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INTERNAL MEDICINE REVIEW

CORE CURRICULUM

SIXTEENTH EDITION

Book 4 of 5

Topics in this volume:

Endocrinology

Hematology

Oncology

Allergy & Immunology

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Editor in Chief

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SIXTEENTH EDITION

INTERNAL MEDICINE REVIEW

CORE CURRICULUM

ENDOCRINOLOGY

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Endocrinology

HELPFUL GENERALITIES

If you want to test for hyposecretion of a hormone, try to stimulate it. Example: In cases of suspected adrenal insufficiency, the ACTH stimulation test is performed to stimulate cortisol production.

If you want to test for hypersecretion of a hormone, try to suppress it. Example: In cases of suspected Cushing syndrome, the dexamethasone suppression test is performed to suppress production of cortisol.

Important characteristics to know about a hormone:

- What is its function?
- Where is it produced and secreted?
- What stimulates and inhibits its release?
- Where are these controls?
- How is it secreted? Is it diurnal or tonic?

Note: Many endocrine glands are responsive to regulatory feedback mechanisms, which determine the extent of hormone secretion by either negative feedback or positive feedback. Negative feedback decreases the deviation from an ideal normal value and is important in maintaining homeostasis. Most endocrine glands are under the control of negative feedback mechanisms.

PRIMARY vs. SECONDARY vs. TERTIARY

With regard to glandular abnormalities:

Primary refers to disease in the gland that secretes the hormone. Example: Primary hypothyroidism means the thyroid gland is diseased and not producing thyroxine.

Secondary refers to disease of the gland that controls the primary gland. Example: Secondary hypothyroidism means the pituitary is diseased and not producing TSH to stimulate the thyroid to make thyroxine.

Tertiary refers to disease of the gland that controls the gland that controls the primary gland. Example: Tertiary hypothyroidism means the hypothalamus is diseased and not producing TRH to stimulate the pituitary to release TSH to stimulate the thyroid to make thyroxine.

Let's do one more example:

Primary hyperaldosteronism means that the disease is in the gland that makes aldosterone, which is the adrenal. This would be an aldosterone-secreting tumor.

Secondary hyperaldosteronism means that the disease is in the gland that controls aldosterone release. The kidney releases renin, which stimulates the adrenal to produce aldosterone. So, in secondary hyperaldosteronism, disease is at the level of the kidney. This would be renovascular disease or a renin-secreting tumor.

POSTERIOR PITUITARY

The pituitary gland is considered the master gland. Functionally, it is comprised of the anterior pituitary and the posterior pituitary, each of which participates in different hormonal axes. Each axis has a different set of hormonal output and controls.

The hypothalamus controls output of the anterior pituitary by means of hormones. It controls the output of the posterior pituitary (neurohypophysis) by direct nerve stimulation. The posterior pituitary stores and releases oxytocin and antidiuretic hormone ([ADH]; also called vasopressin). The anterior pituitary contains osmoreceptors, which control ADH release and are responsible for the sensation of thirst.

Above a certain threshold of serum osmolality (relatively less water than solute), the kidneys have a compensatory and proportionate response of concentrating the urine in response to the secretion of ADH. The threshold set point is decreased (ADH is released at a lower osmolality) by pregnancy and pre-menses; the set point is increased by chronic hypervolemia, acute hypertension, and corticosteroids. Volume contraction both increases the amount of ADH released and decreases the threshold set point.

Serum osmolality can be estimated. Remember the formula: $\text{Osmolality} = 2[Na+] + (\text{Glucose}/18) + (\text{BUN}/2.8)$.

ADH also is released in response to non-osmotic factors; the most potent of these is nausea, which increases ADH levels to several hundred times normal. Thirst begins when serum osmolality exceeds 295 mOsm/L and becomes more intense as serum osmolality increases. Dehydration and hypovolemia also increase thirst and thereby increase the secretion of ADH, but only in extreme circumstances such as shock.

ANTERIOR PITUITARY GLAND

OVERVIEW

The anterior pituitary contains 6 hormones:

1) Adrenocorticotropic hormone (ACTH)
2) Growth hormone (GH)
3) Luteinizing hormone (LH)
4) Follicle-stimulating hormone (FSH)
5) Prolactin (PRL)
6) Thyroid-stimulating hormone (TSH)

The hypothalamus-pituitary-target organ loops stimulate hormone production when serum levels are low and inhibit hormone secretion when serum hormone levels are high. The hypothalamus stimulates pituitary hormone secretion, which then stimulates target organ hormone production. Target organ hormones negatively feed back to both the pituitary and the hypothalamus.

There are 2 types of signals that control the release of anterior pituitary hormones:

1) The stimulatory hormones produced by the hypothalamus (e.g., thyrotropin-releasing hormone)
2) Target organ hormone feedback (e.g., thyroxine, cortisol)

ACTH has a diurnal variation with a peak at 3–4 a.m. and a nadir at 10–11 p.m. ACTH stimulates the adrenal gland to produce corticosteroids and androgens, and it has a regulatory effect on production of mineralocorticoids. ACTH increases in response to corticotropin-releasing hormone (CRH) and physical or psychological stresses.

GH is secreted in a pulsatile fashion and is regulated by 2 hypothalamic-releasing hormones—growth hormone-releasing hormone (**GHRH**) and somatostatin (also known as growth hormone-inhibiting hormone or **GHIH**). GHRH causes release of GH from the pituitary, and somatostatin/GHIH inhibits release of GH from the pituitary. Somatostatin/GHIH also has the capability to inhibit the release of TSH from the pituitary.

LH and **FSH** are produced by gonadotrophs, and production is regulated by pulsatile secretion of gonadotropin-releasing hormone (**GnRH**) from the hypothalamus. **Inhibin** (produced in the ovary and testis) inhibits only FSH secretion.

PRL is different from the other hormones because it is under tonic inhibition by hypothalamic dopamine sent down the pituitary stalk.

TSH secretion is stimulated by hypothalamic thyrotropin-releasing hormone (**TRH**) and inhibited by T_4, T_3, and somatostatin/GHIH.

PITUITARY TUMORS

Overview

Pituitary tumors are most often found incidentally or following imaging of the brain secondary to a patient's symptomatic complaints. Pituitary tumors are due to the abnormal proliferation of cells of the anterior pituitary. The first step in evaluating a pituitary tumor is to determine whether it is functionally abnormal and whether it is secreting an abnormal amount of any of the various hormones.

If functionally abnormal, any of the following cell types can be responsible for the tumor growth and may have any of the following effects:

- **Lactotrophs** (prolactinomas) --› hyperprolactinemia; tied with gonadotrophs as the most common type of macroadenomas
- **Gonadotrophs** → variable presentation:
  - Mass effect + clinically silent
  - Mass effect +/– gonadotropin deficiency/ partial panhypopituitarism
  - Mass effect +/– gonadotropin hypersecretion; tied with lactotrophs for most common type of macroadenomas
- **Somatotrophs** → hypersecretion of GH resulting in acromegaly
- **Corticotrophs** --› hypersecretion of ACTH resulting in Cushing disease
- **Thyrotrophs** → hyperthyroidism = least common
- **Mixed cell type** (somatotrophs + lactotrophs) → features of both acromegaly and hyperprolactinemia

It is important to check prolactin in somatotroph tumors and IGF-1 in lactotroph tumors.

Common mass effect symptoms include headaches, diplopia or visual field defects (bitemporal hemianopsia, most commonly), and seizures. Less commonly, adenomas can extend and cause CSF rhinorrhea. Acute hemorrhage into an adenoma causes apoplexy.

Especially suspect a pituitary adenoma when a patient presents with multiple hormone abnormalities, such as a mixture of hypothyroid and adrenal insufficient symptoms (i.e., reflexes with delayed returns, confusion, alopecia, constipation, menorrhagia or amenorrhea plus hyponatremia, nausea/vomiting, low-grade fever, and postural hypotension).

When given FSH and LH levels, always determine whether the levels are appropriate for the reproductive stage of the female (pre- vs. postmenopausal). For example: If a postmenopausal female patient has inappropriately low or normal FSH and LH levels (should have an elevated FSH level), there is a disruption in production of gonadotropins.

Diagnosis: If a patient's history/PE suggests a pituitary tumor (or if an imaging study done for other reasons shows an incidental pituitary mass), the initial goal is to determine which cell type has expanded into a mass. Start by imaging the tumor with an MRI (if not already done), and assessing the following hormones for excesses or deficiencies:

- Prolactin
- IGF-1 to screen for acromegaly
- 24-hour urine free cortisol concentration or 1 mg overnight dexamethasone suppression test (if suspect cortisol excess) or ACTH stimulation (if suspect cortisol deficiency)
- TSH and free thyroxine (FT_4)
- α subunit, FSH, and LH

α subunits are inactive pieces of glycoprotein and, when found in increased amounts, they support a diagnosis of gonadotroph adenoma. Finding these subunits indicates that a pituitary mass is definitely pituitary in origin (vs. non-pituitary, such as craniopharyngioma). On MRI, craniopharyngiomas present as calcified cystic suprasellar lesions and are considered to be benign. However, they may cause symptoms secondary to mass effect and impingement on the optic nerve.

When and how to properly order these hormone tests is discussed in their representative sections that follow.

Quick Quiz

- What is meant by positive and negative feedback regulation in endocrine diseases? Which is most common: positive or negative feedback?
- What are the definitions of primary, secondary, and tertiary hormone diseases?
- What are the hormones of the posterior pituitary?
- What is the formula to estimate serum osmolality?
- What are the hormones of the anterior pituitary?
- What are typical signs and symptoms of a pituitary tumor?
- Aside from a prolactinoma, what are the other causes of hyperprolactinemia?

Radiologists may occasionally report an "empty sella." An apparent empty sella may be caused by loss of the pituitary, but it may also be normal. 90% of the patients with empty sella syndrome are multiparous women whose pituitary has been displaced and compressed by CSF but functions normally. No treatment is needed for empty sella syndrome if no hormone deficiencies are associated. Of course, the sella may actually be "empty," and the patient may have hypopituitarism.

Hyperprolactinemia and Prolactinomas

A serum prolactin concentration that is repeatedly >20 ng/mL is elevated and is termed "hyperprolactinemia."

A level of 21–40 ng/mL is considered a slight elevation and can be caused by many factors:

- Drugs that are dopamine antagonists; i.e., metoclopramide, verapamil, and certain antipsychotics (phenothiazines, haloperidol, risperidone)
- Diseases of the hypothalamus and/or pituitary stalk that interfere with production or transport of dopamine; e.g., sarcoidosis and trauma
- Pregnancy or estrogen use (Estrogen inhibits dopamine outflow.)
- Nipple stimulation in lactating women
- Chest wall injuries
- Hypothyroidism
- Chronic kidney disease
- Prolactinomas
- Food intake (So prolactin should be checked fasting.)

A serum prolactin concentration > 200 ng/mL almost always is caused by a prolactinoma.

Prolactinomas are the most common functional pituitary tumor. They are usually microadenomas (< 1 cm in diameter), but they can also be space-occupying macroadenomas (≥ 1 cm in diameter) associated with visual field defects. The elevated PRL level decreases the release of GnRH, thereby causing a decrease in LH and FSH. A decreased LH and FSH may result in erectile dysfunction in men and amenorrhea and hirsutism in women. PRL levels generally correlate with tumor size (> 100 μg/L for macroadenomas); if the tumor is ≥ 1 cm, and the PRL level is < 100 μg/L, then the tumor is not a prolactinoma.

Due to amenorrhea, prolactinomas are found earlier in women than in men. Decreased libido is the earliest symptom of a prolactinoma in males and is often ignored; so men tend to present later with visual field defects. By the time most men seek care, the tumor has grown considerably. Galactorrhea occurs in most women with prolactinomas but rarely in men. Long-standing, unrecognized disease is associated with decreased skeletal bone mineralization in both men and women.

Treatment for these tumors is started when the size of the tumor causes neurologic symptoms (headaches, visual field disturbances) or when hypogonadism exists.

Microadenomas usually do not increase to > 1 cm, so observation may be an appropriate option for these patients; however, serial MRIs should be done to assess any change in size. For patients who do require an intervention, therapeutic options include medical and surgical treatment.

For most patients, medical therapy with dopamine agonists such as cabergoline and bromocriptine is the best initial option. Dopamine agonists reduce both the PRL level and tumor size. Cabergoline is better tolerated (twice-weekly dosing and less nausea) and is now available as a generic formulation. Cabergoline is associated with increased cardiac valvulopathy when administered at very high dosages as in the treatment of Parkinson's. Cabergoline is contraindicated in patients with known lung, heart valve, and retroperitoneal fibrotic disease.

Transsphenoidal surgery is used when the patient cannot tolerate drug therapy, or when it is ineffective. Postoperatively, an elevated PRL level is indicative of a recurrence, particularly in the case of macroadenomas. Radiation is usually reserved for postsurgical cases to eradicate any remaining tumor.

When a patient on drug therapy for a prolactinoma becomes pregnant, the drug is stopped, and the patient is observed using a good review of systems, physical exam, and visual fields testing. About 1/3 of macroadenomas enlarge during pregnancy. If the tumor enlarges enough to cause symptoms, bromocriptine can be restarted. If vision is threatened, surgery is a therapeutic option. Both bromocriptine and cabergoline are FDA pregnancy category B drugs.

Acromegaly

Growth hormone (GH) is required for normal growth. GH is suppressed by hyperglycemia, somatostatin, and chronic corticosteroid use and stimulated by hypoglycemia and estrogens.

A single value of GH is not useful in diagnosing acromegaly because its secretion is pulsatile and levels in the blood can vary greatly in a healthy individual. Insulin-like growth factor-1 (IGF-1) is produced by the liver and mediates the growth-promoting effect of GH. Unlike GH, IGF-1 levels are stable throughout the day. IGF-1 is the 1st test done in the workup of acromegaly. Normal levels almost always exclude the diagnosis. If the IGF-1 levels are elevated, perform a GH suppression test (following an oral glucose load). Inadequate suppression confirms the diagnosis of acromegaly.

Gigantism is due to GH excess in childhood, which results in abnormally high linear growth while the epiphyseal growth plates of the long bones are open. Acromegaly is the same disorder of GH excess; however, it occurs during adulthood after the growth plate cartilage fuses. Excessive soft tissue growth is characteristic of acromegaly and may recede following treatment. Long bones changes, however, do not recede following treatment.

Greater than 99% of acromegaly cases are due to a benign, well-defined adenoma that is easily recognized on CT or MRI.

Acromegaly has an insidious onset associated with an increased mortality when untreated and is usually diagnosed late in the course of disease. Affected patients typically are symptomatic in their late 30s to mid 40s.

Signs and symptoms of acromegaly include:

- Enlarging hands and feet
- Coarsening of the facial features
- Deepening of the voice
- Carpal tunnel syndrome
- Acanthosis nigricans
- Skin tags
- Pronounced jaw growth (which leads to multiple dental problems)
- Excessive sweating, body odor
- Sleep apnea

The most important long-term problem associated with acromegaly is cardiovascular disease, including:

- Ischemic heart disease
- Cardiomyopathy
- Diastolic dysfunction
- Hypertension
- Left ventricular hypertrophy
- Increased strokes

Associated diseases include obstructive sleep apnea, insulin resistance and diabetes, and colon polyps that have an increased risk of malignancy.

Screen by checking for a high age-adjusted IGF-1 level. Confirm the diagnosis by demonstrating a failure of GH to suppress after a 75-gm oral glucose load (OGTT). A post-OGTT GH level > 1 ng/mL is diagnostic of acromegaly. Do not order a random GH level. Also check prolactin (elevated due to co-secretion in 25% of GH tumors). Large tumors disrupt thyroid and gonadotropin release, so these levels may also need to be assessed.

Treat all patients with transsphenoidal surgery, even if they are asymptomatic. Give somatostatin analogs (octreotide), +/– dopa agonists (bromocriptine or cabergoline), or GH receptor antagonists (pegvisomant) as adjuvant treatment to patients with residual tumor or to those who are poor surgical candidates. Some experts recommend medical therapy with somatostatin analogs as initial therapy. Radiation is used only as adjuvant treatment. All patients with a diagnosis of acromegaly should have a screening colonoscopy and echocardiogram regardless of age.

Other Pituitary Tumors

We discussed gonadotroph tumors in the Overview. Recall they are tied with prolactinomas for being the most common type of macroadenomas. Gonadotroph tumors can present variably as:

- mass effect and hormonally silent, or
- mass effect with symptoms of hypogonadism/partial panhypopituitarism, or
- mass effect with symptoms of gonadotropin excess (rare).

A diagnosis of gonadotroph adenoma is supported by finding an increase in free α subunits or high levels of FSH and/or LH.

Transsphenoidal surgery is indicated for symptomatic nonfunctioning or gonadotroph tumors.

For asymptomatic patients with preserved endocrine function and no mass encroachment on vital structures, observation with serial imaging studies may be appropriate.

Radiation is an option for certain types of tumors but primarily is used postsurgically to contain residual tumor mass. Patients who have had pituitary radiation need their anterior pituitary function monitored indefinitely.

With severe primary hypothyroidism (disease of the thyroid gland), the pituitary thyrotrophs become hyperplastic and may simulate a tumor—imaging shows a pituitary mass. Free T_4 is low, TRH and TSH levels increase, and the elevated TRH suppresses dopamine, which increases PRL; thus, the patient may be mistakenly diagnosed with a prolactinoma. Treatment with thyroxine replacement causes the thyrotrophs to shrink, and PRL levels to normalize.

Metastatic cancer can be seen in the pituitary—the posterior part of the gland is most often involved. Posterior pituitary mets present as diabetes

Quick Quiz

- How do you test for acromegaly?
- Which cancers metastasize to the pituitary?
- What is the workup for a pituitary incidentaloma?
- What is the clinical presentation of pituitary apoplexy? The treatment?

insipidus. Breast and lung cancer mets are most common. Lymphoma and leukemia can present as primary cancer of the pituitary.

PITUITARY INCIDENTALOMA

Some pituitary tumors are incidentally found when brain imaging is performed for other reasons (termed an "incidentaloma").

Formally test visual fields of patients who have tumors that impinge on the optic nerve or abut the chiasm. Work up the patient for hyper- and hypo-secretion of hormones:

- Measure PRL because prolactinomas are common.
- Check IGF-1 to screen for acromegaly.
- Order either a 24-hour urine free cortisol or a low-dose overnight dexamethasone suppression test if you suspect cortisol excess (e.g., HTN, hyperglycemia, associated physical characteristics). A random ACTH level is not recommended at time of initial screening.
- Check TSH and FT_4.
- Check a morning cortisol to assess hyposecretion.
- Check LH, FSH and testosterone.
- Gonadal function in premenopausal women can be assessed by history and physical exam alone.

If the tumor is nonfunctional, does not impinge on the optic chiasm, and there is no hyposecretion of hormones, then the tumor can be reimaged in about 6 months and again in 1 year to assess growth.

Indications for surgical removal include visual field or other ophthalmologic defects, a lesion in or abutting the optic chiasm or compressing the optic nerve, apoplexy, or discovery of acromegaly or Cushing disease.

Additionally, recognize that the tumor could also be a metastatic focus—lung and breast are most common.

Apoplexy and Sheehan Syndrome

Pituitary apoplexy is a neurosurgical emergency caused by hemorrhage into a pituitary mass. Suspect apoplexy in the patient who presents with a variable onset of severe headache, N/V, meningismus, vertigo, visual defects, and fluctuating consciousness. These symptoms may be superimposed on chronic symptoms of hormone excess or deficiency if there is an underlying adenoma. Laboratory values should show decreased ACTH and cortisol levels. On stimulation with cosyntropin, the cortisol level increases since the adrenals remain intact. The most dangerous situation is an acute, life-threatening hypotension from central or secondary adrenal insufficiency.

The symptoms may occur immediately ("mule kick in the head") or may develop over 1–2 days. Diabetes with microvasculature changes, radiotherapy, and concurrent warfarin use are risk factors. Patients may present with an acute onset and complaints of "the worst headache of my life." Apoplexy and Sheehan syndrome may be difficult to distinguish from subarachnoid hemorrhage. Pituitary hormones are abnormal in apoplexy and Sheehan syndrome.

Diagnose with CT/MRI ("high-density mass in the sella") and differentiate from a leaking aneurysm.

Treatment: If the symptoms are mild, only corticosteroids are necessary. Edema may cause a mass effect and require emergent decompression. Consult a neurosurgeon to make the call on whether to use corticosteroids or take the patient to surgery.

Sheehan syndrome (1/10,000 deliveries) is postpartum hypopituitarism caused by ischemic necrosis due to blood loss and hypovolemic shock during and after childbirth. It always involves the anterior pituitary and sometimes also affects the posterior pituitary, but rarely causes central diabetes insipidus.

In mild cases, the syndrome presents with postpartum amenorrhea and failure to lactate. Severe cases present with symptoms of adrenal insufficiency (weakness, lethargy, anorexia) and failure to lactate.

Other causes of hypopituitarism include pituitary and parasellar tumors, radiation, infections, inflammation, and infiltrative processes, such as sarcoidosis or histiocytosis X.

DIABETES INSIPIDUS

Diabetes insipidus (DI) can be neurogenic (decreased ADH production) or nephrogenic (decreased ADH effect on the kidneys). Neurogenic DI is either genetic (50%) or acquired. The acquired neurogenic form is caused by CNS injury, infiltrative diseases (e.g., eosinophilic granuloma, sarcoidosis, granulomatosis with polyangiitis), or cancer; however, occasionally, it is idiopathic or vascular (e.g., Sheehan syndrome). Nephrogenic DI is also either genetic (due to gene mutations in the ADH receptor or in an aquaporin [aquaporins are discussed in Nephrology, Book 2]) or acquired. Drugs are an important cause of DI, especially lithium. Any cause of hypercalcemia > 11 mg/dL for an extended period also can cause acquired DI. Also know that Sjögren's and sickle cell disease can cause DI.

Understand that expression of DI, whether central (neurogenic) or nephrogenic, is variable with subsets of disease being named "partial central" and "partial nephrogenic" DI. Know how to distinguish central from

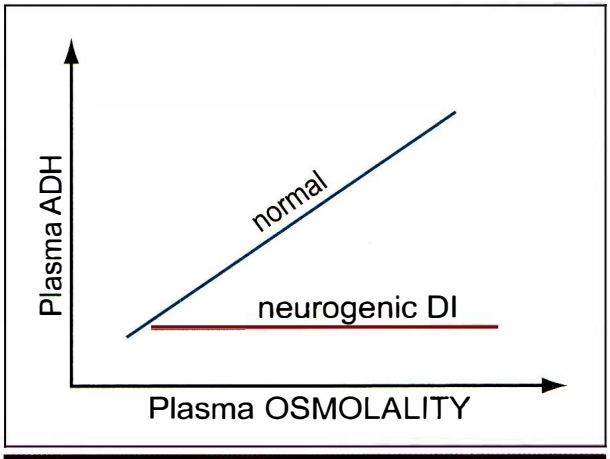


Figure 7-1: Neurogenic DI

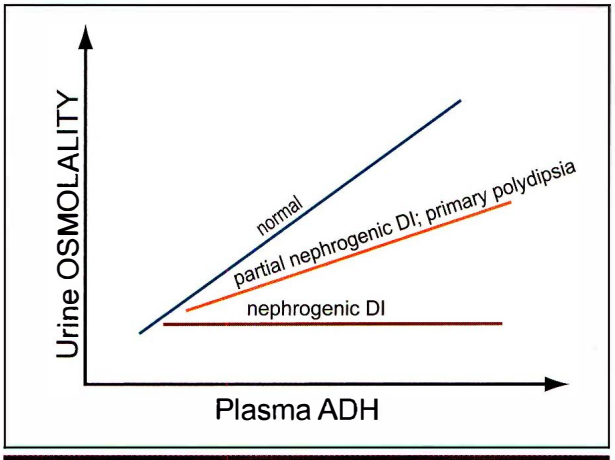


Figure 7-2: Nephrogenic DI

nephrogenic disease. And know that primary polydipsia mimics DI, which should be considered in patients with polydipsia and polyuria. The water deprivation test helps to differentiate between DI and psychogenic polydipsia.

Nocturia usually is the 1st symptom of DI. Volume depletion rarely occurs, except in patients with impaired thirst or decreased access to water; e.g., infants, nursing home patients. With water restriction, DI causes very dilute polyuria (> 3L/day) and hypernatremia.

Diagnose the cause of DI with the water-deprivation test, in which you measure hourly ADH and plasma + urine osmolality. The 2 mechanisms for proper diagnosis can be shown with 2 simple graphs, which are important to know.

The first graph, Figure 7-1, has ADH as a function of plasma osmolality. If ADH does not increase with increasing plasma osmolality, the cause of the DI is central (neurogenic). If only numbers are given (instead of a graph), diagnose central DI when the urine fails to concentrate with water deprivation, but does concentrate after desmopressin administration.

The second graph, Figure 7-2, has urine osmolality as a function of plasma ADH. If there is increasing ADH with no associated increase in urine osmolality, the diagnosis is nephrogenic DI. If only numbers are given, diagnose nephrogenic DI if the urine fails to concentrate with water restriction and desmopressin administration.

Treat neurogenic DI with desmopressin (DDAVP®, Stimate●), either subQ or intranasally. Occasionally, desmopressin may be administered orally to patients with mild neurogenic DI. Nephrogenic DI is treated with a low-sodium diet and thiazide diuretics +/– amiloride.

If the thirst and ADH osmoreceptors are damaged, a patient has recurrent hypernatremic dehydration without thirst (adipsic hypernatremia). ADH does not increase with increasing osmolality but does respond to all the other stimulants mentioned above. To exclude, observe whether the patient develops thirst as serum osmolality increases.

SIADH

Aside from being idiopathic, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has many causes, including CNS trauma or infection, pulmonary disease, drugs, and ectopic hormone production---especially with small cell lung cancer.

Generally, the patient has normal volume status but inappropriate urinary concentration for the hyponatremic, hyposmolar state. Serum osmolality is low, and urine osmolality is inappropriately high (the patient should be excreting water, not absorbing more). See Nephrology, Book 2, for more discussion of SIADH.

THYROID GLAND

NORMAL PHYSIOLOGY

TRH in the hypothalamus stimulates the pituitary to secrete TSH, which then stimulates secretion of thyroxine (T_4) by the thyroid. Triiodothyronine (T_3) is the active hormone, and some is secreted by the thyroid, but 80% is produced by deiodination of T_4 in the peripheral tissues. T_4 binds very tightly to TBG (thyroxine-binding globulin) and weakly to albumin. T_3 also binds to these proteins, but not as strongly. Only a very small fraction of the total T_4 and total T_3 is unbound—and, therefore, free and active. The free component is generally the fraction that you want to measure when testing for thyroid disorders.

THYROID FUNCTION TESTS

"Thyroid function tests" (TFTs) include TSH, FT_4, and sometimes FT_3. The T_3 resin uptake test has been replaced by the FT_4 assay.

When screening for primary thyroid disease, start with a TSH to detect abnormalities of thyroid function—both hyper- and hypothyroidism. If the TSH is high, then order a FT_4 to assess for hypothyroidism. If the TSH is low, then order a FT_3 + FT_4 to assess for hyperthyroidism (Table 7-1).

QuickQuiz

- What happens to the urine specific gravity and serum sodium in a patient with diabetes insipidus who is on water restriction?
- What are the urine specific gravity, serum sodium, and serum osmolality in a patient with SIADH?
- What is the first screening test of choice for hypo- and hyperthyroidism?
- What is the difference between the thyroid uptake and the thyroid scan? What do the different tests tell you?

OTHER THYROID TESTS

Uptake and Scan

If hyperthyroidism is established (with a low TSH and high FT_4), then the next step in the workup is to determine the cause of thyroid dysfunction. Two tests, the radioactive iodine uptake (RAIU) and thyroid scan (also called "scintigraphy"), help to establish a diagnosis by measuring the degree and pattern of iodine uptake by the thyroid. In clinical practice, these tests are often referred to as "the uptake scan," but recognize these are 2 different tests (the uptake and scan). The RAIU uptake measures the degree of iodine uptake (given as a percent uptake) by the thyroid. The scintigraphy scan assesses the pattern of iodine uptake (takes a "picture"). With thyroid scintigraphy, a diffuse, focal, or multifocal pattern is noted and helps to make a specific diagnosis.

RAIU: The patient is given a small dose of radioactive iodine; and then later, a radiation detector over the thyroid determines the percentage of the dose that was taken up by the gland. Know the uptake results (high, low, or normal) for various causes of thyroid disease.

RAIU is increased in:
- Graves disease
- TSH-secreting pituitary tumor
- Hot nodules (solitary or toxic multinodular goiter [MNG]), if hot enough
- hCG secreting tumor
- Iodine deficiency

RAIU is decreased in:
- Thyroiditis
- Excess exogenous T_4 or T_3
- Iodine excess (contrast dye, diet, amiodarone)
- Factitious hyperthyroidism

Thyroid scan (scintigraphy): The patient is given a dose of ^{99m}Tc or radioiodine (^{123}I) and a scintillation scanner produces a rough picture indicating how these isotopes localize in the thyroid. So the scan gives information on the size, shape, and overall activity of the gland. It also shows hot (hyperfunctioning) and cold (underfunctioning) spots. The scan is typically used for assessing goiters and nodular disease. It tells you whether a nodule is hot or cold and single or multiple.

The thyroid RAIU and scintigraphy scan are essential in determining the cause of hyperthyroidism and are never used in the workup of a hypothyroid patient.

Again: RAIU produces a number; the scan produces a picture.

Table 7-1: Overview of Thyroid Function Tests

TSH	FT_4	Clinical Status
High	Low	Primary hypothyroidism, chronic lymphocytic thyroiditis (Hashimoto's)
	Normal	Incipient/subclinical hypothyroidism
	High	Pituitary (secondary; TSH-induced) hyperthyroidism, thyroid hormone resistance syndromes
Low	High	Thyrotoxicosis (primary hyperthyroidism), subacute or silent thyroiditis
	Normal	Euthyroid sick syndrome, incipient/subclinical hyperthyroidism, multinodular goiter with autonomous production
	Low	Pituitary hypothyroidism

Ultrasound

Ultrasound (U/S) is used to determine the size and number of nodules, to determine whether a nodule is cystic or solid, to stratify a nodule's malignancy risk (low, medium, or high), to localize a nodule for fine needle aspiration, to follow up a nodule's size over time when malignancy is suspected, and to follow up a patient after thyroid cancer resection. U/S is discussed further in the section on the workup of thyroid nodules.

When a patient presents with a palpable nodule and is hyperthyroid, a RAIU and scintigraphy should always precede a thyroid ultrasound (U/S). When a patient presents with a palpable nodule and is hypothyroid or euthyroid, the next step in the workup is to go directly to U/S. This is discussed further under Nodule Workup (see page 7-13).

Biopsy

Fine needle aspiration (FNA) is a biopsy method used to evaluate a thyroid nodule (discussed on page 7-13).

HYPOTHYROIDISM

Findings

Chronic autoimmune thyroiditis (previously Hashimoto disease) is the most common cause of hypothyroidism.

It normally presents as gradual hypothyroidism, but it can present with a hyperthyroid phase, so-called "Hashitoxicosis." Other causes of thyroiditis also can be associated with a transient, self-resolving state of hypothyroidism.

Symptoms of hypothyroidism, regardless of cause, include:

- Cold intolerance
- Weight gain
- Fatigue
- Menstrual irregularities
- Mental slowness
- Constipation
- Puffiness in the face
- Extremity swelling
- Hoarseness
- Coarse hair/alopecia
- Brittle nails
- Dyspnea with exercise
- Carpal tunnel syndrome

Signs on physical exam include:

- Cool/Pale skin
- Coarse hair
- Periorbital and non-pitting edema
- Tongue enlargement (severe cases)
- Bradycardia
- Delayed reflexes

Abnormal labs/studies include:

- Hyponatremia
- Normochromic/normocytic anemia (pernicious anemia in 10% of cases)
- Hyperlipidemia (increased total cholesterol and LDL)
- Rare pericardial effusions on echocardiograms and possibly an increased PRL level (although usually < 100)

If a woman has an elevated PRL and amenorrhea, check thyroid function first. The elevated PRL and amenorrhea resolves with thyroxine treatment if they are due to hypothyroidism. If the patient is not hypothyroid, evaluate for a prolactinoma. And if the PRL level is > 200, the woman almost assuredly has a prolactinoma, even if she is also hypothyroid.

Diagnosis of Hypothyroidism

Check the TSH and the FT_4. Values are used together to determine whether the patient is hypothyroid and whether disease is most likely primary (in the thyroid), secondary (in the pituitary), or tertiary (in the hypothalamus):

- High TSH (> 10 mU/L) and low FT_4 = overt primary hypothyroidism.
- High TSH (5–10 mU/L) and normal FT_4 = "subclinical" or incipient primary hypothyroidism. Adrenal insufficiency can also slightly increase the TSH.

Subclinical hypothyroidism is an area of evolving understanding. We know TSH drifts up as we age and possibly as we gain weight. Studies indicate that patients with TSH 5–10 mU/L develop overt hypothyroidism at a rate of about 4% per year. The incidence of overt disease is proportional to the degree of TSH elevation (TSH > 6 mU/L indicates the most risk). A family history of autoimmune thyroid disease and evidence of associated anti-thyroid peroxidase (anti-TPO) are risk factors.

Treating subclinical hypothyroidism to reduce rates of hyperlipidemia and ischemic heart disease is too controversial for testing on Board exams; and in clinical practice, the decision to treat is very individualized. The guidelines at this time generally recommend no treatment for patients whose TSH is < 10 mU/L.

Low or inappropriately normal TSH with a low FT_4 = secondary or tertiary hypothyroidism except in hospitalized, sick patients who may have euthyroid sick syndrome (see page 7-12). Suspect secondary/tertiary disease when you see a deficiency of multiple hormones. (Isolated hypothyroidism due to pituitary or hypothalamic dysfunction almost never occurs.)

Secondary and tertiary diseases are differentiated by imaging the sella; no routine stimulation test is available. TRH is never given to stimulate TSH in order to distinguish secondary from tertiary disease because results are not reliable.

Treatment of Hypothyroidism

Treatment for overt hypothyroidism is levothyroxine (T_4) alone. Adding T_3 might help with some neuropsychological symptoms, but randomized controlled trials show that T_3 does not confer any benefit beyond that achieved with T_4 monotherapy. In addition, T_3 therapy is harder to regulate and may cause hyperthyroid effects, such as atrial fibrillation. T_3 has a short half-life—so short that wild swings in blood levels are noted when T_3 is used therapeutically; therefore, it is not recommended in the treatment of hypothyroidism.

T_4 has a long half-life and takes weeks to equilibrate, so in most cases, you can start patients on 50–100 μg/day.

You need to allow enough time for the blood level to come to a steady state, so don't check the TSH again until a full 6–8 weeks after a dose adjustment. For patients with the potential for coronary artery disease, especially the elderly, start low and slowly titrate up.

QuickQuiz

- What are common signs and symptoms of hypothyroidism? Lab tests?
- How do you make a diagnosis of secondary or tertiary hypothyroidism?
- What are the risks of overtreating hypothyroidism?
- What are signs and symptoms of myxedema coma?
- What is the treatment for myxedema coma?

Follow the TSH to evaluate treatment, and keep the level within the lower half of the normal reference range for your laboratory. Adjust the dose of levothyroxine upward in increments of 12.5–25 μg. Don't overtreat, because you risk inciting complications of hyperthyroidism, such as atrial fibrillation and osteoporosis.

Know that a TSH elevation > 10 mU/L in a patient prescribed > 200 μg/day of T_4 is most commonly due to nonadherence.

Watch out for other conditions and drugs that interfere with absorption of thyroxine, raise TBG levels, or increase the metabolism of T_4 (and that could be a cause of persistently elevated TSH despite usual dosages of T_4): malabsorption syndromes, estrogens, cholestyramine, iron/calcium/aluminum supplements, and resin binders.

If a patient is hypothyroid and needs emergent surgery for another reason, do it! Otherwise, try to restore euthyroidism before surgery.

Always treat pregnant hypothyroid patients and follow their TSH levels during pregnancy because their requirements increase (dose needs to be adjusted upwards 50% or more over the pre-pregnancy dose). Failure to treat maternal hypothyroidism during pregnancy can adversely affect the baby.

Myxedema Coma

Myxedema coma is one of 2 thyroid emergencies (the other being thyroid storm). Mortality is 30–40% and is higher in the elderly and in those with heart disease. The diagnosis depends on recognition of classic signs and symptoms. Management includes providing supportive care and instituting empiric treatment for hypothyroidism, possible adrenal insufficiency, and possible infection until the case is completely investigated.

Any cause of hypothyroidism can lead to myxedema coma. Patients usually present with a history of progressive hypothyroid symptoms. If not diagnosed, long-standing hypothyroidism can develop into myxedema coma; or, patients with known but inadequately treated hypothyroidism can develop coma precipitated by infections, exacerbations of heart disease, opiates, or cold temperatures. For the patient who presents to the emergency department obtunded with multi-system failure, quiz relatives for possible antecedent signs and symptoms of thyroid dysfunction.

Decreased mentation and hypothermia (even body temps down to 74° F!) are the classic findings. Other signs indicate a generalized slowing of systemic processes: hypoventilation, hypoglycemia, hypotension, and bradycardia.

Other symptoms depend on why the patient has thyroid disease:

- If the disease is primary, there may be no other symptoms; but, be aware that, rarely, primary autoimmune processes can affect both the thyroid and the adrenal.
- If the disease is secondary, the patient may have symptoms of other hormone deficiencies—again, adrenal insufficiency is especially important.
- Rarely, a patient can present psychotic ("myxedema madness") instead of obtunded.
- Patients may have a pericardial effusion.
- Up to 25% of patients have seizures.

Other lab abnormalities: hyponatremia, hypoglycemia, anemia, and hyperlipidemia.

Diagnose myxedema coma by history and PE.

Treatment of myxedema coma: Before initiating treatment, draw a serum TSH and FT_4, baseline cortisol, and ACTH to rule out coincident adrenal insufficiency; then give a dose of cosyntropin. Follow up cortisol measurements at 30 and 60 minutes to assess whether the patient has an appropriate rise in response to the ACTH stimulation (see Adrenal Gland on page 7-15).

Treat with either T_3 (preference of some experts because of rapid onset and decreased conversion of T_4 to T_3 during acute illness) or intravenous T_4 (due to reduced absorption with oral) or both T_3 and T_4 (preferred by most experts) using a loading dose and a smaller daily dose thereafter.

Give empiric glucocorticoids until the results of stimulation testing are available to determine whether to continue the steroids long-term. Once adrenal insufficiency has been eliminated, the steroids can be discontinued.

Give empiric broad-spectrum antibiotics until infection is excluded. Pay particular attention to gradually warming the body temperature, maintaining adequate blood pressure with IVF, and normalizing the serum sodium.

Know that the mortality of myxedema coma is directly related to the degree of hypothermia, and that passive rewarming is one of the most important elements of supportive care.

HYPERTHYROIDISM

Findings

The most common cause of hyperthyroidism is autoimmune Graves disease. Other common causes include toxic multinodular goiter (MNG), toxic adenomas, and thyrotoxicosis due to chronic autoimmune thyroiditis (hashitoxicosis). Subacute and postpartum thyroiditis also can cause thyrotoxicosis, but these are typically transient illnesses not associated with long-term primary hyperthyroid disease.

Symptoms of hyperthyroidism, regardless of cause, include:

- Anxiety and restlessness
- Irritability
- Insomnia
- Impaired concentration (even confusion or psychosis)
- Weight loss
- Diarrhea
- Heat intolerance
- Alopecia
- Onycholysis
- Dyspnea
- Menstrual irregularities (oligo- or amenorrhea, impaired fertility)
- In males: gynecomastia, decreased libido, impaired spermatogenesis, and/or erectile dysfunction

Exam may reveal:

- Warm skin
- The "hyperthyroid stare"(exophthalmos)
- Lid-lag
- Hypertension
- Increased heart rate
- Atrial fibrillation or ectopy in up to 20% of patients (more common in elderly)

Abnormal general labs/studies:

- Low total cholesterol and LDL
- Normochromic/normocytic anemia
- Hypercalcemia with increased bone alkaline phosphatase
- Osteopenia/osteoporosis
- Increased cardiac output, dilated cardiomyopathy, and any tachyarrhythmia

Be especially alert to diagnose hyperthyroidism in the elderly patient who may have new-onset atrial fibrillation or depression (termed "apathetic hyperthyroidism"). Hyperthyroidism in the elderly can cause a "failure-to-thrive" picture with apathy, anorexia, and weight loss. In practice and on exams, you may need to distinguish thyroid disease from polymyalgia rheumatica and clinical depression or adjustment disorder.

Graves Disease

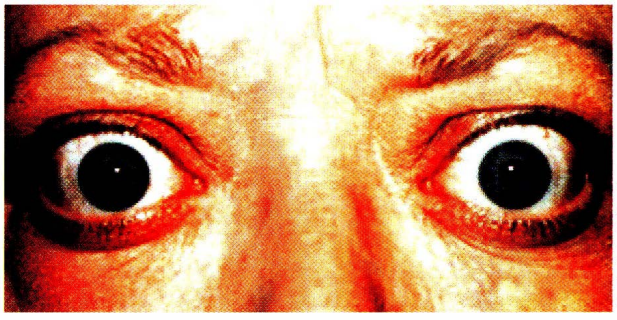
Overview

Graves disease is the most common cause of thyrotoxicosis. It is caused by thyroid-stimulating immunoglobulins, IgG antibodies that bind to and stimulate the TSH receptors in the thyroid gland.

Specific Graves disease physical findings (in addition to those listed above; also see Image 7-1):

- A diffuse, soft, symmetric goiter (but not always).
- Ophthalmopathy: Exophthalmos and periorbital edema with impaired extraocular movements → diplopia, corneal ulcerations, visual impairment. Know that the risk of Graves ophthalmopathy (GO) is increased in both active and passive smokers. Smoking is also associated with progression of GO after RAI therapy and adversely affects the course of GO during treatment with steroids and orbital radiotherapy. Know that 90% of Graves patients have ocular involvement on MRI or CT. Clinically apparent GO requires formal eye testing and imaging to determine the degree of eye inflammation. If a patient with mild-to-moderate GO decides on RAI treatment, pretreatment with steroids is warranted in order to prevent the progressions of GO. RAI is not indicated for patients with severe eye inflammation.
- Dermopathy: Pretibial myxedema is a thickening and redness of the dermis due to a lymphocytic infiltrate that gives it a peau d'orange appearance (looks different from the myxedema seen in hypothyroid patients).
- Immune-mediated hematologic abnormalities, such as pernicious anemia and idiopathic thrombotic purpura.

To diagnose Graves', use a good clinical exam + TFTs + thyroid uptake scan (TUS). TSH is low (usually < 0.01 mU/L), FT_3 and FT_4 are elevated (rarely, only FT_3 is increased with normal FT_4), and the TUS shows increased diffuse uptake. Other common lab abnormalities: elevated alkaline phosphatase, hypercalcemia, anemia, and thrombocytopenia. Autoantibodies are generally not measured, but TSI (thyroid-stimulating immunoglobulins) are positive in > 90% of cases of Graves disease.



Johnathan Trobe / Wikimedia

Image 7-1: Proptosis & lid retraction

QuickQuiz

- What is apathetic hyperthyroidism?
- What specific physical findings confirm the diagnosis of Graves disease?
- What is the result of the thyroid uptake scan in a patient with Graves'?
- What are side effects of medications used to treat Graves'?
- What are the precipitating events leading to thyroid storm?
- In addition to PTU or MMI, beta-blockers, and iodine, what other drug is given to patients to treat thyroid storm?
- What causes subacute thyroiditis?

Treatment of Graves Disease

Treat with antithyroid drugs (methimazole [**MMI**] or propylthiouracil [**PTU**]) and/or thyroid **ablation** with ^{131}I or surgery.

MMI is now the preferred drug in non-pregnant patients because of lower toxicity than PTU. PTU received a FDA boxed warning for increased risk of death due to acute liver failure or severe liver injury, so PTU is no longer 1st line therapy in non-pregnant patients and children. PTU is still 1st line treatment for Graves disease in pregnant patients in the 1st trimester and is still used for thyroid storm.

The most serious side effects of PTU and MMI are hepatic toxicity and agranulocytosis, which are rare and unpredictable. LFTs and CBCs do not require monitoring. Check only if the patient becomes symptomatic (jaundice, dark urine, prolonged fever/sore throat). Side effects almost always disappear when the drug is promptly discontinued.

Beta-blockers help patients with adrenergic symptoms while waiting on the effects of PTU or MMI.

Relapse is much less likely when stimulatory immunoglobulins disappear with treatment, but this happens in a small minority of cases.

In the United States, most patients with Graves disease are treated with thyroid ablation using ^{131}I. Virtually all patients are pretreated with beta-blockers, and many patients are treated with MMI (or PTU) prior to radioiodine ablation. Most patients become hypothyroid months to years after ^{131}I therapy.

Surgery may be indicated in pregnancy, in patients with an associated cold nodule or relapse after radiation, and in some young patients with a large goiter. Worrisome complications of surgery are loss of all parathyroids and damage to recurrent laryngeal nerves.

Thyroid Storm

Storm is the 2nd thyroid emergency that is associated with a high mortality rate (the other is myxedema coma). Storm is most often a precipitated event in patients known or suspected to have undiagnosed or inadequately treated hyperthyroidism. Precipitating events include surgery, infections, or an iodine load, such as amiodarone or contrast dye.

Symptoms of storm are identical to symptoms of hyperthyroidism, only more exaggerated: hypertension, tachycardia, congestive heart failure, fever, psychosis, or delirium. Some patients have constitutional symptoms of nausea, vomiting, and diarrhea. Oddly, some patients develop jaundice. Diagnose the condition with measurement of TSH and FT_4. In virtually all cases, TSH is immeasurable and FT_4 markedly increased.

Storm is characterized by a severe level of metabolic stress that the patient can no longer tolerate. This severe stress results in a relative adrenal insufficiency, even though the adrenal glands may be functioning perfectly and secreting a large amount of cortisol. Patients in storm die from cardiovascular collapse. The most important aspect of treatment is large amounts of glucocorticoids.

Other aspects of treatment include the following:

- Interrupt the physiologic response to excess thyroid hormone: IV propranolol or esmolol.
- Block new hormone synthesis: high-dose thionamide (PTU or MMI).
- Block release of preformed hormone from the gland: stable iodide.
- Block peripheral conversion of T_4 to T_3: iodinated contrast agent, propranolol, and corticosteroids. PTU also does this (but not MMI).
- Give empiric broad-spectrum antimicrobial coverage until infection is excluded.
- Provide supportive care in the ICU with diligent attention to volume status, temperature, and heart rate.

THYROIDITIS

Thyroiditis is divided into the following categories:

- Acute: caused by bacterial infection of the gland (rare).
- Subacute: caused by viruses (also called "granulomatous").
- Chronic: Autoimmune-mediated disease is the most common cause (Hashimoto's). Painless and postpartum thyroiditis are considered variants of "chronic."

Subacute thyroiditis is a common problem in 30–50-year-olds, females > males. It is caused by a viral infection that results in granulomas in the thyroid gland, which becomes fibrotic but returns to normal months later. Patients complain of a very tender neck with pain that may radiate to the ear +/– fever, and are fussy about having their neck examined. As in other causes of thyroiditis, patients may be hypothyroid, hyperthyroid, or euthyroid.

Labs/studies: Initially, T_3 and T_4 are increased, TSH is suppressed, and RAIU is initially decreased. ESR is increased but is too nonspecific to use in diagnosis. Over time, temporary overt hypothyroidism develops in some with low T_4 and increased TSH. RAIU returns to normal. Eventually, T_4 and TSH normalize.

The disorder is self-limited and usually does not require treatment. For severe cases, treat inflammation as needed with ASA or NSAIDs. Glucocorticoids are given as an 8-week taper in refractory/systemic cases. Occasionally, a patient may need beta-blockers to ameliorate the thyrotoxicosis symptoms or levothyroxine for overt hypothyroidism. Reevaluate periodically until the patient's thyroid function normalizes.

Chronic autoimmune thyroiditis (e.g., Hashimoto's) is the most common thyroid problem (4% of the population, affecting women > men) and the most common cause of hypothyroidism. Both genetic and environmental factors are important (however not yet well defined). Cases are clustered in families, and the hypothyroidism is sometimes associated with other autoimmune diseases, such as Type 1 diabetes, primary adrenal insufficiency, pernicious anemia, and vitiligo.

Usually, patients become slowly hypothyroid as the gland is gradually destroyed by autoimmunity, but some patients may present with thyrotoxicosis before disease evolves into overt hypothyroidism. Presenting symptoms, therefore, are variable and depend on whether the disease is causing hypo- or hyperthyroidism. Chronic autoimmune hypothyroidism is characterized by a painless, chronic, lymphocytic infiltration of the gland causing a firm and often irregular goiter which sometimes is confused for multiple nodules (ultrasound helps distinguish). Up to 95% of patients have measurable anti-TPO antibodies. Immune-mediated thyroid cell apoptosis is the ultimate cause of hypothyroidism, but how these antibodies specifically cause cell death is unclear.

Presenting FT_4/FT_3 and TSH may vary on disease presentation:

- Incipient hypothyroidism = normal FT_4, rising TSH (2–10 mU/L)
- Overt hypothyroidism = low FT_4, high TSH (> 10 mU/L)
- Hyperthyroidism = high FT_4/FT_3, low TSH

In an exam situation, most patients with chronic autoimmune hypothyroidism present with hypothyroidism, which does not resolve and must be treated with levothyroxine.

Painless thyroiditis and postpartum thyroiditis are considered variants of chronic thyroiditis because, even though these conditions usually are transient and self-resolve, many patients become hypothyroid with evidence of autoimmunity in the future, especially painless thyroiditis cases.

Patients with **painless thyroiditis** have complaints of either hyper- or hypothyroidism, and some are actually asymptomatic. The disease process generally starts with a hyperthyroid stage (2–4 weeks), which progresses to a hypothyroid stage (4–12 weeks). Most patients recover. The gland shows diffuse, painless enlargement in contrast with subacute thyroiditis. 50% of these patients later develop chronic autoimmune hypothyroidism associated with anti-TPO antibodies.

Postpartum thyroiditis is fairly common, affecting up to 10–15% of postpartum women. Patients present with hyper- or hypothyroid symptoms and a painless goiter. ESR is normal, but many patients do have anti-TPO antibodies. RAIU is decreased. Don't hesitate to treat the hypothyroidism—or to give beta-blockers as needed for thyrotoxicosis. Patients universally recover but need annual follow-up because of the risk of overt hypothyroidism later.

Radiation thyroiditis may develop shortly (7–10 days) after exposure to radiation, which may be in the form of radioactive iodine treatment, radiotherapy of head and neck cancer, or accidental exposure (e.g., nuclear accident).

Remember: RAIU helps distinguish Graves' from thyroiditis as a cause for hyperthyroidism. RAIU is high in Graves and low in patients who are hyperthyroid due to thyroiditis, iodine excess, exogenous T_4 or T_3 ingestion, and struma ovarii (thyroid tissue in an ovarian teratoma). Thyroid scintigraphy scans are diffusely high for both Graves disease and hyperthyroidism caused by thyroiditis, but these are not typically done for non-nodular hyperthyroidism workup.

EUTHYROID SICK SYNDROME

Euthyroid sick syndrome (ESS) is seen in critically ill patients. In states of significant illness, the body does not need much T_3 (the active hormone). Instead, the body converts T_4 to reverse T_3 (rT_3), an inactive compound. The FT_3 is very low while both the FT_4 and TSH are low or low-normal.

In an exam question, the FT_3 usually is not included in the labs. Look for a sick hospitalized patient with a mildly decreased FT_4 and TSH near the lower limit of normal. Your first thought should not be pituitary insufficiency or an exotic hypothalamic disorder. If the patient is very ill, it is more likely non-thyroidal illness. The answer is to remeasure the TSH and FT_4 after the illness is improved. If the exam question insists that you prove your diagnosis, order an rT_3.

Remember 2 things:

1) Do not check TFTs in sick patients unless their acute illness is possibly due to a thyroid emergency (storm or myxedema coma).
2) In ESS, most of the T_3 is in the form of rT_3—rT_3 is high, FT_3 is low, and FT_4/TSH are variable. In central hypothyroidism, the rT_3 is low.

Quick Quiz

- What are the results of the thyroid uptake in patients with thyroiditis (all causes)?
- In what situations is it appropriate to check a sick patient's thyroid function?
- Workup of which nodule can cease after the uptake and scan test—a hot or cold one?
- List some characteristics associated with malignant nodules.
- If the TSH is high and an U/S of a solitary nodule is not concerning for malignancy, what is the most likely diagnosis?

Generally, the diagnosis of ESS is presumptive because central hypothyroidism is a very rare entity. An rT_3 level might be useful if you suspect multiple hormone deficiencies (thus, central disease). In this situation, the sella should be imaged too.

NODULES AND GOITERS

Overview

Nodules can be multiple or single, hot or cold. Most solitary nodules are cold, and most of those are benign. Virtually all hot or purely cystic nodules are benign.

A malignant nodule may be primary thyroid carcinoma or a metastasis. 5% of patients who had neck radiation as a child (especially with > 100 rads) get malignant nodules (mostly papillary carcinoma), and even more get nonmalignant ones (colloid adenoma).

Thyroid nodules are common. Now that ultrasound, CT, and MRI usually are employed to evaluate anterior carotid disease, nodules have been found incidentally but in abundance (up to 76% of the population)! Only about 5% of these nodules are malignant, however.

So the task for the internist is to determine which nodules are malignant and which ones aren't—keeping in mind that most nodules are not malignant. Any topic that requires judicious use of resources is important and likely to be emphasized on exams.

Here are some helpful generalities:

- Autonomously functioning nodules ("hot" nodules) are never malignant. So, a single hot nodule is not evaluated further. Histology from a hot thyroid nodule may be indistinguishable from a follicular thyroid malignancy, which could lead to high false positive rates and possibly unnecessary treatment with surgery or RAI. So, do not ever recommend biopsy for a hot nodule! Never, ever!
- The majority of nodules are cold, and the majority of these are benign, but thyroid malignancies also present as cold nodules.
- Cold nodules in a patient with Graves' still are evaluated because they may be malignant.
- **Multinodular goiters** (MNG) can have both hot and cold nodules. (If a hot nodule is hot enough, it becomes a toxic MNG.) Evaluate the cold nodules because cold nodules in MNG and solitary cold nodules have the same overall malignant risk.
- Do not routinely screen for thyroid nodules with U/S unless the patient has risk factors for malignancy; however, all palpable nodules (including MNGs) should be viewed with U/S as a general rule.

Risk Factors for Thyroid Nodules

Palpable nodules should be considered in terms of risks for malignancy. The following are risk factors that increase the possibility that a nodule is malignant:

- Hx head/neck irradiation
- Family Hx of thyroid cancer
- Age < 20 or > 70 years
- Male
- Growing nodule (if the rate of growth is rapid, you must rule out a thyroid lymphoma)
- Firm or hard consistency
- Lymphadenopathy
- Fixed
- Symptoms of compression in a patient without comorbid goiter: dysphonia, dysphagia, and cough
- U/S features: microcalcifications, marked hypoechogenicity, irregular margins, absence of hypoechoic halo around the nodule, lymphadenopathy, local invasion into adjacent structures

General rule: If a thyroid nodule (single, multiple, or within MNG) has any suspicious characteristics by Hx or U/S, refer for fine needle aspiration (FNA).

Again, do not biopsy hot nodules.

Nodule Workup

2010 American Association of Clinical Endocrinologists (AACE) practice guidelines suggest 2 algorithms—one for the palpable nodule and one for the incidentaloma (nodules found by coincidental imaging). The revised 2010 ATA thyroid nodule guidelines determine FNA based on risk factors, U/S features, and threshold size.

Palpable Nodules

Workup of solitary nodules:

Start with a good Hx and PE with focus on risk factors for malignancy. Then, do a thyroid U/S (even if the nodule was found on CT or MRI) and a TSH.

- Suspicious U/S: Do an FNA. Period. Do an FNA no matter the size or type of nodule or the level of TSH.
- Non-suspicious U/S. Consider the TSH:
  - **High**: Note that high levels of TSH correlate with increased likelihood that a nodule is malignant;

any irregular U/S features are important and should prompt biopsy. Large nodules (> 1 cm) usually are biopsied based on size alone (unless the nodule is "hot"). Evaluate for hypothyroidism by measuring free T_4 and anti-TPO antibodies. Treat hypothyroidism with thyroxine.

- **Low**: Do a scintigraphy scan. If nodule is single and hot, stop! You're done! Remember, do not ever biopsy hot nodules! Histologically, hot nodules can look very similar to cancer and biopsying them often can lead to many false positive readings. Treat hyperthyroidism with radioactive iodine or resection. Multiple nodules and cold nodules are discussed next.
- **Normal**: Most experts FNA this nodule if > 1 cm.

Workup of multinodular goiter (MNG):

In patients with a low or low-normal TSH and a MNG, a scintigraphy scan is done to determine which nodules are hot or cold. Do FNA on all cold nodules and any suspicious nodule seen on U/S. If U/S is not concerning, treat hyperthyroidism with ^{131}I or resection. Long-term treatment with anti-thyroid drugs (e.g., methimazole) may be considered in patients who refuse ^{131}I therapy and are not surgical candidates.

If the TSH is normal and the U/S shows no areas of malignant concern, stop! You're done. Very large nodules (> 1 cm) are often biopsied, though, based on size alone.

Further workup of all nodules: What you do after FNA of these nodules depends on what the pathology shows. Know that any "definitely malignant" or suspicious pathology goes to surgery, and nondiagnostic pathology (up to 20% of FNAs) goes for repeat FNA. More on MNGs on next page.

Incidentalomas

Thyroid nodules accidentally found during imaging for other reasons are referred to as thyroid incidentalomas. By definition, they are not palpable. They are worked up the same as other nodules with initial U/S (if not already done) and TSH. Biopsy any nodule with suspicious U/S characteristics, but when to biopsy based on size alone is more controversial than with a palpable nodule. Most experts definitely biopsy if the nodule is > 2 cm, but how to handle the 1–2-cm incidental nodule with a normal-appearing U/S is debatable. 2010 ATA guidelines determine FNA on U/S appearance (e.g., solid, cystic, mixed) and corresponding size thresholds. Do not biopsy cystic-appearing nodules.

Benign Nodular Disease

For nodules and/or MNG established as benign, treat when symptoms develop, such as compression of the trachea or discomfort in the neck. Recurrence of a cystic nodule after aspiration is considered to be an indication for surgical excision, as is persistent patient anxiety and concern about cosmetic appearance.

Toxic Adenoma

A toxic thyroid adenoma is a benign area of autonomous hyperfunctioning thyroid tissue. Most occur as a single nodule of hyperfunctioning tissue within normal tissue that grows slowly, eventually becoming large enough to suppress TSH production. The end result is an autonomous, hyperfunctioning nodule in the midst of "turned-off" thyroid tissue (a "hot" nodule). These are usually diagnosed by TFTs, which demonstrate overproduction of FT_3/FT_4 and suppression of TSH, and thyroid scan (focal uptake in "hot" nodule).

Treatment of thyroid adenomas: If the patient is hyperthyroid, use ablative treatment or perform surgery. Antithyroid drugs do not work long term. For the euthyroid patient with a thyroid adenoma, do not use suppressive therapy with thyroxine because it does not shrink the size of the adenoma, and you risk inducing hyperthyroidism. If the thyroid adenoma is compressing underlying structures or is cosmetically problematic, surgery is the best treatment. Percutaneous ethanol injection of autonomous functioning thyroid nodules is an alternative to surgery and RAI, with restoration of normal thyroid function in the majority of cases.

Review again: Graves disease has an increased RAIU, while hyperthyroidism caused by thyroiditis has decreased RAIU. Other causes of hyperthyroidism with a low RAIU are over-medication with thyroxine supplements and excess iodine; e.g., amiodarone. Besides Graves disease, other causes of high RAIU thyrotoxicosis are toxic MNG and (occasionally) toxic adenoma.

Thyroid Carcinoma

Thyroid cancer has 4 histologic types:

1) **Papillary** carcinoma: most common, usually indolent, spreads via lymphatics to bone/lungs.
2) **Follicular** carcinoma: less common, mimics normal thyroid tissue with early hematogenous spread to bone/lungs/CNS. Capsular invasion is an important part of staging for follicular thyroid cancer and a total thyroidectomy is needed for adequate staging.
3) **Anaplastic** carcinoma: rare, undifferentiated, and highly malignant; death within 6 months of diagnosis; no good treatment available.
4) **Medullary** (MTC): associated with hyperplasia of parafollicular C cells and elevated serum calcitonin; sporadic or inherited with ~ 15% occurring as component of multiple endocrine neoplasia MEN2A and MEN2B syndromes. MEN cases are associated with point mutations in the *RET* proto-oncogene → constitutive production of kinase that phosphorylates tyrosine residues and transduces signals for uncontrolled cell growth.

Treatment of thyroid cancer begins with a thyroid lobectomy (if papillary cancer is limited to one lobe) or a near-total thyroidectomy (for bilateral papillary thyroid cancer or for any follicular thyroid cancer). A near-total thyroidectomy always leaves part of the posterior

QuickQuiz

- What are the 4 histologic types of thyroid cancer? Which is the most aggressive?
- What is the hormone released by medullary thyroid cancer?
- MEN2A and MEN2B are associated with what histologic type of thyroid cancer?
- What is the gene associated with medullary thyroid cancer?
- Thyroid lymphoma is associated with what autoimmune disease?
- Name 3 different hormones that are produced in the adrenal cortex. (Also see Figure 7-3 on page 7-16.)

capsule around the recurrent laryngeal nerve intact. Frequently, a small amount of residual thyroid tissue also remains, and therefore most thyroid cancer patients need postoperative RAI. Additionally, those patients with risk factors for recurrence such as higher staging or larger adenoma size are also candidates for RAI. (You do not need to know the specific staging systems of the various thyroid cancers.) Following surgery, suppressive thyroxine therapy is necessary but is not started immediately after thyroidectomy. Instead, the TSH is allowed to rise on its own over several weeks, or alternatively, thyrogen is used to increase the TSH. When the TSH is > 30, a thyroglobulin level is measured and the patient is given a high dose of radioactive iodine in an attempt to kill any remaining cancer cells.

Several days after ablation, suppressive doses of thyroxine are started. Most differentiated thyroid cancers (follicular type) remain responsive to TSH, so keeping the TSH suppressed below the lower limit of normal helps prevent recurrence. Oversuppression of TSH may increase the risk of developing complications associated with hyperthyroidism; e.g., tachyarrhythmias, dilated cardiomyopathy, osteoporosis.

Long-term follow-up usually involves one or more of the following: neck ultrasound, total body scans, and/or thyroglobulin levels (as long as the patient doesn't have antithyroglobulin antibodies to interfere with the assay). Thyroglobulin levels following surgery and RAI should be 0, so any rise in thyroglobulin levels suggests recurrent disease (thyroglobulin is expressed only by thyroid tissue).

Thyroid lymphoma is associated with chronic autoimmune thyroiditis. Think about this in a patient with chronic autoimmune thyroiditis who develops a fast-growing thyroid mass. The most common tumor type is a diffuse large B-cell lymphoma, and these are treated with chemotherapy and external beam radiation. Surgery is used only for biopsy and diagnosis.

Goiter

Simple, nontoxic goiter is a diffuse enlargement of the thyroid gland with no metabolic symptoms other than enlargement. It may be caused by a lack of iodine or ingestion of a goitrogen; e.g., cassava root, Brussels sprouts, cauliflower, cabbage; but many cases are idiopathic. Diagnose nontoxic goiter with thyroid function tests: FT_4 and TSH are normal.

Treatment: Remove any goitrogens from the diet. If the cause is low iodine, iodine supplements help.

Multinodular Goiter: Nontoxic and Toxic

Nontoxic MNG is fairly common and occurs more often in women. Cause is multifactorial. Nodules of varying sizes are distributed throughout the gland, but patients are generally asymptomatic and euthyroid with a normal TSH. They come to attention because of the size of their gland or because (rarely) the gland gets large enough to compress surrounding structures.

Diagnosis is suspected when various-sized nodules are palpated in a goiter. Perform U/S to look for dominant nodules and features suspicious for malignancy. Nontoxic MNG has 2 main indications for treatment; otherwise, it is managed conservatively:

1) Symptomatic compression of key structures; e.g., trachea or esophagus
2) Cosmesis: surgical correction of a disfiguration

Standard treatment of nontoxic MNG, if indicated, is ablation with ^{131}I or bilateral subtotal thyroidectomy (if signs/symptoms of compression). Most benign nodules do not change size and remain benign. Thyroxine suppressive therapy typically is not used because it does not shrink most nodules, and long-term therapy risks the development of osteoporosis and atrial fibrillation.

Toxic MNG refers to a MNG with thyrotoxicosis. TSH is suppressed, and FT_3 and FT_4 are often increased. The thyroid scan usually shows 1 or more hot nodules.

Toxic MNG may temporarily be treated with antithyroid medications. Normal treatment is ablative therapy with radioactive iodine. This does not destroy all the nodules, but it does destroy those that are hyperfunctioning. Surgery is used in cases that are refractory, or in symptomatic cases, especially if a large goiter is compressing surrounding structures.

ADRENAL GLAND

OVERVIEW

Cortisol, adrenal androgens, and aldosterone are made in the cortex of the adrenal gland.

The adrenal cortex has 3 zones (remember "GFR"):

1) The outer zona glomerulosa (aldosterone = "salt")
2) The middle zona fasciculata (cortisol = "sugar")
3) The inner zona reticularis (androgens = "sex")

The chromaffin cells in the adrenal medulla mainly manufacture epinephrine.

Hypothalamic corticotropin-releasing hormone (CRH) is secreted in response to a low serum cortisol, stress, and circadian rhythm. CRH causes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which stimulates the adrenal gland to release mineralocorticoids (aldosterone and precursors), glucocorticoids (cortisol and precursors), and androgens (mainly dehydroepiandrosterone [DHEA] and testosterone). ACTH has no effect on epinephrine production from the adrenal medulla.

STEROID SYNTHESIS

Refer to the steroid synthesis diagram (Figure 7-3). This diagram gives you all you need to know for those mind-boggling steroid deficiency questions.

Remember: In response to ACTH, the adrenal gland takes cholesterol and forms 3 products—mineralocorticoids, cortisol, and androgens—through a series of enzyme actions. It makes each of these products in 1 of the 3 layers of the adrenal cortex; hence, these chemicals are often called "adrenocorticoids."

In this diagram [Know it!], the green line represents normal pathways of steroid synthesis. The circles are the genes that code for important enzymes:

- *CYP21A2* = 21-hydroxylase
- *CYP17* = 17α-hydroxylase
- *CYP11B1* = 11β-hydroxylase

An "x" over the circle represents a defect in the gene with subsequent impairment of the enzyme for that step of synthesis. Recognize that whenever a pathway is blocked, precursors build up and push the reactions into the alternate pathways. If you know the effects of the final product of each pathway, then you can easily guess the clinical presentation of excesses that arise when any pathway is blocked and rerouted into other pathways.

Note that the color of the "x" shows what pathway increases if that enzyme is blocked. For example, a defect in either *CYP11B1* or *CYP21A2* results in increased DHEA and decreased aldosterone and cortisol. Not only that, but it causes a buildup in the chemical right before it. For example, a defect in *CYP11B1* causes a buildup of 11-deoxycortisol.

Now, let's go over the actions of the 3 ultimate products:

1) **Mineralocorticoids** (e.g., aldosterone) normally increase Na absorption and K^+/H^+ excretion, so high levels cause hypertension, hypokalemia, and alkalosis.
2) **Glucocorticoids** (e.g., cortisol) stimulate lipolysis, the release of amino acids from the muscles, and gluconeogenesis by the liver. Cortisol inhibits all stages of the inflammatory process and also affects the bones by decreasing the protein matrix. Its immunosuppressive effect is on T cells and their associated cell-mediated immunity and delayed hypersensitivity. Excess cortisol can additionally stimulate mineralocorticoid and androgen receptors with the clinical appearance of aldosterone excess (hypertension, hypokalemia, and alkalosis). Cortisol does not bind androgen receptors.

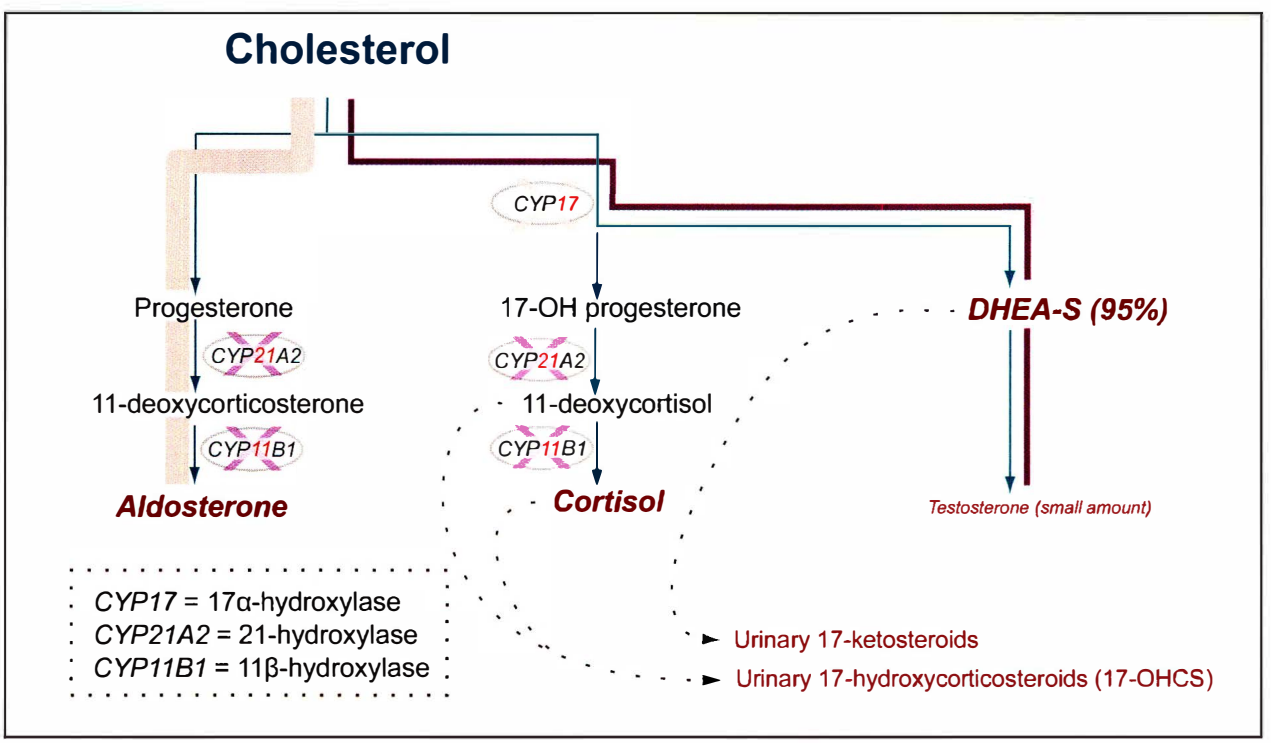


Figure 7-3: Adrenal Steroid Synthesis Pathways

Quick Quiz

- What is produced in the adrenal medulla?
- What genes control steroid synthesis in the adrenal cortex? What cortical hormones are increased and decreased when there is a defect in 21-hydroxylase? 17 α-hydroxylase? 11β-hydroxylase?
- What do mineralocorticoid hormones do?
- What are the effects of excess cortisol?
- What happens to a woman who overproduces adrenal androgens because of a disease process? How does she present?
- Which gene defect is most commonly associated with congenital adrenal hyperplasia?

3) Main androgens produced by the adrenals are **DHEA** and small amounts of **testosterone**.
   - In normal males, adrenal androgens are overshadowed by the effects of testicular androgens.
   - In normal females, the adrenals contribute half of the circulating testosterone. (Ovaries contribute the other 50%.) Together with adrenal DHEA, these androgens slightly virilize the female (small amounts of pubic and axillary hair). In excess, the clinical effects depend on whether disease occurs during gestation (causing ambiguous genitalia in females) or postnatally (causing a lot more hair and abnormal menses). Bottom line: Any time excess hair growth is noted in a female, think about overproduction of androgens by the adrenals or ovaries.

Refer again to the synthesis diagram:
- With defective *CYP21A2* and *CYP11B1*, the increased precursors force the reactions along the purple line with enhanced production of adrenal androgens.
- If *CYP17* is defective, the reaction is forced along the pink line, and more mineralocorticoids are produced.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) is a congenital, autosomal recessive decrease in the production of cortisol. It is caused by defects in the proper expression of any 1 of the 3 genes previously mentioned:
1) *CYP21A2* (95%; enzyme = 21-hydroxylase),
2) *CYP17* (enzyme = 17α-hydroxylase), or
3) *CYP11B1* (enzyme = 11β-hydroxylase).

95% of cases are due to mutations in *CYP21A2*, where 17-hydroxyprogesterone is not converted (and thus accumulates) and cortisol decreases. Complete impairment of *CYP21A2* during gestation forces an increase in DHEA and testosterone (purple line on diagram), which causes ambiguous genitalia in newborn girls.

Postnatal complete *CYP21A2* impairment results in a low cortisol level and an elevated ACTH, which causes hypertrophy of the adrenal gland and:
- increased androgen production (purple line on diagram), with
- subsequent virilization of females, or
- precocious puberty in males.

Late-onset (nonclassical) **CAH** occurs in postpubertal patients and is usually due to partial *CYP21A2* impairment. Genitalia are normal at birth, and the patient presents with signs of androgen excess (acne, hirsutism, accelerated bone age, and irregular menses in females). Labs show an early morning elevation of blood 17-hydroxyprogesterone and increased urinary 17-ketosteroids and blood DHEA. Confirm by observing elevated cortisol precursors (e.g., 17-hydroxyprogesterone) after ACTH stimulation. The most important test to remember for nonclassical CAH due to partial *CYP21A2* impairment is an elevated unstimulated or ACTH-stimulated serum 17-hydroxyprogesterone level.

Less commonly, late-onset CAH is due to impairment of *CYP11B1* with elevated 11-deoxycortisol and 11-deoxycorticosterone (potent mineralocorticoid precursors). Cholesterol is also shunted along the purple line into producing excess DHEA and testosterone. Thus, the clinical presentation is a hypertensive, hypokalemic, metabolic alkalosis with associated hirsutism and menstrual irregularities.

Quick review:

CYP21A2 = 21-hydroxylase deficiency; 95%; pushes pathway into formation of androgens only, with clinical presentation of virilized females (ambiguous genitalia if prenatal; hirsutism and menstrual irregularities if post-natal) and precocious puberty in males.

CYP11B1 = 11β-hydroxylase deficiency; ~ 4%; pushes pathway into formation of androgens and allows for buildup of aldosterone precursors, with clinical presentation of hypertension, hypokalemia, alkalosis + virilization of females or precocious puberty in males.

CYP17 = 17α-hydroxylase deficiency; < 1% [rare!]; pushes pathway into formation of only mineralocorticoids, with hypertension, hypokalemia, alkalosis, and hypogonadism (due to androgen deficiency). (These patients are also deficient of cortisol, but they are generally asymptomatic.) *CYP17* mutations are rare.

CUSHING SYNDROME

Overview

Cushing syndrome occurs when there is excessive adrenal glucocorticoid production causing complaints of proximal muscle weakness and easy fatigability; amenorrhea, hirsutism, and acne in females; easy bruising; and emotional lability (sometimes frank psychosis). Exam reveals facial plethora, thin skin with prominent bright pink-to-purple striae, cervicodorsal fat

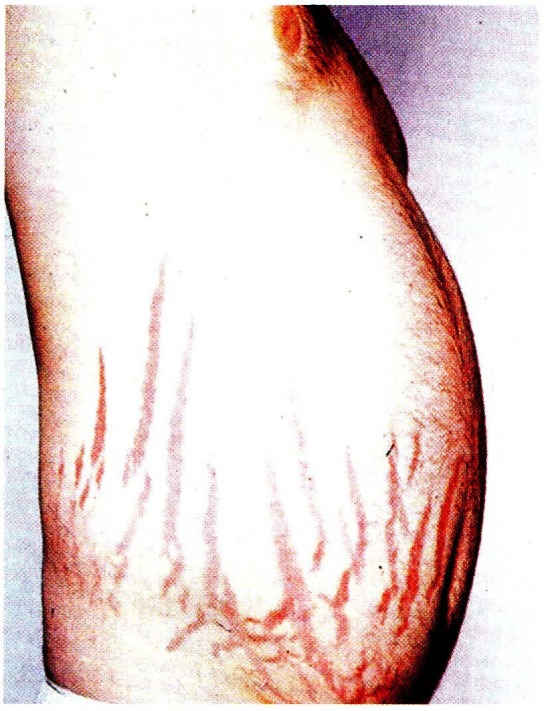


Image 7-2: Abdominal striae in Cushing syndrome.

pad ("buffalo hump"), truncal obesity, and moon facies (Image 7-2). Because cortisol also can stimulate mineralocorticoid receptors, the patient may have edema and hypertension. Comorbid diagnoses include insulin resistance (with Type 2 diabetes in 20%) and osteoporosis.

Labs may show hypokalemia and/or metabolic alkalosis.

Causes of Cushing syndrome in order of most-to-least frequent:

- Iatrogenic cortisol administration
- ACTH-secreting pituitary adenoma (Cushing disease)
- Ectopic ACTH-secreting tumor: bronchogenic, pancreatic, or thymic carcinoma (if age > 60 years, then small cell lung cancer is the most common cause of Cushing's!)
- Non-pituitary–associated, bilateral adrenal hyperplasia
- Adrenal tumors

Obesity, alcoholism, and depression mimic some of the phenotypic features of Cushing's and slightly increase the 24-hour urine cortisol—and/or result in an abnormal low-dose suppression test. These cases are referred to as "**pseudo-Cushing's**"; refer to an endocrinologist.

Cushing syndrome caused by a pituitary microadenoma (disease in the head) is termed Cushing "disease." Next to exogenous steroids, Cushing disease is the most common cause of Cushing syndrome.

Know the following:

- In true **Cushing syndrome**, expect urinary free cortisol to be significantly elevated.
- Recall that ACTH increases the synthesis of not only cortisol but also mineralocorticoids (slightly) and androgens (remember Figure 7-3?). So in **Cushing disease** (disease in the head = pituitary), elevated ACTH stimulates production of adrenal DHEA, and females can present with virilization (hirsutism and acne).
- If an adrenal adenoma is producing the cortisol, ACTH and DHEA are both low.

In clinical practice, Cushing's can be complicated with subtle nuances; so, thankfully, there are endocrinologists who can interpret multiple tests to make a diagnosis. Typical exam question scenarios are straightforward, though, and you can get the right diagnosis using the following strategy.

Cushing Syndrome Workup

1) Initial tests are to establish the presence of cortisol excess.

The suspicion of excess cortisol comes from recognizing the typical clinical presentation. Initial testing uses:

- a 24-hour urine free cortisol (UFC),
- late-night salivary cortisol, and/or
- low-dose dexamethasone suppression test to confirm excess cortisol.

An abnormal test should be confirmed at least once. In the plasma, < 5% of cortisol is free and physiologically active. Only the free cortisol is filtered by the glomerulus, so urinary cortisol is always "free" cortisol and reflects plasma free cortisol levels.

Do not measure plasma total cortisol in a woman on estrogen because estrogen raises sex hormone binding globulin (SHBG), which falsely raises total cortisol.

If your patient is depressed, obese, alcoholic, or sick, check for pseudo-Cushing's before attributing an increased urine cortisol to true Cushing syndrome. Identify pseudo-Cushing's by attempting to suppress cortisol production with low-dose dexamethasone (a synthetic glucocorticoid). Patients with pseudo-Cushing's usually suppress cortisol production with this very small amount of glucocorticoid. True Cushing syndrome does not suppress. If the patient does not suppress cortisol production with the low-dose dexamethasone test and has a high-normal or high UFC, make an endocrine referral.

Remember: Cushing syndrome is the general description for any state of excess cortisol and includes the specific diagnosis of Cushing disease, which refers to an ACTH-secreting pituitary tumor.

2) Is the Cushing syndrome ACTH-dependent or ACTH-independent?

Once you have identified a patient with true Cushing syndrome, check the ACTH level. Normally, a high cortisol completely suppresses ACTH production.

Quick Quiz

- What is pseudo-Cushing's? In what situations does it occur?
- What is the difference between Cushing syndrome and Cushing disease?
- What is the ACTH level in Cushing disease?
- What are your choices for initial tests to evaluate a patient who may have Cushing syndrome?
- Explain what tests are done to differentiate ACTH-dependent Cushing syndrome vs. ACTH-independent Cushing syndrome.
- How does adrenal insufficiency (both primary and secondary) present?

Thus, any measurable ACTH indicates ACTH-dependent Cushing syndrome—either Cushing disease or ectopic ACTH production.

An ACTH too low to be measured indicates ACTH-independent Cushing syndrome—non-pituitary adrenal hyperplasia or adrenal mass.

3) a. If ACTH-dependent Cushing syndrome:

ACTH-dependent Cushing syndrome means the cause is either a pituitary tumor (Cushing disease) or an ectopic, ACTH-secreting tumor. Again ACTH level is elevated.

Image the pituitary with a gadolinium-contrasted MRI and refer the patient to a neurosurgeon if a pituitary tumor is seen.

Some ACTH-producing microadenomas are not visible on MRI. If no pituitary tumor is visible, the patient may have a very small microadenoma, which can sometimes be identified by petrosal sinus venous sampling (detects local production of ACTH). Alternatively, the patient may have an ectopic ACTH-producing tumor, such as primary lung or carcinoid tumors.

To look for these, image the chest and abdomen with high-resolution CT.

You may be asking, "What happened to the high-dose dexamethasone test?" Historically, patients with definite Cushing syndrome were given a high-dose dex suppression test to determine if the source was a pituitary microadenoma (which suppresses with high-dose dex) or an ectopic ACTH-producing tumor or adrenal mass (neither of which suppresses with high-dose dex). Then targeted imaging was performed based on the result.

Measuring ACTH levels is now the best initial test for determining causes of Cushing syndrome—making the high-dose dexamethazone test obsolete. Today, we stratify patients for imaging based on the ACTH result.

We include this topic, however, because general textbooks of medicine are still discussing use of the high-dose dex suppression test to exclude a pituitary microadenoma. In the unlikely event that the high-dose test should show up on exam questions, know:

- Cushing **d**isease, in the head, suppresses with high-**d**ose **d**ex.
- If the patient fails to suppress with high-dose dex, think about ectopic ACTH-producing tumors and adrenal tumors as a cause of Cushing's.

3) b. If ACTH-independent Cushing syndrome:

This patient has high cortisol and low ACTH—most likely an adrenal tumor (adenoma or carcinoma) that is secreting cortisol. Image the adrenals with a contrasted CT and refer to a surgeon for options if a mass is found.

Consider ordering DHEA and testosterone concentrations. Adrenal adenomas have low ACTH and modest DHEA levels, while carcinomas have low ACTH and high DHEA + urine 17-ketosteroids. Again, recall that adrenal tumors do not usually suppress cortisol production in response to high-dose dexamethasone.

ADRENAL INSUFFICIENCY

Adrenal insufficiency (AI) can be primary (Addison disease) or secondary (low ACTH production by the pituitary or withdrawal of glucocorticoids). When AI presents acutely, it is an endocrine emergency.

In industrialized countries, **primary AI** is most often the result of autoimmune adrenalitis (Addison disease, which is sometimes seen in polyglandular autoimmune syndromes I and II); but it can also be caused by granulomatous infections and infiltrative diseases, e.g., HIV/AIDS, CMV, TB, amyloidosis, and sarcoidosis.

Polyglandular autoimmune syndrome I includes chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal/pituitary insufficiencies +/– pernicious anemia, hepatitis, alopecia, chronic autoimmune thyroiditis, and premature gonadal failure.

Polyglandular autoimmune syndrome II includes ≥ 2 of the following: Addison disease, chronic autoimmune thyroiditis, premature ovarian failure, and Type 1 diabetes +/– pernicious anemia, vitiligo, alopecia, sprue, and myasthenia. Watch out for primary AI in patients with AIDS.

The most common cause of **secondary AI** is rapid withdrawal of chronic exogenous glucocorticoids.

Signs and symptoms of AI: The preeminent symptom of adrenal insufficiency is weakness and, as the disease worsens, patients may become bed-bound. Other symptoms include weight loss, N/V, vague abdominal pain, hypoglycemia, and moodiness. Hypercalcemia occurs in 20% of patients due to unknown reasons. Eosinophilia is unusual but is also a clue.

In patients with primary AI (where ACTH is increased), hypotension and hyperpigmentation may be obvious on physical exam. Labs may reveal hyponatremia and

hyperkalemia due to hyperreninemic hypoaldosteronism—since most etiologies of primary AI affect both the zona glomerulosa and zona fasciculata.

Secondary adrenal insufficiency (disease in the pituitary, so ACTH is decreased) is not associated with hyperkalemia because the zona glomerulosa is not diseased and responds normally to angiotensin II.

Diagnosis and treatment of AI: If your patient has acute adrenal insufficiency, it does not matter where the disease is located. It needs to be diagnosed and treated immediately. So your 1st task is simply to determine whether AI exists. You can sort out the level of disease later.

If the patient is in shock and you suspect AI, give fluids and dexamethasone, and perform your stimulation test after the patient stabilizes. Dexamethasone is potent and does not interfere with the cortisol assay, so the post-stimulation cortisol results are reliable. Dexamethasone affects the ACTH level; so if you have time, draw a serum ACTH prior to instituting treatment. Remember that in primary AI, there is usually an associated mineralocorticoid deficiency, so you probably need to also replace mineralocorticoids with fludrocortisone.

In patients who can tolerate an immediate stimulation test: Draw a baseline cortisol level. Then give cosyntropin 0.25 mg IM/IV and recheck cortisol at 30 and 60 minutes. If the stimulated cortisol is not > 18–20 µg/dL, your patient has AI; but you need the ACTH level to determine whether the disease is in the adrenals or the head. The ACTH measurement is a reference test, so it takes days to return. But you're going to give corticosteroids anyway, regardless of level of disease.

Once you know the cosyntropin test is abnormal, check serum aldosterone also. (Often, this can be added to the initial blood sample with the pending ACTH result.)

When your labs return, interpret this way:

Primary AI = abnormal cosyntropin stimulation + high ACTH level and low aldosterone because multiple layers of adrenal are affected by disease process.

Secondary/Tertiary AI = abnormal cosyntropin stimulation + low or low-normal ACTH level and normal aldosterone. Image the sella with MRI.

Clarification: In all causes of AI—primary, secondary, and tertiary—the patients do not respond to ACTH stimulation. This is weird, right? Since secondary and tertiary causes result in a lack of ACTH, shouldn't the adrenals respond if ACTH is supplied? Theoretically, they should—but they don't. Adrenal glands atrophy when they are not stimulated regularly by ACTH. If the gland is not diseased, reinstating ACTH stimulation eventually restores adrenal function, but it takes several days.

In secondary/tertiary AI (disease in pituitary or hypothalamus), the glands do not respond to ACTH stimulation—because they are atrophied. But, they can respond with enough exogenous ACTH over time. In secondary/tertiary AI, serum ACTH is decreased or low-normal. In primary AI (disease in the adrenal cortex), the glands do not respond to ACTH—because they are sick. Serum ACTH is elevated. The point is that even central diseases that result in a failure to produce ACTH result in an abnormal stimulation test.

Schmidt syndrome is the combination of primary adrenal insufficiency and hypothyroidism (and often Type 1 diabetes). Know that you must replace cortisol first because giving thyroid replacement prior to glucocorticoid replacement can increase metabolic demand and cause or worsen shock, leading to death.

MINERALOCORTICOIDS

Overview

Aldosterone is discussed extensively in Nephrology, Book 2. It increases Na^+ resorption and, hence, K^+ and H^+ excretion in the distal tubules. Increased Na^+ resorption means increased water retention and the tendency for hypertension. The release of aldosterone is controlled by both the renin-angiotensin system and the K^+ level.

Review: Renin is released by the healthy kidney from the juxtaglomerular apparatus in response to at least 3 independent factors:

1) Perceived volume depletion, as measured by the juxtaglomerular cells. These are specialized myoepithelial cells cuffing the afferent arteriole.
2) Elevated levels of filtered sodium, as measured by the efferent macula densa cells.
3) Sympathetic nervous system stimulation, which stimulates release of renin in response to assuming the upright posture.

Renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II by ACE—mainly in the lungs. Angiotensin II has pressor effects and stimulates aldosterone release from the zona glomerulosa in the adrenal glands.

Aldosteronism

Primary aldosteronism (disease in the adrenal) is associated with hyporeninemia, hypertension, and hypokalemia—as are other disease states where mineralocorticoid-type activity is in excess, such as Cushing syndrome and licorice ingestion.

Secondary aldosteronism (disease is in the kidney), a hyperreninemic state. Decreased renal blood flow from either renal artery stenosis or fibromuscular dysplasia → increased renin → increased angiotensin II → increased aldosterone.

Note that primary and secondary aldosteronism, licorice ingestion, and Cushing syndrome can all present with hypertension and hypokalemia.

See Nephrology, Book 2, for more on when and whom to screen.

Quick Quiz

- What electrolyte abnormalities are associated with primary adrenal insufficiency? With secondary?
- How do aldosterone levels affect serum Na^+ and K^+?
- What endocrinopathies should you be concerned about in a patient with untreated hypertension and a $K^+ < 2.8$?
- What are the screening tests to differentiate primary and secondary aldosteronism? How do you interpret them?
- Hypoaldosteronism is usually due to what acquired problem?

Test for primary and secondary aldosteronism with paired plasma aldosterone concentration (PAC) and plasma renin activity (PRA). This also can be presented as PAC:PRA ratio. Know that ACEIs/ARBs and aldosterone blockers such as spironolactone or eplerenone interfere with these screening tests. These agents should be stopped prior to performing screening tests. All other antihypertensive medications can be continued. Interpret the results this way:

- Primary aldosteronism: PAC elevated, PRA suppressed → elevated ratio. Think adrenal disease (tumor or hyperplasia).
- Secondary aldosteronism: PAC and PRA both increased with PAC:PRA usually < 10. Think kidney disease (renovascular or renal tumor).
- Cushing's and excessive consumption of black, natural licorice: PAC and PRA both decreased, with PAC:PRA either normal or elevated.

If the PAC, PRA, and PAC:PRA support primary aldosteronism (PAC high; PRA low; PAC:PRA high), confirm the diagnosis of disease in the adrenal by trying to suppress the excess aldosterone. Give 2 liters of normal saline IV over 3–4 hours to the recumbent patient—nonsuppression of PAC indicates primary aldosteronism. An easier method is to give an oral sodium load for 3 days, then measure the PAC. (Again, nonsuppression suggests adrenal disease.)

Once aldo excess is confirmed, image the adrenals with either high-resolution CT or MRI to determine whether the cause is adrenal hyperplasia or tumor (Conn syndrome). Check with your radiologist so the appropriate testing can be done.

If the PAC, PRA, and PAC:PRA suggest renovascular disease (PAC high; PRA high; PAC:PRA < 10), go straight to renal angiography.

These tests are not as easy as they seem. The patients have hypertension, which is often marked. Giving saline runs the risk of significantly increasing blood pressure.

In many centers, arterial duplex, CT angio, and MRA are very sensitive for diagnosing renal artery stenosis. Depending on cost and sensitivity, arterial duplex, CT angio, and MRA may be preferred over the PAC:PRA as the initial test for renovascular disease.

Hypoaldosteronism

The most common cause of hypoaldosteronism is decreased production of renin in diabetic patients with mild renal failure ("hyporeninemic hypoaldosteronism"). It is also seen in patients with chronic interstitial nephritis, chronic NSAID use, and heparin therapy.

Pick up this diagnosis by observing hyperkalemia and normal anion gap metabolic acidosis out of proportion to the renal disease (no aldosterone leads to failure to excrete H^+/K^+ in the distal tubule). Patients are unable to retain sodium in states of volume contraction, and they develop postural hypotension.

Start the workup by excluding AI as a cause of the hyperkalemia: Perform ACTH stimulation test. Next, measure renin and aldosterone levels during upright posturing and salt restriction (they are low in this diagnosis). Treat with a mineralocorticoid (fludrocortisone) and/or furosemide.

PHEOCHROMOCYTOMA

Because these tumors are rare, a group of international pheochromocytoma specialists have formed a collaborative organization called PRESSOR (Pheochromocytoma & Paraganglioma Research Support Organization). In 2005, PRESSOR issued clinical practice guidelines for diagnosis and management based on the current standard of care. Our discussion is based on the 2005 guidelines (find them here: www.pressor.org), on the 2004 WHO classification of neuroendocrine tumors, and the 2010 North American Neuroendocrine Tumor Society guidelines.

Pheochromocytomas are rare tumors that arise from chromaffin tissue, with symptoms due to secretion of catecholamines: epinephrine, norepinephrine, and dopamine. 10% of pheos are extraadrenal tumors that are called extraadrenal paragangliomas. The distinction is important because the risk of malignancy is higher in the extraadrenal masses. 15% of the time, the pheo tumors are multiple. 10–36% are malignant. Germline mutations are found in up to 30%. 5–15% of patients with these tumors do not have hypertension, and many have sustained, not paroxysmal hypertension. Some even have normal blood pressure.

The differential diagnosis includes labile essential hypertension, anxiety, hyperthyroidism, hypoglycemia, and menopausal flushing—most of which are more common than pheo. Carcinoid can mimic pheo but also is quite rare.

Suspect a catecholamine-secreting tumor in patients who have spells of headaches, sweating, and chest palpitations.

The following risk factors increase the likelihood that a patient may have a pheo:

- Combined HTN + DM
- Refractory HTN
- HTN in young person without a family Hx
- Adrenal incidentaloma
- Dilated cardiomyopathy of unknown cause
- Hx HTN during procedures, with ingestion of tyramine-containing foods, or use of MAO inhibitors
- Family Hx of pheochromocytoma (particularly high risk)
- Family Hx of MEN2, neurofibromatosis, or von Hippel-Lindau disease (particularly high risk)

Diagnosis: Controversy still exists, even amongst experts, as to what the best method is for screening. The most sensitive biochemical screening tests for pheochromocytoma are the following:

- Fractionated metanephrines and catecholamines on 24-hour urine (preferred for screening of low-risk individuals). Patients should be weaned off of tricyclic antidepressants and cyclobenzaprine 2 weeks before testing because these meds interfere with the results. (SSRIs are okay.)
- Plasma fractionated metanephrines; sensitivity is high, so a negative test excludes disease. However, specificity is somewhat low and leads to false-positive results, so measure these only in patients who carry a high pretest probability of disease; i.e., MEN2/NF/VHL, incidentaloma with characteristics of pheo, or family Hx of pheo. The test is not recommended for initial screening of a low-risk population.

For the patient with a possible false-positive result and an increase in plasma fractionated metanephrines, a clonidine suppression test can be performed. The plasma level of fractionated metanephrines is measured before and after the patient receives a dose of clonidine. Plasma metanephrines fall if elevated levels are due to essential hypertension but stay increased if they are due to a pheo.

If the biochemical tests suggest a pheo, perform CT or MRI of the abdomen and pelvis to find the tumor.

If imaging does not show a tumor and you still suspect one given the screening tests and history, look for the tumor using a radioactive tracer (^{123}I, metaiodobenzylguanidine [MIBG] scintigraphy, a norepinephrine analog that concentrates in adrenals and pheos), PET scan, or total body MRI.

Genetic screening is available for the following patient groups:

- Pheo associated syndromes such as MEN2, VHL, neurofibromatosis
- Familial paragangliomas and pheos due to germ-line mutations of genes encoding succinate dehydrogenase subunits B, C, and D (SDHB, SDHC, SDHD), which increase malignancy risk
- Those with a family Hx of pheos or paragangliomas

Treat both pheos and paragangliomas with laparoscopic surgery. Because of the high incidence of bilateral adrenal disease in those with hereditary pheo, partial adrenalectomies are advocated in these patients, thereby decreasing the morbidity associated with medical adrenal hormonal therapy. Metastatic foci or locally invasive disease often require open surgical resection for cure.

Preoperatively, treat with combined alpha and beta blockade. Phenoxybenzamine is preferred for 2 weeks prior to surgery; and ~ 3 days before surgery, add a beta-blocker. Remember never to use the beta-blocker first, because it leads to unopposed alpha stimulation and potential for hypertensive crisis. For those with advanced disease and positive [^{123}I]-MIBG scintigraphy, [^{131}I]-MIBG can be used. For rapidly expanding lesions or those with a negative [^{123}I]-MIBG, a chemotherapy regimen of cyclophosphamide, vincristine, and dacarbazine can provide up to 50% tumor regression. Outcomes are poor in patients with an undiagnosed pheo who go to surgery for an unrelated condition because of hypertensive sequelae.

OTHER ADRENAL MASSES

Many adrenal masses are incidentalomas—a mass, larger than 1 cm, discovered by accident on an imaging study. Up to 15% of patients with an incidentaloma have bilateral masses.

Most incidentalomas are nonfunctioning adenomas. If the patient has a history of malignancy, however, then the mass has a 50% chance of being a metastasis.

Without a history of malignancy, the initial 2 steps are to:

1) Exclude a functioning tumor or adrenal hypofunction.
2) Determine whether the mass is a primary malignancy or a metastasis from an unknown primary. The radiographic characteristics (CT, MRI, or PET) can help to distinguish malignant from benign lesions. Metastases tend to be larger, bilateral, irregular, and inhomogeneous.

All patients with adrenal incidentaloma should have the following tests:

- Blood pressure and serum K^+; add PAC:PRA if hypertension or hypokalemia is present. These tests evaluate the zona glomerulosa for hyperaldosteronism.
- 24-hour urine free cortisol or low-dose overnight dex suppression test; these tests evaluate the zona fasciculata for Cushing syndrome.
- Plasma fractionated metanephrines; this test evaluates the adrenal medulla for pheochromocytoma.
- Females with virilization or males with feminization should have estrogens and androgens measured.

If the results of these tests are normal and the mass is < 4 cm, observation is appropriate with repeat imaging in 3–6 months. Know that FNA is not used to determine whether an adrenal mass is an adenoma or a carcinoma

QuickQuiz

- What screenings are employed to test for pheochromocytoma?
- What are the first steps in working up adrenal incidentalomas?
- What is the definition of primary amenorrhea, and what are the common causes? A female patient with short stature, primary amenorrhea, and little or no breast development probably has what genetic defect?
- What is the definition of secondary amenorrhea, and what are the common causes?

because of the concern of seeding malignant cells during the FNA. An FNA, however, is helpful to determine if a mass is a metastasis.

There are 3 indications for adrenalectomy of an incidentaloma:

1) Tests indicate a functioning tumor
2) Mass is > 4–6 cm
3) Imaging characteristics are suspicious for malignancy

HORMONES OF REPRODUCTION

NORMAL PHYSIOLOGY

Follow along in Figure 7-4.

The hypothalamus secretes GnRH in a pulsatile fashion (60–90-minute cycle), which stimulates the anterior pituitary to then pulse out gonadotropins, LH and FSH.

FSH causes the new ovarian follicle to produce 2 hormones: estrogen (builds up the lining of the uterus) and inhibin (suppresses secretion of FSH). Estrogen normally inhibits FSH and LH production. However at mid-cycle, estrogen has a positive feedback effect causing a surge in the LH and FSH, which then stimulates ovulation.

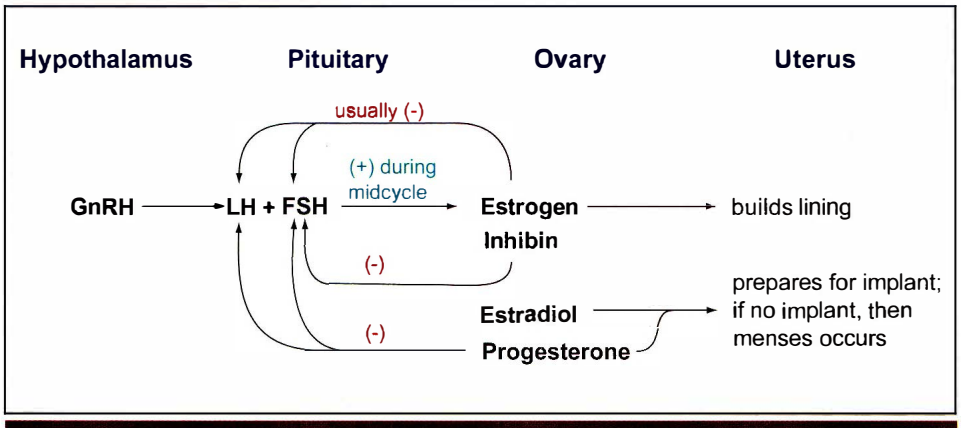


Figure 7-4: Female Hormones of Reproduction

After ovulation, the follicle becomes a corpus luteum that secretes estradiol (main estrogen) and progesterone. Progesterone, in turn, prepares the lining of the uterus for possible implantation and suppresses gonadotropin release.

The theca cells of the ovaries convert circulating androgen precursors (produced by the adrenal gland) into estrogen and a small amount of testosterone. In females, the ovaries and adrenals share the function of producing testosterone––each producing 50%. The major effect of testosterone in females is slight virilization with normal hair development in the pubic and axillary regions.

Amenorrhea

Primary Amenorrhea

Primary amenorrhea in females is diagnosed as a lack of menstruation by age 16 or the lack of development of secondary sex characteristics by age 14. Primary amenorrhea is caused by either a uterine outflow tract abnormality (or absence) or an ovulatory abnormality. Primary amenorrhea is rare, and evaluation is often undertaken by pediatricians; however, you should know a couple of important diagnoses:

- If a patient with primary amenorrhea has short stature, widely spaced nipples, no breast development, webbed neck, and decreased pubic and axillary hair, think of Turner syndrome (karyotype 45,XO).
- If there is no palpable cervix and no uterus, the cause is either a genetic absence of a uterus, in which case she has normal secondary sex characteristics, or androgen insensitivity syndrome (an insensitivity to androgens in a karyotypic female), in which case there is absence of pubic and axillary hair and normal breast development. These patients have an elevated serum testosterone level (within normal range for men).

Secondary Amenorrhea

Secondary amenorrhea is defined as absence of menses for 3–6 months. Know that erratic menstrual cycles are common in the first 1–2 years after menarche and in the 1–2 years prior to menopause.

It is most often caused by pregnancy––once excluded, think about problems with ovulation. Start with a good H&P, looking for signs/symptoms of pituitary disease, systemic disease, and androgen excess, plus a battery of lab tests.

Androgen excess is discussed under Adrenal Gland—Overview and Steroid Synthesis. You might want to go back and review quickly (page 7-15).

Initial labs should include: a pregnancy test and FSH + LH. If the woman is hirsute, and particularly if she is virilized (deepening voice, balding), measure serum total testosterone and DHEA, too. What happens next depends on your test results. The easiest lab to interpret as a cause of amenorrhea is the positive pregnancy test. Next easiest are abnormal gonadotropins (FSH and LH).

Increased FSH and LH levels in the amenorrheic woman tells you that the pituitary has lost negative feedback from the ovaries. The only condition that causes this is ovarian failure. If the woman is < 40 years old, this is called "premature ovarian failure" (POF) and, if the woman is older, "menopausal ovarian failure." (Average age of menopause = 52 years.) In POF cases, consider associated Turner syndrome, galactosemia, or autoimmune polyglandular syndrome, although POF does occur idiopathically in many women.

Decreased FSH and LH levels in the amenorrheic woman tells you that the pituitary is not making the hormones, either because it is diseased or because the hypothalamus is not sending out gonadotropin-releasing hormone (GnRH). This latter state is called "hypogonadotropic hypogonadism," and it has several causes. "Disease" of the pituitary does not always mean disease of gonadotrophs. Recall from the discussion on pituitary adenomas (page 7-2) that prolactinomas and primary hypothyroidism can affect gonadotrophs and levels of FSH + LH as well.

So, check on the following for the amenorrheic woman with low FSH and LH:

- Review of systems and drug use: antiepileptic drugs or psychotropic meds. Is this functional hypothalamic amenorrhea (see below)?
- Prolactin level.
- TSH.
- MRI, if above does not give diagnosis.

Functional hypothalamic amenorrhea (FHA) is caused by stress from an eating disorder and/or prolonged, intense exercise; e.g., long-distance running (but not swimming!). FSH/LH and estrogen are decreased. Measure PRL and TSH to exclude hyperprolactinemia and hypothyroidism before making this diagnosis.

Amenorrhea with Hirsutism

Overview

The amenorrheic woman with virilizing signs needs a good physical exam (evaluate for adnexal masses) and follow-up of blood DHEA and testosterone levels.

The major diagnoses that cause amenorrhea and virilization are polycystic ovarian syndrome (PCOS) and tumors of the adrenal or ovary. Recall from the Steroid Synthesis discussion (page 7-16) that, in the female, both the ovaries and the adrenals contribute to androgen production, almost equally. Usually, normal androgen production causes only growth of pubic and axillary hair. Excess growth of hair in these areas and/or other "masculinizing" signs should prompt concern about either PCOS or adrenal/ovarian tumors.

Polycystic Ovarian Syndrome (PCOS)

PCOS consists of amenorrhea or oligomenorrhea with signs or biochemical evidence of androgen excess (hirsutism, acne, male-pattern balding, or mild increases in DHEA and/or testosterone). It is associated with obesity, insulin resistance, frank diabetes, hyperlipidemia, and obstructive sleep apnea.

In PCOS, the ovaries and adrenals produce excess androgens and estrogens (a result of peripheral aromatization of the androgens) for unclear reasons. The continuous secretion of estrogen decreases FSH secretion but enhances LH secretion such that the LH:FSH ratio often is > 2 (probably > 3 on a Board exam).

The increased LH causes ovarian stromal hyperplasia (more theca cells!) and more production of androgens. It's a chronic cycle! The presence of ovarian cysts as a criterion for PCOS is debatable, as many patients have normal ovaries without any cysts.

While PCOS is associated with small increases in androgens, know that serious increases in these androgens (2–4x upper limit of normal) obligate you to look at the ovaries or adrenals for tumors.

Treatment of PCOS first includes education about weight loss (which treats most) and then is dependent on the degree of hyperandrogenism and whether pregnancy is desired:

- No hirsutism and no desire for pregnancy: Prescribe oral contraceptives or medroxyprogesterone every 1–3 months to induce withdrawal bleeding and to protect the endometrium from hyperplasia.
- Hirsute and no desire for pregnancy: Prescribe combined estrogen-progesterone oral contraceptives. Hirsute symptoms can also be ameliorated with depilatories/shaving. An insulin sensitizer, such as metformin or a thiazolidinedione, may also confer a very modest additional benefit on hirsutism.
- Hirsute and desires pregnancy: Induce ovulation with clomiphene with or without metformin.

Also screen for insulin resistance (oral glucose tolerance test is suggested) in both obese and lean women with PCOS.

Hirsutism

This section is simply a more targeted discussion of hirsutism—a specific virilizing sign (Table 7-2). The history and physical exam are keys in evaluating a hirsute woman. An objective assessment of hair growth and distribution should be made during the

QuickQuiz

- What are the initial labs for the workup of secondary amenorrhea, once pregnancy is excluded?
- What do elevated FSH and LH levels in an amenorrheic woman tell you?
- What testing is done for a woman with secondary amenorrhea who has low FSH and LH levels?
- How does a woman with PCOS present?
- Patients with PCOS should be evaluated for what additional diagnosis?
- What is the most common cause of primary hypogonadism in males?

physical. A scoring system (Ferriman-Gallwey) may be useful to determine whether a patient truly has worrisome features.

The scale shows photos of hair growth in parts of the body subject to androgens: upper lip, chin, chest, abdomen, pelvis, upper arms, thighs, upper back, and lower back. For each location, the amount of hair is assessed and graded on a scale of 0 to 4. This scale is widely available on the Internet under the search terms "Ferriman-Gallwey score." A score > 8 merits further evaluation, especially when the hirsutism is associated with other virilizing signs/symptoms.

In truth, the objective scoring system is not used much in practice. The presence of virilization (clitoromegaly, deepening of the voice, male-pattern balding) and de-feminization (breast atrophy) is more clinically useful.

Recall that the workup for the virilized female includes evaluation of ovarian and adrenal androgens: DHEA and testosterone.

Lab results for these tests in the virilized woman with:

- Mild elevations of DHEA and testosterone are consistent with PCOS.
- Elevated testosterone and very high DHEA are consistent with an adrenal carcinoma.
- Very high testosterone with normal DHEA is consistent with an ovarian stromal tumor; e.g., arrhenoblastoma = Sertoli-Leydig cancer = < 10% of ovarian cancers.

Remember that hirsutism may also be due to late-onset, partial congenital adrenal hyperplasia, which is usually caused by a *CYP21A2* gene defect (→ 21-hydroxylase deficiency). Labs show elevated blood 17-hydroxyprogesterone and increased urinary 17-ketosteroids and blood DHEA (Figure 7-3 on page 7-16).

Cushing disease (in the pituitary) and prolactinoma are uncommon causes of hirsutism. Drugs associated with hirsutism include minoxidil, cyclosporine, and phenytoin.

MEN

In men, luteinizing hormone (LH) stimulates Leydig cells (L stimulates L) to produce testosterone, which in turn inhibits FSH and LH secretion. FSH stimulates the Sertoli cells to secrete inhibin B and androgen-binding globulin, which in turn bind the testosterone, keeping high intratubular levels (allowing maturation of the spermatozoa). Hence, both FSH and LH are required for spermatogenesis.

Primary hypogonadism is usually due to Klinefelter syndrome (47,XXY or mosaic 46,XY/47,XXY). The genetic abnormality results in defective testosterone synthesis by the Leydig cells. Therefore, the testes do not grow properly, and they fail to adequately produce androgens for the life of the male. Clinical presentation is small testes, long arms and legs, fertility problems, lack of virilization (sparse hair growth and muscle mass), and gynecomastia. Some patients have learning disabilities. The expression of this genetic abnormality is somewhat variable, although not fully understood. Occasionally, mosaic individuals are fertile. Testosterone is decreased, and serum LH and FSH are elevated. Diagnose with a karyotype. Treat Klinefelter syndrome with testosterone. Fertility can happen with *in vitro* techniques harvesting spermatozoa from the testes of Klinefelter patients.

Table 7-2: Hirsutism Workup: Lab Results vs. Disease Entities

Serum Hormone Levels	Cushing Disease (central)	Adrenal Cancer	Ovarian Cancer (stromal)	CAH	PCOS
Testosterone level	N, +	N, +	+++	N, +	N, +
DHEA level or urinary 17-ketosteroids	N, +	+++	N, +	N, +	N, +
LH/FSH	N	N	N	N	> 2

N = Normal, + = increased. Notes: 1) DHEA is a precursor to 17-ketosteroids. 2) PCOS is polycystic ovarian syndrome. CAH is congenital adrenal hyperplasia. Results in PCOS, idiopathic, and CAH are similar except for the LH/FSH level. 3) See text to further define CAH. 4) Ovarian cancer has a high testosterone level, whereas adrenal cancer has a high DHEA level. 5) Only "central" Cushing "disease" causes hirsutism; elevations in only cortisol occur in adrenal adenomas (low DHEA and ACTH levels).

Secondary hypogonadism is due to an abnormal hypothalamic-pituitary axis, so testosterone level is low and FSH and LH are low or inappropriately normal. Causes of secondary hypogonadism are either acquired or congenital:

- Hyperprolactinemia.
- Long-standing abuse of exogenous testosterone (anabolic steroids).
- Cushing syndrome (excessive glucocorticoids from any source).
- Congenital gonadotropin deficiency. If some male relatives of the patient have similar hypogonadism, the patient probably has Kallmann syndrome (= GnRH deficiency + anosmia [inability to smell]). Kallmann's is often associated with midline defects such as cleft palate and horseshoe kidney (Figure 7-5).

Erectile dysfunction is discussed in General Internal Medicine, Book 5.

Gynecomastia in men results from an altered estrogen to androgen ratio. Unilateral or bilateral gynecomastia is normal at male puberty. Males who have increased aromatization of circulating androgens into estrogen have this. Also, conditions that produce excess testosterone can result in excess estradiol because of the aromatization. Gynecomastia is seen in advanced age, obesity, cirrhosis, hyperthyroidism, Klinefelter's, germ cell tumors, and certain drugs. In males with gynecomastia and a testicular mass, an elevated hCG and low LH (due to high estradiol levels) suggest germ cell cancer. This is discussed further in Oncology, Book 4.

LIPOPROTEINS

REVIEW

Chylomicrons

Lipoprotein review: Follow along in Figure 7-6.

All **lipoproteins** are particles with a hydrophobic core (triglycerides and/or cholesterol), surrounded by a hydrophilic phospholipid outer layer that facilitates transport through the serum. Apolipoproteins are embedded and bind enzymes or receptors. **Chylomicrons** (with apo B48, CII, and E) are large globules that consist of mostly triglycerides but some cholesterol, and are formed in the intestinal epithelium from dietary fats. The apo B48 on their surface is unique to chylomicrons. Chylomicrons enter the circulation by way of the intestinal lymph ducts. In the circulation, chylomicrons attach to peripheral binding sites in muscles and fat, where the CII apolipoproteins on the surface of the chylomicrons activate lipoprotein lipase (LPL).

The activated LPL removes the triglycerides from the inside of the chylomicrons by breaking down the triglycerides into free fatty acids (FFA), which are either utilized or stored. The shrunken remnant, now high in cholesterol (relative to triglycerides), is called (appropriately enough) a chylomicron remnant. It is taken up by the liver via the liver receptors specific for apolipoprotein E. The liver degrades the remnants, and the cholesterol goes either into bile or on to further synthesis reactions.

To review: The apo B48 is a chylomicron marker; apo CII activates the LPL to suck out the triglycerides; and the apo E is a marker recognized by the liver. If there is a deficiency of either apo CII or LPL, the patient has hyperchylomicronemia, which may cause acute pancreatitis and eruptive xanthomas.

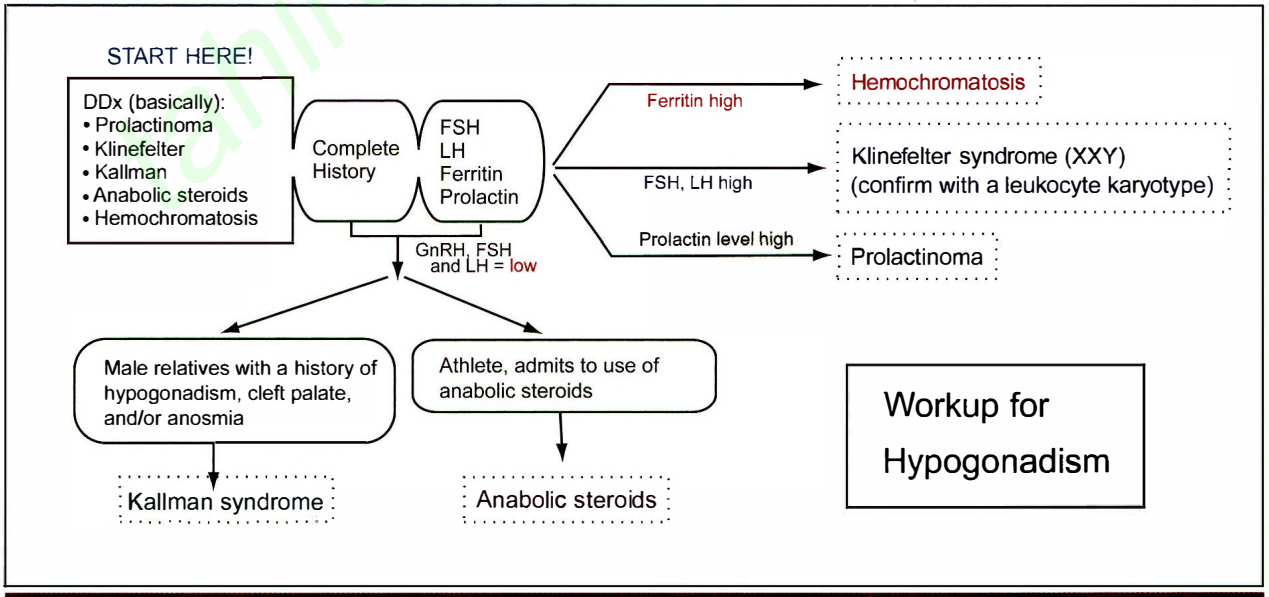


Figure 7-5: Hypogonadism Workup for Males

Quick Quiz

- Differentiate Kallmann syndrome from Klinefelter's.
- In what medical situations do you see gynecomastia, normally and in disease states?
- In what situations are LDL receptors down-regulated? Up-regulated?

VLDL

Very low-density lipoprotein ([**VLDL**]; with apo B100, CII, and E) is synthesized by the liver to supply energy to the body. All subsequent lipoproteins except HDL have apo B100. VLDL is similar to chylomicrons, except that it is smaller and contains less triglyceride and more cholesterol. VLDL function is analogous to chylomicrons in that VLDL transports triglycerides to the capillaries of the muscle and fat and is metabolized by the peripheral LPL (activated by CII).

IDL

Following its excretion from the liver and catalyzation by LPL, VLDL forms a remnant called **intermediate-density lipoproteins** (**IDL**). These still have the triglycerides and some cholesterol. 1/2 of IDL are identified and consumed by the liver via the LDL receptor, which recognizes apo E and apo B100. The other 1/2 remain in the plasma, where they lose the rest of the triglycerides and all of the apolipoproteins, except B100, and thereby are converted to **low-density lipoprotein** (**LDL**). If there is a deficiency of apo E, patients have a high IDL.

LDL

LDL is formed from IDL. LDL (cholesterol only; apo B100 only!) provides cholesterol for the synthesis of hormones, cell membranes, and bile acids. The only apolipoprotein on LDL you need to remember is apo B100 (whew)!

LDL is either taken up by a specific LDL receptor (2/3) or scavenged (1/3)—usually by monocytes or smooth muscle cells. The LDL receptor is present on all cells, but it is much denser in the liver (80%). This receptor binds lipoproteins with apolipoproteins E and B100. Affinity is greater for those with both apo E and apo B100, which is why there is no accumulation of IDL in a healthy person.

LDL receptors are down-regulated or decreased:

- When dietary cholesterol or saturated fats are high
- With age (increasing cholesterol with age)
- In patients with familial hypercholesterolemia, hetero = 50%, homozygotes = 0

LDL receptors are up-regulated or increased:

- When dietary cholesterol or saturated fats are low
- By estrogen
- By thyroxine
- By the "statins" (HMG-CoA reductase inhibitors)
- By a decrease in bile acid uptake from the intestines (as with bile acid resins)

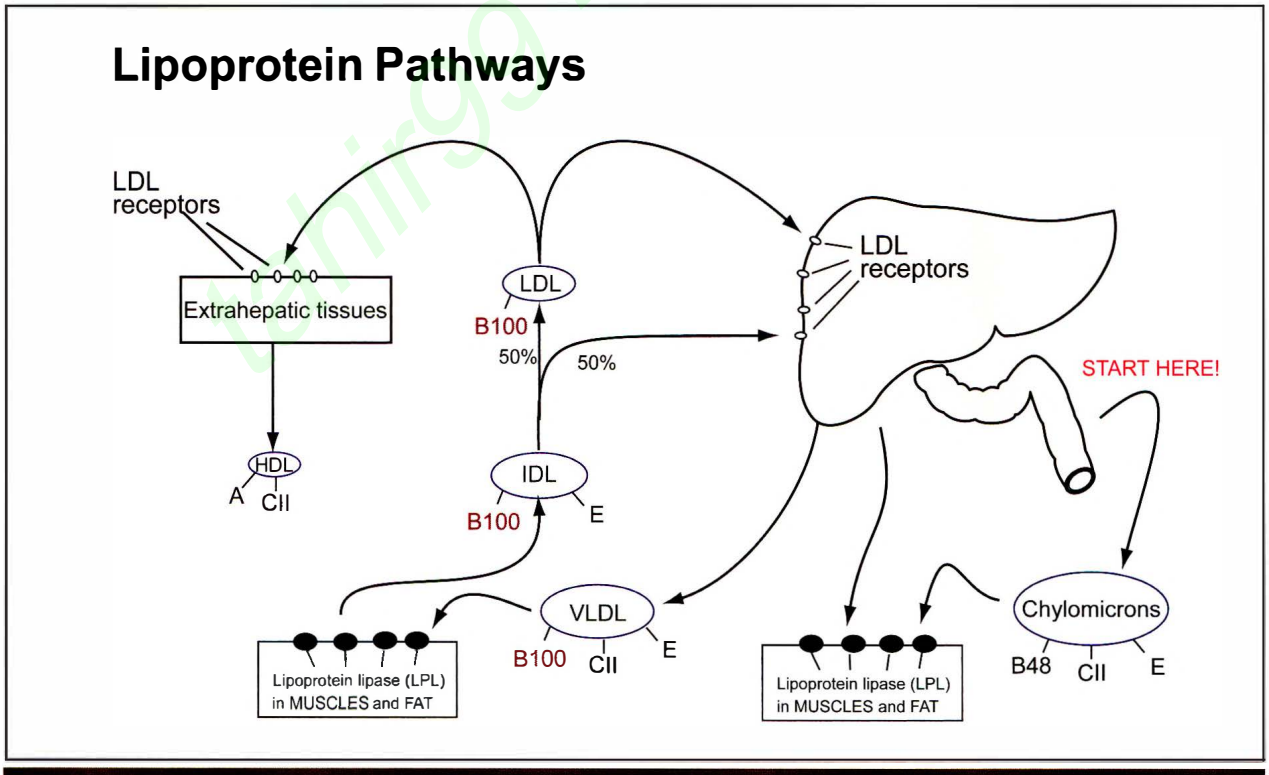


Figure 7-6: Lipoprotein Pathways

Lipoprotein a (Lp(a)) is covalently bound by a disulfide bond to the Apo B100 of LDL. Genetic and epidemiologic studies have identified Lp(a) as an independent risk factor for coronary heart disease and stroke. Its exact mechanism is still unknown; however, because of the high homology of apolipoprotein(a) and plasminogen, it has been hypothesized that Lp(a) is pro-thrombotic. Lp(a) levels are genetically inherited and are twice as high in African-Americans as in Caucasians. Nicotinic acid and mipomersen, an antisense oligonucleotide to apo B100, are the only known drugs that decrease Lp(a). Nicotinic acid decreases Lp(a) only in those patients with concomitant hypertriglyceridemia. Mipomersen, however, decreases Lp(a) levels by 21–27% in patients with familial hypercholesterolemia and severe hypercholesterolemia.

Small LDL particle size is also associated with an increased risk of CHD and endothelial dysfunction. The smaller particles are more easily oxidized, bind arterial wall proteoglycans with more affinity, and bind the LDL receptor with less affinity, thereby reducing their clearance from the blood stream. These mechanisms contribute to their pro-atherogenic nature. Also, the presence of small, dense LDL particles seems to parallel a state of decreased **high-density lipoprotein (HDL)**.

HDL

HDL is mainly composed of protein and phospholipids with very little cholesterol or triglycerides. It scavenges the unesterified cholesterol from cell breakdown. HDL contains mainly apo AI and AII but also apo C.

Apo AI helps esterify the scavenged cholesterol. Then, it is transferred to IDL or LDL and removed via the liver. In this way, the HDL is a sort of reverse transport system.

ABCA1 is a transmembrane protein that helps to move cholesterol from inside the cell to the cell membrane. ABCA1 is expressed when cholesterol loads onto the cell surface and is removed when the apolipoproteins pick up the cholesterol.

Problems arise in HDL levels when something goes wrong with apo AI or ABCA1 (gene or protein). Low HDL is common in cases of premature CHD and is usually either isolated or occurs in combination with elevated triglycerides (TG). Low HDL occurs because of low levels of apo AI (termed hypoalphalipoproteinemia) and happens because the synthesis of apo A is reduced or its breakdown is increased. (There are diseases associated with these, but you don't need to know them in-depth [well, for now anyway!].)

When the HDL level is low, the apo CII level lowers because HDL also acts as a reservoir for apo CII. Because CII activates LPL, there is decreased processing of VLDL and chylomicrons by LPL in the muscle and fat. The end result can be hypertriglyceridemia—as in familial hypertriglyceridemia.

HEREDITARY DYSLIPIDEMIAS

Overview

Dyslipidemias can be classified as familial/primary or acquired/secondary (due to DM2, hypothyroidism, nephrotic syndrome). Of the familial dyslipidemias, known monogenic causes include mutations in the LDL receptor, the PCSK9 enzyme, and the microsomal triglyceride transfer protein (MTTP). It is important to know that the majority of cases of dyslipidemia seen in an internist's clinic are polygenic in origin, which may contribute to the variable response rates to different lipid-lowering therapies. However, regardless of the genetic etiology of a particular dyslipidemia, clinical management is primarily determined based on clinical history, family history, CV risk assessment, and, most importantly, serum LDL-C.

Many cases of premature CHD are related to a familial dyslipidemia. Start screening for lipid disorders at age 20 using the basic fasting lipid panel (FLP). Some experts are looking for the less common familial dyslipidemias by measuring apo B100, apo AI, and Lp(a) when they observe CHD in a patient with a normal lipid profile or if there is a strong family history of CHD and/or ischemic events.

LDL-Associated Dyslipidemias

The familial dyslipidemias below with the "*" are the conditions most likely to be tested on exams.

Familial combined hyperlipidemia* (FCHL) is the most common dyslipidemia and very common in the general population. 1% of the population is autosomal dominant for FCHL, and up to 10% of those with premature CHD have it. It is the most common cause of lactescent plasma. FCHL has an extremely variable presentation with varying elevations of LDL and VLDL. In FCHL, there is increased production of both apo B100 and VLDL, and the increased VLDL stresses the pathways toward increased LDL production. The LDL levels in FCHL are usually less than those in FH (< 230; see next).

Familial hypercholesterolemia* (FH) presents as premature atherosclerosis and tendon xanthomas on physical exam. Homozygous FH (1:1,000,000 incidence) is uncommon, and patients present with an extremely high LDL (usually > 400 mg/dL). Homozygous FH patients have no functional LDL receptors, so they are typically unresponsive to statins. Heterozygous FH is more common with an incidence of 1:500. Heterozygous FH patients have baseline LDL-C levels > 200 mg/dL and have variable response to statins.

Diagnosis is suggested by family history of premature CHD, tendon xanthomas, elevated LDL levels, and an LDL:apo B ratio < 1.2 (vs. > 1.4 in normals).

Familial defective apolipoprotein B100 is an autosomal dominant genetic disorder that causes a problem on the LDL particle at the apo B100 ligand. Like heterozygous FH, LDL levels are 2–2.5x higher than

Quick Quiz

- Which familial dyslipidemia is the most common? What lipoproteins are elevated?
- What lipid test result suggests the need to work up familial hypoalphalipoproteinemia?
- What lab tests should be included in general lipid screening?
- What is the primary endpoint of lipid screening done for primary prevention of CHD?

normal. These 2 disorders have to be distinguished using genetic techniques.

Hyperapobetalipoproteinemia is also caused by excess production of apo B, but LDL levels are normal. Suspect this in patients with premature CHD, especially if they have prominent xanthelasma. Labs show a normal LDL but increased apo B with LDL:apo B < 1.2.

Polygenic hypercholesterolemia is another cause of premature CHD that clusters in families. LDL is increased, but the genetic specifics are unclear.

Other Dyslipidemias

Familial hypertriglyceridemia* contrasts with FCHL in that the apo B and VLDL numbers are normal, but VLDL size is larger and less dense. Like FCHL, it is an autosomal dominant inheritance!

Dysbetalipoproteinemia is autosomal recessive and presents with a high IDL, meaning elevated triglycerides and cholesterol. The IDL has an abnormal apo E, which interferes with the attachment of IDL on the LDL receptor in the liver. The patient must be homozygous (E2/E2) for the defect—plus have DM, be obese, or have an alcohol problem to have significantly elevated IDL levels.

HDL-Associated Dyslipidemias

Familial hypoalphalipoproteinemia is autosomal dominant and results from a mutation in the gene for apo AI (*APOA1*), or for the genes *ABCA1,* or *LCAT*. It results in an isolated low HDL. Current data say the condition is seen in 6% of Japanese patients who have low HDL.

Familial HDL deficiency is also autosomal dominant and is caused by mutations in the gene encoding *ABCA1*. Theoretically, the altered intracellular transport of cholesterol that occurs with an *ABCA1* mutation is associated with increased catabolism of apo AI. It results in an isolated low HDL with premature CHD.

Tangier disease is also due to an *ABCA1* mutation leading to increased catabolism of apo AI. Patients heterozygous for the mutation have low HDL (50% of normal), and homozygous patients have no HDL. This leads to very defective cholesterol handling and diffuse deposition of foam cells causing hepatosplenomegaly, neuropathy, and premature CHD.

EVALUATION OF HYPERLIPIDEMIA

"High cholesterol" means elevated LDL. "High triglycerides" means elevated chylomicrons, elevated VLDL, elevated IDL, or all. Low HDL is a predictor of CHD. Therefore, general cholesterol screening uses the FLP that includes total cholesterol, LDL, HDL, and triglycerides. LDL is calculated and is the value you care about most (discussed next).

TREATMENT OF HYPERLIPIDEMIA

Overview

Treatment exists as:

- **Primary** prevention (in patients without known CHD)
- **Secondary** prevention (in patients with known CHD or with diseases that carry the same risk as CHD, termed "CHD equivalents")

Six large trials have established that primary prevention for dyslipidemia reduces CHD. The most influential U.S. practice guidelines come from the NIH-sponsored National Cholesterol Education Program (NCEP) and were titled, "Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2004 Adult Treatment Panel III)." New ACC/AHA (with the NHLBI) guidelines on atherosclerotic cardiovascular disease (ASCVD) prevention were published in late 2013. These guidelines have not been endorsed by the National Lipid Association (NLA).

Our discussion of lipids is based on 2004 NCEP ATP III, 2013 ACC/AHA guidelines, 2013 NLA response statement, and on the current body of literature. Both traditional and new management guidelines are listed here because there may be a delay in updating this information to the Boards and because some of the recommendations in the new guidelines are controversial (see page 7-31).

General Concepts of Primary Prevention

Start screening using the fasting lipid panel (FLP) at age 20, with follow-up in 5 years if normal or yearly if borderline and < 2 CHD risk factors. If abnormal, start your treatment and follow up in 4–6 weeks.

The primary screening endpoint is LDL. LDL is usually a derived value:

$$\text{LDL} = \text{Total cholesterol} - \text{HDL} - \text{VLDL}$$

$$= \text{Total cholesterol} - \text{HDL} - \text{triglycerides}/5$$

(valid only if triglycerides < 400 mg/dL)

Following achievement of LDL targets, non-HDL cholesterol is a secondary target in patients with hypertriglyceridemia > 200:

$$\text{Non-HDL} = \text{Total cholesterol} - \text{HDL}$$

The non-HDL result is theoretically equivalent to the sum of the remaining atherogenic lipoproteins: LDL + Lp(a) + IDL + VLDL, and may do a better job of predicting plaque formation than just measurement of LDL in those patients with elevated LDL and triglycerides. Watch how this shakes out in the highly anticipated ATP IV updates.

ATP III recommends a priority level of treatment:

- Elevated LDL, then
- Elevated non-HDL, then
- Low HDL

This stratification of priority tells you to correct an elevated LDL first. Do not get distracted by a low HDL or high TG, and prescribe drugs for these until you've addressed the LDL.

After obtaining the FLP, identify whether the patient has any CHD/CHD equivalents—if these are present, treat for "secondary prevention"—and other risk factors for CAD. From this information, determine a patient's risk category and establish the goal LDL.

NCEP ATP III Guidelines

Overview

Again: LDL level is the main lab test used for determining treatment thresholds and goals. [Know all this perfectly!] It is summarized in Table 7-3. When using the table, remember that "CHD equivalents" are considered the same as having CHD. Again, these are considered superceded by some experts by the 2013 ACC/AHA guidelines (page 7-31).

CHD: Risk Factors and CHD Equivalents

1) High LDL is a major risk factor for CHD; high HDL is good and a negative risk factor:

LDL cholesterol:

- Very high: ≥ 190
- High: ≥ 160
- Borderline high: 130–159
- Near optimal: 100–129
- Optimal: < 100

Total cholesterol levels are a bit simpler and used as a reference, but they are not used as treatment goals:

- High: ≥ 240
- Borderline high: 200–239
- Desirable: < 200

HDL limits are:

- < 40 = low
- ≥ 60 = high (which is good and allows you to subtract 1 risk factor!)

2) [Know.] The CHD-equivalent diseases are:

- Diabetes
- Other clinical forms of atherosclerotic disease, such as peripheral arterial disease, abdominal aortic aneurysm, transient ischemic attack, or stroke
- A 10-year risk of CHD of > 20% (using Framingham risk calculators)
- Chronic kidney disease (added by the National Kidney Foundation)

For the target LDL, CHD equivalents are treated the same as having known CHD.

3) The major non-LDL risk factors for CHD are:

- Age: men ≥ 45 years old; women ≥ 55 years old
- Family history of premature CHD (< 55 years old in male, 1st degree relatives; < 65 years old in female, 1st degree relatives)
- Current cigarette smoking
- Hypertension (> 140/90 or on medication)
- HDL cholesterol < 40

0–1 risk factor correlates with a ≤ 10% 10-year risk for CHD; 2+ risk factors correlate with a 10–20% risk for CHD.

HDL cholesterol > 60 mg/dL is a negative risk factor, and you can use it as a "–1" when adding up risk factors.

The goal of treatment is to reduce LDL according to the risk factors. The secondary target is to address metabolic risk, which consists of addressing factors such as: abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, and prothrombotic and proinflammatory conditions.

Table 7-3: NCEP ATP III Primary Prevention Initiation and Goals Based on LDL Cholesterol

I. Initiation of Therapeutic Lifestyle Changes (TLC)

	Initiation Level ≥:	LDL Goal (mg/dL) <:
No CHD, 0–1 risk factors	160	160
No CHD, ≥ 2 risk factors	130	130
With CHD/CHD equivalents	100	100 < 70 optional

II. Addition of Drug Therapy

	Consideration Level ≥:	LDL Goal (mg/dL) Less than:
No CHD, 0–1 risk factors	190	160
No CHD, ≥ 2 risk factors	160	130
With CHD/CHD equivalents	130	100 < 70 optional

Hint: Just remember > 160/130/100 as the initiation of TLC and 160/130/100 is the goal for both therapies. Add 30 to each initiation level number to determine the point at which you consider adding drug therapy to TLC.
Know that, contrary to this table, statins have now been shown to be beneficial for all patients with CHD/CHD equivalents with or without hyperlipidemia!

Quick Quiz

- Explain the ATP III treatment priority for lipid abnormalities.
- List the CHD-equivalent diseases.
- Per ATP III, what are the non-LDL risk factors for CHD that are considered when you stratify patients for primary prevention of CHD?
- Per ATP III, at what LDL level is TLC started on a 38-year-old man with diabetes? At what level would you start drug therapy?
- Per ACC/AHA ASCVD guidelines, name the 4 statin benefit groups.
- How is a "high intensity" statin defined? A "moderate intensity" statin?

ATP III: Treating for Primary Prevention

Start with **Therapeutic Lifestyle Changes** (**TLC**), which consist of dietary therapy, exercise, and weight loss (Table 7-3).

With 0–1 risk factor: Start TLC when LDL ≥ 160 (goal of therapy is LDL < 160); start drugs at ≥ 190.

With ≥ 2 risk factors: Start TLC when LDL ≥ 130 (goal of therapy is LDL < 130); start drugs at ≥ 160, except in the patient who has a 10-year CHD risk of > 10%. Start that patient on drugs when the LDL is ≥ 130.

ATP III: Treating for Secondary Prevention

Treat those with CHD/CHD equivalents more aggressively than those with 2 risk factors (in primary prevention, above):

- If LDL > 100, start TLC.
- If LDL > 130, start TLC + drug therapy.

In a patient with CHD/CHD equivalents, the goal is to get LDL to < 100. The 2004 ATP III update allows for optional reduction of LDL to < 70 in CHD/CHD equivalents. In 2007, several diabetes and cardiology practice guidelines began to recommend a target LDL of < 70 in patients with CHD, and this has become the national standard.

Statins are 1st line drugs because they improve mortality.

On an exam question, if you are presented with a patient who has limited resources but needs treatment for secondary prevention of CHD, always give this patient a statin. The statins have the highest mortality benefit. Niacin would seem to be a good choice because it is less expensive, but the mortality benefit of niacin is less than statins (and there are many inexpensive generic statins available now in the U.S.).

Follow-up

The maximum effect occurs 4–6 weeks after starting treatment, so wait 6–8 weeks before changing therapy. When LDL < 100 mg/dL, recheck every 2–3 months for the 1st year, then 2x/yr.

2013 ACC / AHA Clinical Practice Guideline on Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease (ASCVD) Risk in Adults

Recommended changes in management:

- Identifies 4 "statin benefit" patient groups in which to focus efforts to reduce ASCVD events in primary and secondary prevention; this is a departure from "treat-to-target" approach for LDL and non-HDL goals.
- These 4 "statin benefit" patient groups are those with:
  1) clinical atherosclerotic cardiovascular disease,
  2) familial hypercholesterolemia,
  3) diabetics 40–75 years of age with LDL-cholesterol levels between 70 and 189 mg/dL and no evidence of atherosclerotic cardiovascular disease, and
  4) diabetics with low lipid levels but a 10-year risk of atherosclerotic cardiovascular disease > 7.5%.
- Identifies which high-intensity statin therapy (resulting in > 50% reduction of LDL) and moderate-intensity statin therapy (30 to < 50% reduction of LDL) should be used in those most likely to benefit.
- TLC should serve as the backbone to any ASCVD prevention clinical management plan.
- Advocates the use of new pooled cohort equations that estimate 10-year risk in both Caucasian and African-American men and women for primary prevention.
- Identifies high-risk groups that may not benefit from primary prevention.
- Advocates consideration of the net benefit of statin therapy; identifies important safety considerations and potential adverse effects.
- Offers guidance on management of statin-associated adverse effects such as muscle symptoms.
- Other factors such as inflammatory biomarkers and noninvasive tests may inform treatment of individuals not in the 4 statin benefit patient groups.
- Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their adverse effects in prevention of ASCVD.
- For questions regarding complex lipid disorders for which little or no randomized controlled trial data are available, the guidelines recommend referral to clinicians with lipid expertise for further management.

Note: These guidelines are still considered controversial in that some experts believe that the guidelines-based risk calculator published on the ACC website overstates CV risks by 75–150%, thereby increasing statin recommendations. Additionally, the National Lipid Association

(NLA) has decided to not endorse these guidelines for reasons listed below.

NLA Response Statement on 2013 ACC / AHA Clinical Practice Guidelines

ACC/AHA guideline recommendations limited their review to only high quality RCTs, but NLA believes that other important types of clinical evidence should have been included in order to further address gaps in clinical care.

NLA questions the need to remove LDL and non-HDL treatment targets that have been so widely endorsed and recognized by the clinical community.

NLA finds an absence of discussion regarding other therapeutic options for patients on high-dose statins who still exhibit high residual risk and/or significantly elevated LDL-C levels.

NLA finds a need for more discussion on managing special populations such as older patients (> 75 years of age), those with familial hypertriglyceridemia (FH), those who are statin-intolerant, and younger high-risk patients (< 40 years of age).

Dietary Therapy

Diet is always the 1st line of treatment for the hyperlipidemias. Total fat consumption should be < 30% of daily calories. More specifically, saturated fat should be < 7% of daily calories, and cholesterol should be < 200 mg/d.

Regarding types of fats:

- Hydrogenated ("trans fats") vegetable oils (margarines) not only raise LDL but also lower HDL—doubly bad!
- Decreasing dietary saturated fats increases LDL receptors and so decreases LDL, but HDL also decreases!
- Similarly, changing to a diet high in polyunsaturated fats decreases LDL and VLDL, as well as HDL. In all of these cases, the LDL/HDL ratio is the same or increased—not good!
- On the other hand, monounsaturated fats (olive/peanut/canola oils) decrease LDL, but not HDL—good!
- Omega-3 fatty acids decrease only VLDL (triglycerides).

Table 7-4 summarizes this information.

Drugs for Dyslipidemias

Of the following drugs, statins decrease cardiac events and cardiac mortality by about 25% and overall mortality by 15%. Niacin decreases cardiac events and has inconsistent effects on mortality. Gemfibrozil and cholestyramine show a decrease in cardiac endpoints but no decrease in overall mortality. See Figure 7-7 and Table 7-5 on page 7-34.

HMG CoA reductase inhibitors are the **statins**: lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin. These are the primary cholesterol-lowering drugs. HMG CoA reductase is the enzyme in the rate-limiting step of lipid metabolism. Statins inhibit this enzyme and, thereby, up-regulate the LDL receptors—as do the bile acids.

Statins cause a decrease in LDL and may decrease VLDL. There are only modest gains in HDL with statins. As mentioned, all persons with CHD should be on a statin long-term, if they can tolerate it.

Statins may cause myalgias, an elevated CPK, and, rarely, rhabdomyolysis. Check liver transaminases if the patient develops nausea, abdominal pain, or other signs/symptoms of hepatotoxicity.

The risk of myopathy with statins increases significantly when used in combination with cyclosporine, gemfibrozil (but not as much with fenofibrate!), erythromycin, and ketoconazole.

Statins can cause mild elevations in blood sugar level. Statins may cause memory loss and confusion in some people. The FDA added blood sugar and cognitive changes to the warnings in 2012. Both are generally reversible with stopping the drug.

Inhibitor of intestinal cholesterol absorption (ezetimibe): 2nd line LDL-lowering drug (after statins). It is approved for use alone or in combination with a statin or fenofibrate to reduce LDL and apo B in patients with primary or mixed hyperlipidemias. It is also approved for use with atorvastatin or simvastatin to reduce LDL in patients with familial homozygous hypercholesterolemia. Alone, ezetimibe can reduce LDL by up to 17%; in combination with a statin, it provides a further 14% reduction in LDL over the effect of the statin. Ezetimibe can cause myopathy and increases the risk of statin-induced myopathy during combination therapy. Avoid using ezetimibe with gemfibrozil. Moderate or severe hepatic impairment is a contraindication.

Table 7-4: Dietary Therapy and Cholesterol

Diet Modification	LDL	HDL	LDL/HDL	Comments
Change to hydrogenated vegetable oils (trans)	Increase	Decrease	Increase	Doubly bad!
Decrease saturated fats	Decrease	Decrease	Same or increase	Neutral to bad
Change to polyunsaturated fats	Decrease	Decrease	Same or increase	Bad
Change to monounsaturated fats	Decrease	May increase	Decrease	Good!

Quick Quiz

- Which fats are the "good" fats? The "bad" fats?
- What class of drugs is recommended 1st line to reduce LDL?
- What are the major side effects of statins?
- What are side effects of colesevelam?
- What is the main action of the fibrate drugs?

The most interesting news about ezetimibe comes from the clinical trial, ENHANCE (efficacy of simvastatin 80 mg alone or in combination with ezetimibe, using the well-established carotid intima-media thickness [IMT] as a surrogate endpoint in patients with heterozygous familial hypercholesterolemia [FH]). This 2-drug combination lowered LDL and raised HDL significantly better than simvastatin alone, but the IMT was no different between the groups.

The significance of ENHANCE is that it raised more questions than it answered about LDL reduction. Was IMT the best endpoint to use for these FH patients? Is there a threshold below which further reduction of LDL does not provide clinical benefit? Ongoing trials are addressing these issues.

Bile acid resins (cholestyramine, colestipol, and colesevelam) are also 2nd line LDL-lowering drugs. Similar to ezetimibe, bile acid resins are used primarily as adjuvant therapy in combination with statins or monotherapy in patients who cannot take statins. Resins decrease LDL, slightly increase HDL, and may increase triglycerides. By absorbing bile acids in the intestine, and thereby preventing their re-uptake, they cause up-regulation of the LDL receptors in the liver, which increases the processing of serum LDL needed to synthesize replacement bile acids. Although the HDL level remains the same, the LDL/HDL ratio decreases.

Bile acid resins may also cause an increase in the synthesis of VLDL, so the patient may get an increase of triglycerides. Side effects of these resins are nausea, vomiting, constipation, and bloating. The resins can absorb other oral drugs, so give any other medicines 1 hour before or 4 hours after the resins.

Fibric acid derivatives (mainly gemfibrozil and fenofibrate) are used primarily to treat hypertriglyceridemia. These drugs decrease VLDL and raise HDL. Their main mechanism of action is increasing the activity of LPL on VLDL—thus increasing its rate of conversion to IDL. Some of this IDL is then converted to LDL, occasionally causing an increase in LDL. Other actions are increased production of apo AI and AII, which increases HDL and increases excretion of cholesterol into the bile.

Fenofibrate is the latest fibric acid derivative; it appears to have more efficacy than gemfibrozil in lowering LDL, and it does not inhibit statin breakdown (thus contributing to statin myopathy). Fenofibrate is the drug of choice when combining a fibrate with a statin.

The recent ACCORD trial included diabetic patients who were treated with a statin vs. statin plus fibrate to determine if the addition of the fibric acid derivative reduced rates of non-fatal MI, stroke, or cardiovascular death. The end result: The addition did not change these endpoints. So, the current standard is to reduce LDL to < 70 in high-risk patients using drugs that specifically target LDL, e.g., statins.

Clofibrate is another fibrate that is available but should not be used because of its association with GI cancers.

Nicotinic acid (= niacin) is great if the patient can tolerate it. It is by far the least expensive agent of those listed. It lowers triglycerides and cholesterol (LDL) and increases HDL. It is the most effective drug available for raising HDL (up to 30%). It lowers triglycerides by blocking the production of VLDL (and therefore LDL). Initially,

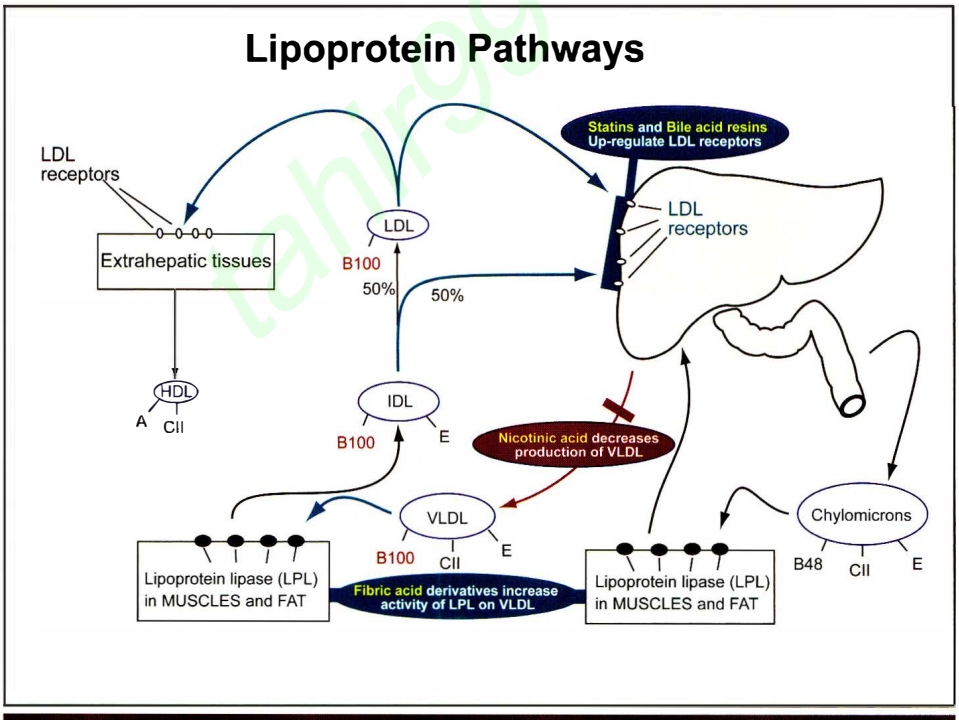


Figure 7-7: Effect of Drugs on the Lipoprotein Pathways

Table 7-5: Uses of Currently Available Lipid Drugs

Drug	Use	Side Effects
Statins	Drug of choice for LDL reduction	Myalgias, myositis, elevated transaminases
Ezetimibe	Alternative drug for LDL reduction	Myopathy, elevated transaminases
Bile resins	Alternative drug for LDL reduction	N/V, constipation, bloating
Fibric acid derivatives	Drug of choice for TG reduction	Possible: abdominal pain, GB disease, malignancy
Nicotinic acid	Alternative drug for LDL and TG reduction	Flushing, dry skin, N/V/abdominal pain

give nicotinic acid 100 mg tid, then raise it 100 mg tid each week to the full dose of 1–2 gm tid. Important metabolic side effects include hyperuricemia and insulin resistance; gout and diabetes mellitus are relative contraindications. Annoying side effects include flushing (especially), dry skin, and nausea/abdominal pain. ASA 325 mg given 30 minutes before the dose blocks the flushing reaction. This reaction usually disappears after a week or two. Niacin has been shown to reduce cardiovascular events, but the data are not as strong as the data for statins. The recent AIM-HIGH trial fails to show a clinical benefit of adding niacin to statin therapy even though lipid levels improved.

Omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, in moderate doses, appear to decrease mortality and sudden cardiac death in patients with known CHD. High doses cause a decrease in platelet and neutrophil aggregation, decreased BP, and decreased triglycerides (VLDL) but with an increased LDL. Very high doses may decrease angioplasty restenosis rate. Generally, if a patient has CHD, adding fatty fish (salmon, mackerel, herring, sardines, albacore tuna) to their diet twice a week or a daily fish supplement is recommended.

Summary (see Table 7-5):

- Statins block HMG CoA reductase. Ezetimibe inhibits intestinal cholesterol absorption. Nicotinic acid decreases triglycerides by blocking synthesis of VLDL.
- Statins and nicotinic acid are the only drugs that both decrease LDL and increase HDL.
- Ezetimibe is used in conjunction with either a statin or fenofibrate to reduce LDL and/or non-HDL.
- Both fibric acid derivatives (gemfibrozil, fenofibrate) and nicotinic acid decrease triglycerides; but, whereas nicotinic acid also decreases LDL (good), gemfibrozil may increase the levels of LDL (bad). Fenofibrate increases LDL less than gemfibrozil.
- Combining gemfibrozil with statins significantly increases the risk of myositis. Use fenofibrate if you need to combine with a statin.
- What increases HDL? Nicotinic acid, fibrates, statins, omega-3 fish oils, moderate alcohol intake, exercise, stopping smoking, losing weight if obese, and reducing intake of trans fats.
- What lowers HDL? Beta-blockers (except labetalol), smoking, getting fat, and eating a diet high in hydrogenated (trans) fats or polyunsaturated fats.
- What has no effect on HDL? Bile resins. Monounsaturated fats (peanut, olive, and canola oils) have no effect or may raise HDL only slightly.

Treatment Scenarios

What drugs are indicated for the following if the TLC is insufficient?

Remember: Priority of treatment is LDL first, then non-HDL, then HDL. For secondary treatment goals, many experts recommend focusing on lowering all non-HDL cholesterol first and then raising HDL. All patients with CHD/CHD equivalents should receive statin therapy regardless of lipid levels.

Treatment scenarios:

- Increased LDL, normal TG, normal HDL: statin.
- Increased LDL, normal TG, decreased HDL: statin first. Based on NCEP guidelines, consider adding GI-active drug (ezetimibe or resin) or niacin to achieve further reduction in LDL and raise HDL. Based on 2013 ACC/AHA guidelines, do not add any additional non-statin therapies.
- Increased LDL, increased TG, normal HDL: statin first. Based on NCEP guidelines, consider adding fibrate or niacin to achieve further reduction in LDL/TG. Based on 2013 ACC/AHA guidelines, do not add any additional nonstatin therapies.
- Increased LDL, increased TG, low HDL: statin first. Based on NCEP guidelines, consider adding niacin, ezetimibe, and/or fibrate to achieve further reduction in LDL/TG and raise HDL. HDL is the last abnormality you treat. Based on 2013 ACC/AHA guidelines, do not add any additional nonstatin therapies.
- Normal LDL, increased TG, normal HDL: Isolated high triglycerides are not as associated with CHD. TG > 1,000–2,000 increases risk for pancreatitis; treat with niacin or fibrate or fish oil. Use statin plus niacin or fibrate or fish oil if the patient has CHD. Consider statin, niacin, fibrate, or fish oil if patient has a family history of early CHD or many risk factors.
- Normal LDL, increased TG, low HDL: fibrate or niacin; see comments under isolated increased TG, just above.

Quick Quiz

- What are relative contraindications to niacin?
- What activities increase HDL? Lower HDL?
- What happens to the lipid panel in ACS?

- Normal LDL, normal TG, low HDL: statin first then niacin, or fibrate; probably need to treat only those with CHD/CHD equivalents.
- Clinical evidence of ASCVD, candidate for statin therapy and already on TLC, and age ≤ 75 years: high-intensity statin or moderate-intensity statin (if not a candidate for high-intensity statin).
- Clinical evidence of ASCVD, candidate for statin therapy and already on TLC, and age > 75 years or not a candidate for high-intensity statin: moderate-intensity statin.
- No clinical evidence of ASCVD, already on TLC: high-intensity statin or moderate-intensity statin (if not a candidate for high-intensity statin)
- Diabetes Type 1 or 2, age 40–75 years and estimated 10-year ASCVD risk < 7.5%: moderate-intensity statin.
- Diabetes Type 1 or 2, age 40–75 years and estimated 10-year ASCVD risk ≥ 7.5%: high-intensity statin.
- Any patient with estimated 10-year ASCVD risk ≥ 7.5%: moderate-to-high intensity statin.

Also consider adverse drug effects, drug-drug interactions, and patient preferences for statin treatment.

LIPIDS IN ACUTE CORONARY SYNDROME

Statins do more to reduce CHD mortality than just reducing LDL. They stabilize plaques, reduce inflammation and thrombogenicity, and reverse endothelial dysfunction.

Give all patients with acute coronary syndrome (ACS) a high-dose statin no matter what the LDL measures. If the patient is already taking a statin, increase the dose for the acute event. (Continuing the statin during an ACS hospitalization has been associated with an improved outcome.) Some experts specifically recommend atorvastatin based on data that high-dose atorvastatin decreases mortality during ACS, but other experts believe the benefit is a drug-class effect. (Data do not compare 2 high-dose regimens.) Exam questions probably will not ask you to pick a specific statin; more likely, they'll ask you to select a choice among different classes of drugs. Any high-dose statin regimen has more side effects (especially myalgias) than low/moderate regimens.

Remember: A recent MI or any serious illness may affect the lipid panel. These effects include decreasing LDL and HDL levels and raising or lowering triglyceride levels. So do not use the FLP drawn at admission for ACS to determine how to treat the patient. Start the statin at a high dose. Redraw the FLP 8 weeks later for a better idea of the patient's true lipid abnormalities.

GOAL LEVELS OF LDL IN PATIENTS WITH CHD

Know all of the following (based on NCEP ATP III guidelines):

Give all patients with CHD/CHD equivalents long-term statin therapy for secondary prevention, even if their LDL is in the normal range. The data indicate that patients should generally be prescribed a dosage of statin that lowers LDL at least 30–40% from the patient's baseline LDL level.

The target LDL is less well-defined, but the trend is to treat to an LDL < 70 because of data showing a reduction in "CHD event rates" (NCEP ATP III).

The 2004 NCEP update recommended a target LDL < 100 in all patients with CHD and a target LDL < 70 as "optional" in high-risk patients. However, many experts and some practice guidelines from major societies are suggesting a target LDL < 70 for those with known CHD.

Experts caution, however, that if a patient with CHD is unable to achieve an LDL < 70 with statin therapy, there is no evidence to support adding a 2nd drug.

Patients intensively treated may experience more serious side effects from the addition of a new medication than they receive benefit from further reduction in LDL.

On a Board exam, it's probably safe to assume your target LDL for these patients is < 100. Because of all the controversy, the exam is unlikely to focus on < 100 vs. < 70. Do not get distracted by the HDL and TG levels. Do what you need to do to get the LDL below target per the patient's risk assessment.

Reevaluate the lipids after initiating treatment to reduce LDL, and then consider interventions to reduce non-HDL and/or raise HDL.

DIABETES MELLITUS

OVERVIEW

The U.S. is seeing an epidemic of metabolic syndrome and diabetes mellitus that parallels the epidemic of U.S. obesity. If you were born in 2000, your risk of developing any kind of DM is 33% (males) and 39% (females)! Diabetics have twice the death rate of non-diabetics from CHD. Early initiation of excellent glycemic control reduces the risk of CHD by 50% in patients with Type 1 diabetes. Life span in diabetics is reduced by 12 years (males) and 19 years (females).

Classification of diabetes is based more on mechanism of dysfunction (Type 1 or 2) than on whether the patient requires insulin for treatment.

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have practice guidelines for management. Fortunately, they pretty much agree on the major items!

Know these categories:

- **Prediabetes** includes both impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).
- **Type 1 immune-mediated** (T1DM, 10% of DM): previously "insulin-dependent DM" and "juvenile-onset DM." The term insulin-dependent DM (IDDM) is not used anymore.
- **Type 1 idiopathic** DM is a rare form of insulinopenia without autoantibodies and with a strong inheritance pattern. Insulin requirements often fluctuate.
- **Type 2** DM (T2DM, 90% of DM): previously "non-insulin–dependent DM" and "adult-onset DM." The term non-insulin–dependent DM (NIDDM) is not used anymore.
- **Chemical** DM: Certain drugs can induce T2DM in patients with insulin resistance or impair the action of insulin (niacin, steroids, thiazides, oral contraceptives, beta-blockers).
- **Gestational** DM.

Diabetes also is caused by endocrinopathies (Cushing's, acromegaly), and injury to the endocrine pancreas due to trauma, surgery, inflammatory disorders, or toxins.

MODY is "maturity-onset diabetes of the young" and is a rare genetic defect in the beta cell.

LADA is "latent autoimmune diabetes in adults"; a late onset of an immune-mediated course often in non-obese adults. LADA has been referred to as Type 1.5 DM! These adult patients often require insulin early in their DM due to the auto-antibodies targeting the pancreas.

DIAGNOSIS AND SCREENING

Some simple basics first. Let's say that CF = clotting factors and WP = the watery part of blood. Glucose, electrolytes, CF, and other proteins float around in the WP.

To make **serum**, let whole blood clot in a red-top tube. The clotting factors are used up when generating clot. Centrifuge the tube to remove the clot and other cells. What remains is "serum."

To make **plasma**, mix whole blood with an anticoagulant (purple-top tube), and then centrifuge it to remove only the cells. What remains is "plasma."

Therefore:

- Whole blood = (cells + CF + WP)
- Serum = WP – (cells + CF)
- Plasma = (WP + CF) – cells

Serum and plasma glucoses are basically the same, except plasma includes the clotting factors. Whole blood glucose values are about 15% less than serum/plasma values. Serum and plasma are obtained by venipuncture. (What you get depends on which tube you put the blood in.) Serum, plasma, and whole blood (venipuncture) glucose measurements can be very different from finger stick measurements.

Finger sticks obtain whole blood from capillaries. Capillary whole blood glucoses are subject to much variability. Finger sticks are acceptable for self-monitoring of known diabetics, but only plasma or serum should be used for diagnosis of diabetes. So remember: Finger stick (capillary whole blood) glucoses are not equivalent to serum/plasma glucoses.

Normal fasting plasma glucose (FPG) is < 100 mg/dL.

Diagnosis of prediabetes (use 1 of the following):

1) Impaired fasting glucose (IFG) = FPG 100–125 mg/dL.
2) Impaired glucose tolerance (IGT) = 2-hr plasma glucose of 140–199 mg/dL after a 75-gm oral glucose load; i.e., during an oral glucose tolerance test (OGTT). The OGTT is more sensitive than FPG for diagnosing prediabetes and is considered the best test by AACE, but they realize it is rather impractical in most offices—and the screening guidelines take this into account.

An HbA1c = 5.7–6.4% is supportive of prediabetes; retest patients with results in this range using the FPG or OGTT.

Diagnosis of diabetes (use 1 of the following):

1) FPG ≥ 126 mg/dL
2) Random plasma glucose ≥ 200 mg/dL with symptoms (polyuria, polydipsia)
3) A1c ≥ 6.5%
4) 2-hr plasma glucose ≥ 200 mg/dL after a 75-gm OGTT

Hyperglycemia should be confirmed by retesting at least once unless there are clear signs of metabolic decompensation (DKA, hyperosmolar coma).

When confirming the diagnosis, the recommendation is to repeat the same test that was used initially.

Know that the best test for diagnosing overt T2DM is the fasting plasma glucose. About 20% of patients screened with the HbA1c have false-negative tests, compared to using the FPG or OGTT.

Additionally, the A1c result can be misleading in some patient groups; e.g., African-Americans, those with hemoglobinopathies and thalassemias, patients with iron deficiency or hemolytic anemias, and those with hepatic or renal diseases.

AACE recommends screening the following patients for DM annually beginning at age 30 years (FPG preferred):

- 1st degree relative with diabetes
- CHD
- Acanthosis nigricans and is overweight (BMI ≥ 25 kg/m^2) or obese
- Sedentary
- Non-Caucasian race
- Hx of IGT
- HTN
- Hyperlipidemia

QuickQuiz

- What are the new categories of diabetes mellitus?
- Define prediabetes and chemical diabetes.
- Define MODY and LADA.
- When are finger stick glucoses useful? When should they not be used?
- What are the criteria for the diagnosis of prediabetes?
- What diseases can lead to a false value of HbA1c?
- What is the significance of diagnosing prediabetes?
- What autoimmune diseases are also associated with T1DM?
- What is the primary treatment for T1DM?

- Hx of gestational diabetes
- Hx of delivery of > 9-lb infant
- Polycystic ovaries
- Psychiatric disease (specifically schizophrenia)

ADA practice guidelines are slightly less rigorous, recommending screening younger patients only if they are overweight (BMI ≥ 25 kg/m^2) with any of the risk factors listed above. Without these risk factors, both ADA and AACE say to start screening at age 45.

PREDIABETES

Overview

Prediabetics have a 6-fold risk of developing overt T2DM; 1/3 of them do. 1/3 stay prediabetic, and 1/3 normalize. The condition is quite important to discover because some prediabetics develop microvascular disease. Also, overt diabetes increases a patient's risk of CHD by 50%!

Goals and Types of Treatment

Promoting a "healthy lifestyle" is your best bet for helping the prediabetic. Weight loss of 5–10% with maintenance can prevent development of overt DM; so does regular exercise (30–60 minutes, moderate intensity, 5 days/week) and a low-sodium/high-fiber diet (low in saturated and trans fats) with moderation of alcohol.

No drugs are approved yet, although metformin, acarbose, glitazones, and GLP-1 agonists have been studied, with strong evidence in their favor. Some studies say you can consider one of these drugs in high-risk prediabetics.

Lipid, blood pressure goals, and aspirin therapy should be the same as for the diabetic (see below).

AACE recommends monitoring the prediabetic with an annual OGTT (although they accept this is difficult to accomplish) and urine test for microalbuminuria. Perform twice yearly FPG, HbA1c (to assess if patient is developing overt DM), and FLP. Note: AACE has published a prediabetes algorithm that stresses lifestyle modification as well as use of medically assisted weight loss.

TYPE 1 DM

Overview

T1DM is marked by cell-mediated beta cell destruction causing absolute insulin deficiency. 90% of patients have autoantibodies against:

- islet cells,
- insulin,
- glutamic acid decarboxylase [GAD], and/or
- tyrosine phosphatases IA-2 and IA-2ß).

Anti-GAD antibody titers are generally the most clinically useful. T1DM is caused by genetic (→ immunologic) and environmental factors that are not yet entirely elucidated. Identical twins have a 30–70% concordance rate. It appears that polymorphisms in the HLA region of chromosome 6 (region that encodes the major histocompatibility complex, MHC) result in some kind of immunologic malfunction.

Quick review: The MHC directs the immune response by presenting antigen to T cells. Human leukocyte antigen (HLA) loci are part of the MHC; the alleles in these loci are defined as A, B, C, and D. DR3 and DR4 alleles are 2 in the set of D alleles.

95% of patients with T1DM have HLA DR3 or DR4. Still, in addition to MHC, there are a lot of other loci proven to contribute to T1DM. Certain environmental factors, such as viruses, may also be important.

T1DM patients are prone to ketosis, depending on how much insulin is being produced. Do not forget that T1DM is associated with other autoimmune diseases; e.g., thyroid, adrenal, celiac disease, vitiligo, B_{12} deficiency, and myasthenia).

Treatment of T1DM

Treatment of hyperglycemia in T1DM has been shown to definitively reduce micro- and macrovascular complications.

Treat with insulin. Oral hypoglycemics are ineffective. See Table 7-6 on page 7-38.

Insulin regimens consist of 3 main groups:

1) Long-acting insulin to serve as basal insulin:
   - Glargine (Lantus®)
   - Detemir (Levemir®)
2) Intermediate-acting to cover fasting and pre-meals: NPH (Humulin N®, Novolin N®)

3) Short-acting insulin to cover pre-meals:
- Regular (Humulin R®, Novolin R®)
- Lispro (Humalog®)
- Aspart (NovoLog®)
- Glulisine (Apidra®)

Premixed insulin combinations (e.g., "70/30" of NPH/R) are not recommended to treat patients with T1DM.

Fixed daily doses of each type of insulin do not always correct hyperglycemia, especially in patients whose intake of carbohydrates varies dramatically. A recent approach is to use nutritional counseling to teach patients how to effectively estimate the grams of carbohydrate in their next meal. Then, they use a pre-established carbohydrate:insulin ratio to calculate the dose of their pre-meal short-acting insulin. (For example, if using regular insulin and the patient's individualized C:I ratio is 15:1, then when the intake is estimated at 130 gm of carbs, the dose would be 130/15, or ~ 8.5 u of short-acting pre-meal). This route for dosing gives patients a little more dietary flexibility and still prevents hyperglycemia. The counseling aspect is important because both physicians and diabetic patients erroneously estimate the carbohydrate content of most meals.

Alternatively, patients also can be treated with a continuous pump that uses rapid-acting insulin to provide a basal rate, with programmed increases prior to meals. The programming is based on preprandial (before meal) blood sugars. The pumps appear to improve glucose control slightly over standard injections.

Pumps and intensive insulin regimens carry a danger of hypoglycemia, and this may be fatal if it occurs at night or is otherwise unrecognized, especially in someone with coronary artery disease. Malfunction of the pump also can result in quick ketoacidosis.

Know that nocturnal hypoglycemia is a problem, not only because it is potentially lethal, but also because episodes lead to feeling poorly the next day with marked fatigue and a measurable decrease in productivity.

Notes for T1DM

Brittle DM: Possible etiologic factors include increased growth hormone in puberty (increases resistance to insulin), gastroparesis, poor communications, and malingering. It usually reflects psychological issues.

Honeymoon effect: indicates improvement of hyperglycemia after diagnosis and institution of treatment. Sometimes, patients can be removed from medication entirely for a short while. Eventually, however, they require reinstitution of treatment. Some patients have increased insulin secretion and decreased insulin resistance in the 1st year. This additionally may be due to a decrease in the initial precipitating stress.

Table 7-6: Insulin Preparations

	Onset	Peak	Duration	Cost	Miscellaneous
Human Insulin Preparations: Peaks and duration do not simulate natural basal and post-meal insulin activity.					
Intermediate-acting					
NPH (Humulin N®, Novolin N®)	2 hours	6–10 hours	18–28 hours	$	
Short-acting					
Regular (Humulin R®, Novolin R®)	30–60 minutes	2–4 hours	5–8 hours	$	
Insulin Analogs: Result in better simulation of natural insulin activity.					
Long-acting					
Glargine (Lantus®)	2 hours	None!	20–24 hours	$$$	Less nocturnal hypoglycemia compared to NPH
Detemir (Levemir®)	2 hours	3–9 hours	6–24 hours (dose-dependent)	$$$	Less nocturnal hypoglycemia compared to NPH
Short-acting					
Lispro (Humalog®)	5–15 minutes	45–75 minutes	2–4 hours	$$$	Less hypoglycemia compared to Regular
Aspart (NovoLog®)	5–15 minutes	45–75 minutes	2–4 hours	$$$	Less hypoglycemia compared to Regular
Glulisine (Apidra®)	5–15 minutes	45–75 minutes	2–4 hours	$$$	Less hypoglycemia compared to Regular

Quick Quiz

- Explain the honeymoon effect.
- What is the difference between dawn phenomenon and Somogyi effect?
- What are the most common causes of morning hyperglycemia in DM?
- What are the mechanisms leading to development of T2DM?
- What conditions are associated with acanthosis nigricans?
- What is the 1st treatment for T2DM?

Dawn phenomenon: increased blood glucose between 4 and 7 a.m. with no preceding hypoglycemia. It also may occur in healthy people. The cause is transient, mild insulin resistance due to the normal early-morning rise in cortisol and GH.

Somogyi effect: The Somogyi effect is the theory that nocturnal hypoglycemia stimulates the adrenal to release glucocorticoids that, subsequently, increase early morning glucoses. The suggested treatment has been to decrease the evening insulin to prevent the nocturnal hypoglycemia. As stated in the Dawn phenomenon, nocturnal growth hormone secretion and hypoinsulinemia are the most common causes of morning hyperglycemia, not nocturnal hypoglycemia.

We mention this Somogyi effect only to tell you that the theory has been definitively disproven; so on a Board exam, it would be incorrect to reduce the evening NPH in patients with nocturnal hypoglycemia and morning hyperglycemia. Early morning hyperglycemia usually can be treated by delaying the evening long-acting insulin until bedtime, so that the peak (if using NPH) occurs ~ 8 hours after the dose and coincides with waking/breakfast. Alternatively, a long-acting insulin analog (glargine or detemir) can be substituted for the NPH. These insulins have a less dramatic peak and decline, compared with NPH.

TYPE 2 DM

Etiology

90% of patients with diabetes have T2DM. The disease is considered strongly hereditary (multifactorial and polygenic), but we have yet to identify any major genes. Concordance of T2DM in monozygotic twins is 70–90%. Obesity increases insulin resistance, and ~ 80% of patients with T2DM are obese. T2DM patients with a combination of central obesity, HTN, and dyslipidemia are known as having a "metabolic syndrome." Pregnancy also increases resistance due to placental hormones.

T2DM causes impaired glucose handling at many sites.

Know the defects that result in T2DM:

- Insulin resistance in muscle and fat tissues
- Gradual reduction in insulin secretion by the pancreas
- Unregulated hepatic gluconeogenesis and glucagon secretion
- Reduction in gastrointestinal incretins (glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide)

Hyperosmolar nonketotic states are a problem in T2DM, although some patients present with DKA. Hyperosmolar coma has many precipitating factors, including volume depletion, drugs (e.g., glucocorticoids), and any serious illness.

Note: Insulin resistance is also associated with acanthosis nigricans. This velvety, dark rash in flexural areas occurs in conditions associated with insulin resistance, such as PCOS, Cushing's, certain medications (e.g., niacin, corticosteroids), and acromegaly. Rapid onset of widespread acanthosis nigricans in the older patient suggests GI malignancy.

Treatment of T2DM

Overview

Therapeutic Lifestyle Changes (TLC) are still the 1st treatment (diet and exercise, weight loss). After TLC, prescribe oral hypoglycemics +/– insulin. Typically, insulin is prescribed as a "last resort" option after all other possible oral and injectable medications are tried or ruled out. This is because, in general, insulin therapy leads to weight gain over time.

No head-to-head studies of medication regimens have been done yet, so focus on knowing the mechanisms of action of each class of drugs, when the different drugs are prescribed, and the side effects/contraindications.

The medications used in treatment of T2DM:

- Oral hypoglycemics
  - Secretagogues (sulfonylureas, meglitinides)
  - Biguanide (metformin)
  - Thiazolidinediones/glitazones (rosi-, pio-)
  - α-glucosidase inhibitors (acarbose, miglitol)
- Newer agents (oral or injectable)
  - Amylin analogs (pramlintide)
  - Glucagon-like peptide-1 (GLP-1; exenatide, liraglutide)
  - Dipeptidyl-peptidase 4 inhibitors (DPP4I; sitagliptin)
  - Bromocriptine
  - SGLT-2 inhibitor (sodium glucose co-transport inhibitors; canagliflozin)
- Insulin

Oral Hypoglycemics

For general competency and for exam questions, it is important to know the mechanisms of action of each class of oral hypoglycemic drugs (Table 7-7).

Secretagogues

The sulfonylureas and meglitinides increase insulin secretion but do so by different, although similar, mechanisms of action.

Sulfonylureas: These are either 1st generation: acetohexamide, chlorpropamide, tolazamide, and tolbutamide; or 2nd generation: glipizide, glyburide, and glimepiride.

2nd generation drugs are preferred over 1st generation and are less expensive.

Even though glyburide is a 2nd generation drug, its half-life is very long, and patients (especially elderly) are at risk for severe hypoglycemia. The use of glyburide is no longer preferred by the ADA; use the other 2nd generation drugs instead.

Sulfonylureas are approved for use in combination with most other drugs except meglitinides; especially useful in patients who cannot take metformin as a preferred 1st drug.

Weight gain is a common side effect of sulfonylureas.

The half-life of these drugs is long, and hypoglycemia can persist in states of overdose or renal impairment. Severe hypoglycemia caused by an overdose of sulfonylureas mandates an admission to the hospital because the resultant persistent hypoglycemia may require days of high-dose IV glucose therapy.

Use sulfonylureas with caution in the elderly and in patients with declining renal function; glipizide has a relatively shorter half-life and is safer in these conditions.

Meglitinides: These drugs are rapid-acting with a very short half-life. Representatives are repaglinide, repaglinide + metformin (a biguanide), and nateglinide. Major effect is on postprandial glucose.

As with sulfonylureas, weight gain is also a common side effect of the meglitinides.

This class can be used in patients with chronic kidney disease.

Biguanides

Biguanides reduce hepatic glucose production.

Metformin (MET) is the only one on the market in the U.S. Other formulations are extended-release MET, MET in combination with glyburide as a single tablet, and many others. Metformin is the preferred 1st line drug for any patient with T2DM, unless the patient meets a need for immediate insulin (discussed below). Start with 500 mg bid and gradually increase to a maximum of 1,700–2,550 mg/day in divided doses.

Side effects from MET monotherapy are less than with sulfonylureas, especially no weight gain and less hypoglycemia.

Also favorable: decreases LDL and TGs.

Major side effects of MET that sometimes limit use:

- Dose-related abdominal pain and diarrhea and propensity for causing lactic acidosis.
- Contraindicated in renal dysfunction (males with serum creatinine ≥ 1.5, females with ≥ 1.4, or "abnormal" creatinine clearance [GFR < 30 cc/min is usually used in the U.S.]), decompensated CHF, and acute or chronic metabolic acidosis.
- Hold MET in acutely ill patients and in those scheduled for contrast procedures or surgery—because both might cause renal failure → lactic acidosis.

Biguanides are approved for use in a variety of combinations with other oral agents and insulin.

Thiazolidinediones (TZDs)

Also called "glitazones," TZDs enhance insulin sensitivity and may help preserve some function of pancreatic beta cells. 2 are currently approved in the U.S.: rosiglitazone and pioglitazone. Currently, the ADA does not recommend use of rosiglitazone because of questions regarding its cardiovascular risk. However, in mid 2013, following a re-adjudication of rosiglitazone safety data, the FDA concluded that rosiglitazone does not increase the risk for adverse cardiovascular outcomes and eased the prescribing restrictions in the U.S., making the drug more readily available to patients.

Pioglitazone has not been shown to have the same cardiac risks and is marketed in combination with other agents:

- Pio + metformin
- Pio + glimepiride

Table 7-7: Oral Hypoglycemic Agents

	Efficacy in Lowering HbA1c	Average Cost/Month
Metformin	1–2%	$4.00 (retail pharmacy with prescription program)
Sulfonylureas	1–2%	$4.00 (retail pharmacy with prescription program)
TZDs	0.5–1.4%	variable
Acarbose	0.5–0.8%	variable
Meglitinide	0.5–2%	variable
Exenatide	0.5–1%	$$$
Sitagliptin	0.5–0.8%	$$$
Pramlintide	0.2–0.5%	$$$
Canagliflozin	0.7–1%	$$$

QuickQuiz

- What are the mechanisms of action of the main classes of oral hypoglycemics?
- What are the metformin contraindications? Thiazolidinediones?

Favorable effects: modest reduction in blood pressure, increased HDL, and decreased TGs.

Serious adverse effects: fluid retention and increased risk of exacerbating stable heart failure, weight gain, and increased risk of fractures (definitely in women, probably in men). Pioglitazone may be associated with bladder cancer and should not be used in patients with a history of such. Monitor liver transaminases occasionally because of risk of hepatotoxicity. Hypoglycemia is a definite risk when combined with insulin.

α-Glucosidase Inhibitors (AGIs)

AGIs delay carbohydrate absorption in the gut. Representatives: acarbose and miglitol. Biggest effect is on postprandial glucose. Common side effects: flatulence, diarrhea, abdominal bloating. AGIs are approved for monotherapy and in combination with sulfonylureas.

Newer Agents

Amylin Analogs

Amylin is a hormone secreted by pancreatic beta cells along with insulin and helps to regulate glucose influx by suppressing glucagon and slowing stomach emptying.

Pramlintide is an analog that comes as an injection given before meals. It is intended to be used with prandial insulin, because it helps insulin to work more effectively.

Cut the insulin dose by 50% when initiating treatment. Gastroparesis and insensitivity to hypoglycemia are contraindications.

Glucagon-like Peptide-1 (GLP-1) Agonists

These drugs were initially called "incretin mimetics." Incretin hormones are secreted by the gut (GLP-1 is an example) and regulate glucose by stimulating insulin release, inhibiting postprandial glucagon release, slowing nutrient absorption, and accelerating satiety.

Exenatide is an injection approved for combination with MET, sulfonylureas, and TZDs as well as basal insulin.

Side effects include vomiting and diarrhea, which can be significant. Recent data associate this drug with pancreatitis (that may be hemorrhagic), but the drug has not been established as an actual cause. Extended release exenatide is available for once weekly injection.

Liraglutide injection is also available. It is currently contraindicated in patients with a family history of medullary thyroid cancer, including MEN2 syndromes, because of C-cell hyperplasia (seen only in rodents so far and not in humans).

These drugs are recommended as 1st line drugs only for patients who cannot tolerate or take potent oral hypoglycemics; e.g., metformin, sulfonylureas, or TZDs. They are add-on drugs, otherwise, and especially benefit patients with obesity who cannot tolerate an increase in insulin.

Dipeptidyl-Peptidase 4 Inhibitors (DPP4I)

These drugs slow the inactivation of natural incretins, such as GLP-1, thereby increasing its concentration. Representative drugs: sitagliptin, sitagliptin in combination with MET, and saxagliptin, vildagliptin, and linagliptin. Approved for use alone or in combination with MET or TZD.

The biggest effect is on decreasing postprandial glucose. DPP4Is are associated with fewer instances of hypoglycemia, but sitagliptin may cause pancreatitis (like exenatide) and upper respiratory infections. Occasionally, these drugs cause severe skin reactions, such as blistering, angioedema, and anaphylaxis.

Like GLP-1 antagonists, DPP4Is are reserved as 1st line drugs only for patients who are intolerant or cannot take metformin, sulfonylureas, or TZDs. They are add-on drugs, otherwise, and especially benefit patients with obesity who cannot tolerate an increase in insulin.

Bromocriptine

Bromocriptine is a dopamine agonist previously used to treat pituitary tumors, hyperprolactinemia, and Parkinson disease. It was approved in 2009 for treatment of Type 2 DM. It is rarely used because of its mild glucose-lowering effect and GI side effects.

Sodium-Glucose Co-transport Inhibitors (SGLT-2 Inhibitors)

SGLT-2 inhibitors block the co-transport of sodium and glucose in the proximal tubule, reducing glucose reabsorption and causing renal excretion of glucose. These drugs do not cause hypoglycemia, and they lead to modest weight loss. There is an increased risk of vulvovaginal infections in females.

Canagliflozin is the 1st agent in this class that works by inhibiting glucose reabsorption in the renal tubules. It is an oral agent approved as monotherapy and in combination with metformin, sulfonylureas, glitazones, and insulin. It is contraindicated in Type 1 diabetes and in patients with a GFR < 45. Common side effects are dehydration, renal impairment, urinary tract infections, and genital mycotic infections.

Insulins

The same insulins used in T1DM are used in T2DM. Know that the newer formulations (long- and short-acting) are not more effective at lowering A1c than the older NPH insulin and regular, although they often are preferred because they are easier for patients. Patients with T2DM sometimes can tolerate the fixed insulin preparations (e.g., "70/30" of NPH/regular). (See Table 7-6 on page 7-38.)

As in patients with T1DM, patients with T2DM who take insulin sometimes can benefit from using the carbohydrate:insulin ratio when determining pre-meal insulin doses.

Nocturnal hypoglycemia also may lead to poor daily functioning in patients with T2DM, just as in patients with T1DM.

According to both the ADA and the AACE, insulin should be added after oral drugs are used except in the following special situations, where insulin should be instituted early:

- Patients who have consistently high random plasma glucoses (> 300–350 mg/dL)
- A1c > 10–12%
- A1c > 9% with symptoms
- Signs of ketosis on physical exam
- Severe symptoms of hyperglycemia or history of DKA

In these groups, oral agents can be added later, after the glucoses have stabilized with insulin—and, eventually, you may be able to stop the insulin entirely.

In patients without symptoms, both the ADA and AACE suggest starting patients out on 2 or 3 medications if the A1c is > 9%.

The ADA preferred regimen for insulin is "basal-bolus" dosing, where patients are given a long-acting insulin that keeps glucoses controlled during the fasting state, and short-acting insulin is given preprandially (just before meals). Recognize that patients who are hospitalized, or are fasting for whatever reason, should not have their basal insulin discontinued simply because they are not eating. Stop the rapid-acting prandial (mealtime) insulins. But continue the basal insulin because its function is to deal with the hyperglycemia that occurs regardless of whether food is present, though it might need to be reduced by 30% to 50%.

Both the ADA and AACE suggest waiting to add insulin (meaning, use oral agents first), except in the above groups, because of the side effects of weight gain (~ 2–4 kg) and hypoglycemia associated with insulin use.

Sequence of Drug Regimens

Use the potent oral hypoglycemics first—sulfonylureas, MET, TZDs (Table 7-7 on page 7-40).

MET (with lifestyle changes) is the preferred initial treatment in all patients with T2DM unless a contraindication exists or the patient cannot tolerate it. Intensify treatment (add drugs) if the A1c is ≥ 7% (6.5% per AACE) after 3 months.

AACE management (2013) is based on degree of persistent hyperglycemia as measured by hemoglobin A1c at presentation:

- A1c < 7.5% = one drug: MET, GLP-1 agonist, DPP4I, AGI, SGLT inhibitor, TZD, insulin secretagogues
- A1c > 7.5% = dual therapy: MET + GLP-1 agonist, DPP4I, TZD, SGLT inhibitor, basal insulin, colesevelam, bromocriptine, AGI, insulin secretagogue
- A1c 7–8% = combination orals +/– insulin; choices of combinations: secretagogue + MET, secretagogue + TZD, secretagogue + AGI, TZD + MET, DPP4I + MET, DPP4I + TZD, secretagogue + MET + TZD

If the A1c is ≥ 6.5 (AACE) or 7% (ADA) after 3 months of the above therapy, add a second drug (dual therapy).

Wait another 3 months and reassess. If A1c is still ≥ 6.5 or 7%, intensify again by adding another of the potent drugs not yet used (triple therapy). Wait another 3 months, and if not at goal, proceed to or intensify insulin therapy:

- A1c > 9% without symptoms = dual or triple therapy (per regimen above).
- A1c > 9% with symptoms or >10–12% = intensive insulin. (Long-acting analogs or NPH + short-acting analogs; premixed insulins work, too. Insulin pumps are good for patients who require multiple injections. Insulins are described above in the section on treatment for T1DM.)
- ADA (2012/2013) does not suggest a hierarchy of drug choices after initial therapy with metformin, but recommends combination therapy with an additional 1–2 orals or injectable agents.

The ultimate intensive regimen would be intensive insulin + MET +/– TZD +/– GLP-1 agonist +/– SGLT inhibitor. **Intensive insulin** means combinations of long-, intermediate-, and short-acting preparations with frequent self-monitoring of blood glucoses.

For patients having trouble with their weight, know that adding a GLP-1 agonist is the best option to control blood glucoses and encourage weight loss.

GLYCEMIC TREATMENT GOALS

For both T1DM and T2DM, keep the glucose level "as close to normal as possible." Recommendations between the advisory groups differ only slightly in targets:

	FPG (mg/dL)	2-hour Postprandial (mg/dL)	HbA1c (%)
AACE	< 110	< 140	≤ 6.5
ADA	90–130	< 180	< 7.0*

*Note: Data have emerged (ADVANCE, VADT, and ACCORD studies) that show that "intensive"

Quick Quiz

- In what T2DM situations should patients be prescribed insulin early in treatment?
- What are the initial drugs used to treat newly diagnosed T2DM?
- What are the treatment goals for glucose and HbA1c?
- Describe the relationship between HbA1c and pre- and postprandial blood glucoses.
- Hyperglycemia after eating is associated with what diabetic complications?
- What antihypertensives are recommended for diabetics with hypertension?

glycemic control (compared to standard control) either has no long-term benefit or actually causes harm in some groups of patients. Therefore, the target HbA1c has been loosened to < 8% for the following groups:

- History of severe hypoglycemia
- Limited life expectancy
- Advanced complications
- Extensive comorbidities
- Long-standing DM with difficulty attaining low A1c

If the A1c remains elevated, but the FPG are controlled, start checking postprandial glucose levels.

Also know that preprandial hyperglycemia contributes more to high average blood glucose when the A1c is elevated. Once the A1c is < 7.5–8%, postprandial hyperglycemia contributes more to high average blood glucose and has been linked to macrovascular complications.

When using insulin to treat DM, consider checking the postprandial glucose periodically, even when the A1c is normal, so you do not miss periods of hyperglycemia.

Some patients who are hospitalized do worse when their blood glucoses are tightly controlled, so these are the current recommendations:

- Non-critical patients: Keep FPG < 140 and random glucoses < 180 using the patient's typical basal regimen and a titrated prandial regimen. A "corrective dose" of insulin is appropriate if needed to correct prandial hyperglycemia, but use of the "sliding scale" is discouraged.
- Critical patients: Keep glucose 140–180 using IV insulin as needed.

ANCILLARY MANAGEMENT

Hypertension

ADA recommendations say to treat first with ACEI or ARB. If additional drugs are required, add a diuretic next (loop, if the GFR is estimated at < 30 cc/min), then a beta-blocker. Non-dihydropyridine calcium channel blockers are recommended last. Goal: < 140/90 for all diabetic patients, but < 130/80 or lower without medication side effects for diabetic patients with micro- and macrovascular disease as per JNC 8.

For the rare patient with DM who is not hypertensive, use an ACEI if significant microalbuminuria or macroalbuminuria is present.

Dyslipidemia

Treat aggressively with whatever agents are suitable to target the patient's specific type of dyslipidemia.

Statins are the drug of choice for any patient with an elevated LDL.

Goals (mg/dL):

- LDL < 100 in all (some now say < 70)
- LDL < 70 in diabetics with CHD
- HDL > 40 (males) and > 50 (females)
- TG < 150

ADA goes a little further and recommends statins in all diabetics who are > 40 years of age with ≥ 1 additional risk factor for CHD, regardless of the lipid profile.

Aspirin

Aspirin use in diabetics is controversial, because we now understand that not all diabetics have the same risk for heart disease, despite DM being listed as a CHD risk-equivalent in the NCEP guidelines.

The current ADA recommendation is to use a prediction model to estimate the patient's 10-year risk for ischemic heart disease (Framingham is one; the United Kingdom Prospective Diabetes Study (UKPDS) risk engine is another that has been validated in diabetics, specifically).

Based on the 10-year risk, give ASA for primary prevention as follows:

- < 5% risk: no ASA.
- > 10% risk: give ASA.
- 5–10%: Talk to the patient and individualize your recommendation.

Diabetics with known heart disease should get a daily aspirin as secondary prevention. ASA-allergic patients can take clopidogrel.

DIABETIC COMPLICATIONS

Overview

Diabetes causes microvascular disease (eyes, kidneys, nerves) and macrovascular disease (coronary and peripheral atherosclerosis → CHD and stroke).

Postprandial hyperglycemia has been specifically associated with macrovascular complications. Tobacco greatly accelerates this process.

Prediabetes has been specifically associated with microvascular and macrovascular disease (although the process continues as long as the patient is hyperglycemic).

The following 3 microvascular complications usually appear 10–15 years after the onset of DM (but T2DM may be present 5–10 years before being diagnosed):

1) **Retinopathy** correlates with duration and control of DM. Early findings include dot hemorrhages (no additional treatment), but photocoagulation is needed if neovascularization occurs (a late finding). Retinopathy may worsen transiently with initiation of tight glycemic control. Retinopathy almost universally precedes nephropathy. If a diabetic without retinopathy develops nephrotic-range proteinuria, the patient should be evaluated for other causes of nephrotic syndrome.
2) **Nephropathy** is heralded by persistent microalbuminuria. Remember that treating hypertension with either ACEI or ARB decreases the rate of progression (by decreasing intraglomerular pressure). ADA and AACE recommend reduced protein diet (0.8–1.0 g/kg/d) in early chronic kidney disease and low-protein diet (0.8 g/kg/d) in advanced kidney disease.
3) **Neuropathy** includes autonomic neuropathy, axonal (Schwann cell) degeneration, symmetric polyneuropathy, erectile dysfunction, and gastroparesis. Both alcohol and tobacco use increase the rate of development of neuropathy. Diabetic mononeuropathy usually affects the 3rd and 6th cranial nerves, the peroneal nerve (foot drop), and the radial nerve (wrist drop). Strict glycemic control decreases the risk of developing neuropathy and improves nerve conduction. The pain associated with diabetic sensory dysfunction is difficult to treat. Recommended drugs for treatment include amitriptyline, venlafaxine, duloxetine, and pregabalin.

You should definitely know the major diabetes studies and how glycemic control affects diabetic complications:

- Microvascular complications are reduced in both T1DM and T2DM with tight control of blood glucoses. This was demonstrated for T1DM by the Diabetes Control and Complications Trial (DCCT) and for T2DM by the UKPDS and the Japanese Kumamoto study.
- Macrovascular complications: A reduction with tight control of glucose has been harder to show. Recent long-term secondary analyses of intensively treated DCCT and UKPDS patients (A1c ~ 7%) show a reduction in cardiovascular outcomes, although the reduction was not statistically significant at the time of the original studies—the significance evolved as the patients aged.

Monitoring

Patients need annual evaluations for microvascular complications (after 5 years in T1DM and immediately in T2DM).

Be sure to do the following:

- Do a urine spot albumin:creatinine as a test for nephropathy (normal < 30 mg/g). Microalbuminuria is 30–300 mg/g.
- Check creatinine and estimate GFR.
- Send them to an ophthalmologist for a slit lamp exam and rapidly refer macular edema or proliferative retinopathy. It is now acceptable to use fundus photography in clinical situations when experienced ophthalmologists are unavailable.
- Inspect the feet visually and perform a sensory evaluation using the 10-gm monofilament, pinprick, temperature, and vibration. Know that loss of vibratory sense and sensation to the 10-gm monofilament predicts foot ulcers.
- Know that asymptomatic diabetics should not be routinely screened for ischemic heart disease; outcomes are unchanged, provided that you are treating their CHD risk factors. Use of coronary CT may benefit some asymptomatic diabetics; we discuss this in Cardiology, Book 3.

HYPERGLYCEMIC STATES

Ketoacidosis

Diabetic ketoacidosis (DKA) is sometimes the initial presentation of T1DM, but it can also occur in T2DM (even in patients treated with oral meds).

It is caused by a state of complete or partial insulin deficiency leading to massive lipolysis. Lipolysis causes a release of free fatty acids and the ketone bodies—beta-hydroxybutyrate, and acetoacetate. These products cause volume depletion from massive osmotic diuresis and high anion gap acidosis (because ketones are acids).

Symptoms include nausea, vomiting, abdominal pain, polyuria, and lethargy. Ask about symptoms of infection (pneumonia, UTI)—often a precipitating condition for DKA.

On clinical exam, hypotension is noted in patients with severe volume depletion. Fruity breath and a Kussmaul respiratory pattern suggest ketoacidosis. Severe cases are marked by confusion or obtundation.

Diagnosis: DKA is diagnosed by a high anion gap acidosis and hyperglycemia. Secondary derangements include total body potassium and phosphorus deficits (even though both may be normal at presentation because of the acidosis and hemoconcentration). Serum Na^+ is usually decreased because of the osmotic shift of water from inside cells to the intravascular space caused by the hyperglycemia, a phenomenon referred to as pseudohyponatremia. Adjust the serum sodium upwards 1.6 mEq for every 100 mg/dL increase in blood glucose over 100 mg/dL before diagnosing any disease of water balance.

Treatment: Give normal saline (~ 2–3 liters), then either continue the saline or switch to 0.45% saline based on the serum sodium (corrected for hyperglycemia).

Quick Quiz

- Name 3 diabetic microvascular complications and characterize their screening and treatment.
- What microvascular complication occurs first in a diabetic, retinopathy or nephropathy?
- Discuss the major diabetes studies that show a correlation between reducing blood glucoses and subsequent micro- and macrovascular complications.
- What tests make up the annual screening for a diabetic?
- List the symptoms of DKA.
- What lab abnormalities occur in the patient with DKA?
- What is the formula used for correction of pseudohyponatremia due to hyperglycemia?
- When is bicarbonate given to treat DKA?
- What medications commonly given to diabetics are contraindicated in pregnancy?
- What is the Whipple triad?

Start IV insulin at 0.1 units/kg/hr. When glucose is < 200 mg/dL, add D5W to the 0.45% fluids. Keep the IV insulin going until the acidosis is resolved, and the anion gap is normal; the insulin is required to stop production of the ketoacids.

If the K^+ is normal at the start of treatment, give KCl immediately because there is usually a several-hundred mEq deficit. In cases of very low K^+, < 3.3 mEq/dL, hold insulin until the K^+ is ≥ 3.3. K^+ is shifted into the cells by both the reversal of acidosis and the action of insulin, further aggravating the hypokalemia and possibly leading to cardiac arrest. Also monitor the heart-wave morphology and rhythm for any K^+-associated changes.

Bicarbonate is given only for pH < 7.0, especially if the patient is having respiratory or hemodynamic collapse.

Know that the Acetest® tablets detect only acetoacetate, not the beta-hydroxybutyrate. When the patient has ketoacidosis, there can be much more of the beta-hydroxybutyrate than the acetoacetate.

If the patient is being treated for DKA and seems to be getting better but the ketones start rising, the beta-hydroxybutyrate is being converted to acetoacetate as the acidosis resolves. Follow resolution with pH and anion gap. The anion gap reflects both types of ketones.

Hyperglycemic Hyperosmolar State (HHS)

This hyperglycemic complication happens in T2DM and is caused by partial insulin deficiency and decreased intake of fluids. Usually, the patient is elderly and has a prolonged history of developing illness marked by lethargy, weight loss, and polyuria.

Exam is consistent with severe dehydration and volume depletion. These patients are not acidotic, so they do not have the fruity breath or Kussmaul respirations.

Labs show hyperglycemia and evidence of dehydration/volume depletion (Na^+ deficit—noted after correction for the hyperglycemia) and azotemia. If a high anion gap metabolic acidosis is present, it is mild and due to lactate.

Treat HHS similarly to DKA, with IV fluid resuscitation and insulin bolus + infusion. Be sure to adjust the serum sodium for the hyperglycemia to determine if a free water deficit exists, then replace it gradually over the next 24–48 hours. Potassium replacement is usually required.

GESTATIONAL DIABETES

With pregnancy in diabetic women, strict control even before conception is important. Maintain FPG < 100 mg/dL and A1c < 7%. Before conception, control of blood glucose reduces fetal malformation; during pregnancy, it reduces miscarriages, fetal anomalies/death, and newborn problems. Tight glycemic control decreases the risk of macrosomia (birth weight ≥ 9–10 lb) and shoulder dystocia in the newborn.

During pregnancy, a diabetic patient requires ~ 50% more insulin due to increased resistance from placental hormones. This increased requirement is gone immediately after delivery, so anticipate a reduction in insulin dosage of at least 33% postpartum and observe the patient carefully the day after delivery.

Know that these medications commonly employed in diabetic management are contraindicated in pregnancy:

- Statins and ACEIs are category X and should be discontinued before pregnancy.
- ARBs are category C (1st trimester) and D (later trimesters).
- Many oral hypoglycemics are category C.

C = Some adverse effect in animal studies or no controlled studies in women. Use only if potential benefit outweighs potential risk to fetus.

D = Positive evidence of human fetal risk. But may be acceptable despite the risk; e.g., life-threatening illness.

X = Causes fetal abnormalities. Do not use.

HYPOGLYCEMIA

OVERVIEW

The diagnosis of hypoglycemia is not based on an absolute blood glucose level; it requires fulfillment of the **Whipple triad**:

1) Signs and symptoms consistent with hypoglycemia
2) Associated low glucose level (< 55 mg/dL)
3) Relief of symptoms with supplemental glucose

Symptoms are autonomic (palpitations, tremor, sweating, paresthesias) and neuroglycopenic due to CNS glucose deprivation (confusion, impaired consciousness, seizures). Usually, autonomic symptoms happen first. Signs of hypoglycemia are nonspecific (pallor, sweating, anxiety).

There are 2 categories of hypoglycemia: reactive (sometimes called "postprandial") and nonreactive (sometimes called "fasting").

REACTIVE HYPOGLYCEMIA

Reactive, or postprandial, hypoglycemia develops in response to a nutrient challenge. You see it in a few patients with T2DM and in some post-GI surgical patients, when gastric contents get dumped into the small intestine too quickly with a brisk release of incretins. "Idiopathic reactive hypoglycemia" requires fulfillment of the Whipple triad to be a true diagnosis. Some patients have symptoms but normal blood glucoses; they need no further workup, in spite of their insistence. Never order an OGTT to work up this entity. On exams, OGTT is a common distractor from the correct answer.

NONREACTIVE HYPOGLYCEMIA

Nonreactive, or fasting, hypoglycemia can be further subdivided into iatrogenic (most common overall cause) and fasting/factitious.

In the fasting/factitious type, the patient is unable to maintain glucose levels with fasting. Most common causes: alcohol abuse, drugs (oral hypoglycemics, pentamidine), sepsis, and renal failure.

Causes of nonreactive hypoglycemia most commonly tested on exams:

- Factitious taking of oral hypoglycemics/insulin: common---especially suspect if the patient is in the medical field or has a family member with DM
- Hormone deficiencies: adrenal insufficiency
- Insulinoma from a pancreatic islet cell tumor
- Autoimmune etiology: rapidly changing levels of anti-insulin antibodies

4 tests are used in the workup of confirmed, nonreactive hypoglycemia brought about by a supervised fast (sometimes up to 72 hours; see Figure 7-8):

1) Serum insulin
2) Serum proinsulin
3) C-peptide
4) Urinary/Plasma sulfonylurea test

Insulin is high or inappropriately normal during the hypoglycemic episode:

- With factitious etiology, patients can have high insulin levels, sometimes > 100 μU/mL, due to self-administration.
- Patients with insulinomas usually have an insulin level > 6 μU/mL during an episode of hypoglycemia.

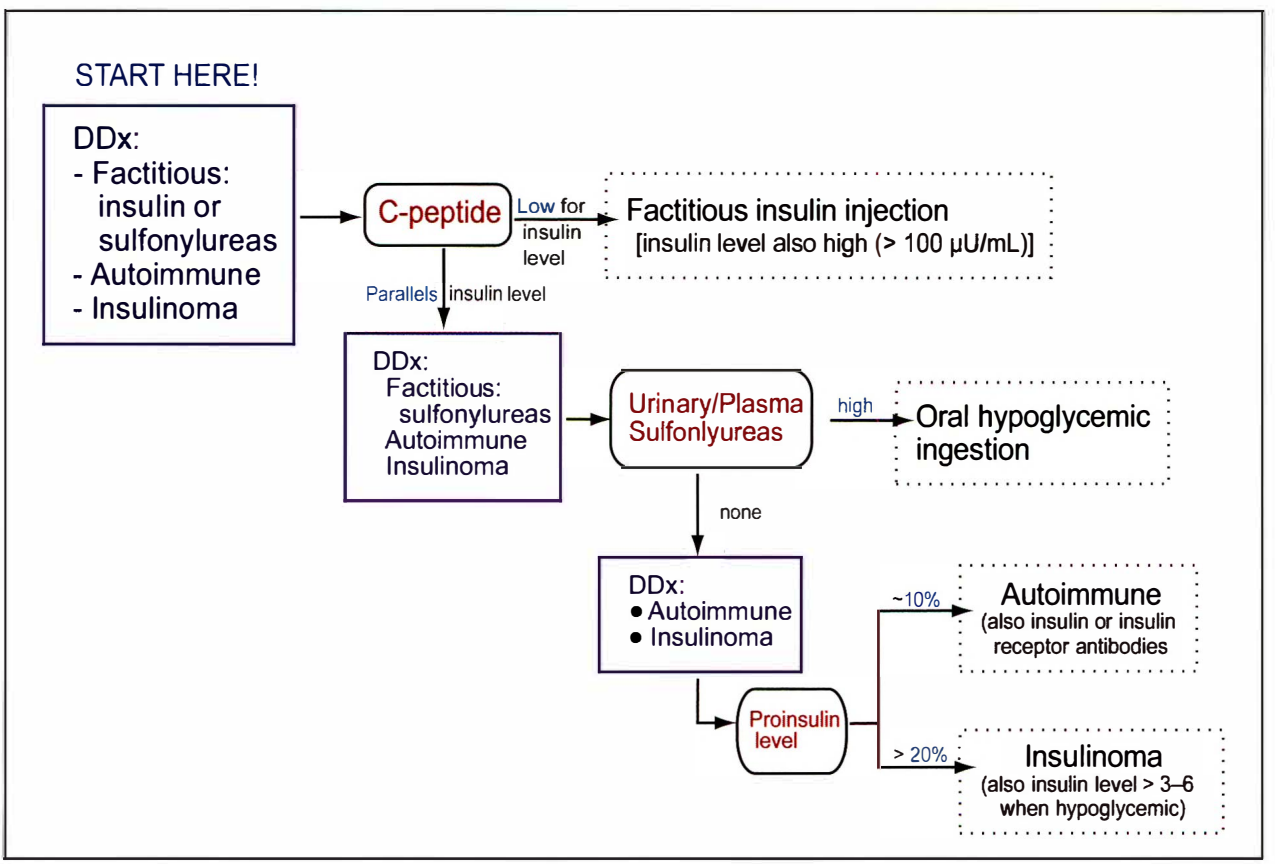


Figure 7-8: Workup of Nonreactive Hypoglycemia

QuickQuiz

- What laboratory tests help you determine if someone is factitiously self-injecting insulin to induce hypoglycemia?
- What is the classic radiographic finding on hand films of patients who have primary hyperparathyroidism?
- A normal iPTH level in the setting of hypercalcemia suggests what diagnosis?

- Autoimmune etiology also results in inappropriately high insulin levels. Antibodies to insulin and insulin receptors can be measured, but proinsulin (next) is typically done instead.

Proinsulin (the precursor of insulin): Insulinomas tend to cause a higher proportion of proinsulin in the serum. Normal level is 10% of total insulin. With insulinomas, the level is > 20%, and often 30–40%.

C-peptide is produced in a 1:1 ratio with insulin when they are both cleaved from proinsulin. Therefore, with endogenous insulin production (including sulfonylurea-induced and insulinoma), the C-peptide level parallels serum insulin values. C-peptide is low (usually not measurable) with insulin injection.

Urinary/Plasma sulfonylurea test rules in or out oral hypoglycemic use but can result in a false negative. Follow your clinical suspicions. A newer screen using mass spectrometry can detect all sulfonylureas, as well as meglitinide and repaglinide.

BONE / CALCIUM DISORDERS

NORMAL CALCIUM PHYSIOLOGY

Normal calcium physiology: Calcium is absorbed from the duodenum, stored in the bone, and excreted by the kidneys.

Increase in Serum Calcium

Two endogenous hormones increase serum calcium level: 1,25-$(OH)_2$-vitamin D and parathyroid hormone (PTH).

Vitamin D is made in the skin after a reaction with sunlight but is inert until it is sequentially hydroxylated, first in the liver (to form 25-OH-D), and then in the kidney (1,25-$(OH)_2$-D). 1,25-$(OH)_2$-D, in turn, increases Ca^{2+} and phosphorus absorption from the gut.

PTH increases calcium in the blood through the following:

- Stimulates release of bone calcium stores by indirect stimulation of osteoclasts (**c** = **c**hew bone)
- Increases renal tubular Ca^{2+} resorption and renal tubular phosphorus excretion
- Increases the production of 1,25-$(OH)_2$-D by increasing activity of kidney hydroxylase

Serum free Ca^{2+} works via a negative feedback on the parathyroids. High serum Ca^{2+} decreases production of PTH, and low serum Ca^{2+} increases production.

Decrease in Serum Calcium

Calcitonin, from the thyroid parafollicular cells (C cells), can be considered a PTH antagonist. It slows down the osteoclasts, causing a decrease in bone resorption and increases renal calcium clearance.

Normal levels of glucocorticoids help maintain osteo**b**last (**b** = **b**uild bone) function, but excess decreases the bone protein matrix and cause calciuria.

Estrogen (like calcitonin) decreases bone resorption and (like glucocorticoids) may increase osteoblastic activity—so it has a double bone-building function.

HYPERCALCEMIA

Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is often found incidentally after noting high serum calcium on screening laboratory studies. 80% of cases are caused by parathyroid adenomas. Natural history includes ~ 25% progression. Patients have decreased density of cortical bone (distal radius), a 2–3x increased risk of fractures, and may have complaints of bone pain.

The classic signs and symptoms in a symptomatic PHPT patient have often been described as "bones, stones, abdominal moans, and psychic groans."

Subperiosteal bone resorption (termed "osteitis fibrosa cystica"), with a moth-eaten appearance to the radial side of phalangeal cortices on finger radiographs, is the classic finding indicating prolonged PTH excess. This finding is occurring much less now than in the past, probably due to automated lab tests and earlier recognition. If an exam question shows you radiographs of a patient's hands, think about primary hyperparathyroidism.

Diagnosis of PHPT is made by finding a normal or an elevated intact PTH (iPTH) in a patient with elevated calcium. Serum phosphorus is usually low-normal to low.

Know that patients with drug-induced (lithium, thiazides) hypercalcemia and benign familial hypocalciuric hypercalcemia (FHH) may present with PTH levels above normal; and ~ 25% of patients with primary hyperparathyroidism have normal or high-normal iPTH. Even a normal iPTH is compatible with the diagnosis of primary hyperparathyroidism—because an otherwise healthy person has a suppressed iPTH in the presence of hypercalcemia.

Abdominal x-rays and measurement of 24-hour urinary calcium are no longer recommended. Also, hypercalciuria (if there is no history of stones) is no longer an indication for surgery.

Treatment of PHPT: Medically managed patients should have their serum calcium and creatinine measured yearly and bone density scans every 1–2 years. Also check their 25-$(OH)_2$-D levels and give supplementation if the level is < 20 ng/dL. Know that you should not tell patients to restrict their calcium intake; diet advice should be the same as for patients without primary hyperparathyroidism.

No specific drug is recommended by the guidelines because long-term data in these patients are scarce. However, bisphosphonates build bone in the L-spine and hips without changing serum calcium. Cinacalcet is also being investigated because it normalizes calcium levels—but does not build bone.

Symptomatic PHPT patients (e.g., nephrolithiasis or osteoporosis) go to surgery.

Asymptomatic patients are more difficult to manage. Guidelines released in 2009 from the Workshop on Hyperparathyroidism say to manage most asymptomatic patients medically, with good follow-up.

Additionally, the following PHPT patients are referred for surgery:

- GFR < 60 cc/minute/1.73 m^2 (CKD stage 3)
- T-score of –2.5 or less at L-spine, femur, hip or 33% radius
- Z-score of –2.5 or less in premenopausal women and men < 50 years
- Age < 50 years

All potential surgical candidates should have a serum calcium > 1 mg/dL above normal (at least).

Note: A urine calcium > 300 is no longer considered an indication for parathyroid surgery; however, a urine calcium (that is low) in the setting of a high serum calcium consistent with a diagnosis of FHH is needed to prevent unnecessary surgery.

Sestamibi scans and ultrasound are standard preoperative evaluations to localize the adenomas.

Secondary hyperparathyroidism is the overproduction of parathyroid hormone secondary to a chronic abnormal stimulus for its production. Typically, this is due to chronic renal failure and/or vitamin D deficiency.

Tertiary hyperparathyroidism is seen in patients with chronic secondary hyperparathyroidism and often after renal transplantation. These autonomous, hypertrophied parathyroid glands fail to return to normal and continue to oversecrete parathyroid hormone, despite elevated serum calcium levels. Often serum phosphate levels also are elevated.

Summary: Hypercalcemic patients with elevated or normal iPTH and low phosphorus = primary hyperparathyroidism. If symptomatic (e.g., kidney stones) or low bone density, do surgery. Secondary hyperparathyroidism = consider vitamin D deficiency and CKD as the cause. Tertiary hyperparathyroidism = hyperparathyroidism persisting after renal transplantation.

Other Causes of Hypercalcemia

Vitamins and Medications

Vitamin D excess, vitamin A excess (causes calcium release from bones), thiazide diuretics (decreases calcium excretion), and lithium (increases PTH threshold by requiring calcium to be at a higher level to shut off PTH production) can cause hypercalcemia.

Genetic Causes of Hypercalcemia

Benign familial hypocalciuric hypercalcemia (FHH) is autosomal dominant with normal or slightly elevated iPTH and elevated calcium—same as what can occur in patients with primary hyperparathyroidism. FHH requires no treatment, so it is important to differentiate from other causes of hypercalcemia (especially primary hyperparathyroidism). If suspected, measure calcium and creatinine in the serum and urine, then calculate the calcium:creatinine clearance ratio. If the ratio is < 0.01, the diagnosis is FHH; if > 0.02, FHH is excluded, and the diagnosis is most likely primary hyperparathyroidism. The problem is in the calcium sensor, which requires a higher calcium level before turning off PTH secretion.

Malignancy and Hypercalcemia

There are 3 groups of malignancies that cause hypercalcemia: myeloma, some solid tumors, and tumors with bone metastases. Myeloma produces several osteoclast-activating factors, causing breakdown of bone.

Some solid tumors secrete a PTH-related protein (PTHrP), in which the N-terminal (amino) end is identical to iPTH. But the mid- and carboxy-terminal portions are different, so it is not picked up by the iPTH assay. The elevated calcium causes a negative feedback on the production of PTH by the parathyroid glands.

Bone metastases account for 1/2 of all patients with elevated calcium and malignancy; they produce local osteoclast activation substances.

Several granulomatous diseases cause hypercalcemia by means of increased 1,25-$(OH)_2$-D production by the macrophages. Macrophages (and lymphocytes) have an unregulated 1α-hydroxylase, which converts 25-OH-D into 1,25-$(OH)_2$-D. These granulomatous diseases include sarcoidosis, tuberculosis, berylliosis, histoplasmosis, and leprosy. Treat with corticosteroids if it's safe (if the patient is not infected). Immobilization is a mechanical cause of elevated calcium, but only in the setting of high bone turnover—hyperthyroidism, Paget disease, and adolescence. The high calcium causes a decrease in iPTH.

Treatment of Hypercalcemia

Immediately give 3–4 L of normal saline to treat volume depletion caused by salt wasting associated with high urinary calciums. We used to add loop diuretics to

QuickQuiz

- What periodic exams do patients with primary hyperparathyroidism need if they are being medically managed?
- What are the indications for surgical treatment of primary hyperparathyroidism?
- What are the common causes of secondary hyperparathyroidism?
- Define tertiary hyperparathyroidism. When is it likely to be seen?
- What are other causes of hypercalcemia, besides primary hyperparathyroidism?
- How can you differentiate FHH from primary hyperparathyroidism?
- What malignancies are associated with hypercalcemia?
- What is the treatment for hypercalcemia?
- Why can hyperphosphatemia cause hypocalcemia?
- What is osteomalacia? How does it present and how do you screen for it?
- What is the most common cause of vitamin D deficiency?
- What lab value is used to measure vitamin D levels?

promote calciuria once volume status was corrected, but this is not done anymore because the efficacy of bisphosphonates and calcitonin outweigh the electrolyte complications of the diuretic.

Bisphosphonates interfere with bone resorption in areas of high turnover, such as sites of malignancy, and usually are used in conjunction with saline infusions and calcitonin to treat moderate-to-severe hypercalcemia.

Pamidronate and zoledronic acid are representative drugs, favored by most because of their rapid onset of action and intravenous formulation. Know that these drugs are associated with osteonecrosis of the jaw in patients with multiple myeloma and metastatic bone disease.

Give glucocorticoids for sarcoidosis and myeloma. Mobilize patients.

HYPOCALCEMIA

Overview

Low serum calcium is caused by the following:

- Hypoparathyroidism is due to decreased PTH secretion:
  - primary hypoparathyroidism,
  - thyroid surgery with loss of parathyroid glands, or
  - severe hypomagnesemia (Mg < 0.8 mEq/L; required for PTH release and its effect on target organs) due to bowel disease or alcohol abuse.
- Vitamin D deficiency.
- Loss of calcium in cases of severe, acute pancreatitis: formation of calcium "soap."
- Acute, severe hyperphosphatemia, in renal excretion of phosphorus which calcium chelates with the phosphorus.
- Pseudohypoparathyroidism (Types Ia, Ib, Ic, II) is due to increased PTH resistance. It is a rare genetic disease due to a mutation in the PTH receptor gene. These patients have an appropriately elevated PTH (in response to the hypocalcemia). In addition to hypocalcemia, patients with Type Ia have short 4th metacarpals and short stature. This phenotype of Type Ia is due to yet another mutation of the PTH receptor gene and may occur alone.

When patients with shortened 4th metacarpals and short stature have a normal biochemical profile, they have pseudo-pseudohypoparathyroidism. Very simple! Do not let this confiise you! These patients have only the mutation for the Ia phenotype but are otherwise completely normal and have normal calcium homeostasis.

Osteomalacia

Osteomalacia is a condition of demineralized bone, which occasionally presents with hypocalcemia. It is most commonly caused by vitamin D deficiency (called rickets when it occurs in youth, causing listlessness, irritability, and bowing of the legs). Older patients present with bone pain and proximal muscle weakness. Patients of all ages have diffuse demineralization. In adults, know that "bilateral symmetric pseudofractures" establish the diagnosis. If there are no fractures, you need an iliac crest bone biopsy with tetracycline double-labeling to show the mineralization defect, but usually osteomalacia is diagnosed clinically without a biopsy. Once the diagnosis is established, work up the cause (many possibilities).

The usual cause of vitamin D deficiency is inadequate intake of vitamin D and/or malabsorption. It's quite common in the elderly and in northern latitudes. Vitamin D deficiency is also more common in people who use a lot of sunscreen and/or avoid sunlight.

Studies link vitamin D deficiency with falls, fractures, increased risk of cancer, and CHD, so the Boards should have a renewed interest in your knowledge about the condition. Look for osteomalacia in the older man, hospitalized for weeks, who develops bone pain with radiographs that show hair-line fractures.

Check 25-OH-D levels if you suspect vitamin D deficiency (not 1,25-$(OH)_2$-D!).

Renal osteodystrophy and adynamic bone disease are discussed in Nephrology, Book 2. Osteoporosis is discussed under Geriatrics in General Internal Medicine, Book 5.

Table 7-8: Lab in Diseases Affecting Calcium

	PO_4	Ca^{2+}	Alk Phos	iPTH	25-OH-D	1,25-$(OH)_2$-D
Osteomalacia from Vit D def*	↓	↓	↑	↑	↓	n/a
Chronic renal failure	↑	↓	n/a	↑	normal	↓
Primary hyperparathyroidism**	n/a	↑	↑	↑	n/a	n/a
Hypercalcemia of malignancy***	n/a	↑	↑	↓	n/a	n/a

* Do not need to check 1,25-$(OH)_2$-D for osteomalacia from Vit D deficiency. If 25-OH-D is low, then 1,25-$(OH)_2$-D will be low.
** High Ca and high iPTH = primary hyperparathyroidism (elevated iPTH should not be elevated if the calcium is high; it should be suppressed).
*** Other findings for hypercalcemia of malignancy: diagnosis of myeloma or obvious bony metastases.

REVIEW OF CALCIUM-RELATED LABS

Know Table 7-8.

MULTIPLE ENDOCRINE NEOPLASIA

Multiple endocrine neoplasia (MEN, Table 7-9): All are autosomal dominant—with varying expression! These are categorized as MEN1, MEN2A, and MEN2B.

MEN1: It can have quite a variety of symptoms, but they are all caused by hyperplasia, adenomas, and/or cancers of the **p**arathyroid, **p**ituitary, or the islet cells of the **p**ancreas (think "**PPP**"). Suspect this in a patient with hypoglycemia and hypercalcemia. There is often a strong family history of peptic ulcer disease. Phenotypic expression within a family might be quite variable; one relative may have all 3 components whereas another relative may have only 1 of the endocrinopathies.

MEN2A: Medullary thyroid cancer occurs in virtually all patients with MEN2A or MEN2B and often occurs early in life. Pheochromocytoma occurs frequently; parathyroid hyperplasia occurs in 25–50%.

MEN2B is also associated with medullary thyroid carcinoma, and 1/2 have pheochromocytoma, but only rarely do they have parathyroid hyperplasia. This type is easy to differentiate from the others because of the mucosal neuromas easily seen on physical exam. Life expectancy in MEN2B is 30 years, whereas it is 60 years in MEN2A—suggesting that these are different clinical syndromes.

For MEN1, the pancreatic adenoma may functionally be a glucagonoma, which is a very rare malignant tumor of pancreatic islet cells that produces glucagon and is associated with a blistering dermatitis, diabetes, cheilitis, diarrhea, weight loss, and cognitive impairment. The skin and tongue changes are due to a glucagon-induced amino acid deficiency.

Risk factor for a glucagonoma is MEN1. Think about it in patients with a family history of MEN1 who present with a triad of mild hyperglycemia, glossitis with a "beefy red tongue," and a distinctive blistering erythematous rash that is often found in the groin region (termed "migratory necrolytic erythema"). The skin and tongue changes are due to a glucagon-induced amino acid deficiency.

Diagnose by measuring a glucagon level—one of the rare instances where it is useful to measure a random hormone! A level > 500 pg/mL is supportive (mean ~ 1,400 pg/mL). Imaging of the pancreas with a helical CT is useful in patients suspected of having the tumor because of increased glucagon levels.

In the majority, the glucagonoma has already metastasized (liver, lymph nodes, bone, adrenals, kidney, lung) at diagnosis.

Remember: Both MEN2A and MEN2B have medullary thyroid cancer and pheochromocytoma.

Look at Table 7-9 for the following:

- A causes hypercalcemia, but generally no symptoms.
- B may cause Cushing disease, but usually no symptoms unless advanced.
- C can cause a patient to present with hypoglycemic episodes or peptic ulcer disease.
- D is detected by a calcitonin level.
- E can present as hypertension but typically is asymptomatic.

If a patient with an elevated iPTH has a family history of one brother having "medullary cancer" and another having a "parathyroid tumor," what tests should you do on the patient?

Table 7-9: Multiple Endocrine Neoplasia

Type	Clinical
1	A, B, C
2A	A, D, E
2B	D, E, F

A) Parathyroid hyperplasia
B) Pituitary adenomas
C) Pancreatic islet cell tumors causing hypersecretion of either insulin or gastrin
D) From C-cell hyperplasia to medullary cancer
E) Pheochromocytoma
F) Abnormal physical appearance: marfanoid body type, multiple neuromas of the conjunctiva, lips, labia, tongue, mucosa, larynx. "Blubbery lips."

Answer: (think MEN2A) Check calcitonin and free plasma metanephrines. In an exam setting, you may see only one of these in the answer choices.

The RET proto-oncogene test for hereditary medullary thyroid cancer (MTC) can also be very useful and offers the potential for prophylactic surgical intervention prior to the development of MTC in family members who are at risk. Calcitonin elevation correlates with tumor burden and may be the first sign of recurrent persistent disease. Calcitonin doubling time has been shown to be accurate in predicting prognosis. Elevated calcitonin levels can cause symptoms such as flushing, diarrhea, and weight loss; these patients may benefit from somatostatin analogues if their disease is recurrent postoperatively.

For those with sporadic MTC, disease cannot be controlled by current therapies. Drugs that modify signaling pathways (e.g., phosphatidyl-inositol 3-kinase/Akt) and glycogen synthase kinase-3 pathways are currently in clinical trials.

FOR FURTHER READING

[Guidelines in blue]

ANTERIOR PITUITARY GLAND

Bujawansa S, Thondam SK, et al. Presentation, management and outcomes in acute pituitary apoplexy: A large single centre experience from the United Kingdom. *Clin Endocrinol* (Oxf). 2013 Aug 5.

Colao A, Savastano S. Medical treatment of prolactinomas. *Nat Rev Endocrinol*. 2011 May;7(5):267–278.

Gueorguiev M, Grossman AB, et al. Pituitary tumors in 2010: a new therapeutic era for pituitary tumors. *Nat Rev Endocrinol*. 2011 Feb;7(2):71–73.

Heaney AP. Clinical review: Pituitary carcinoma: difficult diagnosis and treatment. *J Clin Endocrinol Metab*. 2011 Dec;96(12):3649–3660.

Maiter D, Primeau V. 2012 update in the treatment of prolactinomas. *Ann Endocrinol* (Paris). 2012 Apr;73(2):90–98.

Matsuwaki T, Khan KN, et al. Evaluation of obstetrical factors related to Sheehan syndrome. *J Obstet Gynaecol Res*. 2013 Aug 15.

Melmed S. Medical progress: Acromegaly. *N Engl J Med*. 2006;355(24):2558.

Molitch ME. Management of incidentally found nonfunctional pituitary tumors. *Neurosurg Clin N Am*. 2012 Oct;23(4):543–553.

Nussey S, Whitehead S. Chapter 7. *The Pituitary Gland in Endocrinology: An Integrated Approach*. UK Oxford: BIOS Scientific Publishers; 2001. http://www.ncbi.nlm.nih.gov/books/NBK27/

Orija IB, Weil RJ, et al. Pituitary incidentaloma. *Best Pract Res Clin Endocrinol Metab*. 2012 Feb;26(1):47–68.

Ribeiro-Oliveira A Jr, Barkan A. The changing face of acromegaly--advances in diagnosis and treatment. *Nat Rev Endocrinol*. 2012 Oct;8(10):605–611.

AACE Guideline Update: Diagnosis and treatment of acromegaly, 2011. https://www.aace.com/files/acromegaly-guidelines.pdf

DIABETES INSIPIDUS

Bellastella A, Bizzaro A, et al. Subclinical diabetes insipidus. *Best Pract Res Clin Endocrinol Metab*. 2012 Aug;26(4):471–483.

Devin JK. Hypopituitarism and central diabetes insipidus: perioperative diagnosis and management. *Neurosurg Clin N Am*. 2012 Oct;23(4):679–689.

Devuyst O. Physiopathology and diagnosis of nephrogenic diabetes insipidus. *Ann Endocrinol* (Paris). 2012 Apr;73(2):128–129.

SIADH

Esposito P, Piotti G, et al. The syndrome of inappropriate antidiuresis: pathophysiology, clinical management and new therapeutic options. *Nephron Clin Pract*. 2011;119(1):c62–73; discussion c73.

Fenske W, Allolio B, et al. The syndrome of inappropriate secretion of antidiuretic hormone: diagnostic and therapeutic advances. *Horm Metab Res*. 2010 Sep;42(10):691–702.

THYROID GLAND

Allahabadia A, Razvi S, et al. Diagnosis and treatment of primary hypothyroidism. *BMJ*. 2009 Mar 26;338:b725.

Bahn RS. Autoimmunity and Graves' disease. *Clin Pharmacol Ther*. 2012 Apr;91(4):577–579.

Desailloud R, Hober D, et al. Viruses and thyroiditis: an update. *Virol J*. 2009 Jan 12;6:5.

Economidou F, Douka E, et al. Thyroid function during critical illness. *Hormones* (Athens). 2011 Apr-Jun;10(2):117–124.

Gaitonde DY, Rowley KD, et al. Hypothyroidism: an update. *Am Fam Physician*. 2012 Aug 1;86(3):244–251.

Gurgul E, Sowinski J, et al. Primary hyperthyroidism—diagnosis and treatment. Indications and contraindications for radioiodine therapy. *Nucl Med Rev Cent East Eur*. 2011;14(1):29–32.

Hybenova M, Hrda P, et al. The role of environmental factors in autoimmune thyroiditis. *Neuro Endocrinol Lett*. 2010;31(3):283–289.

Klubo-Gwiezdzinska J, Wartofsky L. Thyroid emergencies. *Med Clin North Am*. 2012 Mar;96(2):385–403.

Mai VQ, Burch HB. A stepwise approach to the evaluation and treatment of subclinical hyperthyroidism. *Endocr Pract*. 2012 Sep-Oct;18(5):772–780.

McDermott MT. Hyperthyroidism. *Ann Intern Med*. 2012 Jul 3;157(1):ITC1–16.

Medeiros-Neto G, Camargo RY, et al. Approach to and treatment of goiters. *Med Clin North Am*. 2012 Mar;96(2):351–368.

Paes JE, Burman KD, et al. Acute bacterial suppurative thyroiditis: a clinical review and expert opinion. *Thyroid*. 2010 Mar;20(3):247–255.

Persani L. Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. *J Clin Endocrinol Metab*. 2012 Sep;97(9):3068–3078.

Samuels MH. Subacute, silent, and postpartum thyroiditis. *Med Clin North Am*. 2012 Mar;96(2):223–233.

Shivaraj G, Prakash BD, et al. function tests: a review. *Eur Rev Med Pharmacol Sci*. 2009 Sep-Oct;13(5):341–349.

Tagoe CE, Zezon A, et al. Rheumatic manifestations of autoimmune thyroid disease: the other autoimmune disease. *J Rheumatol*. 2012 Jun;39(6):1125–1129.

Theoharis C, Roman S, et al. The molecular diagnosis and management of thyroid neoplasms. *Curr Opin Oncol*. 2012 Jan;24(1):35–41.

Villar HC, Saconato H, et al. Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database Syst Rev*. 2007.

AACE/AME/ETA Clinical Guidelines: Diagnosis and management of thyroid nodules, 2010. https://www.aace.com/files/thyroid-guidelines.pdf

AACE Guideline: Evaluation and treatment of hyperthyroidism and hypothyroidism, updated 2006. https://www.aace.com/files/hypo_hyper.pdf

American Thyroid Association Guidelines Task Force, Kloos RT, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009 Jun;19(6):565–612. Erratum in: *Thyroid*. 2009 Nov;19(11):1295.

Bahn RS, Burch HB, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract*. 2011 May-Jun;17(3):456–520.

Chen H, Sippel RS, et al; North American Neuroendocrine Tumor Society (NANETS). The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. *Pancreas*. 2010 Aug;39(6):775–783.

DeGroot L, Abalovich M, et al. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2012; 97: 2543–2565.

FDA MedWatch Update: PTU associated with risk of serious liver injury, 2009. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm164162.htm

Garber JR, Cobin RH, et al; American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012 Nov–Dec;18(6):988–1028. Erratum in: *Endocr Pract*. 2013 Jan–Feb;19(1):175.

Gharib H, Papini E, et al. AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European-Thyroid Association Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. Endocr Pract. 2010 May–Jun;16 Suppl 1:1–43.

Hyperthyroidism and other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists, 2011. https://www.aace.com/files/hyper-guidelines-2011.pdf

Mallick UK; American Thyroid Association. The revised American Thyroid Association management guidelines 2009 for patients with differentiated thyroid cancer: an evidence-based risk-adapted approach. *Clin Oncol* (R Coll Radiol). 2010 Aug;22(6):472–474.

Smallridge RC, Ain KB, et al; American Thyroid Association Anaplastic Thyroid Cancer Guidelines Taskforce. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*. 2012 Nov;22(11):1104–1139.

Tuttle RM, Ball DW, et al. National Comprehensive Cancer Network. Thyroid carcinoma. *J Natl Compr Canc Netw*. 2010 Nov;8(11):1228–1274.

ADRENAL GLAND

Auchus RJ, Arlt W. Approach to the patient: the adult with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2013 Jul;98(7):2645–2655.

Auchus RJ. Congenital adrenal hyperplasia in adults. *Curr Opin Endocrinol Diabetes Obes*. 2010 Jun;17(3):210–216.

Claahsen-van der Grinten HL, Stikkelbroeck NM, et al. Congenital adrenal hyperplasia—pharmacologic interventions from the prenatal phase to adulthood. *Pharmacol Ther*. 2011 Oct;132(1):1–14.

Gorman LS. The adrenal gland: common disease states and suspected new applications. *Clin Lab Sci*. 2013 Spring;26(2):118–125.

Guaraldi F, Salvatori R. Cushing syndrome: maybe not so uncommon of an endocrine disease. *J Am Board Fam Med*. 2012 Mar-Apr;25(2):199–208.

Ito Y, Takeda R, et al. Subclinical primary aldosteronism. *Best Pract Res Clin Endocrinol Metab*. 2012 Aug;26(4):485–495.

Neary N, Nieman L, et al. Adrenal insufficiency: etiology, diagnosis and treatment. *Curr Opin Endocrinol Diabetes Obes*. 2010 Jun;17(3):217–223.

Reddy P. Clinical approach to adrenal insufficiency in hospitalised patients. *Int J Clin Pract*. 2011 Oct;65(10):1059–1066.

Rossi GP. Diagnosis and treatment of primary aldosteronism. *Rev Endocr Metab Disord*. 2011 Mar;12(1):27–36.

Satre TJ, Kovach F. Clinical inquiries. What's the most practical way to rule out adrenal insufficiency? *J Fam Pract*. 2009 May;58(5):281a-b.

Witchel SF. Non-classic congenital adrenal hyperplasia. *Steroids*. 2013 Aug;78(8):747–750.

Chen H, Sippel RS, et al. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. *Pancreas*. 2010 Aug;39(6):775–783.

Endocrine Society Guideline: Case detection, diagnosis, and treatment of patients with primary aldosteronism, 2008. https://www.endocrine.org/~/media/endosociety/Files/Publications/Clinical Practice Guidelines/Final-Standalone-PA-Guideline.pdf

Endocrine Society Guideline: The diagnosis of Cushing's syndrome, 2008. https://www.endocrine.org/~/media/endosociety/Files/Publications/Clinical Practice Guidelines/Cushings_Guideline.pdf

Funder JW, Carey RM, et al; Endocrine Society. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008 Sep;93(9):3266–3281.

Nieman LK, Biller BM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008 May;93(5):1526–1540.

Pheochromocytoma and Paraganglioma Research Support Organization (PRESSOR). Facts in Brief. http://www.pressor.org/facts.php

Speiser PW, Azziz R, et al; Endocrine Society. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010 Sep;95(9):4133–4160. Erratum in: *J Clin Endocrinol Metab*. 2010 Nov;95(11):5137.

Zeiger MA, Thompson GB, et al; American Association of Clinical Endocrinologists; American Association of Endocrine Surgeons. The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. *Endocr Pract*. 2009 Jul-Aug;15 Suppl 1:1–20.

HORMONES OF REPRODUCTION (WOMEN)

Heiman DL. Amenorrhea. Prim Care. 2009 Mar;36(1):1–17, vii.

Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril*. 2006 Nov;86(5 Suppl 1):S148–155.

ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No.108: Polycystic ovary syndrome. *Obstet Gynecol*. 2009 Oct;114(4):936–949.

Azziz R, Carmina E, et al; Task Force on the Phenotype of the Polycystic Ovary Syndrome of The Androgen Excess and PCOS Society. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril*. 2009 Feb;91(2):456–488.

Endocrine Society Guideline: Evaluation and treatment of hirsutism in premenopausal women, 2008. https://www.endocrine.org/~/media/endosociety/Files/Publications/Clinical Practice Guidelines/Hirsutism_Guideline.pdf

Martin KA, Chang RJ, et al. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008 Apr;93(4):1105–1120.

HORMONES OF REPRODUCTION (MEN)

Johnson RE, Murad MH, et al. Gynecomastia: pathophysiology, evaluation, and management. *Mayo Clin Proc*. 2009 Nov;84(11):1010–1015.

Morcos RN, Kizy T. Gynecomastia: when is treatment indicated? *J Fam Pract*. 2012 Dec;61(12):719–725.

Radicioni AF, Ferlin A, et al. Consensus statement on diagnosis and clinical management of Klinefelter syndrome. *J Endocrinol Invest*. 2010 Dec;33(11):839–850.

Bhasin S, Cunningham GR, et al. Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010 June;95(6):2536.

Montague DK, Erectile Dysfunction Guideline Update Panel, et al. The management of erectile dysfunction: an update. Linthicum (MD): American Urologic Association Education and Research, Inc.; 2006 May. Reaffirmed 2009. http://www.guideline.gov/content.aspx?id=10018&search=erectile+dysfunction

Qaseem A, Snow V, et al. Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Hormonal testing and pharmacologic treatment of erectile dysfunction: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2009 Nov 3;151(9):639–649.

Wang C, Nieschlag E, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male*. 2009 Mar;12(1):5–12.

LIPOPROTEINS

Balci B. The modification of serum lipids after acute coronary syndrome and importance in clinical practice. *Curr Cardiol Rev*. 2011 Nov;7(4):272–276.

Brouwers MC, van Greevenbroeck MM, et al. The genetics of familial combined hyperlipidaemia. *Nat Rev Endocrinol*. 2012 Feb 14;8(6):352–362.

Ito MK. Dyslipidemia: management using optimal lipid-lowering therapy. *Ann Pharmacother*. 2012 Oct;46(10):1368–1381.

Kelly RB. Diet and exercise in the management of hyperlipidemia. *Am Fam Physician*. 2010 May 1;81(9):1097–1102.

Kwiterovich PO Jr. Diagnosis and management of familial dyslipoproteinemias. *Curr Cardiol Rep*. 2013 Jun;15(6):371.

Vale N, Nordmann AJ, et al. Statins for acute coronary syndrome. *Cochrane Database Syst Rev*. 2011 Jun 15;(6):CD006870.

Vigna GB, Fellin R. Pharmacotherapy of dyslipidemias in the adult population. *Expert Opin Pharmacother*. 2010 Dec;11(18):3041–3052.

Yusuf S, Lonn E, et al. Lipid lowering for primary prevention. *Lancet*. 2009 Apr 4;373(9670):1152–1155. Review. Erratum in: *Lancet*. 2009 Jul 4–2009 Jul 10;374(9683):28.

ACP Guideline: Lipid control in the management of Type 2 diabetes mellitus, 2004. http://www.annals.org/cgi/reprint/140/8/644.pdf

Berglund L, Brunzell JD, et al; Endocrine Society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012 Sep;97(9):2969–2989.

FDA Drug Safety Podcast: Revised dose limitation for Zocor (simvastatin) when taken with amiodarone, 2011. http://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm283898.htm

Goldberg AC, Hopkins PN, et al; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011 Jun;5(3 Suppl):S1–8.

Ito MK, McGowan MP, et al; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Management of familial hypercholesterolemias in adult patients: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011 Jun;5(3 Suppl):S38–45.

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002 Dec 17;106(25):3143–3421.

National Institutes of Health. National Cholesterol Education Program (NCEP). Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2004. http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm

NKF KDOQI Guideline: Recommendations for diabetes and chronic kidney disease, 2007. http://www.kidney.org/professionals/kdoqi/guideline_diabetes/guide4.htm

Robinson JG, Goldberg AC; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Treatment of adults with familial hypercholesterolemia and evidence for treatment: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011 Jun;5(3 Suppl):S18–29.

DIABETES MELLITUS

Allcock DM, Sowers JR. Best strategies for hypertension management in type 2 diabetes and obesity. *Curr Diab Rep*. 2010 Apr;10(2):139–144.

Buse JB, Ginsberg HN, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: A scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2007;115:114.

Buysschaert M, Bergman M. Definition of prediabetes. *Med Clin North Am*. 2011 Mar;95(2):289–297, vii.

Chehade JM, Gladysz M, et al. Dyslipidemia in type 2 diabetes: prevalence, pathophysiology, and management. *Drugs*. 2013 Mar;73(4):327–339.

Erlich DR, Slawson DC, et al. Diabetes update: new drugs to manage type 2 diabetes. *FP Essent*. 2013 May;408:20–24.

Ferrannini E, Gastaldelli A, et al. Pathophysiology of prediabetes. *Med Clin North Am*. 2011 Mar;95(2):327–339, vii–viii.

Garber AJ, Handelsman Y, et al. Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocr Pract*. 2008 Oct;14(7):933–946.

King P, Peacock I, et al. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol*.1999 Nov;48(5):643–648.

Merger SR, Leslie RD, et al. The broad clinical phenotype of Type 1 diabetes at presentation. *Diabet Med*. 2013 Feb;30(2):170–178.

Morsink LM, Smits MM, et al. Advances in pharmacologic therapies for type 2 diabetes. *Curr Atheroscler Rep*. 2013 Feb;15(2):302.

National Institutes of Health. Diabetes Control and Complications Trial (DCCT). CinicalTrials.gov. http://clinicaltrials.gov/show/NCT00360815

Ohkubo Y, Kishikawa H, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995 May;28(2):103–117. Analysis at: http://www.trialresultscenter.org/study7377-Kumamoto-(primary-prev).htm

Ovadia C, Dixit A. The management of gestational diabetes. *Curr Diabetes Rev*. 2012 Jul 1;8(4):247–56.

Patel P, Macerollo A, et al. Diabetes mellitus: diagnosis and screening. *Am Fam Physician*. 2010 Apr 1;81(7):863–870.

Ratner RE, Sathasivam A. Treatment recommendations for prediabetes. *Med Clin North Am*. 2011 Mar;95(2):385–395, viii–ix.

Rubin DJ, Golden SH. Hypoglycemia in non-critically ill, hospitalized patients with diabetes: evaluation, prevention, and management. *Hosp Pract* (1995). 2013 Feb;41(1):109–116.

Rybicka M, Krysiak R, et al. The dawn phenomenon and the Somogyi effect—two phenomena of morning hyperglycaemia. *Endokrynol Pol*. 2011;62(3):276–284.

Shaw J. Diagnosis of prediabetes. *Med Clin North Am*. 2011 Mar;95(2):341–352, viii.

Steenkamp DW, Alexanian SM, et al. Adult hyperglycemic crisis: a review and perspective. *Curr Diab Rep*. 2013 Feb;13(1):130–137.

Stolar M. Glycemic control and complications in type 2 diabetes mellitus. *Am J Med*. 2010 Mar;123(3 Suppl):S3–11.

Tack J, Arts J, et al. Pathophysiology, diagnosis and management of postoperative dumping syndrome. *Nat Rev Gastroenterol Hepatol*. 2009 Oct;6(10):583–590.

Umpierez GE. How to manage type 2 diabetes in medical and surgical patients in the hospital. *Cleve Clin J Med*. 2011 Jun;78(6):379–384.

Unger J, Parkin C. Recognition, prevention, and proactive management of hypoglycemia in patients with type 1 diabetes mellitus. *Postgrad Med*. 2011 Jul;123(4):71–80.

U.S. Preventive Services Task Force. Screening for type 2 diabetes mellitus in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008 Jun 3;148(11):846–854.

Valensi P, Picard S, et al. Lipids, lipid-lowering therapy and diabetes complications. *Diabetes Metab*. 2011 Feb;37(1):15–24.

Vandorsten JP, Dodson WC, et al. NIH consensus development conference: diagnosing gestational diabetes mellitus. *NIH Consens State Sci Statements*. 2013 Mar 6;29(1):1–31.

Wilson JF. In clinic. Diabetic ketoacidosis. *Ann Intern Med*. 2010 Jan 5;152(1):Entire Issue.

AACE Consensus Statement: Diagnosis and management of pre-diabetes in the continuum of hyperglycemia—when do the risks of diabetes begin? 2008. https://www.aace.com/files/prediabetesconsensus.pdf

ADA/AACE Consensus Statement: Inpatient glycemic control, 2009. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2681039/

ADA Consensus Statement: Hyperglycemic crises in adult patients with diabetes, 2009. http://care.diabetesjournals.org/content/32/7/1335

ADA Consensus Statement: Medical management of hyperglycemia in Type 2 diabetes, 2009. http://care.diabetesjournals.org/content/32/1/193.

ADA Guidelines: Executive Summary: Standards of medical care in diabetes, 2012. http://care.diabetesjournals.org/content/35/Supplement_1/S4.full.pdf+html

ADA Guidelines: Summary of revisions for the 2012 clinical practice recommendations. http://care.diabetesjournals.org/content/35/Supplement_1/S3.full.pdf+html

American Association of Clinical Endocrinologists Medical Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan - © 2011. https://www.aace.com/files/dm-guidelines-ccp.pdf

American Diabetes Association. Clinical Practice Guidelines. http://professional.diabetes.org/ResourcesForProfessionals.aspx?cid=84160

American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care*. 2013 Jan;36 Suppl 1:S11–66.

Committee on Obstetric Practice. ACOG Committee Opinion No. 435: postpartum screening for abnormal glucose tolerance in women who had gestational diabetes mellitus. *Obstet Gynecol*. 2009 Jun;113(6):1419–1421.

Endo Society Guideline: Primary prevention of cardiovascular disease and Type 2 diabetes in patients at metabolic risk, 2008. https://www.endocrine.org/~/media/endosociety/Files/Publications/Clinical Practice Guidelines/Metabolic-Syndrome-Guideline-Standalone.pdf

Handelsman Y, Mechanick JI, et al; AACE Task Force for Developing Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract*. 2011 Mar–Apr;17 Suppl 2:1–53.

James PA, Oparil S, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA®. 2014;311(5):507.

Novo S, Balbarini A, et al. Guidelines Committee of the International Union of Angiology; Scientific Committee of the International Union of Angiology; Council of Vascular Medicine of the International Union of Angiology. The metabolic syndrome: definition, diagnosis and management. *Int Angiol*. 2008 Jun;27(3):220–231.

Rosenzweig JL, Ferrannini E, et al. Endocrine Society. Primary prevention of cardiovascular disease and type 2 diabetes in patients at metabolic risk: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008 Oct;93(10):3671–3689.

BONE / CALCIUM DISORDERS

Bhan A, Rao AD, et al. Osteomalacia as a result of vitamin D deficiency. *Endocrinol Metab Clin North Am*. 2010 Jun;39(2):321–331, table of contents.

Bilezikian JP. Primary hyperparathyroidism. *Endocr Pract*. 2012 Sep-Oct;18(5):781–790.

Endres DB. Investigation of hypercalcemia. *Clin Biochem*. 2012 Aug;45(12):954–963.

Fong J, Khan A. Hypocalcemia: updates in diagnosis and management for primary care. *Can Fam Physician*. 2012 Feb;58(2):158–162.

Gaztambide S, Vazquez F, et al. Diagnosis and treatment of multiple endocrine neoplasia type 1 (MEN1). *Minerva Endocrinol*. 2013 Mar;38(1):17–28.

Machens A, Dralle H. Multiple endocrine neoplasia type 2: achievements and current challenges. *Clinics* (Sao Paulo). 2012;67 Suppl 1:113–118.

Nussey S, Whitehead S, et al. Chapter 5: *The parathyroid glands and vitamin D in Endocrinology: An Integrated Approach*. Oxford: BIOS Scientific Publishers; 2001. http://www.ncbi.nlm.nih.gov/books/NBK22/

Pallan S, Rahman MO, et al. Diagnosis and management of primary hyperparathyroidism. *BMJ*. 2012 Mar 19;344:e1013.

Powell AC, Libutti SK, et al. Multiple endocrine neoplasia type 1: clinical manifestations and management. *Cancer Treat Res*. 2010;153:287–302.

Thakker RV. Multiple endocrine neoplasia type 1 (MEN1). *Best Pract Res Clin Endocrinol Metab*. 2010 Jun;24(3):355–370.

Traugott AL, Moley JF, et al. Multiple endocrine neoplasia type 2: clinical manifestations and management. *Cancer Treat Res*. 2010;153:321–337.

Wohllk N, Schweizer H, et al. Multiple endocrine neoplasia type 2. *Best Pract Res Clin Endocrinol Metab*. 2010 Jun;24(3):371–387.

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, July 2011; 96(7):191.

Thakker RV, Newey PJ, et al. Endocrine Society. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*. 2012 Sep;97(9):2990–3011.

AACE

AACE Consensus Statement: Diagnosis and management of pre-diabetes in the continuum of hyperglycemia—when do the risks of diabetes begin? 2008. https://www.aace.com/files/prediabetesconsensus.pdf

American Association of Clinical Endocrinologists Medical Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan - © 2011. https://www.aace.com/files/dm-guidelines-ccp.pdf

Handelsman Y, et al; AACE Task Force for Developing Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract*. 2011 Mar-Apr;17 Suppl 2:1–53.

ACOG

Committee on Obstetric Practice. ACOG Committee Opinion No. 435: postpartum screening for abnormal glucose tolerance in women who had gestational diabetes mellitus. *Obstet Gynecol*. 2009 Jun;113(6):1419–1421.

JNC8

James PA, Oparil S, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *ESO JAMA*[R], 2014;311(5):507.

ENDOCRINE SOCIETY

Endo Society Guideline: Primary prevention of cardiovascular disease and Type 2 diabetes in patients at metabolic risk, 2008. http://www.endo-society.org/guidelines/final/upload/Metabolic-Syndrome-Guideline-Standalone.pdf

Rosenzweig JL, et al. Endocrine Society. Primary prevention of cardiovascular disease and type 2 diabetes in patients at metabolic risk: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008 Oct;93(10):3671–3689.

INTERNATIONAL UNION OF ANGIOLOGY

Novo S, et al. Guidelines Committee of the International Union of Angiology; Scientific Committee of the International Union of Angiology; Council of Vascular Medicine of the International Union of Angiology. The metabolic syndrome: definition, diagnosis and management. *Int Angiol*. 2008 Jun;27(3):220–231.

USPSTF

U.S. Preventive Services Task Force. Screening for type 2 diabetes mellitus in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008 Jun 3;148(11):846–854

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NORMAL ERYTHROPOIESIS

Erythropoietin regulates red cell production. Normal erythropoiesis involves the maturation of pluripotent stem cells into proerythroblasts → erythroblasts → reticulocytes (Figure 8-1). Immature RBCs, which have lost their nucleus but retained their RNA, can be identified on a standard Wright's stained peripheral blood smear because the cytoplasmic RNA stains a gray-purple color (polychromasia). These same cells, also called reticulocytes, can be quantified by special stains or flow cytometry, yielding a reticulocyte count.

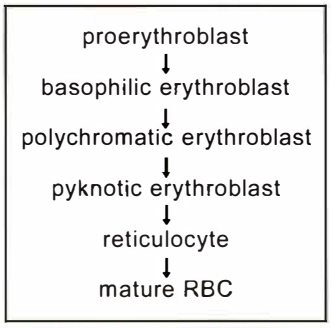

Figure 8-1: Erythropoiesis

The mature red blood cells contain no RNA and survive for approximately 120 days. Throughout their life span, RBCs pass repeatedly through the spleen, where old or damaged cells are ingested by macrophages. The hemoglobin is catabolized into its heme (protoporphyrin ring + iron) and globin components.

The porphyrin ring is metabolized into unconjugated (indirect, water insoluble) bilirubin, which, when bound to albumin (now water soluble), is then transported to the liver, where it is conjugated. Iron released from heme (or absorbed in the intestine from the diet) is transported by transferrin, the blood plasma protein, to the bone marrow and to other tissues where it is stored as ferritin and hemosiderin.

IRON

Iron is absorbed from the gut by means of ferroportin, a transmembrane protein that transports iron through the cell walls of enterocytes and macrophages and subsequently releases this iron to transferrin in the hepatoportal circulation. Ferroportin itself is controlled by hepcidin, the key regulator hormone for iron hemostasis.

Hepcidin levels are decreased in low iron states and increased in iron overload states. Hepcidin binds ferroportin, causing a decrease in the release of iron into the bloodstream. So, high levels of hepcidin cause decreased iron absorption, while low levels allow for increased iron absorption.

Hepcidin is also an acute phase protein that is increased in response to inflammatory cytokines (especially interleukin-6).

MECHANISMS OF ANEMIA

Overview

The approach to the anemic patient should be methodical. Excluding acute hemorrhage and rare sequestration, all anemias can be broadly classified as either hypoproliferative or survival defects. The etiology of most anemias is determined using the history, a physical exam, the reticulocyte count, a thoughtful evaluation of the CBC (focusing on the MCV and RDW), and the peripheral blood smear. Refer to Table 8-1 as you go through this material. Several images of normal blood smears and marrow aspirates are shown for your review on the next page (Image 8-1 through Image 8-6).

Causes and mechanisms of anemia:

1) **Production** defects result from chronic disease, acute inflammatory conditions, impaired renal function, hypometabolic states (e.g., hypothyroidism, hypogonadism, adrenal insufficiency), and bone marrow damage. Very little polychromasia and few reticulocytes are seen.
2) **Maturation** defects:
   - Cytoplasmic: All are related to impaired hemoglobin synthesis—iron deficiency, sideroblastic anemia (the inability to incorporate iron into hemoglobin: protoporphyrin deficiency, myelodysplastic syndrome, drugs, toxins), and globin synthesis deficiency (thalassemias).
   - Nuclear: DNA synthesis defects (folate and B_{12} deficiencies, myelodysplastic syndrome).
3) **Survival** defects result in premature destruction of the RBC.
   - Intrinsic (inherited): membrane cytoskeletal protein (spherocytosis, elliptocytosis), metabolic enzymes (G6PD deficiency), or hemoglobinopathies (sickle cell disease, thalassemias).
   - Extrinsic (acquired): antibody- or complement-mediated, microangiopathy, mechanical heart valves (autoimmune hemolysis, malaria, and DIC, TTP, HUS, or HELLP).
4) **Sequestration**: hypersplenism (portal hypertension, early childhood sickle cell disease).
5) **Blood loss**, with resultant iron deficiency, is the most common cause of anemia in the U.S.

Laboratory Results

Iron Studies

Free iron is produced from hemoglobin breakdown by RBC macrophages and by absorption from the duodenum. Free iron is toxic to the tissues.

Transferrin is a blood plasma protein that binds iron and transports it to the tissues. Transferrin receptors on cells bind this iron-containing transferrin and absorb it into vesicles.

Table 8-1: Summary — Causes and Mechanisms of Anemia

		Reticulocyte Count	Morphology	Etiology	Examples
1) Production defect		Decreased	Normal	1) Decreased erythropoietin 2) Bone marrow failure	1) Chronic renal disease 2) Aplastic anemia
2) Maturation defect	Cytoplasmic	Decreased	Hypochromic Microcytic	1) Impaired Hgb synthesis 2) Protoporphyrin deficiency 3) Globin synthesis deficiency	1) Fe deficiency 2) Sideroblastic anemia 3) Thalassemias 4) Myelodysplastic syndrome 5) Drugs, toxins
	Nuclear	Decreased	Megaloblastic	DNA synthesis defects	B_{12}, folate deficiencies
3) Survival defect	Intrinsic (inherited)	Increased	Specific changes; e.g., spherocytes, sickle cells, bite cells	1) Membrane cytoskeleton protein 2) Metabolic enzymes 3) Hemoglobinopathies	1) Spherocytosis, elliptocytosis 2) G6PD deficiency 3) SS disease, HbC, HbD, HbE, thalassemias
	Extrinsic (acquired)	Increased	Specific changes; e.g., spherocytes, schistocytes	1) Antibody- or complement-mediated 2) Microangiopathy 3) Mechanical heart valves	1) Autoimmune hemolysis, malaria 2) DIC, TTP/HUS 3) HELLP
4) Sequestration		Increased	Normal	Hypersplenism	Portal hypertension or early childhood sickle cell disease
5) Blood loss		Increased if iron stores are adequate	Normal or hypochromic	GI hemorrhage	Peptic ulcer disease

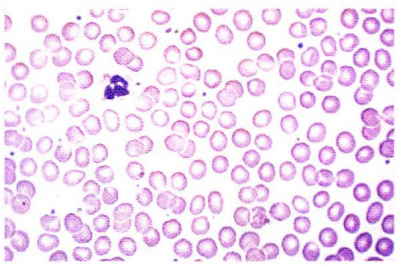

Image 8-1: Normal peripheral smear: low-power view, RBCs, platelets, and segmented neutrophil.

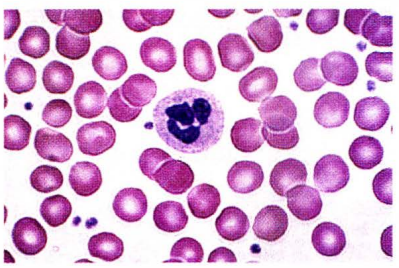

Image 8-2: Normal peripheral smear: low-oil view. Normocytic, normochromic RBCs, platelets, and normal segmented neutrophil.

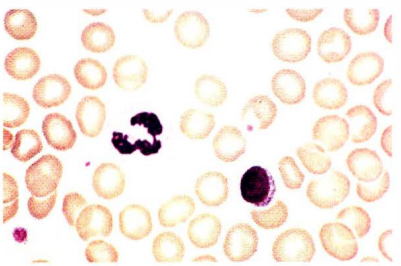

Image 8-3: Normal peripheral smear: high-dry view. RBCs, platelets, normal segmented neutrophil, and a normal lymphocyte.

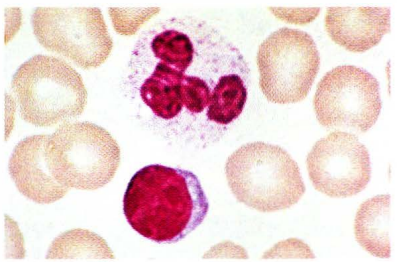

Image 8-4: Normal peripheral smear: high-oil view. Normal RBCs, segmented neutrophil, and lymphocyte. No platelets are visible in this field.

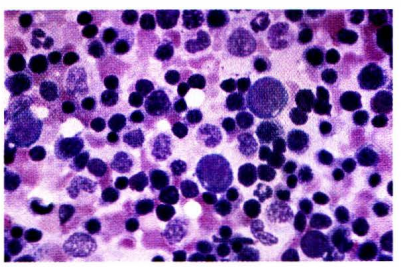

Image 8-5: Normal BM aspirate: low-power view. M:E (myloid to erythroid) ratio is usually 3:1. This field has more than the normal number of erythroid precursors. Many of the erythroid precursors have dark, condensed nuclei.

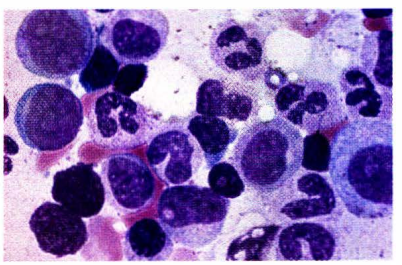

Image 8-6: Normal BM aspirate: low-oil view. Five erythroid precursors (dark condensed nuclei). Remaining cells are myeloid precursors/cells—from myoblasts to segs.

QuickQuiz

- List some extrinsic survival defects that cause anemia. (Table 8-1)
- Is reticulocytosis increased or decreased for each of these: Production defect? Maturation defect? Survival defect? (Table 8-1)
- When are Howell-Jolly bodies seen? (Table 8-2)

Soluble transferrin receptor (sTfR) concentration is elevated in iron deficiency and normal in anemia of chronic disease (ACD). It is mainly used for differentiating ACD from iron deficiency anemia.

Serum iron is a measurement of circulating iron bound to transferrin.

Total iron-binding capacity (TIBC) indirectly measures transferrin by determining the total amount of iron the blood can bind. Generally, it is not necessary to order both a transferrin level and TIBC.

The ratio of serum iron to TIBC, measured as a percentage, is called **transferrin saturation**.

Within the cell, iron is stored in protein complexes as **ferritin** or **hemosiderin**.

In equilibrium conditions, serum ferritin level is a good indicator of total iron stores. It is low in iron deficiency anemia, high-normal to high in anemia of chronic disease, and high in hemochromatosis.

Ferritin is also an acute-phase reactant and can be elevated with inflammation or chronic disease, although inflammation generally should lead to only a 3x increase in ferritin levels. A low C-reactive protein (CRP) helps rule out inflammation. Additionally, a high ferritin level is often a side effect of certain malignancies, especially hematologic cancer.

Working up Anemia

Work up anemia by analyzing the peripheral blood smear (see Table 8-2), reticulocyte count, and serum iron studies (Fe, TIBC, ferritin), then calculate the transferrin saturation (Fe/TIBC). Look at the measurements of the red cell indices for density (normochromia or hypochromia) and size (microcytosis or macrocytosis). Anisocytosis is reflected by an increase in the red cell distribution width (RDW). Finally, look at the descriptions of the red cells. Certainly, you can look at the smears yourself rather than relying on the hematology lab for measurements and descriptions. (See Image 8-7 through Image 8-12 on the following page.)

Production and maturation defects lead to low reticulocyte counts (< 2% or < 100,000), whereas shortened red cell survival, splenic sequestration, or blood loss stimulate a high reticulocyte count as new red cells are produced. Prior to interpretation, the reticulocyte count needs to be adjusted for the degree of anemia by correcting for the hematocrit and the reticulocyte maturation time (reticulocyte production index).

SPECIFIC ETIOLOGIES OF ANEMIA

Production Defects

Anemia of chronic disease ([ACD]; anemia of [chronic] inflammation) results from RBCs not functioning normally and causing impaired iron utilization, despite normal or increased iron stores.

In inflammatory states, macrophages produce IL-6, which induces the production of hepcidin by the liver. Hepcidin then inhibits iron absorption from the GI tract and decreases release of iron from macrophages.

Erythropoietin level is typically above normal but is lower than would be expected for the degree of anemia. In addition, there is no real increase in erythropoiesis in response to the higher erythropoietin level.

Table 8-2: Significance of Specific Changes in the Peripheral Smear

Finding	Meaning
RBC fragments (schistocytes)	Microangiopathic hemolytic anemia (seen in TTP, HUS, HELLP, DIC, and occasionally vasculitis), severe burns, and valve hemolysis
Spherocytes	Autoimmune hemolytic anemia and hereditary spherocytosis
Target cells	Significant liver disease, but also seen in thalassemia and other hemoglobinopathies
Teardrop cells	Classic for myelofibrosis and other infiltrating bone marrow processes Also seen with thalassemia
Burr cells (echinocytes) vs. spur cells (acanthocytes)	Burr cells (Image 8-14) are seen in uremic patients. These are distinct and different from spur cells (Image 8-13), which are seen in liver diseases.
Howell-Jolly bodies	Splenectomy or functional asplenia. Howell-Jolly bodies are the result of fragmentation of the nucleus (karyorrhexis), causing the formation of small black "pellets." This occurs normally, and the spleen efficiently removes them.
Hypersegmented PMNs	Megaloblastic anemia (pernicious anemia/B_{12} deficiency, folate deficiency)

Table 8-3: Some Laboratory Characteristics of Fe Deficiency and Anemia of Chronic Disease

	Fe Deficiency	ACD
Serum Fe	Low	Low
TIBC	High	Low
Transferrin Saturation	Low	Low to normal
Ferritin	Low	High/high-normal
Soluble Transferrin Receptor	High	Normal

The most common causes of ACD are chronic rheumatic, infectious, and neoplastic diseases. ACD and iron deficiency anemia may coexist, so it is best to work up all anemias in patients with chronic illness (Table 8-3).

Labs in ACD:

- RBCs are typically normochromic and normocytic (occasionally hypochromic microcytic) with a low reticulocyte count.
- Serum Fe and TIBC are low.
- Fe/TIBC is normal (or barely low).
- Ferritin is increased or high-normal.
- The soluble transferrin receptor test helps differentiate ACD from iron deficiency anemia and is normal in ACD (increased in Fe deficiency).

Anemia of chronic kidney disease is due to decreased erythropoietin production and is commonly responsive to recombinant erythropoietin. There may also be increased hepcidin in these patients. 20% of diabetics with stage 3 CKD have anemia. This topic is discussed more fully in Nephrology, Book 2.

Anemia of hypometabolic states can result from deficiencies in thyroid hormone, glucocorticoids, testosterone, or growth hormone and may be one of the presenting features of hypothyroidism, primary adrenal insufficiency, or pituitary disease (hypogonadism or panhypopituitarism).

Anemia from bone marrow damage includes the following:

- Aplastic anemia: pancytopenia secondary to a primary stem cell disorder, an autoimmune process, or drug.
- Pure red cell aplasia: severe anemia due to decreased RBC precursors in the bone marrow. This can be congenital due to abnormal stem cells or acquired due to viral infection, thymoma (paraneoplastic), autoimmunity, lymphoproliferative disorders, or drugs. Suspect parvovirus B19 in these severe anemia patients who also have an HIV infection or sickle cell anemia.
- Marrow infiltrative disorders: Fibrosis, granulomas, or malignancy can cause changes in the peripheral blood smear, including teardrop cells, as well as immature red and white blood cells. These leukoerythroblastic changes reflect a weakened bone marrow (myelophthisis).

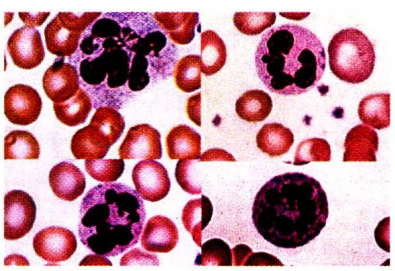

Image 8-7: Various views of hypersegmented neutrophils.

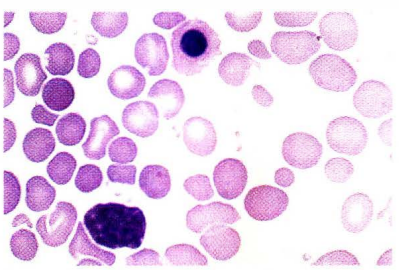

Image 8-8: This field shows hemolytic anemia with RBC fragments, a nucleated RBC, and spherocytes.

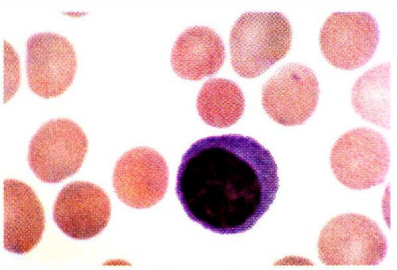

Image 8-9: Hereditary spherocytosis. Note the lack of central pallor. The normal-sized lymphocyte shows that these are microcytic spherocytes.

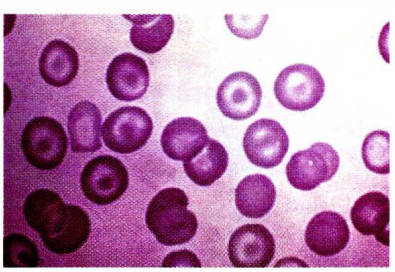

Image 8-10: Target cells. Low-oil view.

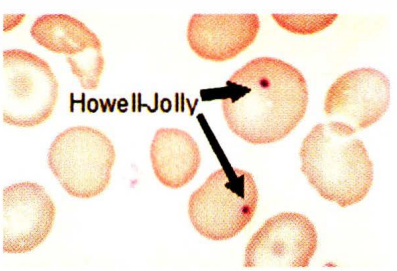

Image 8-11: Post splenectomy: Howell-Jolly bodies are the dense inclusion bodies in the RBCs. Also see target cells and a burr cell in this field.

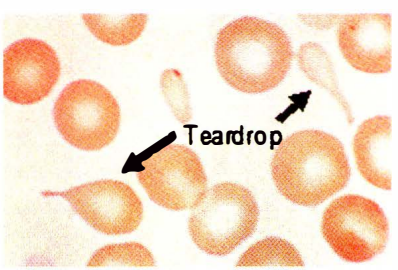

Image 8-12: Teardrop cells. This patient has myeloid metaplasia. Also seen in thalassemias and other hemoglobinopathies.

QuickQuiz

- Characterize the lab values in iron deficiency anemia vs. anemia of chronic disease.
- What are common causes of iron deficiency anemia?

Maturation Defects

Cytoplasmic Maturation Defects

Iron Deficiency Anemia

Iron is essential for the production of hemoglobin, and a deficiency leads to impaired erythropoiesis and iron deficiency anemia (IDA).

Signs and symptoms include fatigue, pallor, weakness, irritability, and poor exercise tolerance. IDA is one of the major causes of restless leg syndrome. Pica for ice (termed "pagophagia") is occasionally seen and pretty specific for IDA. Beeturia occurs in ~ 75% of patients with iron deficiency when eating beets leads to excreting red urine (also in ~ 10% of normal population).

Labs in IDA:

Red cells are microcytic (MCV < 80 mm^3) and hypochromic (decreased MCHC) with a low reticulocyte count.

Serum iron (SI) is low. Low SI causes increased production of transferrin, which is measured as total iron binding capacity (TIBC). So TIBC is elevated, and the ratio of the low SI to the elevated TIBC is usually < 10% (normal 25- 40%).

The serum ferritin level is considered the best test for assessing iron stores. In the patient with no known inflammatory or infectious disease, a ferritin level ≤ 40 ng/mL is 98% sensitive and 98% specific for IDA. When the level is < 15, the diagnosis is virtually always IDA, no matter what the disease state.

Remember that ferritin is an acute phase reactant and can increase during states of inflammation, so this test has poor sensitivity for IDA in patients who have ongoing inflammation. Soluble transferrin receptor (sTfR) concentration is normally elevated in iron deficiency and normal in anemia of inflammation.

Once you diagnose iron deficiency anemia, you must pursue the etiology:

- Chronic blood loss (most common) from either the gastrointestinal (especially PUD, malignancies) or genitourinary tracts (e.g., menorrhagia)
- Pregnancy, which can cause iron deficiency because of increased iron requirements
- Lack of dietary iron
- Malabsorption (e.g., celiac disease or gastric bypass surgery)
- Chronic low-grade intravascular hemolysis (as in paroxysmal nocturnal hemoglobinuria)

Celiac disease is a common cause of chronic, unresponsive IDA in a young person with a history of bulky, foul-smelling stools.

Thalassemias

Normal hemoglobin is a tetramer with 2 α- and 2 β-globin chains. These tetramers are covalently linked to heme, a complex of ferrous iron and protoporphyrin. A normal Hb electrophoresis pattern would be HbA ($\alpha_2\beta_2$) > 97.5%, HbA_2 ($\alpha_2\delta_2$) < 2.5%. δ and γ are β-like globins; δ is an adult form, and γ is fetal.

Thalassemias are inherited disorders characterized most commonly by absent or decreased production of either the α chain (α-thalassemia) or the β chain (β-thalassemia) leading to decreased production of hemoglobin tetramers and fewer red blood cells. In addition, there is unbalanced globin chain synthesis, and homotetramers are formed, which are insoluble and precipitate in RBCs. These precipitated chains lead to RBC hemolysis and ineffective erythropoiesis. These processes result in anemia. Mutations may be deletional or nondeletional and affect many different aspects of transcription and translation.

α-thalassemia: Chromosome 16 contains 2 copies of the α-gene at 2 different loci on each of the 2 genes. There are, therefore, 4 α-genes in normal individuals. The clinical manifestations correlate with the number of α-genes that are affected: the more loci affected, the worse the symptoms. This type is seen in African, Mediterranean, and Southeast Asian populations.

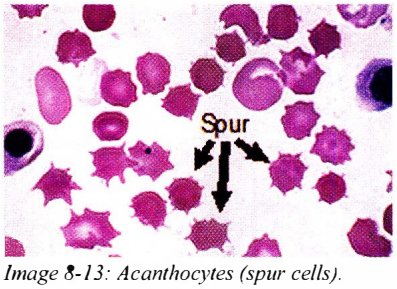

Image 8-13: Acanthocytes (spur cells). Nucleated RBCs. Spur cells are RBCs with multiple irregular projections that vary in length, width, and regularity. Usual cause is hepatic failure.

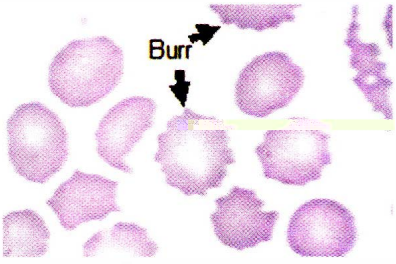

Image 8-14: Echinocytes or burr cells in uremia. These are RBCs with regular, short, spiney projections. These membrane changes disappear when uremia is corrected.

There are 4 types of α-thalassemia:

1) α-thalassemia trait: 1 locus, (αα/α-), asymptomatic, no hematologic abnormalities.
2) α-thalassemia minor: 2 loci, (α-/α-) or (αα/--), asymptomatic, MCV low, little to no anemia.
3) Hb H: 3 loci, (α-/--). Unpaired β chains form β_4 tetramers called HbH—these form inclusions in peripheral cells but not in the marrow. Clinical features are intermediate and variable and can include moderately severe hemolytic anemia but often with avoidance of transfusions until adulthood.
4) Hb Bart's: 4 loci, (--/--). No effective hemoglobin is produced beyond the embryonic stage. γ_4 tetramers (Hb Bart's) form and have such high oxygen affinity that they do not deliver any oxygen to the tissues, causing death *in utero* (hydrops fetalis).

β-thalassemia: caused by a range of mutations within the β-globin locus of chromosome 11. This type is seen in Mediterranean, Middle Eastern, and Asian populations. There are 3 categories of β-thalassemia:

1) β-thalassemia minor (heterozygotes): mild or no anemia, with a disproportionately high number of microcytes. These patients are asymptomatic and have no clinical sequelae. In most patients, this disorder has 2- to 3-fold elevations of HbA_2 ($\alpha_2\delta_2$) and slight increases in HbF ($\alpha_2\gamma_2$) on hemoglobin electrophoresis.
2) β-thalassemia major (homozygous): Patients with β-thalassemia major, termed "Cooley anemia," have essentially no β-globin production. The remaining, highly insoluble α-globin precipitates into homotetramers, or inclusion bodies, which are toxic to erythrocytes and cause them to die within the marrow. Surviving erythrocytes carry inclusion bodies that are detected by the spleen, leading to removal of the erythrocytes and chronic hemolytic anemia. The resulting severe anemia (developing over the 1st year of life) results in elevated erythropoietin levels and thus, erythroid hyperplasia. If the erythroid hyperplasia is severe, it can lead to extramedullary hematopoiesis in the liver and spleen and an expanded bone marrow with the latter, giving children "chipmunk facies." Often, patients are transfusion-dependent and develop iron overload. Bilirubin gallstone disease is common. Hemoglobin electrophoresis shows high Hb F and HbA_2.
3) β-thalassemia intermedia (homozygous): Not all patients with homozygous defects of β-globin production have the full clinical severity described above. Modulating factors are: minor qualitative defects of the β-globin; coinheritance of α-thalassemia trait, leading to decreased formation of the toxic RBC inclusion and therefore less precipitation of insoluble homotetramers and less hemolysis; and increased production of Hb F. The term "β-thalassemia intermedia" is used to convey this heterogeneity and to describe those patients who range from the asymptomatic to the transfusion-dependent states.

Know that thalassemias are often misdiagnosed as iron deficiency anemia and, subsequently, incorrectly given iron replacement. Iron therapy does not improve the microcytosis, and, even worse, it can cause secondary hemochromatosis. Remember that thalassemias can be diagnosed by excluding iron deficiency with a CBC, reticulocyte count, and iron studies (+/– soluble transferrin receptor). The microcytosis can be evaluated further with a hemoglobin electrophoresis (normal in α-thalassemia and increased A_2 component in β-thalassemia).

In clinical practice, adult patients with a microcytosis and normal iron studies are assumed to have thalassemia, and the electrophoresis is rarely ordered. Nonetheless, it is helpful to confirm the diagnosis with Hgb electrophoresis if there is some doubt.

Nuclear Maturation Defects

Megaloblastic anemias result from impaired DNA synthesis. They are often the result of deficiencies of B_{12} and/or folate but may also result from drugs that impair DNA metabolism.

Folate deficiency is caused by:

- Poor diet
- Increased demand (pregnancy)
- Alcohol use

B_{12} deficiency can result from:

- Pernicious anemia (due to autoimmune destruction of parietal cells that produce intrinsic factor)
- Strict vegetarian diet
- Alcohol use
- Inability to release B_{12} from food sources (common in the elderly, atrophic gastritis, and acid-suppressing medications)
- Malabsorption affecting B_{12} absorption in the terminal ileum (e.g., inflammatory bowel disease), bacterial overgrowth, fish tapeworm, and pancreatic insufficiency

Know that the marrow is disturbed in these nutritional deficiencies, and multiple cell lines can be affected as the deficiencies progress. The megaloblastic RBCs are destroyed in the marrow (termed "intramedullary hemolysis"), and erythropoiesis is ineffective. Surviving RBCs are macrocytic, and neutrophils are hypersegmented (defined as at least 5 lobes in 5% of neutrophils or any neutrophil with 6 lobes). Platelets can be decreased as well.

Think about a megaloblastic process in patients who present with a macrocytic anemia, pancytopenia, and slight indirect hyperbilirubinemia (from the continuous low-level intramedullary hemolysis).

In addition to anemia, deficiencies in B_{12} also produce gastrointestinal effects (smooth sore tongue, diarrhea) and neurological deficits (ranging from paresthesias to frank psychosis). B_{12} deficiency may be present without

Quick Quiz

- Characterize the CBC in patients with α-thal minor.
- What is the characteristic Hgb electrophoresis finding in patients with β-thal minor?
- How many lobes must a neutrophil have to be considered "hypersegmented"?
- Which megaloblastic anemia is associated with neurologic disease?
- What are the MMA and homocysteine levels in B_{12} and folate deficiencies?
- What general lab tests are abnormal in hemolytic states?

anemia but with serious neurologic problems. Know that folate deficiency is not associated with neurologic impairment.

Diagnose B_{12} deficiency at level < 200 pg/mL. If the level is borderline low (200–400 pg/mL), check methylmalonic acid (MMA) and homocysteine (HC). Both are elevated in B_{12} deficiency. Only the HC is elevated in folate deficiency—and the serum folate level is decreased.

Once B_{12} deficiency is diagnosed, the etiology should be pursued. For pernicious anemia (PA), the presence of anti-intrinsic factor (IF) antibodies supports the diagnosis, but sensitivity of the test is only ~ 70%. If you highly suspect pernicious anemia, but IF antibodies are absent, check the serum gastrin and pepsinogen levels. In PA, the serum gastrin is increased, and the pepsinogen I level is decreased. The ratio of pepsinogen I to pepsinogen II is also used, and it is low in PA. The Schilling test, in which the fate of radiolabeled B_{12} ingested by the patient is followed, was previously used to confirm the diagnosis but is rarely used and generally not available anymore.

Treat B_{12} deficiency with daily injections for 1 week, then weekly injections for 1 month, then monthly. Treat folate deficiency with daily oral replacement.

Survival Defects

Overview

Hemolytic anemias can be grouped by the underlying cause of premature RBC destruction.

Intrinsic:

- Molecular defect inside the cell (G6PD deficiency, hemoglobinopathies)
- An abnormality in membrane structure or function (hereditary spherocytosis)

Extrinsic: an environmental factor outside the cell (DIC, autoantibodies, TTP/HUS, HELLP).

Review of Coombs Tests

Direct antiglobulin test (DAT)—antibodies against IgG or C3 are prepared in an animal and then mixed with the patient's blood. A positive test occurs if the patient's RBCs agglutinate—meaning there is IgG (or C3) on the surface of the patient's RBCs.

Indirect antiglobulin test (IAT) is done to see if the patient's serum contains antibodies that would cause agglutination of other RBCs (i.e., with transfusion). The Rh- and ABO-compatible RBCs are mixed with the patient's serum, and again, a positive test occurs if these RBCs agglutinate.

Figure 8-2: Coombs Tests

Additionally, hemolytic anemias can be grouped as intravascular or extravascular. Hemolysis is termed "extravascular" when RBCs are outside the vascular space, trapped in the reticuloendothelial system (mainly the spleen), and engulfed by macrophages. "Intravascular" hemolysis occurs when RBCs are lysed within the lumen of the blood vessels. This can result from non-immunological mechanisms including DIC, TTP/HUS, HELLP, and severe heart valve abnormalities that shear red cells.

Supplemental Lab Tests

Haptoglobin low = hemolysis. In both intravascular and extravascular hemolysis, released hemoglobin is quickly bound to haptoglobin and then engulfed by macrophages. The resultant low level of haptoglobin can be used to diagnose hemolysis—but does not help distinguish the type.

Bilirubin. Heme loses the iron and is converted to bilirubin and cleared in the urine or stool. With excessive hemolysis of either type, more of the bilirubin is unconjugated (indirect).

Urine hemosiderin high = intravascular hemolysis. Iron is more frequently lost in the urine with intravascular hemolysis and can be detected by the urine hemosiderin test.

LDH levels elevated = intra- and extravascular hemolysis.

Coombs test positive = antibody- or complement-mediated hemolysis. The direct antiglobulin test (DAT), or direct Coombs test, can help identify antibody or complement on the red cell surface, which may mediate hemolysis (Figure 8-2).

Intrinsic Survival Defects

G6PD Deficiency

Over 400 variants of the X-linked *G6PD* gene exist—affecting over 200 million people. These result in

variable deficiencies in the reduced state of glutathione—this reduced state being a protective mechanism against oxidative stress. Common oxidative stressors are infections, medications (including dapsone, sulfa drugs, and antimalarials), fava beans, and diabetic ketoacidosis.

Hemolysis in G6PD deficiency can be mild to massive. G6PD levels normally decline over the RBC lifespan, so measured levels of G6PD may be normal during an acute hemolytic episode if young cells enrich the test population; i.e., a false-negative test is possible during acute hemolysis with brisk reticulocytosis. Measure G6PD levels 2–3 months after the hemolytic event to avoid a false-negative result. Other hematologic findings (and buzzwords) include Heinz bodies (chunks of denatured hemoglobin) on special smears and "bite cells" in peripheral blood. Coombs test is negative.

Pyruvate Kinase Deficiency

Although G6PD deficiency is more common than pyruvate kinase deficiency, the latter is more likely to result in a symptomatic hemolytic anemia. Pyruvate kinase deficiency and other enzyme deficiencies within the glycolytic pathway are subject to hemolytic crisis without exposure to oxidative stress. In fact, the mechanism of hemolysis is not clearly understood. The peripheral blood smear does not reveal characteristic RBC abnormalities, as might be seen in other types of hemolysis.

Sickle Cell Syndromes

Sickle cell syndromes result from a mutation in the β-globulin gene ($\beta^{6Glu \rightarrow Val}$), in which valine is substituted in place of glutamine. When both β-globin chains are affected, **sickle cell anemia** (**SCA**) results. The deoxygenated hemoglobin S stiffens and distorts the RBC membrane, gives the characteristic sickle shape, and prevents the cells from passing through small vessels.

Know that parvovirus B19 may cause either a pure red cell aplasia or a worsening of anemia by decreasing erythropoiesis in the face of chronic hemolysis.

Clinical manifestations of SCA are the result of small vessel blockage, downstream tissue infarction, and chronic hemolysis. Recurrent microinfarcts of the kidney lead to isosthenuria (inability to concentrate urine). Recurrent infarcts of the spleen lead to functional asplenia with increased risk of infection from encapsulated organisms, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, and from *Salmonella*. To protect against these organisms, penicillin prophylaxis is used in children until age 5. All patients should be given pneumococcal, meningococcal, *H. influenzae*, hepatitis B, and influenza vaccines. Acute chest syndrome (chest pain and desaturation of oxygen) is thought to represent microinfarctions of the lung. The acute chest syndrome is a hematologic emergency which may require red cell exchange transfusion.

Other sickle cell syndromes can result when only 1 β-globin gene is affected:

- **Sickle cell trait** (HbS/A): Half the hemoglobin in each RBC is HbS and half HbA. Patients are asymptomatic or demonstrate renal papillary necrosis, painless hematuria, and isosthenuria.
- **Hemoglobin SC disease** ($\beta^{6Glu \rightarrow Val}\beta^{6Glu \rightarrow Lys}$): RBCs are rigid—but not sickled—and have a short lifespan. Splenic sequestration is common and can occur both in children and adults (unlike in sickle cell anemia), because the spleen does not always undergo early autoinfarction. Consider sequestration in patients with SC who present with a tender spleen and worsening of anemia. Retinal problems are also common.
- Other hemoglobin disorders may be seen in combination with HbS (double heterozygotes). They include sickle/β-thalassemia and HbS/D. Clinical features are varied.

Diagnose a sickle syndrome with hemoglobin electrophoresis. You can screen prospective parents for the carrier state and provide genetic counseling.

Treatment of SCA is largely supportive, although bone marrow transplantation is being increasingly utilized.

Exchange transfusion is sometimes required for treatment of priapism, cerebral sickling, aplastic crisis, and acute chest syndrome. Occasionally, more conservative therapy with a simple transfusion and/or supportive care treats these presentations. A partial exchange transfusion program is reserved for those with a history of stroke. Folate supplementation is important. Medications such as hydroxyurea are used to increase HbF production, which offers some protection against sickle crisis.

Hereditary Spherocytosis and Elliptocytosis

These are autosomal dominant disorders of the RBC cytoskeleton that result in loss of membrane flexibility and are associated with chronic hemolysis. These disorders are seen in Northern European populations.

Complications of spherocytosis and elliptocytosis may include cholelithiasis, due to bilirubin stones, and splenomegaly. Splenectomy is sometimes required to prolong red cell survival. Think about these disorders in patients who demonstrate evidence of hemolysis and have spherocytes or elliptocytes on their peripheral smear. Coombs test is negative.

The osmotic fragility test may assist in diagnosing hereditary spherocytosis. (The reduced surface:volume ratio makes spherocytes more susceptible to osmotic stress.) The eosin-5-maleimide (EMA) binding test is a newer rapid test that does not require much blood and gives results in 2 hours (great for newborns). Sophisticated molecular membrane studies (usually available at research institutions) can be done to make a definitive diagnosis (e.g., sodium dodecyl sulfate polyacrylamide gel electrophoresis), but it does not change management.

- What cells are seen in the peripheral blood of patients with G6PD deficiency?
- Which virus is implicated in the development of aplastic crisis or worsening of anemia in patients with sickle cell disease?
- What cells are seen on peripheral smear in patients with hereditary spherocytosis?
- What is the clinical presentation of PNH?
- What tests are used to diagnose PNH?
- Which leukemia/lymphoma is associated with autoimmune hemolytic anemia?

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is a rare acquired stem cell disorder resulting from a defective *PIGA* gene. The result is the loss of a membrane-bound protein, which, when present, anchors other proteins to the cell membrane. Some of these anchored proteins serve to protect the cell against complement-mediated lysis. Without the anchor protein, this protection is lost.

Clinical presentation includes a variable degree of intravascular hemolysis, which may lead to chronic hemoglobinuria and iron deficiency. Classic symptoms include episodic abdominal pain and chest pain due to diffuse esophageal spasms that coincide with hemoglobinuria. The other major potential complication is arterial or venous thrombosis (especially of abdominal veins; think about PNH in cases of Budd-Chiari syndrome). Rarely, transformations to aplastic anemia, acute leukemia, and myelofibrosis occur.

Diagnosis is made using specific flow cytometry assays for CD55 (decay accelerating factor) and CD59 (homologous restriction factor)—proteins that are lost from the cell membrane when the anchor protein is absent.

Definitive treatment is allogeneic bone marrow transplant. Otherwise, treat hemolysis with corticosteroids. Use anticoagulants to treat thrombotic events. Eculizumab, an antibody to C5 terminal component, has been shown to decrease hemolysis and the need for transfusion.

Extrinsic Survival Defects

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) is regularly caused by IgG or IgM antibodies. Antibodies that react with RBC membrane proteins are often IgG. These antibodies induce hemolysis either by stimulating macrophages and other cells in the spleen and reticuloendothelial system to gradually snip portions of membrane away (causing spherocytes) or by causing complement-mediated destruction.

IgG antibodies react best at body temperature (so-called "warm antibodies"). They may be idiopathic or secondary to neoplasm or connective tissue disease. In autoimmune hemolytic anemia, the direct Coombs (direct antiglobulin) test, which detects antibodies on the RBC surface, is positive using antibodies to IgG. Treat with corticosteroids. Splenectomy is reserved for refractory cases. The anti-CD20 monoclonal antibody rituximab is sometimes also used in difficult-to-treat patients.

IgM antibodies often bind to polysaccharides or complement. These antibodies react better at room temperature (so-called "cold antibodies"). IgM antibodies are not detected on the RBC surface by direct Coombs testing. Instead, the complement components whose binding they induce are detected with a positive direct result using antibodies to C3 (indicates ability to fix complement), not IgG (because the hemolysis is caused by antibodies to IgM). RBC clumping is often seen on the peripheral smear.

These IgM autoantibodies may be secondary to:

- neoplasm (especially CLL and lymphoma),
- infection (especially *Mycoplasma pneumoniae* and infectious mononucleosis), or
- SLE.

Treatment is best accomplished by maintaining a warm environment and identifying and treating the underlying cause. Steroids are ineffective.

Drug-Associated Hemolysis

Many drugs may cause hemolysis. Penicillin bound to red cells may elicit an antibody response that can cause hemolysis. Quinine, methyldopa, and certain cephalosporin antibiotics are also known culprits. The pattern of abnormal Coombs testing varies with the type of drug.

Sequestration

This type of anemia occurs with overactive, often enlarged spleens in a variety of disorders, especially portal hypertension where red cells, white cells, and platelets may be sequestered. In early childhood with HbS/C and HbS/β-thalassemia (before splenic infarction and fibrosis are seen), splenic sequestration may occur.

Blood Loss

Anemia from blood loss is often obvious from injuries or GU and GI tract loss, but may be less obvious in intrapulmonary, retroperitoneal, and rectus abdominis sites. And remember again, any Fe deficiency anemia is considered to be due to blood loss until proven otherwise.

Liver Disease

Anemia is common in liver disease, depending on the cause:

- Cirrhosis causes spur cell anemia (Image 8-13 on page 8-5), due to abnormal cholesterol production. Red cells change shape and are hemolyzed.
- Portal hypertension causes splenic sequestration and cytopenias.
- Alcohol abuse is associated with nutritional (megaloblastic) anemias, especially folate.
- EtOH also directly inhibits erythropoietin production and erythropoiesis.
- Viral hepatitis can cause anemia through direct inhibition of the marrow and via autoimmune hemolysis.
- GI blood loss is common, especially if the patient has esophageal varices.

Chronic Kidney Disease

Anemia in CKD is discussed extensively in Nephrology, Book 2.

Cancer Patients

Cancer patients may have coexisting causes of anemia. Consider these possibilities:

- Bone marrow infiltration by cancer cells
- Chemotherapy-induced anemia
- Infection causing bone marrow suppression
- Medications including antibiotics/antivirals
- Autoimmune hemolytic anemia (e.g., lymphoproliferative disorders such as CLL)
- Sequestration
- Anemia of chronic disease (anemia of inflammation)
- Blood loss from bleeding tumors
- Fe deficiency (especially in GI cancers)
- Malnutrition

Treatment is often supportive, with transfusions provided as needed. Erythropoietin-stimulating agents are almost never indicated except in very specific scenarios, including some cases of myelodysplastic syndrome. These agents can be considered when chemotherapy for non-curative intent causes symptomatic anemia—but even in this context, they are still controversial.

MISCELLANEOUS DISORDERS THAT AFFECT RBCs

METHEMOGLOBINEMIA

Oxidation of heme iron from the ferrous Fe^{2+} to the ferric Fe^{3+} state forms altered hemoglobin (methemoglobin), which has an impaired ability to bind oxygen. Methemoglobin gives the blood a dark color, so patients appear cyanotic despite a normal P_aO_2 on arterial blood gas. Pulse oximetry is not reliable, but co-oximetry reveals low oxygen saturation. Symptoms include headache, dizziness, dyspnea, tachypnea, tachycardia, and obtundation. Severe tissue hypoxia and death can result as levels rise. Causes are hereditary and/or acquired and may include industrial chemicals and drugs: nitrates/nitrites (nitroglycerin, amyl nitrate ["poppers"], nitroprusside—but not nitrous oxide), phenazopyridine (OTC bladder analgesic), dapsone, sulfonamides, and anesthetics (oral benzocaine, lidocaine). Treat severe cases with methylene blue.

PORPHYRIAS

The porphyrias are inherited (most) or acquired metabolic disorders in which heme biosynthetic pathway enzymes are deficient, resulting in excess accumulation and excretion of porphyrins and their precursors. Porphyria cutanea tarda (PCT), the most common of the porphyrias, is an acquired mutation.

The porphyrias are classified as either acute or cutaneous. **Acute porphyrias** affect the neurologic system causing neurovisceral abdominal pain (most common), psychiatric disorders, and other neurologic manifestations (neuropathic pain, encephalopathy). **Cutaneous porphyrias** cause either acute nonblistering or chronic blistering reactions (PCT) in sun-exposed areas.

Clinical manifestations can be extremely subtle and can mimic many other disorders.

Initial treatment in the absence of neurologic symptoms or organ failure is the administration of dextrose via intravenous infusion. Severe cases are treated with intravenous hematin. Both of these treatments decrease heme synthesis and slow the buildup of the toxic precursors.

HEREDITARY HEMOCHROMATOSIS

Hereditary hemochromatosis (HH) is an iron-overload disorder due to 1 or more mutations, with the *HFE* gene mutations being most common. These mutations cause the body's appetite for iron to be insensitive to the presence of adequate iron stores. The 2 most common *HFE* mutations are *C282Y* and *H63D*. Caucasians have the highest incidence of *C282Y* homozygosity, followed by Native Americans. Compound heterozygosity (*C282Y* with *H63D*) and heterozygosity for either *C282Y* or *H63D* are the next most common genotypes.

Other genotypic variations include mutations in genes that code for the transferrin receptor, ferroportin, and hepcidin, a peptide that plays a central role in human iron metabolism. HH is ordinarily inherited in an autosomal recessive fashion.

Clinical disease does not develop in all patients who inherit the mutations, even with *C282Y* homozygosity. The phenotype of skin pigmentation, arthropathy, cirrhosis, cardiomyopathy, and endocrinopathies that characterize fully penetrant HH may require 1 or more mutations in the *HFE* gene plus inheritance of 1 or more

QuickQuiz

- What is the most common neurologic manifestation of porphyria?
- What is the typical presentation of hereditary hemochromatosis?
- Which test is used to diagnose hereditary hemochromatosis?

of the other genetic variations and/or exposure to environmental risk factors; e.g., excessive alcohol use.

The HFE protein is expressed in the deep crypt cells of the duodenum and normally acts as a sensor of the body's iron stores, modulating the uptake of transferrin-bound iron into these cells. *HFE* mutations decrease this transferrin receptor-mediated uptake of iron into crypt cells, sending a false signal of low iron stores to the intestinal cells, causing an up-regulation of the intestinal iron transporter, DVMT, in the lumen. This unchecked absorption of intestinal iron leads to elevated levels of serum ferritin, with concomitant iron deposition into multiple organ systems, including the liver, heart, skin, gonads, joints, and pancreas.

Although classically described as a triad of cirrhosis, bronzed skin pigmentation, and diabetes mellitus, HH is now more commonly diagnosed at an earlier stage in the disease. Patients most often present in middle age with early signs and symptoms of iron overload, including (from most to least common):

- Fatigue and weakness
- Abnormal liver transaminases
- Bronzing of the skin
- Diabetes mellitus
- Joint pain +/– crystalline arthropathy (CPPD)
- Erectile dysfunction

Women may present with symptoms in their mid-to-late 50s, after menopause, because the monthly menses served as adequate phlebotomy during their younger years. All patients are at increased risk for infection with *Listeria* (because the excess iron impairs macrophage function) and with bacteria that utilize iron as a substrate (e.g., *Vibrio* and *Yersinia* species).

The most sensitive test to diagnose HH is transferrin saturation (serum Fe/TIBC x 100%). Once HH is suspected based on a transferrin saturation of > 45%, the diagnostic workup should include iron studies to further quantify iron overload. A ferritin level > 1,000 ng/mL indicates iron overload. Genetic testing can be done for the most common underlying genetic mutations. Liver biopsy, the diagnostic gold standard, now is largely used as a prognostic indicator or in cases in which laboratory and genetic testing is equivocal. MRI can detect iron in the liver, heart, joints, and pituitary (experienced facility only).

First-degree family members should also be tested for the disease, but the role for population screening for HH remains uncertain. Early diagnosis of HH is extremely important, however, because devastating consequences of the disease are easily preventable with timely treatment.

Phlebotomy remains the foundation of management of iron overload. Since it is not known who will develop cirrhosis and hepatocellular carcinoma, treatment is recommended for those with elevated liver iron content. Initially, one to two 500 mL units of blood (each containing about 250 mg of iron) should be removed weekly until the serum ferritin is 20–50 ng/mL, and the transferrin saturation is less than 30%. The typical patient requires removal of 20–25 units of blood to complete this 1st stage.

Lifelong maintenance phlebotomy, usually 2–4 times per year, is then needed to keep serum ferritin levels below 50–100 ng/mL and transferrin saturations below 50%, with regular monitoring of serum hemoglobin. Although this regimen does not reverse previously established cirrhosis or other sequelae of iron deposition, progression can be slowed, and new disease development can be prevented.

Patients should avoid uncooked seafood because of the risk of disseminated *Vibrio vulnificus*.

HEMOSTASIS

OVERVIEW

Coagulation after a vascular injury consists of 2 stages: primary hemostasis and secondary hemostasis. Primary hemostasis is the function of the platelets, whereas secondary hemostasis is dependent upon the coagulation factors.

PRIMARY HEMOSTASIS

Primary hemostasis consists of platelet plug formation, vascular spasm, and capillary endothelial adhesion, with capillaries collapsing and sticking closed when empty. This fix is temporary and lasts for only 12–24 hours. (This is why hemophiliacs often do not have a deep bleed until 12–24 hours after trauma.)

Platelet plug formation = platelet attachment → platelet activation → platelet aggregation.

After endothelial injury, platelets rapidly attach to the newly exposed subendothelial collagen. The von Willebrand factor, released from the endothelium, reacts with the platelet surface glycoprotein Ib/IX to increase "stickiness" of platelets to each other and to exposed collagen. Platelets are then activated, releasing cytokines, including ADP and arachidonic acid, which further stimulate platelet release and aggregation. Arachidonic acid is converted by cyclooxygenase into precursors of thromboxane A_2. Thromboxane A_2 recruits more platelets and exposes platelet surface glycoprotein IIb/IIIa. Thromboxane A_2 is also a potent vasoconstrictor. Fibrinogen then cross-connects the IIb/IIIa protein on platelets to form platelet plugs.

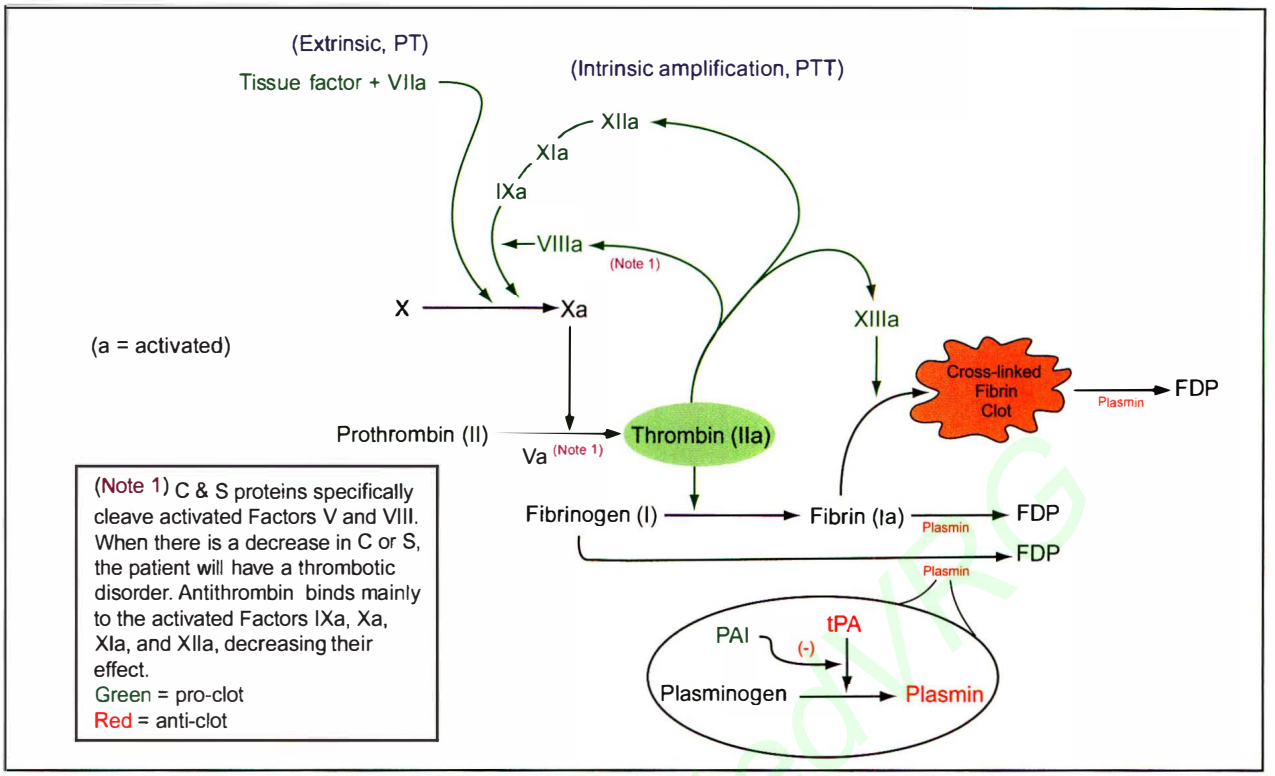

Figure 8-3: Clotting Cascade

There are several FDA-approved IIb/IIIa receptor inhibitors available. Approved indications include unstable angina and adjunctive therapy during coronary angioplasty. Aspirin irreversibly acetylates cyclooxygenase and thus decreases platelet function. Chronic ASA use of as little as 40 mg/day causes suppression of 95% of the thromboxane A_2. NSAIDs bind reversibly with cyclooxygenase; they may block the desired effect of ASA if they are administered at the same time. Clopidogrel irreversibly inhibits ADP binding to the platelet receptor, resulting in decreased platelet aggregation.

SECONDARY HEMOSTASIS

The Coagulation Cascade

All coagulation is initiated by tissue factor (released at the site of injury) interacting with Factor VII. The intrinsic pathway factors (VIII, IX, and XI) serve solely to amplify this formation of thrombin—and can do so only after a small amount of thrombin is formed by the extrinsic pathway. Tissue factor is in short supply and short-lived—so the extrinsic pathway can produce only a small amount of thrombin.

Thrombin is the key. As you can see in Figure 8-3, this little bit of thrombin immediately starts building more thrombin while it builds the thrombus.

Thrombin does the following:

- Converts fibrinogen to fibrin
- Activates Factor XIII, which causes this fibrin to cross-link and form the thrombus
- Activates Factor XII, which, in turn, activates Factor XI, which, in turn, activates Factor IX
- Activates VIII; Factors VIIIa and IXa together activate X again

So, the first 2 processes help make the thrombus while the second 2 are part of a powerful "intrinsic" amplification system that makes more thrombin.

Okay, so how does the body stop this process? Thrombus dissolution, or fibrinolysis, is initiated by tissue plasminogen activator (tPA) and released from the endothelial cells. tPA converts plasminogen to plasmin, which then breaks down fibrin and fibrinogen and limits the size of the thrombus. Proteins C and S are natural anticoagulants; they inactivate Factors Va and VIIIa. Protein C also blocks the inhibitor of tPA (plasminogen activator inhibitor-I). In healthy people, this results in fibrinolysis. In the absence of proteins C and S, thrombosis goes unchecked.

AN APPROACH TO THE PATIENT

It is often possible to differentiate between a primary and a secondary hemostatic problem at the bedside:

- **Primary hemostatic problems** (90% involve either platelet dysfunction or low platelets) result in multiple, tiny, superficial hemorrhages, causing petechiae, purpura (large petechiae), ecchymoses, and mucocutaneous bleeding.
- **Secondary hemostatic disorders**, on the other hand, such as hemophilia, develop deep tissue bleeding, including hematomas or hemarthroses.

QuickQuiz

- Explain how aspirin and NSAIDs work to decrease platelet function.
- At the bedside, how can you tell whether a hemostatic problem is primary or secondary?
- What are the 4 tests initially used to evaluate a bleeding disorder? How are they used?

Typically, 4 tests can quickly assess coagulation and platelet status:

1) Prothrombin time (PT) measures the function of extrinsic and common pathways.
2) Activated partial thromboplastin time (PTT or aPTT) measures the function of the intrinsic amplification.
3) Platelet count.
4) Platelet function tests evaluate platelet aggregation when stimulated by epinephrine, ADP, and collagen.

DISORDERS OF PRIMARY HEMOSTASIS

Overview

Disorders of primary hemostasis involve the skin and vascular endothelium as well as platelets. This review focuses on the latter, which includes both quantitative and qualitative defects.

Thrombocytopenia has multiple etiologies, which can be categorized into defects of production, sequestration, and destruction.

Pseudothrombocytopenia (i.e., artifact) occurs fairly often—so the 1st test to do after observing a low platelet count result is a repeat platelet count. A peripheral blood smear to look for platelet clumping, which is perceived by automated counters as a low platelet count, is also helpful.

You can see abnormal platelet function after aspirin ingestion and in von Willebrand disease, Bernard-Soulier (giant platelet) syndrome, Glanzmann thrombasthenia, paraproteinemia (multiple myeloma), chronic kidney disease, and connective tissue disease.

Primary Hemostasis Disorders: Thrombocytopenias

Overview

Thrombocytopenia has 3 causes: impaired bone marrow production, splenic sequestration, or decreased platelet survival (destruction).

1) Impaired production: due to bone marrow failure from toxins (including alcohol), infiltration, aplasia, sepsis, and HIV infection. Often there is concomitant anemia and/or leukopenia.
2) Hypersplenism: Thrombocytopenia is usually modest and accompanied by a reduction in the other cell lines (leukopenia and anemia).
3) Survival defects:
   - Consumptive process such as DIC, HIT (heparin-induced thrombocytopenia), TTP/HUS, and HELLP.
   - Immune thrombocytopenia (ITP; see next), either idiopathic or drug-induced. Common drug offenders include quinidine, rifampin, sulfonamide combinations, and digoxin. If the platelet count is $> 20 \times 10^9$/L, there is usually no serious spontaneous bleeding. When the count is < 10,000, the risk of serious bleeding increases and platelet transfusions are often considered. Do not transfuse platelets if you suspect HIT or TTP unless the patient has active life-threatening bleeding.

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is an autoimmune syndrome that occurs in children and adults. In children, it often has an acute presentation, occurs after a viral illness, and is commonly self-limited with a good prognosis. Chronic ITP generally occurs in adults and has a relapsing course. Both acute and chronic ITP are associated with IgG antibodies directed against the GPIIb/GPIIIa glycoproteins on platelets. When associated with an underlying disease in which antiplatelet antibodies are formed, patients are said to have "secondary ITP."

Underlying diseases that may be associated with secondary ITP include: viruses (e.g., HIV, hepatitis C), SLE, antiphospholipid syndrome, and CLL. Recall that many of these same diseases also are associated with autoimmune hemolytic anemias.

The adult patient with ITP usually presents with easy bruising, petechiae, and nonpalpable purpura—which differentiates this from Henoch-Schönlein purpura (HSP) in which the purpura is palpable. Patients with ITP have mucosal bleeding (gingival, menorrhagia, epistaxis). When ITP occurs in an elderly patient, the patient may present with a GI or nervous system bleed.

Platelets in patients with ITP are often hyperfunctional, and, even with severe thrombocytopenia, significant spontaneous bleeding is rare.

Primary ITP is a diagnosis of exclusion, so rule out other causes. Do not order an antiplatelet antibody test. The result is too nonspecific to be helpful!

Do the following:

- As with all cases of thrombocytopenia, repeat the platelet count.
- Examine the peripheral smear to make sure platelets aren't clumping, and that schistocytes are absent (if present, suggests TTP is underlying diagnosis, not ITP). Around 1/1,000 automated platelet counts are falsely low. Clumping is caused by platelet activation by EDTA. Collecting the sample in a citrate tube corrects this problem.

- The peripheral smear in ITP typically reveals few (but giant) platelets, and normal RBCs and WBCs.
- Patients > 60 years of age may need a bone marrow biopsy to exclude myelodysplasia before diagnosing them with ITP. In ITP, marrow cellularity is normal with evidence of megakaryocyte hyperplasia.

Treat chronic ITP only if symptomatic or if the platelet count is very low:

- Corticosteroids (prednisone 1mg/kg or equivalent daily) are 1st line treatment.
- Give IV immunoglobulin (IVIG) as a 2nd line treatment to satiate voracious macrophages, which then become less hungry for antibody-coated platelets, leading to an increase in platelet count. IVIG is useful if a rapid improvement in platelet count is desired, as in a pre-op or bleeding patient. Response, however, is regularly transient—lasting only several weeks.
- Before sending a patient for surgery, many hematologists try anti-D immunoglobulin if patients are Rh-positive and have a functional spleen. This induces a mild hemolytic state, with resultant RBC stromal release and uptake by reticuloendothelial cells. The uptake of RBC stroma (as with IVIG) interferes with the ingestion of antibody-coated platelets and results in the elevation of platelet counts. Response to IVIG predicts a good response to splenectomy.
- Splenectomy induces a complete response in 2/3 of patients, but there may be relapses.

Splenectomy is indicated in any 1 of the following:

- No response to steroids
- Frequent relapses
- Unable to taper off steroids within 3–6 months

Remember: All patients should receive vaccinations for pneumococcus, *H. influenzae*, and *Neisseria meningitidis* at least 2 weeks prior to elective splenectomy because splenectomized patients are at an increased risk of infections from these organisms.

A few drugs are available for ITP refractory to steroids, IVIG, and splenectomy:

- Rituximab is an alternative to splenectomy, particularly if there is no response to IVIG. Rituximab is a monoclonal antibody directed against CD20 present on B lymphocytes.
- Romiplostim and eltrombopag are new thrombopoietin receptor agonists now FDA-approved for refractory ITP.

Give platelet transfusions if there are signs of severe bleeding and prior to invasive procedures. While platelet counts may not rise, transfusions may be hemostatically effective. Even so, they are not effective for long-term management.

Thrombotic Thrombocytopenic Purpura

Acquired thrombotic thrombocytopenic purpura (**TTP**) and the atypical hemolytic uremic syndrome (**aHUS**) in adults were once considered variants on a spectrum of disease, although it is now understood they have different pathophysiology. In general, there are 2 types of TTP (inherited and acquired) and 2 types of HUS (atypical HUS and typical/childhood/diarrhea-associated HUS).

Inherited TTP is a defect in the *ADAMTS* gene causing a deficiency in the ADAMTS13 enzyme; it affects only newborns and children. Acquired TTP affects adults and is due to an inhibitor causing decreased activity of ADAMTS13 enzyme. This enzyme is responsible for cleaving ultra-large multimers of von Willebrand factor.

TTP is a fulminant disorder of increased platelet consumption, with high mortality, that is marked by thrombocytopenia and microangiopathic hemolytic anemia.

TTP generally affects younger adults, with a peak in the 3rd decade of life. Most commonly, TTP is idiopathic, but also is associated with:

- drug exposures (quinine, cancer chemotherapy, clopidogrel, ticlopidine),
- post-hematopoietic stem cell transplant,
- pregnancy,
- oral contraceptives,
- disseminated occult mucin-producing adenocarcinomas,
- HIV infection,
- SLE, and
- antiphospholipid syndrome (APS).

Clinical manifestations of TTP:

1) Anemia (microangiopathic hemolytic anemia with schistocytes on peripheral blood smear)
2) Thrombocytopenia
3) Neurological changes (e.g., confusion, severe headache, seizure)
4) Fever
5) Renal failure (unusual in TTP)

The dyad of thrombocytopenia and microangiopathic hemolytic anemia is sufficient to narrow the differential to TTP vs. aHUS (vs. HELLP if pregnant). TTP typically presents with neurologic involvement and minimal or no renal dysfunction. Patients infrequently present with all 5 findings.

Peripheral blood smear shows thrombocytopenia and anemia with schistocytes. Labs commonly indicate a Coombs-negative hemolysis with an elevated LDH and indirect bilirubin, +/– increased creatinine. Unlike in DIC, the PT, PTT, fibrinogen, Factor V, and Factor VIII usually are normal because the coagulation cascade is not activated in TTP.

Quick Quiz

- What are the 1st and 2nd line treatments for ITP?
- Problems with which enzyme is the cause of TTP?
- What 5 clinical manifestations occur with TTP? With aHUS?
- What is the treatment of choice for TTP? For aHUS?
- What bacterial infection is associated with diarrhea-associated HUS?
- What do the letters in HELLP syndrome stand for? In which patients does it occur?
- Does HIT Type II cause bleeding or thrombosis?

Low functional ADAMTS13 enzyme levels can be used to support a TTP diagnosis, but results are generally not available in a timely manner.

Treat TTP with plasma exchange using fresh frozen plasma or cryosupernatant (plasma from which cryoprecipitate has been removed—because the cryoprecipitate contains vWF multimers that might contribute to increased clotting). Know that there are 2 situations where plasmapheresis has not been shown to have any effect:

1) Cancer chemotherapy drugs
2) Post-hematopoietic stem cell transplant

LDH levels serve as a marker of hemolysis and platelet destruction and should be followed to gauge the effect of therapy.

Unless life-threatening bleeding is present, do not give platelet transfusions, because extra platelets will simply be consumed and cause more thrombosis. If the patient does not respond to plasmapheresis, corticosteroids and/or rituximab are additional options.

Atypical Hemolytic Uremic Syndrome

Atypical HUS (**aHUS**) is confused with TTP because aHUS has the same 5 manifestations and same labs as TTP except that renal involvement occurs and neurologic involvement either does not occur or is minimal.

There are many causes of aHUS—all related to disorders in complement regulation. ADAMTS13 enzyme levels are > 10% and generally stay within normal reference intervals.

Treatment is eculizumab, a monoclonal antibody that selectively inhibits the terminal complement cascade. Note that eculizumab predisposes the patient to fulminant meningococcal infections. For some types of aHUS, eculizumab is not effective and plasma exchange transfusion is done.

Diarrhea-Associated HUS

A childhood form of HUS exists that is often precipitated by infection with enterohemorrhagic *E. coli* (O157:H7) and is associated with a prodrome of bloody diarrhea. This presentation has been termed "diarrhea-associated HUS" or "childhood HUS" to differentiate the disease from aHUS. Treatment is supportive. Cases typically self-resolve.

HELLP Syndrome

The **HELLP** syndrome (**h**emolysis, **e**levated **l**iver enzymes, and **l**ow **p**latelets) occurs in 20% of patients with preeclampsia and in 10% of patients with eclampsia. The anemia is microangiopathic, with schistocytes on the peripheral blood smear (as with TTP and aHUS). Hepatic rupture is an uncommon, but potentially devastating, complication. Treatment is delivery of the fetus, with no role for plasma exchange. Both HELLP syndrome and TTP/HUS can occur in the peripartum period, so it is important to consider each in the evaluation. TTP/HUS additionally has fever, renal involvement, and/or neurologic symptoms.

Heparin-Induced Thrombocytopenia (HIT)

Overview

HIT Type I is a clinically insignificant, nonimmune drop in platelets after starting heparin; platelets return to normal within 2 days.

HIT Type II occurs when an antibody is formed that recognizes heparin/platelet factor 4 (heparin-PF4) complexes. The antibody activates platelets, causing clumping and thrombocytopenia within 5–10 days of heparin initiation. Previous exposure to heparin and an anamnestic response may shorten the onset to < 12 hours. Venous and/or arterial thrombosis, not bleeding, is the major complication of HIT-II. Always suspect HIT-II in a patient presenting with clot 1–2 weeks after a hospitalization, even if the platelet count is normal. (The highest risk of thrombosis occurs when platelet count has returned to normal.)

Two different clinical scoring systems, the 4 Ts and HIT Expert Probability (HEP) Score, are available to assess the clinical likelihood of HIT-II (see below).

Immunoassays that detect antibodies against platelet factor 4 complexes are of limited value; they are sensitive, but not specific. Serotonin release assay is specific and sensitive but has a long turnaround time.

The 4 Ts

This clinical scoring system includes an evaluation of 4 "Ts."

Thrombocytopenia—is it present?

- 2 points: > 50% fall but remains > 20,000
- 1 point: 30–50% fall or nadir 10,000–19,000
- 0 points: < 30% fall or falls below 10,000

Timing of the thrombocytopenia:

- 2 points: between days 5–10 of heparin exposure
- 2 points: ≤ 1 day, if anamnestic response and heparin exposure within past 30 days
- 1 point: unclear but probably between days 5–10 of heparin exposure
- 1 point: after day 10 of heparin exposure
- 1 point: ≤ 1 day, if anamnestic response and heparin exposure within past 30–100 days
- 0 points: ≤ 4 days without previous HIT-II

Thrombosis (or other sequelae):

- 2 points: new clot, necrotic skin lesion, or systemic reaction after heparin bolus
- 1 point: recurrent clot or worsening of clot, skin lesion (non-necrotic), possible clot

Thrombocytopenia---other causes?

- 2 points: no obvious other causes
- 1 point: possible other causes
- 0 points: definite other cause

Probability of HIT-II:

- High probability: 6–8 points
- Intermediate probability: 4–5 points
- Low probability: 0–3 points

HIT Expert Probability (HEP) Score

A newer scoring system based on the opinion of 26 HIT experts has, in initial tests, performed better than the above 4 Ts. HEP performed better for improved interobserver agreement and correlation with lab testing. Even non-experts used the scoring system and ended up with results consistent with expert opinion.

The HEP Score is generated from the percentage of decrease in platelets, timing, nadir, thrombosis, skin necrosis, acute systemic reaction to heparin, bleeding, and other causes. Multicenter validation is still needed.

Treatment of HIT-II

Stop all heparin exposure (including low-molecular-weight heparin [LMWH]), even though this does not fully resolve the problem. This is because once the antibodies to heparin-PF4 complex are formed, the antibodies continue to bind to PF4 alone and, thus, continue to activate platelets, causing clots. LMWH should not be substituted because of antibody cross-reactivity.

Treat this hypercoagulable state with direct thrombin inhibitors (lepirudin or argatroban) at the time of diagnosis, even in the face of thrombocytopenia, whether or not a clot is present. Continue to administer the anticoagulant until the platelet count recovers. Remember that argatroban artificially elevates the INR; goal INR during argatroban/warfarin overlap is > 4. Use lepirudin with caution in patients with renal insufficiency (requires dose reduction).

Warfarin should not be started until the platelet count returns to normal. Do not start warfarin alone, since it transiently lowers levels of proteins C and S and can contribute to clot formation. Warfarin should be continued for at least 3 months. There is no role for platelet transfusions.

Once again: Remember that TTP and HIT are thrombotic thrombocytopenic disorders. So you never give these patients platelet transfusions for the thrombocytopenia unless there is life-threatening bleeding present.

Dilutional Thrombocytopenia

Dilutional thrombocytopenia occurs when massive transfusions of platelet-poor blood products are given, typically after major trauma. Treat with platelets.

Post-Transfusion Purpura

Post-transfusion purpura is rare, occurring primarily in women sensitized by pregnancy. It occurs ~ 1 week after transfusion and can last days to weeks. The platelet count is extremely low, and the patient may present with petechiae or purpura. An anti-HPA-1a antibody (human platelet antigen-1a) is formed by alloimmunization from previous blood transfusions or pregnancies, and, inexplicably, it reacts against the patient's HPA-1a negative platelets and causes thrombocytopenia.

Unlike patients with TTP, patients with post-transfusion purpura do not have evidence of microangiopathic hemolytic anemia on the peripheral smear (no schistocytes) and no CNS or renal failure.

Treat with IVIG. Steroids and plasma exchange have also been used, but the responses are slower than with IVIG. Platelet transfusions are not very effective because the transfused platelets also are destroyed by the underlying process.

Thrombocytopenia: Quinine and Other Medications

Quinine is an important cause of thrombocytopenia. It is available over the counter and used for nocturnal leg cramps. It also was once the "tonic" in gin and tonic and, in the 1970s, this side effect was described as "cocktail purpura." Now, however, tonic water contains only a medically insignificant amount of quinine. Other drugs that may cause thrombocytopenia include sulfa combinations, rifampin, digoxin, and vancomycin.

Other Causes of Thrombocytopenia

If there is a dramatic drop in platelets from one day to the next (e.g., 300K to 5K), suspect artifact. The EDTA anticoagulant in blood collection tubes may cause platelet clumping in some patients, resulting in a reading of low platelets and "giant platelets" by an automated counter.

Clinical question: When a previously healthy patient presents with petechiae, ecchymosis, normal mental status, thrombocytopenia, and anemia, what further evaluation is required?

Quick Quiz

- What is the treatment for HIT?
- When does post-transfusion purpura occur?
- What are the 2 most common types of vWD?
- What are Factor VIII activity levels in patients with vWD?
- What are the differences between Bernard-Soulier syndrome and Glanzmann thrombasthenia?

Answer: Do a peripheral blood smear, PT, and LDH. If there are schistocytes, a normal PT, and the LDH is elevated, the patient likely has TTP. If there are no schistocytes, a normal PT, and the LDH is normal, the patient likely has ITP. This is a very important distinction because TTP is a medical emergency even if the patient is feeling fine. The patient can have a precipitous stroke or deterioration in cognition or renal function. Check renal chemistries (BUN, creatinine) to evaluate for renal dysfunction, which is seen in TTP.

Platelet Function Disorders

von Willebrand Disease

von Willebrand disease (vWD) is the most common inherited bleeding disorder. Patients typically have mucocutaneous bleeding, including epistaxis, menorrhagia, postpartum and surgical bleeding, bleeding after dental extractions, and excessive bruising.

The von Willebrand factor (vWF) binds platelets to exposed subendothelial collagen and to other platelets with the platelet receptors Ib/IX and IIb/IIIa, respectively.

vWF is also the carrier protein for Factor VIII, which is degraded in its absence.

Inheritance pattern of von Willebrand disease is usually autosomal dominant. Penetrance is variable, with some patients experiencing bleeding only after surgery or major trauma and others suffering from frequent spontaneous bleeds of the mucosal surfaces of the gastrointestinal and genitourinary tracts.

Individuals with type O blood have lower baseline levels of vWF. Levels of vWF increase during pregnancy and with estrogen use.

The PTT is often increased because of decreased levels of Factor VIII. The bleeding time is prolonged.

Classification of vWD:

1) **Type 1**: a quantitative defect and the most common type (~ 75%).
2) **Type 2**: 4 subtypes (A, B, M, N)—all qualitative defects.
   - Type **2A**: the 2nd most common type of vWD (10–15%) and the result of too little of the large vWF multimer (the same one that causes TTP).
   - Type **2B**: Mutant vWF has increased affinity for platelets, causing spontaneous binding of large vWF multimers to platelets and subsequent clearing of the complex. Causes mild thrombocytopenia. Do not use desmopressin (DDAVP®) to treat because it causes increased release of mutant vWF and increased clearance of platelet-vWF complex, exacerbating thrombocytopenia.
   - Type **2M**: decreased affinity for platelets.
   - Type **2N**: an abnormal vWF protein with impaired ability to bind Factor VIII. This leads to loss of protection for Factor VIII while in circulation and therefore increased Factor VIII clearance and decreased Factor VIII levels. Presentation is similar to classic hemophilia.
3) **Type 3**: rare and severe. Autosomal recessive. Minimal-to-undetectable levels of vWF lead to spontaneous bleeding. The presentation also resembles that of classic hemophilia.

Diagnosis of Type I is confirmed with the combination of the following:

- Abnormal platelet function tests
- Decreased vWF antigen
- Proportional decrease in Factor VIII activity
- Proportional decrease in biologic activity as measured by the ristocetin cofactor assay (rCoF)

Note that the proportional decrease in vWF antigen and Factor VIII activity indicates that the decreased activity is due to a decrease in the concentration of vWF—not dysfunctional vWF.

Patients with mild defects may have varying laboratory test results over time, often requiring repeated testing to confirm the diagnosis.

Treat mild-to-moderate cases of vWD with desmopressin (except Type 2B), which causes a release of vWF and Factor VIII from endothelial cells. For active bleeding, use Factor VIII concentrates, which typically have some vWF as well. Cryoprecipitate is almost never required.

Note: Desmopressin (DDAVP®) is a synthetic analog of antidiuretic hormone (ADH, vasopressin), which boosts plasma levels of Factor VIII and vWF. It does not have vasopressor activity and it is not effective in severe vWD or severe Factor VIII deficiency.

Desmopressin can worsen Type 2B vWD. Watch for hyponatremia when treating with desmopressin.

Other Platelet Function Disorders

In **Bernard-Soulier** syndrome, patients have severely decreased platelet adhesion because they have no glycoprotein Ib (platelets cannot bind vWF). The peripheral smear demonstrates giant platelets. These patients also have a modestly low platelet count, due to

Table 8-4: Bleeding Disorder Evaluation: PT, PTT, Bleeding Time, and Platelet Aggregation

Lab Results	Etiology
1) Elevated PT and PTT	1) Factor deficiency from common pathway 2) Multiple factor deficiency 3) Warfarin affects II, VII, IX, and X, so it can affect both PT and PTT, but PT is more sensitive to warfarin
2) Elevated PT, nl PTT	Factor VII deficiency
3) Elevated PTT, nl PT: Immediate and sustained (2 hr) correction of PTT by addition of normal plasma	Factor VIII, IX, XI, or XII deficiency
4) Elevated PTT, nl PT: PTT not corrected (or no sustained correction at 2 hr) by addition of normal plasma	Inhibitor syndrome (circulating anticoagulant): If clotting: antiphospholipid synd (esp. lupus anticoagulant) – PTT not normalized immediately If bleeding: Factor VIII inhibitor – PTT initially normalized but not normalized at 2 hrs
5) Elevated PTT, nl PT—but no clinical bleeding disorder	Factor XII deficiency
6) Normal, except elevated bleeding time: a) Elevated bleeding time with nl plt aggregation b) Elevated bleeding time with nl plt aggregation and decreased plt count c) Elevated bleeding time with abn plt aggregation	Platelet problem von Willebrand disease (has decreased plt adhesion but normal aggregation) Bernard-Soulier (giant plt) synd (absent gplb) has similar presentation as vWD except lab also shows decreased plt count Glanzmann thrombasthenia (absent gpIIb-IIIa)

accelerated platelet clearance. The inheritance pattern is autosomal recessive.

Glanzmann thrombasthenia results from deficient glycoprotein IIb/IIIa complex (so fibrinogen does not cross-connect). Platelet count is normal. The inheritance pattern is autosomal recessive.

ASA/NSAIDs: Platelet-release defects are often caused by NSAIDs and ASA, which block the synthesis of thromboxane A_2 by binding to cyclooxygenase. The effects of ASA and clopidogrel last for the lifetime of the platelets, and those of non-ASA NSAIDs are transient.

Paraproteinemia, as in MM or connective tissue disease, can cause platelet dysfunction. In these disorders, the paraprotein coats the platelets, inhibiting their function and interfering with fibrin formation.

Uremia causes platelet dysfunction. Treat with platelet transfusions (for active bleeding), conjugated estrogens, or desmopressin (pre-surgery). Conjugated estrogens have a longer effect than desmopressin in uremia.

DISORDERS OF SECONDARY HEMOSTASIS

Review the following 3 variations of the PT and PTT:

1) PT high but the PTT is normal: There is a problem with the vitamin K–dependent Factors II, V, VII, X, or with fibrinogen. (See Figure 8-3.)The most common cause is the use of warfarin (a vitamin K inhibitor). Vitamin K deficiency in the malnourished or postoperative patient also occurs (see page 8-20).
2) PT is normal but PTT is high: There is a problem with Factors VIII, IX, XI, or XII. The most common cause is heparin contaminating the blood sent to the laboratory. In the bleeding patient, think inhibitor to Factor VIII (see below). In the thrombotic patient, think antiphospholipid syndrome (discussed in Rheumatology, Book 3).
3) PT and PTT are both high: There is a defect in the common pathway or else a multiple factor deficiency involving both pathways.

Regarding #2: If there is a greatly increased PTT with a normal PT and normal platelet count, 1st check a heparin-neutralization study. If there is no correction, then do a mixing study to see if the problem is factor deficiency vs. factor inhibitor.

Review: Mixing studies are done on plasma to differentiate factor deficiency from factor inhibitor. In a mixing study, the patient's plasma is mixed 50:50 with normal plasma. If the patient's prolonged PTT is due to factor deficiency, the mixing with normal plasma provides the missing factor and corrects the problem. If the PTT is still prolonged after the 1:1 mix with normal plasma, the problem is likely to be an inhibitor, usually a lupus anticoagulant (antiphospholipid syndrome) or Factor VIII inhibitor.

Some factor inhibitors take time to react with the factor. Factor VIII inhibitors are especially likely to be time-dependent. For example, with acquired idiopathic or postpartum Factor VIII inhibitor antibodies, the PTT may initially correct to normal with the mixing study, but after incubation with the normal serum for 2 hours, the inhibiting antibody begins to bind to the added Factor VIII, and the PTT is once again prolonged.

QuickQuiz

- Characterize the PT and PTT in patients with antiphospholipid syndrome.
- What are mixing studies, and when are they used?
- What is the usual cause when a mixing study shows the PTT initially normalizing, but 2 hours later it is again prolonged?
- What determines the risk of bleeding in a patient with Factor VIII deficiency (hemophilia A)?
- When do you begin the treatment of a bleeding episode in a patient with Factor VIII deficiency?
- What is the clinical presentation of Factor XI deficiency?
- How do patients present if they have Factor XII deficiency?

The thrombin time measures the time of conversion of fibrinogen to fibrin. An increased thrombin time reflects decreased or defective fibrinogen, elevated fibrin degradation products, or heparin or heparin-like anticoagulants.

Refer to both Figure 8-3 on page 8-12 and Table 8-4 as you go through the following material.

Hereditary Coagulation Deficiencies

Factors VIII and IX Deficiencies

Hemophilia is due to a Factor **VIII** (A) or **IX** (B) deficiency. In the intrinsic pathway, activated Factor VIII accelerates by 1,000-fold the cleavage of Factor X by activated Factor IX. With either Factor VIII or IX deficiency, the PTT is increased and the PT is normal.

Clinical presentation is similar in both Factor VIII and IX deficiencies, with easy bruising, muscle and joint hemorrhages, and prolonged hemorrhage after surgery or trauma, but no excessive bleeding after minor cuts.

Both Factor VIII and Factor IX deficiencies are X-linked recessive. (Daughters with only 1 chromosome affected are carriers and exhibit no symptoms.)

In Factor VIII deficiency, the risk of bleeding correlates with Factor VIII serum levels. Patients with levels < 1% of normal have severe disease (bleeding even without trauma); patients with levels > 5% have mild disease.

Use desmopressin for mild Factor VIII deficiency. It works by causing a release of vWF and Factor VIII stores from endothelial cells. It is used as treatment for an acute hemorrhage and prophylactically for a tooth extraction in patients with Factor VIII levels > 5%.

Treat an acute bleed in a patient with a more severe Factor VIII deficiency with human Factor VIII concentrate. Previously, human Factor VIII concentrates carried a risk of transmission of hepatitis viruses and HIV. Since 1985, all plasma used to produce Factor VIII concentrate has been screened for the HIV and hepatitis C viruses, and steps that specifically inactivate these viruses are included in the production process. Recombinant Factor VIII also is an approved treatment.

Symptoms of a bleed often precede objective evidence by several days, and patients frequently inform their physician when a bleed is beginning. Early treatment delays or prevents hemophilia arthropathy, is cost effective, and can be lifesaving. Some centers advocate 2–3x weekly prophylactic Factor VIII infusions to keep levels above 1% and thus reduce bleeding risk. Prophylactic factor administration has been shown to reduce the incidence of arthropathy in adult hemophiliacs, but the product is expensive and may be associated with an increased rate of development of Factor VIII inhibitors. Avoid use of ASA in patients with hemophilia.

Factor IX deficiency is clinically indistinguishable from hemophilia A. Hemophilia B is only 1/10 as common as hemophilia A.

Manage acute bleeding episodes with either recombinant or highly purified human Factor IX concentrate. The original (less purified) human Factor IX concentrates contained trace amounts of other activated clotting factors, which could cause thrombosis.

Factor XI Deficiency

Factor XI deficiency is an autosomal recessive disorder that is less common than hemophilia A or B. The risk of bleeding depends more on the gene mutation leading to the disorder than on the actual serum level of Factor XI. The disorder is more common in certain ethnic groups, including Ashkenazi Jews.

Patients with Factor XI deficiency tend to bleed at mucosal sites (epistaxis and menorrhagia), where fibrinolytic activity is high. Surgery at sites with less fibrinolytic activity (orthopedic surgery, appendectomy) tends to have fewer bleeding complications.

Acute bleeds can be managed with fresh frozen plasma, recombinant Factor XI, or desmopressin.

Factor XII Deficiency

Patients with a decreased **Factor XII** (Hageman factor) have a normal PT and a very prolonged PTT (as with Factor VIII, IX, and XI deficiencies), but they do not have a clinical bleeding disorder and can even undergo surgery without worry of bleeding.

Factor XIII Deficiency

Factor XIII deficiency is an autosomal recessive disorder. Severe bleeding results from the inability to cross-link fibrin strands. Coagulation tests, including PT, PTT, and platelet function studies, are normal. Think about this in patients who have late postsurgical bleeding and poor wound healing.

Diagnose Factor XIII deficiency by performing a specialized clot lysis assay, in which dissolution of clot is attempted using urea. If the clot is solubilized with urea, then a Factor XIII deficiency exists. Treat with small amounts of fresh frozen plasma or specialized plasma derivative every 3–4 weeks.

And ...

As mentioned before, while people with platelet dysfunction tend to experience mucosal bleeding (bruising, nosebleeds, and menorrhagia), people with coagulation factor disorders tend to experience discrete episodes of deep tissue bleeding (hemarthroses, muscle hematomas, retroperitoneal hemorrhage). So, if platelets are absolutely required for thrombus formation, just like coagulation factors are required, why does a deficiency cause only mucosal bleeding? The answer is that early thrombus formation does not require many platelets to do the job.

What bleeding disorders may appear with a normal platelet count, PT, PTT, and bleeding time? The major disorders to consider are:

- Mild von Willebrand disease
- Mild hemophilia
- Factor XIII deficiency

Acquired Coagulation Deficiencies

DIC

Overview

Disseminated intravascular coagulation (DIC) is one of the most common acquired coagulopathies. It is always a secondary condition, so the underlying disease must be treated for the DIC to resolve.

DIC occurs in diseases that promote tissue factor release, including the following:

- Massive trauma
- Production of tumor necrosis factor, especially seen in solid tumors
- Sepsis, especially with endotoxin release
- Retained placental tissue in obstetric patients with placenta abruptio, dead fetus, or amniotic fluid embolus
- Acute promyelocytic leukemia (aPML, AML M3)

Acute (Decompensated) DIC

Large amounts of released tissue factor activate Factor VII and initiate the coagulation cascade. There is excessive thrombin and plasmin produced, resulting in both increased clot formation (via thrombin cleaving fibrinogen to fibrin) and clot breakdown (via plasmin degradation of fibrin clots). The plasmin breaks down fibrinogen and fibrin into fibrinogen/fibrin degradation products (FDPs, also called fibrin split products).

The massive depletion of coagulation factors and platelets and the increased fibrin split products (including D-dimer) may result in bleeding. Symptoms of DIC result from bleeding or microvascular thrombosis, as well as the underlying disorder.

Diagnosis of DIC:

- **PT** and **PTT** prolonged (remember, normal in TTP).
- **Thrombocytopenia** (from consumption).
- **Fibrinogen** level is decreased and trends downward during the disease process.
- **Thrombin time** is increased (due to both decreased fibrinogen and increased FDPs).
- **Schistocytes** (RBC fragments) are found in the peripheral smear in up to 1/2 of patients, which indicate microangiopathic hemolytic anemia (the fibrin strands span the small blood vessels and shear the RBCs).
- **FDP/D-dimer** increased. These are almost always elevated in DIC but also occur in many other conditions. FDP and D-dimer are therefore a sensitive, but not specific test.

Chronic (Compensated) DIC

Patients with chronic DIC can have either bleeding or thrombotic disorders. The thrombotic disorders range from migratory chronic thrombophlebitis (Trousseau syndrome) to pulmonary emboli.

Chronic DIC virtually always occurs in association with solid tumors.

With chronic DIC, a slower consumption of coagulation factors is compensated by increased synthesis of these same coagulation factors. Because of this, the lab results vary from acute DIC and all may be normal except FDP/D-dimer (elevated).

In the setting of an underlying malignancy, diagnosis of chronic DIC can be made with the finding of microangiopathic hemolytic anemia on peripheral smear and increased FDP/D-dimer.

Treatment of DIC

Treat the underlying disorder, or the DIC does not stop. With severe bleeding, give fresh frozen plasma and platelets. Heparin is not usually effective except in specific, unusual clinical situations (e.g., chronic DIC due to malignancy).

You can give cryoprecipitate if the fibrinogen level is very low, and you can use FFP to replace other coagulation factors. Platelets are given only if there is an acute bleed or to prepare a patient for surgery.

Vitamin K Deficiency

Vitamin K deficiency causes decreased production of the vitamin K-dependent factors (II, VII, IX, X) and proteins C and S.

Quick Quiz

- What special diagnostic test is used to diagnose Factor XIII deficiency?
- What disease states are associated with chronic DIC?
- How does the PT and PTT differ in DIC vs. TTP?
- How do broad-spectrum antibiotics cause vitamin K deficiency? How do certain cephalosporins cause vitamin K deficiency?
- Patients with which deficiencies are more likely to experience a venous thrombosis during initial anticoagulation with warfarin?

Causes of vitamin K deficiency include decreased dietary intake, malabsorption, antibiotic use, and decreased storage resulting from liver disease.

Especially know the probable cause of a prolonged PT in patients on either total parenteral nutrition (cause is decreased vitamin K intake) or certain cephalosporins (cause is antagonism of vitamin K by the N-methylthiotetrazole [NMTT] or similar side chains on cefotetan or cefoperazone). Other broad-spectrum antibiotics can cause vitamin K deficiency by reducing the burden of organisms in the intestine that synthesize vitamin K. The PT is prolonged, and the PTT is often normal. To further differentiate from DIC, check thrombin time and D-dimer, which are normal in patients with vitamin K deficiency.

Treat acute bleeds with fresh frozen plasma (FFP). Patients who are not bleeding can often be managed with vitamin K. Oral forms are more predictably absorbed (if the patient has a normal GI tract) than subcutaneous injections. IV vitamin K carries a very small risk for anaphylaxis. IM vitamin K should not be administered due to risk of hematoma formation. Vitamin K may take approximately 8 hours to work, so you should use FFP for immediate treatment if there is life-threatening hemorrhage.

Warfarin antagonizes vitamin K (causing an effective vitamin K deficiency). Initiation of warfarin therapy carries a theoretical increased risk of thrombosis as the levels of proteins C and S drop (the proteins with the shortest half-lives). This initial thrombotic effect may, for a short time, outweigh the antithrombotic effect on Factor VII; this is more likely with large loading doses of warfarin or if the patient is already protein C-deficient (pretreat with heparin). One-third of patients who develop warfarin-related skin necrosis have a protein C deficiency.

Any new medications or dietary changes should be reported by patients, since these may inhibit or potentiate warfarin's effect.

Primary Fibrinolysis

Primary fibrinolysis is a rare disorder often associated with prostate cancer and/or surgery. This disorder occurs when plasmin is released into the circulation in response to endothelial agents like tissue plasminogen activator (tPA). The pathophysiology differs from that of secondary fibrinolytic states, such as DIC, which occur in response to thrombi formation in the microvasculature.

Both primary and secondary fibrinolysis cause abnormalities of the PT, PTT, fibrinogen level, FDPs, and D-dimer; however, patients with primary fibrinolysis often have a normal platelet count.

Factor VIII Inhibitor

Factor VIII inhibitors are associated with:

- hemophilia,
- malignancies (CLL, adenocarcinomas),
- infections,
- pregnancy or the postpartum state,
- autoimmune disorders (SLE, RA),
- aging, and
- drugs.

However, many cases are idiopathic. Most patients who develop a Factor VIII inhibitor have never had a blood transfusion. Patients with an inhibitor present with severe bleeding, similar to hemophilia. In contrast to the lupus anticoagulant, mixing normal and patient's plasma may (initially) correct the PTT, but after a 2-hour incubation, the inhibitor antibody inactivates Factor VIII, and the PTT again becomes prolonged. Therefore, a mixing study that does not maintain a sustained normalization of the PTT suggests a Factor VIII inhibitor rather than factor deficiency.

THROMBOTIC DISORDERS

Overview

Virchow triad describes 3 factors that predispose patients to thrombosis:

1) Stasis
2) Vascular damage
3) Hypercoagulable state

Hypercoagulable states include both acquired and hereditary disorders.

Note that patients may develop a thromboembolic event only after they have multiple prothrombotic conditions. For example, a woman with a hypercoagulable state caused by *Factor V Leiden* mutation may not have her 1st deep vein thrombosis until she is pregnant or is immobilized after knee surgery.

Acquired Thrombotic Disorders

The acquired disorders include the following:

- Malignancy
- Pregnancy (especially immediate postpartum period)
- Smoking
- Estrogen use (OCPs, hormone replacement)
- Immobilization
- Major surgery
- Heparin-induced thrombocytopenia
- Myeloproliferative disorders (especially polycythemia vera and essential thrombocytosis)
- Antiphospholipid syndrome (APS)
- PNH
- Multiple myeloma

Antiphospholipid Syndrome (APS)

APS is a term used to describe the clinical relationship between a hypercoagulable state and the presence of antiphospholipid antibodies. It is discussed further in Rheumatology, Book 3.

Inherited Thrombotic Disorders

Overview

The most common inherited causes of venous thromboembolism are the *Factor V Leiden* gene mutation and the prothrombin gene mutation (*G20210A*). These mutations typically cause thrombosis before 50 years of age and more often present when other acquired risks for clotting are superimposed (e.g., pregnancy, oral contraceptives, immobility).

Although Factor V and prothrombin gene mutations are more common, patients with protein C, S, or antithrombin deficiencies are more likely to thrombose and to have recurrent thromboses. In patients > 50 years of age, think about the acquired causes of thromboembolism.

Thrombophilia means increased tendency to form thromboses.

Activated Protein C Resistance / *Factor V Leiden* Mutation

The *Factor V Leiden* mutation causes a resistance to the normally inhibitory effects of protein C, so the disease is called "activated protein C resistance" or "APC resistance." In the healthy patient, activated protein C cleaves activated Factors Va and VIIIa, rendering them inactive. Resistance to activated protein C leads to an unchecked hypercoagulable state. Heterozygosity for the *Factor V Leiden* mutation increases the lifetime risk for thrombosis 7-fold; homozygosity raises the risk 20-fold.

Prothrombin Gene Mutation

Prothrombin gene mutation is a gain-of-function mutation that results in increased levels of prothrombin (Factor II in the coagulation cascade). Heterozygous carriers of the *G20210A* mutation have 2–3x increased risk of venous, and possibly arterial, thrombosis.

Antithrombin Deficiencies

Antithrombin ([AT]; previously referred to as antithrombin III) inactivates thrombin both with and without the presence of heparin. In the presence of heparin, the antithrombin effects are accelerated roughly 4,000-fold. Antithrombin deficiencies include both quantitative (type 1) and qualitative (type 2) defects. Typically, 1st thrombotic events occur at a young age, and AT deficiencies are associated with a risk of venous thromboembolism of ~ 1%/year. Approximately 65% of patients heterozygous for AT have a thrombotic event by age 50. Homozygous AT deficiency is fatal *in utero*.

Type 1 is diagnosed by immunoassay and type 2 by functional studies (AT-heparin cofactor assay).

Protein C and S Deficiencies

Protein C and S deficiencies result in loss of the normal cleaving of Factors Va and VIIIa. The deficiencies are normally autosomal dominant. Both protein C and S are vitamin K-dependent proteins. Patients with protein C deficiency are at increased risk of developing skin necrosis while on warfarin. This is because protein C, with a very short half-life (6 hrs) compared with the other vitamin K-dependent clotting factors, is rapidly depleted with warfarin initiation, resulting in a transient hypercoagulable state.

Testing for Thrombophilia

Patients are said to be "strongly thrombophilic" if:

- 1st clot prior to age 50,
- recurrent thrombosis, or
- 1st degree family members with clots prior to age 50.

Screen these patients for all of the following:

- APC resistance (*Factor V Leiden*)
- Prothrombin *G20210A* mutation
- Protein C, S, and antithrombin deficiencies
- APS

Again, the less common deficiencies (APS, protein C, S, and antithrombin deficiencies) are more severe and have recurrent clots more often than those with APC resistance and prothrombin *G20210A* mutations.

A patient is "weakly thrombophilic" if the 1st clot occurs after age 50. In this group, an inherited thrombophilia is less likely. An acquired hypercoagulable state is most likely due to a malignancy. In most patients, a primary malignancy is already diagnosed at the time of clot. Screen for the following:

- APS, especially if the patient has any signs or symptoms of SLE

Quick Quiz

- What are the most common genetic mutations that cause venous thrombosis?
- What battery of tests is done on patients with possible inherited thrombophilia?
- What are established indications for an IVC filter in a patient with a deep venous thrombosis?

- Malignancy (solid tumors, lymphomas, myeloproliferative disorders)
- Use of certain drugs (hydralazine, procainamide, HCTZ, propranolol, phenytoin, or phenothiazines)

Remember that acute thrombosis can transiently lower levels of antithrombin, protein C, and protein S. Heparin can cause decreased antithrombin levels. Warfarin can decrease functional (and to a lesser extent, quantitative) levels of protein C and S and can (albeit rarely) raise antithrombin levels. In addition, warfarin yields a false-positive test for lupus anticoagulant. So wait to test for C, S, and antithrombin deficiencies until 2 weeks after completion of the initial 3–6 months of anticoagulation.

Management of Thrombosis

An extensive discussion of deep venous thromboses and pulmonary emboli (DVT/PE) is included in Pulmonary Medicine, Book 2.

Acceptable drugs for treatment of an established thrombosis include low-molecular-weight heparin (LMWH), unfractionated (UF) heparin, and fondaparinux. Recently, the oral Factor Xa inhibitors rivaroxaban and apixaban were approved to treat symptomatic venous thromboembolism. Caution is advised with renal failure. While the oral direct thrombin inhibitor dabigatran is approved for stroke reduction in nonvalvular atrial fibrillation, its use in venous thromboembolism is considered off-label. UF heparin is more expensive due to the need for monitoring of the PTT, but the infusion is easily titrated to meet the needs of an unstable patient. Thus, UF heparin usually is recommended in unstable patients.

Treatment of isolated calf vein thrombosis is guided by whether or not the patient is symptomatic. Options include anticoagulation or observation only, with serial ultrasound over the next 2 weeks to determine whether the clot is extending proximally.

LMWH and fondaparinux are not recommended in patients with low creatinine clearance (GFR < 30 cc/min). UF heparin is recommended in this group. LMWH is recommended, except in the unstable and in those with low creatinine clearance, because of mortality benefits and lower cost.

Be sure to monitor the platelet count in any patient taking a heparin product because of the possibility of HIT-II.

Warfarin can be started simultaneous with the heparin product or fondaparinux. Both drugs should be continued for at least 5 days with subsequent discontinuation of heparin/fondaparinux after the INR has been therapeutic for at least 48 hours.

Thrombolytic therapy is reserved for patients who are unstable due to a pulmonary embolism or a massive ileofemoral thrombus.

Duration of anticoagulation is somewhat controversial for certain patient groups, but general guidelines include the following:

- If the patient has a provoked thrombosis with transient risk factor (OCP use, surgery, immobilization, HIT-II): anticoagulate with goal INR 2–3 for at least 3 months.
- An unprovoked thrombosis: Anticoagulate with goal INR 2–3 for at least 3 months. The ACCP recommends indefinite anticoagulation be considered and benefits weighed against the risks.
- Recurrent thromboses, one unprovoked life-threatening thrombosis, one spontaneous thrombosis with APS: indefinite anticoagulation.
- A thrombosis in the setting of pregnancy or active malignancy: LMWH is more effective for preventing future thrombosis and for treatment of an acute thrombosis. Remember that warfarin is contraindicated in pregnancy because it is teratogenic and causes fetal bleeding. Unfractionated heparin is an alternative, but it is considered least favorable because of the need to use an increased dose during pregnancy and to monitor the PTT, in addition to the long-term risk of bone demineralization.

Consider an IVC filter in the following situations:

- When anticoagulation is contraindicated
- When there is a failure of anticoagulation
- In the presence of severe cardiopulmonary comorbidities, making a new PE life-threatening

Prior to surgery, consult the latest recommendations by the ACCP for discontinuation and resumption of anticoagulation therapy.

FIBRINOLYTIC TREATMENT

Urokinase and streptokinase cause a systemic lytic state. tPA is more specific; it increases the conversion of plasminogen to plasmin in the presence of fibrin, so most of the plasmin made is localized to the fibrin clot.

However, tPA also results in systemic lysis. These drugs are occasionally used to lyse a life-threatening pulmonary embolism (very specific situations) or an acute stroke or MI.

TRANSFUSION MEDICINE

RBC Transfusions

Whole blood is rarely used. Exceptions include major hemorrhage from trauma or from pediatric cardiac surgery. A donated unit of whole blood is normally separated into platelets, plasma, and packed RBCs. Alloimmunization can be a problem in multiple-transfused patients. In absence of ongoing losses, 1 unit of packed RBCs should increase the hemoglobin by 1 g/dL.

Platelet Transfusions

Wait to transfuse most patients with thrombocytopenia if they are not bleeding. A low platelet count that is > 10 x 10^9/L is acceptable for nonbleeding patients with acute leukemia. Platelet counts of 50 x 10^9/L are adequate for most interventional procedures (higher number often used for neurosurgical procedures). Patients with ITP almost never require platelet transfusions, even with very low platelet counts. Their younger platelets seem to work better, and transfusion does not result in an appreciable rise in the platelet count but may be hemostatically effective.

Know that platelet transfusions should not be given to patients with HIT or TTP/HUS unless there is life-threatening bleeding, because of increased risk of thrombosis.

WBC Transfusions

WBC transfusions are only rarely performed. G-CSF or GM-CSF is used instead to increase the neutrophil count—most commonly in patients receiving myelosuppressive chemotherapy.

Plasma and Cryoprecipitate Transfusions

Fresh frozen plasma (FFP) is transfused to replace coagulation factors. Use it to reverse anticoagulation in the context of dangerous bleeding when the PT and/or PTT are supratherapeutic.

Cryoprecipitate is a plasma component enriched in fibrinogen. It is used in conditions like DIC to replace fibrinogen (indicated when fibrinogen < 100 mg/dL).

Transfusion Reactions

Acute hemolytic transfusion reaction is a medical emergency caused by rapid, intravascular hemolysis, commonly due to an ABO incompatibility—and most often a result of a clerical error.

The initial signs may be only fever and chills. So, if a patient receiving a transfusion develops fever and chills, stop the transfusion immediately—prognosis worsens as more blood is given. Provide supportive care, including normal saline infusion.

Diagnostic tests include Coombs testing, serum-free hemoglobin, hemolysis labs (indirect bilirubin, haptoglobin, LDH), urine for hemoglobin testing, and repeat type and cross on transfused RBCs, as well as any blood left in the transfusion bag. Plasma is pink and peripheral smear shows schistocytes.

Alert the blood bank immediately because another patient may also be receiving the wrong blood.

Delayed hemolytic transfusion reaction is caused by extravascular hemolysis associated with Rh incompatibility or minor antigen mismatches. Patients present approximately 7 days after transfusion with anemia, mild fever, and mild unconjugated bilirubin elevation.

No treatment is necessary in the absence of brisk hemolysis. Future transfusions should be matched appropriately.

Febrile transfusion reactions. Fever and chills after a transfusion are common and represent nonhemolytic reactions to leukocytes in the blood product. A normal peripheral smear differentiates this mild, benign reaction from the more dangerous acute hemolysis.

Stop the transfusion and assess for hemolysis by sending off the same labs in the "acute hemolytic" category above. If the Coombs is negative, the symptoms are probably due to anti-HLA antibodies against the WBCs, which are transfused along with the component blood product.

Give antipyretics. Filters are used to remove WBCs in the transfused product (leukocyte-depletion) to minimize this reaction. But filters do not remove cytokines, which can also cause the reaction.

Post-transfusion purpura is discussed on page 8-16.

Transfusional hemosiderosis is iron overload from chronic repeat transfusions, usually in patients with sickle cell disease, thalassemia, or transfusion-dependent myeloproliferative or myelodysplastic disorders. Each 250 cc of packed RBCs contains approximately 250 mg of iron. Patients can become symptomatic after as few as 20 units. After 100 units (20–25 grams of iron), patients almost always show some symptoms of iron overload, which include:

- Glucose intolerance
- Cirrhosis
- Cardiomyopathy
- Hypogonadism

Diagnosis of transfusional hemosiderosis is established by an elevated ferritin and an iron-laden liver biopsy. As with hemochromatosis, MRI can detect iron in the liver, heart, joints, and pituitary (experienced facility only). Start iron chelation treatment (deferoxamine) before symptoms appear, because symptoms are typically not reversible. Consider chelation after 20–25 units of packed red cells (approximately 5 grams of iron) if transfusions are ongoing.

Transfusion-related acute lung injury (TRALI) is a severe pulmonary reaction caused by antibodies present in transfused FFP. The timing of TRALI is typically

Quick Quiz

- Which patients, except in the case of life-threatening bleeding, should not be given platelet transfusions, regardless of the degree of thrombocytopenia?
- What is the most common reason for an acute hemolytic transfusion reaction? What is the clinical presentation?
- What types of transfusions are most associated with transfusion-related bacterial infections? Why?
- What are the lab findings in a patient with aplastic anemia?

during or shortly after transfusion (1–2 hours), but TRALI can be more delayed, occurring up to 6 hours after transfusion. Clinically, there is sudden onset of respiratory distress. This may include alveolitis, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome (ARDS). Treatment is supportive and may include mechanical ventilation. Stop the transfusion and never use blood products from that donor again!

Pre-transplant alloimmunization can occur if transfusions are given before transplant. To reduce risk:

- Do not use family members as donors.
- Use leukocyte-poor irradiated blood components.
- Use single-donor platelets if needed.

Allergic reactions to transfused blood: Simple urticaria and anaphylaxis can occur. Know that recipient IgA deficiency leads to anti-IgA antibody formation, and donor blood with normal IgA levels can provoke anaphylaxis. IgA-deficient donors should be used for such recipients.

Infectious complications are most likely to occur with platelet products because they are stored at room temperature. Skin flora and gram-negative bacteria (*E. coli*, *Yersinia*, and *Pseudomonas*) are the usual organisms. Blood banks now screen for the most common infectious agents as follows:

- HIV-1 and -2: EIA antibody screen and nucleic acid amplification, with confirmation of positive results using Western blot or immunofluorescence test; window of risk for undetectable infection now only 11 days; risk of contracting HIV-1 or -2 from U.S. blood supply is 1 in 2 million.
- HTLV-1 and -2: qualitative antibody screen. Risk is < 1 in 2 million.
- HCV: EIA antibody plus nucleic acid testing; window of risk is 8–10 days; risk of contracting HCV from U.S. blood supply is 1 in 1.3 million.
- HBV: EIA for anti-HBc; risk of contracting HBV from U.S. blood supply is 1 in 200,000–500,000.
- West Nile virus: nucleic acid testing.
- *T. pallidum*: syphilis-specific antibodies using agglutination.
- *T. cruzi*: Trypanosomiasis is of particular concern in South America. Many U.S. blood banks are implementing universal screening using an EIA test for *T. cruzi* antibody, with a confirmatory radioimmunoprecipitation assay (RIPA).
- CMV: EIA for antibody; only CMV-negative blood is transfused in CMV-negative transplant patients, and leukocyte-depleted blood is used to further reduce risk.
- Less common organisms also can cause disease: *Babesia* and malaria (these are rare).

Hypotensive reactions can be seen in patients on ACE inhibitors, whose blood is filtered through coils, such as those used to filter out WBCs. Kinin activation is the probable cause. Prestorage filtration eliminates this problem.

Graft vs. host (GVH) reaction. Immunocompromised patients may develop GVH from lymphocytes in transfused blood. Also in immunocompetent patients, 1st degree relative donations carry some risk because they may be HLA-haploidentical, and lymphocytes may engraft. Order irradiated blood in both circumstances in order to ensure that the potentially harmful lymphocytes have been destroyed.

DISORDERS OF THE BONE MARROW

APLASTIC ANEMIA

Aplastic anemia is an absence of hematopoietic stem cells that results in pancytopenia and a hypocellular marrow. It can be acquired or inherited. The etiology of acquired aplastic anemia is unknown in most cases.

Dose-related causes include benzene and other industrial chemicals, pesticides, and radiation. Idiosyncratic drug causes include sulfa, carbamazepine, valproate, phenytoin, gold, chloramphenicol, and nifedipine.

Aplastic anemia is occasionally associated with viral infections with parvovirus B19, hepatitis viruses, and HIV. Other associated illnesses include thymoma, paroxysmal nocturnal hemoglobinuria, and systemic lupus erythematosus.

The presentation is determined by which cell lines are affected most: fatigue and weakness, if anemia; infections, if neutropenic; bleeding, if thrombocytopenic.

Aplastic anemia presents with pancytopenia, decreased reticulocyte count, and a hypocellular marrow (< 20%) with normal maturation of the cell lines. Differential diagnosis includes other causes of pancytopenia, such as B_{12} or folic acid deficiency, primary hematologic malignancies, MDS, infiltration of bone marrow with neoplastic cells, or fibrosis.

Aplastic anemia is classified as "severe" if:

- Marrow cellularity is < 25% of normal, or
- If the marrow is hypocellular and < 30% of the cells are hematopoietic, and at least 2 of the following 3 conditions are met:
  - ANC < 500/mm^3
  - Platelets < 20,000/mm^3
  - Reticulocytes < 1% corrected for hematocrit

Classification is "very severe" if "severe criteria" are met but ANC < 200/mm^3. A low absolute neutrophil count has poor prognostic significance. Younger age and higher cell counts are predictive of a better response rate to treatment.

Definitive treatment of aplastic anemia is with bone marrow transplantation for patients who are young and have an HLA-matched family member (10-year survival > 80%).

If there is no suitable donor or the patient is > 45 years of age, immunosuppress using either antithymocyte globulin or antilymphocyte globulin in combination with corticosteroids and cyclosporine. The complete response rate is 65%, although relapses are common.

Hematopoietic growth factors are undergoing evaluation and are not yet recommended treatment.

For all patients, treatment includes withdrawal of any possible offending medications. In addition, if thymoma is found, surgical excision is indicated.

Know that patients with aplastic anemia are at increased risk of developing acute leukemia.

THE ACUTE LEUKEMIAS

Overview

The acute leukemias are clonal disorders of early hematopoietic stem cells.

Normal hematopoiesis begins with pluripotent stem cells, which, in addition to reproducing themselves, are capable of differentiating into cells of either the myeloid lineage (granulocytes, monocytes, erythrocytes, and megakaryocytes) or the lymphocyte lineage (B or T cells).

Acute leukemias occur when cells of either the early myeloid (AML) or early lymphoid (ALL) lines lose their ability to differentiate, while retaining their ability to replicate. These blast cells accumulate in the bone marrow and crowd out normal hematopoiesis. The blast cells often spill out into the peripheral circulation but may be contained within the marrow.

Suspect acute leukemia when blasts (immature cells) are seen in the peripheral blood smear, without mature cells. Note that chronic leukemias have overproduction of 1 or more developing cell lines but not of blasts.

Patients present with symptoms related to cytopenias (infections, fatigue, mucosal bleeding).

Diagnosis and prognosis are made using morphologic analysis, cytogenetic studies (karyotype), cytochemical analysis (PAS, peroxidase, esterase, Sudan black), molecular markers, and cell surface markers (flow cytometry and immunophenotyping for CD markers).

Treatment for most acute leukemias involves an induction phase, where all hematopoiesis is suppressed with high-dose chemotherapy, with the hope that normal hematopoiesis returns without the leukemic clone. Successful induction involves a prolonged period of pancytopenia, during which the patient is highly susceptible to infection.

Myeloid growth factors are often used to shorten the time spent in a neutropenic state. Though these agents may reduce the length of hospitalization and decrease the incidence of infection, they have not been proven to increase survival (with the exception of a single study in the elderly). Supportive care with blood and platelet transfusions also is given during this time.

Once remission is achieved and cell counts have recovered, consolidation therapy is used to prolong remission and survival.

Gene expression profiling, utilizing DNA microarrays, is becoming an increasingly important tool to assist with prognosis and to guide therapy.

Acute Myelogenous Leukemia (AML)

During normal hematopoiesis, myeloid blast cells (Image 8-15 and Image 8-17) differentiate into granulocytes, monocytes, erythrocytes, or megakaryocytes. AML is a clonal disorder of the early myeloid cells where there is overproduction of myeloblasts with reduced production of red cells, platelets, and mature granulocytes. The blast forms accumulate in the peripheral blood, marrow, and, sometimes, lymphoid tissues.

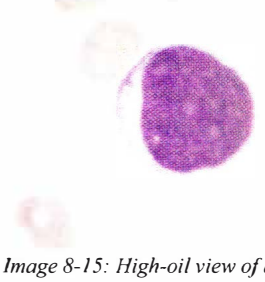

Image 8-15: High-oil view of a normal myeloblast. Few cytoplasmic granules. Several nucleoli.

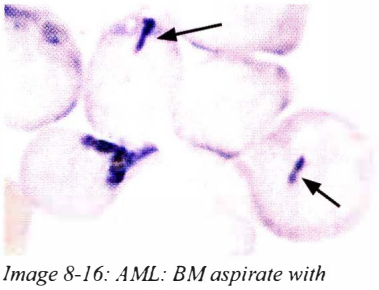

Image 8-16: AML: BM aspirate with peroxidase-positive blasts and 2 peroxidase-positive Auer rods.

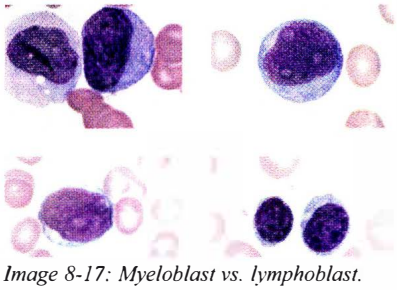

Image 8-17: Myeloblast vs. lymphoblast. UL: young mono and a myeloblast. UR: myeloblast. LL: lymphoblast. LR: normal lymphocytes are smaller.

QuickQuiz

- How can you tell the difference between acute and chronic leukemias?
- What is the treatment for leukemic patients who have hyperviscosity symptoms due to a large number of circulating blasts?
- What percentage of marrow blasts defines AML?
- What is a characteristic peripheral blood finding in a patient with AML?

The disorder can develop from exposure to chemicals such as benzene and certain chemotherapeutic agents. It may also arise after transformation from myeloproliferative disorders, myelodysplastic disorders, aplastic anemia, and PNH. Typically, these secondary leukemias have a worse prognosis than *de novo* AML.

Symptoms related to disordered hematopoiesis result in patients seeking medical care, but bone pain is uncommon. When fever is present, it's usually from infection; this leukemia rarely involves the CNS.

[Know.] Large numbers of blasts in the peripheral blood (> 100,000 cells/mm^3) can increase blood viscosity and cause end-organ disease such as brain ischemia and hemorrhage (presents as altered sensorium) and sludging in the pulmonary vasculature (presents as respiratory distress). This leukostasis is a medical emergency, and urgent treatment includes leukapheresis or hydroxyurea.

Thrombocytopenia predisposes to hemorrhage, especially in the presence of a high blast count. Qualitative and quantitative WBC problems predispose to serious infection of all kinds. Concurrent anemia requires RBC transfusions.

Diagnose AML by bone marrow biopsy if blasts are seen in the peripheral blood: Marrow blasts ≥ 20% is acute leukemia. Commonly, the blasts of AML and ALL look alike, and you cannot tell the type of leukemia by observation alone, so cytochemical tests, immunophenotyping, and chromosomal analysis are performed on marrow cells. Know, however, that finding Auer rods inside peripheral blood blast cells (Image 8-16) makes the diagnosis of AML. Auer rods are azurophilic needle-shaped crystals found in the cytoplasm of AML blasts.

AML can be categorized using the older French-American-British (FAB) classification (Table 8-5) or the newer (2008) World Health Organization (WHO) system. FAB contains classes M0–M7 with categories ranging from poorly differentiated to megakaryocytic. WHO classifies AML based on cytogenetics, clinical disease, and immunophenotype, with categories ranging from "AML with recurrent cytogenetic abnormalities" to "AML, not otherwise specified."

Except for 1 category (FAB M3, acute promyelocytic leukemia [aPML]), the specifics of both systems are not important for the general internist. aPML, however, is important because these patients have cytogenetic abnormalities that carry a favorable prognosis when the patient is treated with an ATRA drug (discussed next). So, remember the subset of AML that is treated with an ATRA drug: M3, acute promyelocytic leukemia, aPML.

Currently, several factors are used to establish AML prognosis. Cytogenetic findings represent one of the most powerful prognostic indicators. The karyotype can be used to classify patients into different risk groups:

- **Favorable** karyotype → t(8;21), t(15;17), or inv(16)
- **Intermediate** karyotype → normal karyotype or t(19;11)
- **Unfavorable** karyotype → inv(3), 5/del(5q), monosomy 7, or a more complex karyotype (3 or more aberrations)

Other unfavorable prognosticators for AML include:

- Age > 60
- Poor performance status
- WBC count > 100,000/mm^3
- Prior disease of the bone marrow (myelodysplasia or myeloproliferative disorder)
- Mutations in FLT3 (a receptor tyrosine kinase), found in 20–30% of patients with AML

Mutations in nucleophosmin (*NPM1*) gene, found in approximately 25% of patients with *de novo* AML and up to 50% of patients with normal karyotype *de novo* AML, are associated with a favorable prognosis (unlike *FLT3* mutations—and as long as no *FLT3* mutation is present).

CEBPA gene mutations are also associated with a favorable prognosis. Know that the molecular diagnostic field of AML is rapidly evolving with new favorable and unfavorable mutations continuously being discovered.

Table 8-5: French-American-British Classification of Acute Myeloid Subtypes with Some Distinguishing Characteristics

M0	Acute myeloblastic, poorly differentiated	5–10%
M1	Myeloblastic, without maturation	5–10%
M2	Myeloblastic, with maturation; associated with t(8;21) (favorable cytogenetics)	25–30%
M3	Acute promyelocytic leukemia, favorable prognosis, t(15;17), associated with DIC	3–15%
M4	Myelomonocytic, associated with inv(16) (favorable cytogenetics)	15–30%
M5	Monocytic	10–20%
M6	Erythroleukemia, poor prognosis	3–7%
M7	Megakaryocytic, associated with marrow fibrosis, unfavorable prognosis	3–6%

Acute promyelocytic leukemia (aPML; AML M3 type) is characterized by a translocation between chromosomes 15 and 17, involving the promyelocytic leukemia gene and retinoic acid receptor α gene (PML-RARα).

Treatment of aPML differs from treatment of other types of AML. Prognosis for aPML is very favorable, and therapy is associated with a remission rate of > 80% and a cure rate of > 70%. These rates are much better than with other forms of AML. Treatment includes all-trans retinoic acid (ATRA), which is used to induce differentiation, along with daunorubicin.

Know that "differentiation syndrome" (formerly "ATRA syndrome") is an adverse effect of ATRA therapy and clinically presents as fever, volume overload with pleural and pericardial effusions, respiratory distress, and hypotension. It can be life-threatening. Treat with high-dose dexamethasone and withhold ATRA if necessary.

Patients with aPML are also at increased risk for developing DIC due to release of procoagulants from cytoplasmic granules. The diagnosis of aPML needs to be made quickly because DIC can change aPML from a curable disease into a fatal one within hours.

An important distinction in AML is whether the disease is *de novo* AML or CML in degenerated blast crisis. CML in blast crisis arises because of the presence of the Philadelphia chromosome (*BCR-ABL* gene translocation) and is vulnerable to treatment with a tyrosine kinase inhibitor such as imatinib.

Standard induction therapy for AML (non-aPML) is a combination of 7 days of cytosine arabinoside (ara-C) and 3 days of daunorubicin ("7 + 3"). Consolidation therapy can take the form of further chemotherapy with the same agents as above. With standard therapy, for patients > 60 years of age, remission is achieved in ~ 40–50%, but long-term, event-free survival is achieved in < 10%. For patients < 60 years of age, long-term survival, on average, is 20–30%.

Allogeneic stem cell transplantation is an important treatment option in patients with AML. It is typically reserved for patients < 60 years of age. Morbidity and mortality are reduced if a histocompatible sibling donor is utilized rather than a matched unrelated donor. Over the last decade, a new technique called nonmyeloablative stem cell transplant has been developed. The difference, compared to standard allogeneic transplant, is that the pre-stem cell rescue chemotherapy is very modest in dosing. This technique has decreased immediate transplant mortality.

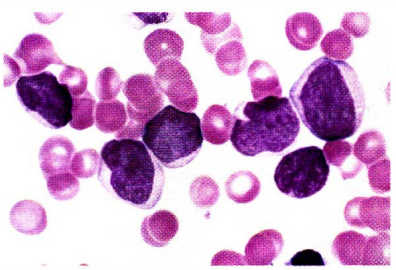

Image 8-18: ALL: many lymphoblasts. Note how large the blasts are compared to RBCs.

However, it is still associated with GVH. For patients < 60, considerations for transplant should include comorbid conditions, relapse/remission status, and cytogenetics.

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is a clonal disorder of early lymphocytic precursors. The blasts of ALL may be of B- or T-cell lineage (see Image 8-18). While ALL is primarily a disorder of children, there is a bimodal age distribution with increased incidence also in older patients. ALL represents ~ 20% of adult leukemias.

The WHO classification divides ALL into 3 categories: precursor B-cell (frequency 70–75%), precursor T-cell (frequency 20–25%), and mature B-cell ALL (Burkitt lymphoma/leukemia, frequency 5%). Among the precursor B and T-cell types, the groups are further delineated into either ALL (if the marrow contains > 25% blasts) or lymphoblastic leukemia (LBL, if mediastinal or other mass is present and marrow contains < 25% blasts). ALL and LBL are essentially the same disease process. The T-cell neoplasm more often presents as LBL, with > 50% of the cases involving a mediastinal mass.

Clinically, patients often present with cytopenias; constitutional symptoms; symptoms of CNS involvement (e.g., cranial nerve and/or retinal abnormalities and symptoms of meningeal irritation); and enlargement of the liver, spleen, lymph nodes, and testicles due to extramedullary deposits of blast cells.

The peripheral blood smear may show leukopenia or leukocytosis with blast counts above 100,000/mm^3. Definitive diagnosis and important prognosticators are made by immunophenotyping and chromosomal analysis of the leukemic cells.

Unfavorable prognostic factors in ALL:

- Age > 60
- WBC > 100,000/mm^3
- Mature B- or early T-cell types
- Persistent minimal residual disease, as detected by flow cytometry after remission is achieved
- t(9;22) translocation = Philadelphia chromosome (unlike in CML, where the translocation is favorable)
- t(4;11) = *MLL-AF4* fusion gene

Treatment is with multiple chemotherapy agents used in induction, consolidation, and maintenance phases. Prednisone, vincristine, and daunorubicin form the foundation, and cyclophosphamide + L-asparaginase are often added (may increase response). Complete response rates are in excess of 80%.

Post-remission therapy in ALL includes CNS chemoprophylaxis (with or without cranial radiation), consolidative therapy, and 2–3 years of maintenance therapy.

For patients without unfavorable prognostic factors, chemotherapy alone results in a 60% long-term, disease-free

Quick Quiz

- Characterize the AML M3 type genetic translocation, and describe how it affects treatment. What is the prognosis for aPML?
- Which FAB category of AML is associated with DIC?
- What physical findings do patients with ALL often present with?
- What ALL cytogenetic abnormality is associated with a poor prognosis?

survival. For patients with 1 or more unfavorable prognostic indicators, consider bone marrow transplantation.

Supportive care is an important component of treatment. In addition to the effects of cytopenias, patients often have hyperuricemia, hyperphosphatemia, and hypocalcemia—all secondary to the high cell turnover.

MYELODYSPLASTIC SYNDROME

Myelodysplastic syndrome (MDS) includes clonal stem cell disorders characterized by ineffective blood cell production and variable progression to acute leukemia. MDS occurs *de novo* or secondary to previous chemotherapy. While both MDS and the myeloproliferative disorders (see below) are clonal stem cell disorders, only patients with MDS exhibit cytopenias and inadequate (dysplastic) maturation of blood cells.

MDS presents with symptoms secondary to cytopenias (weakness, infection, bleeding). Platelets may be dysfunctional and result in bleeding out of proportion to the degree of thrombocytopenia. Patients who have MDS with > 20% blasts are now considered to have AML.

Unfavorable prognosticators for MDS:

- High percentage of bone marrow blasts
- Number of "cytopenias"
- Cytogenetic abnormalities, especially chromosome 7 anomalies
- Increasing age

Favorable prognosticator: the deletion of chromosome 5q or 20q.

The World Health Organization separates MDS into 8 groups, which incorporate the known prognostic factors:

1) Refractory anemia (RA)
2) RA with ringed sideroblasts (RARS; ringed sideroblasts are nucleated RBCs with iron granules in the cytoplasm) (See Image 8-19 and Image 8-20.)
3) Refractory cytopenia with multilineage dysplasia (RCMD)
4) RCMD with ringed sideroblasts (RCMD-RS)
5) RA with excess blasts1 (< 5% blasts) (See Image 8-21.)
6) RA with excess blasts2 (5–19% blasts)
7) MDS-unclassified
8) MDS with del(5q) ("5q- syndrome"): occurs more frequently in women and is associated with thrombocytosis and a more favorable prognosis

Differential diagnoses include B_{12}/folate deficiency, aplastic anemias, and myelofibrosis. Bone marrow biopsy reveals a hypercellular marrow (peripheral cytopenias are due to ineffective hematopoiesis) and dyserythropoiesis.

The International Prognostic Scoring System (IPSS) helps risk stratify patients and predict survival. Points are assigned based on percentage of blasts (the most important prognostic indicator), number of cytopenias, and karyotype. (Good cytogenetics includes 5q- and 20q-; poor cytogenetics includes chromosome 7 anomalies.)

Median survival approximates 5 months for high-risk scores compared to 5.7 years for low-risk scores.

Treatment depends on patient age, comorbidities, and aggressiveness of disease. Treatment is supportive, although allogeneic bone marrow transplant is considered in young patients who are high-risk or have evolving disease. Azacitidine and decitabine are hypomethylating agents with activity in patients with MDS. Mortality in MDS is usually a result of cytopenias or progression to AML.

Know 5q- syndrome: Patients with the favorable 5q- deletion have refractory anemia and thrombocytosis.

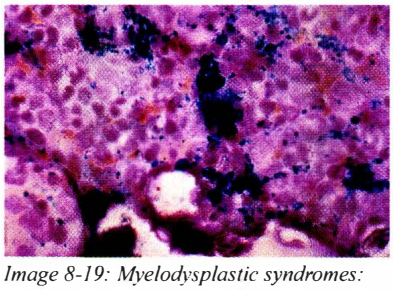

Image 8-19: Myelodysplastic syndromes: This patient has refractory anemia with ringed sideroblasts (RARS). Low-power view of bone marrow aspirate stained for iron shows increased iron stores (dark blue).

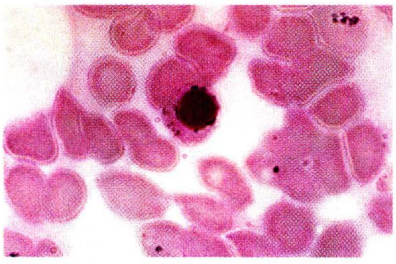

Image 8-20: Myelodysplastic syndromes: A ringed sideroblast is seen in this patient with RARS. Note: The sideroblast is the erythroblast with a perinuclear "string of pearls" formed by intramitochondrial granules of iron.

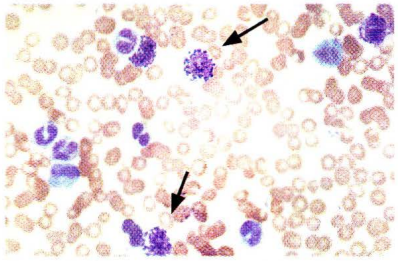

Image 8-21: Increased basophils. Common finding in the myeloproliferative syndromes.

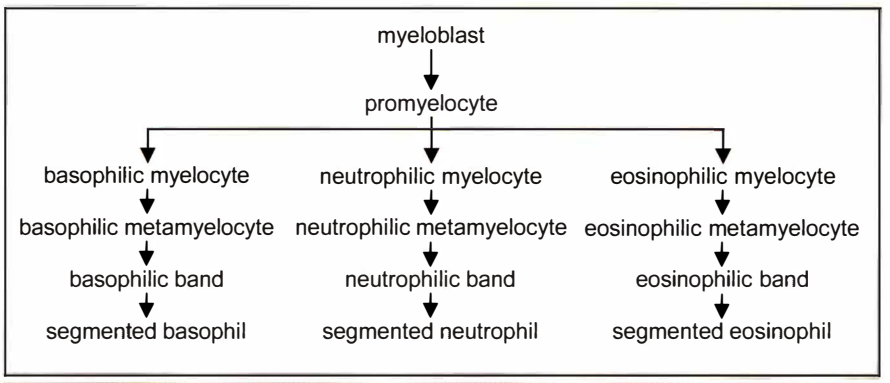

Figure 8-4: Granulopoiesis

Know that these patients generally respond to lenalidomide therapy and have prolonged survival with decreased risk of transformation to AML.

Chronic myelomonocytic leukemia (CMML) is now classified as an overlap myelodysplastic/myeloproliferative disorder. Patients are older with a poorer prognosis. Peripheral blood shows monocytosis with increased myeloid/erythroid precursors. Bone marrow is hypercellular with dysplasia (as in MDS). Patients with CMML should be checked for the t(5;12)(q33;p13) oncogenic product. (The *PDGFRB* gene [platelet-derived growth factor-b] moves adjacent to the *TEL* gene.) These patients may respond to imatinib therapy (tyrosine kinase inhibitor).

MYELOPROLIFERATIVE DISORDERS

Overview

The myeloproliferative disorders (MPDs) are clonal malignancies of early hematopoietic stem cells, characterized by loss of the regulation of cell proliferation. The result is the overproduction of the entire pyramid of maturation of granulocytes, erythrocytes, and platelets (see Image 8-22 through Image 8-23). (Contrast this with acute leukemia, marked by maturation arrest and proliferation of blasts.) MPDs variably progress to acute leukemias or myelodysplasia (Figure 8-4). There appears to be some familial pattern of inheritance, but we do not yet know the mechanism.

The 4 most common MPDs:

1) Chronic myelogenous leukemia (CML)
2) Essential thrombocythemia (ET)
3) Polycythemia vera (PV)
4) Primary myelofibrosis ([MF]; the rarest of these 4 MPDs)

JAK2 (Janus kinase, a tyrosine kinase) is an intracellular signaling molecule that is coupled to cell surface hematopoietic growth factor receptors (like the erythropoietin receptor). A *JAK2* gene mutation causes constitutive activation of the JAK2 kinase domain, inducing unregulated erythrocytosis. The mutation is found in almost all patients with PV and ~ 50% of those with ET or MF. There is no known prognostic significance. Inheritance of this mutation does not appear to be the mechanism for the familial clustering of disease.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a clonal stem cell disorder of myeloid cells. The clinical hallmark is one of uncontrolled production of mature but dysfunctional neutrophils. Most patients present in the chronic phase with an elevated white blood cell count and a predominance of granulocytes. There is often an elevated basophil count and a low leukocyte alkaline phosphatase (LAP) score. The expanded myeloid pool may lead to organ infiltration, causing hepatosplenomegaly.

The diagnosis of CML is dependent on detection of the Philadelphia chromosome, t(9;22), or its products: BCR-ABL fusion mRNA or the BCR-ABL protein, which is a tyrosine kinase. Over 90% of patients demonstrate this abnormality at the time of diagnosis.

Uncontrolled replication of the myeloid stem cells as the disease progresses inevitably leads to further genetic errors. The myeloid cells begin to lose their ability to differentiate from their blast stages, and the disease degenerates into acute leukemia (AML or ALL). This 2nd, or accelerated, phase of CML is characterized by increasing numbers of blasts and basophils and a declining platelet count.

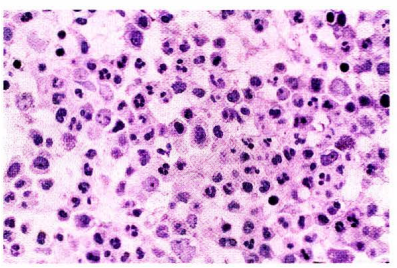

Image 8-22: Myeloproliferative syndromes: CML. Hypercellular marrow. Low power. Myeloid elements are clearly more abundant than the normal 3:1 myeloid:erythroid (M:E) ratio.

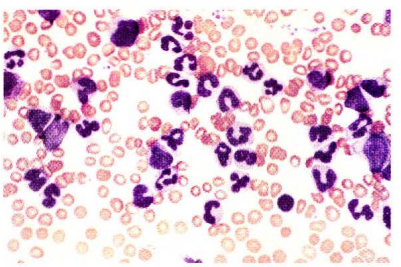

Image 8-23: Myeloproliferative syndromes: CML. Peripheral smear with the pyramid of maturation of granulocytes: promyelocytes, myelocytes, metamyelocytes, bands, and segmented neutrophils.

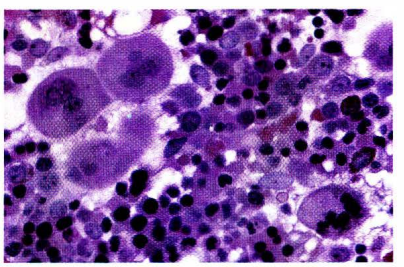

Image 8-24: Myeloproliferative syndromes: Polycythemia. BM Bx shows increased megakaryocytes and greatly increased erythroid precursors (with black condensed nuclei) and a decreased M:E ratio.

Quick Quiz

- What is 5q- syndrome?
- What is the main difference between the MPDs and acute leukemia?
- What are the 4 most common MPDs?
- JAK2 is found in what disease states?
- CML is associated with which cytogenetic abnormality in > 90% of cases?
- What is the current standard of care for treating CML?
- What side effects are associated with imatinib?
- What symptoms necessitate treatment in patients with ET?

The patient is considered to be in the blast phase once the percentage of blasts has progressed to > 20%. Survival is greatly diminished once this "blast crisis" has occurred.

Most (85–90% of patients) present in stable chronic phase while 10–15% may present in accelerated or blast phase. Fewer patients are now progressing to blast phase because of improvements in treatment during the chronic phase.

A tyrosine kinase inhibitor (TKI; imatinib, nilotinib, and dasatinib) is 1st line treatment of CML in chronic phase. The new 2nd generation TKIs, dasatinib and nilotinib, also are approved for frontline treatment of CML. These agents provide faster hematological and cytogenetic responses than imatinib. It is unclear thus far if this corresponds to improved overall survival. Dasatinib and nilotinib should be used in disease resistant to imatinib.

Side effects of TKIs include edema, exacerbation of congestive heart failure, and worsening of LV dysfunction, hepatotoxicity, cytopenias, and hemorrhage. Also, TKIs are teratogens and should not be used in women of childbearing age.

Allogeneic hematopoietic stem cell transplantation remains the only proven curative therapy for CML and is considered in patients who develop TKI resistance or complications. Dasatinib causes pleural effusions and cytopenias. Nilotinib is known to cause GI and liver toxicity as well as cytopenias.

Essential Thrombocythemia

Essential thrombocythemia (ET) is the least aggressive of the myeloproliferative disorders. Suspect ET when a high platelet count is noted on a routine CBC. Although patients with ET have a normal life expectancy, they are at risk for thrombosis (venous and arterial) and hemorrhage.

Risk factors for clot with ET:

- Age > 60
- Previous history of thrombosis

Diagnosis requires exclusion of causes of secondary thrombocytosis (e.g., infection, inflammation, tissue injury, trauma, ischemia, post-splenectomy, surgery, and especially, iron deficiency anemia).

Clinical presentation includes symptoms related to microthrombi (e.g., headaches, visual disturbances, and erythromelalgia), as well as symptoms referable to larger clots (including miscarriages) and bleeding. **Erythromelalgia** is paroxymal vasodilation of small arteries of the feet (mainly) and hands, causing burning pain, swelling, and erythema.

Treatment for ET should be limited to patients with significant erythromelalgia—managed with aspirin—and those at high risk for thrombosis (i.e., age > 60 or history of thromboembolism):

- High-risk patients: Cytoreductive therapy with hydroxyurea; goal is to reduce the platelet count below 400,000/mm^3.
- Everyone else: Prescribe aspirin to prevent thrombosis (especially if erythromelalgia is significant).

For surgical patients with ET, there is a high perioperative risk of thrombosis and bleeding complications. Very high platelet counts preoperatively should be reduced prior to surgery (with platelet pheresis if urgent surgery is required).

Like PV, ET can progress to myelofibrosis and acute leukemia. It is not known if treatment with hydroxyurea accelerates leukemic conversion. Treatment with JAK2 inhibitors remains in the clinical trials phase.

Polycythemia Vera

Polycythemia vera (PV) is characterized by an increased red cell mass in the absence of erythropoietin and in association with the *JAK2* mutation. (See Image 8-24.)

An increased red cell mass most often results from erythropoietin stimulation, which may result from a primary or secondary disorder. Common secondary causes of increased red cell mass include hypoxemia (obstructive sleep apnea, COPD, smoking, right-to-left cardiac shunts, high altitude, carbon monoxide poisoning), tumor secretion of erythropoietin (renal cell carcinoma, hepatocellular carcinoma), and androgens.

Patients with PV often present with an increased hematocrit with leukocytosis and thrombocytosis, the latter often causing erythromelalgia (see above). Other common symptoms are headache, weakness, and dizziness, which are thought to be secondary to hyperviscosity from the elevated hematocrit. Patients with PV often complain of pruritus (perhaps secondary to increased histamine levels) after a hot bath or shower. Gout can result from rapid cellular turnover. Splenomegaly is common.

Increased mortality in patients with PV is related to thrombosis (venous or arterial)—an elevated hematocrit is prothrombotic. Mortality also results from conversion to AML and myelofibrosis.

There is no consensus on an exact diagnostic protocol. The proposed WHO criteria are:

Major criteria:

- Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume
- Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation

Minor criteria:

- Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
- Serum erythropoietin level below the reference range for normal
- Endogenous erythroid colony formation *in vitro*

Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the 1st major criterion together with 2 minor criteria.

Treatment of PV is phlebotomy to a goal hematocrit of < 45% (to induce an iron-deficient state), which reduces mortality but may transiently increase the rate of thrombosis.

Low-dose ASA lowers the risk of thrombosis during this period. Cytoreduction therapy with hydroxyurea lowers this thrombotic risk but may accelerate the leukemic transformation. Once again, JAK2 inhibitor therapy remains in the clinical trials phase.

Primary Myelofibrosis

Primary myelofibrosis (MF) is a clonal stem cell disorder of unknown cause that results in hyperplasia of atypical megakaryocytes. These megakaryocytes stimulate a nonclonal proliferation of fibroblasts, which then go on to cause fibrosis of the bone marrow. Secondary marrow fibrosis may result from transforming PV and ET.

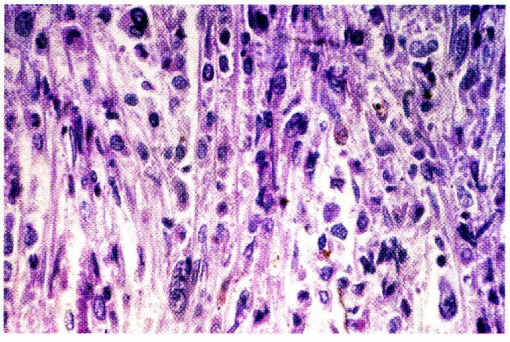

Image 8-25: Myeloproliferative syndromes: Myelophthisis (replacement of bone marrow by a disease process)—in this case, myelofibrosis (replacement by reticulin).

The most common symptom is fatigue. Early satiety and abdominal fullness also are common, attributable to hepatosplenomegaly. Screening labs show marked anemia and variable changes in white cells and platelets, with cytopenias developing as disease progresses. Serum LDH may be increased.

The peripheral blood smear often shows teardrop cells—a finding that is common to diseases that infiltrate the marrow (metastatic cancer, TB, fungal infections). (See Image 8-25.) Marrow aspirate often results in a "dry tap."

Allogeneic hematopoietic stem cell transplantation remains the only chance for cure, but this therapy is limited to younger patients. For the vast majority of patients, treatment is primarily supportive, including splenectomy for severe splenomegaly. The oral JAK2 inhibitor ruxolitinib is approved to treat primary myelofibrosis. Studies show significant improvement in weight loss, fatigue, and splenic volume, but no trial so far has shown an improvement in survival.

LYMPHOPROLIFERATIVE DISORDERS

OVERVIEW

These disorders range from slow-growing asymptomatic tumors to the most aggressive malignancies. Some present mainly as lymphomas (solid tumors) and others more like leukemias (involving blood and bone marrow). Others present with features of both.

OVERVIEW OF NON-HODGKIN LYMPHOMA

The term non-Hodgkin lymphoma (NHL) encompasses a group of disorders characterized by clonal proliferation of lymphocytes—B, T, or natural killer cells. See Table 8-6 for prevalence of cell-type neoplasms. The term lymphoma is used when the neoplastic cells grow as a solid mass in the lymph nodes, spleen, bone marrow, or solid organs. The term leukemia is used when the neoplastic cells are found in the blood. It is not unusual to see overlap of these 2 entities. For example, patients with chronic lymphocytic leukemia (CLL) often have a solid component to their disease, termed small lymphocytic lymphoma (SLL). When present, the combined diagnosis of CLL/SLL is used. In other words, many lymphomas have small components of leukemia to them, and some leukemias have a component of lymphoma.

NHL is associated with Epstein-Barr virus (EBV), human T-cell lymphotrophic virus 1 (HTLV-1), and human herpesvirus 8.

Patients with NHL often present with palpable adenopathy and constitutional symptoms (e.g., weight loss, fever, night sweats).

Nodal growth may also occur in nonpalpable areas as well, resulting in hepatosplenomegaly.

QuickQuiz

- What peripheral blood finding is seen in patients with myelofibrosis?
- What is the common physical finding on initial presentation of NHL?
- An NHL that produces an IgM monoclonal gammopathy, and is associated with hyperviscosity, is termed what?
- What are the 2 general types of NHL?

Airway obstruction or superior vena caval syndrome can result from nodal growth in the mediastinum; bowel or ureter obstruction may result from growth in the mesentery or retroperitoneum.

Some lymphomas produce an IgM monoclonal gamma globulin that can lead to hyperviscosity (Waldenström macroglobulinemia) or autoimmune cytopenias (Coombs + anemia and/or thrombocytopenia), while others (CLL/SLL) cause agammaglobulinemia that leads to frequent infections. Cytopenias also may develop from hypersplenism and from bone marrow infiltration.

Diagnosis of lymphoma is made by an excisional biopsy of a lymph node, which allows the pathologist to observe both the appearance of the cells and the architecture of the lymph node. Immunohistologic stains and flow cytometry also are performed. If there is a sizable leukemic component to the lymphoma, as in CLL/SLL, the diagnosis can be made by flow cytometry of the peripheral lymphocytes, looking for characteristic cell surface markers.

Once the diagnosis is made, staging is carried out using physical exam and CT scans of the neck, chest, abdomen, and pelvis. A bone marrow biopsy can be helpful to determine the nature of cytopenias if present.

Positron emission tomography (PET) scanning can be integrated into initial diagnostics and used in follow-up after treatment. PET uses radiolabeled glucose to image glycolysis *in vivo*. Areas that are relatively metabolically active (brain, heart, kidneys) "take up" the glucose and image brightly. Active malignancies also take up the tracer and become "PET" or "FDG avid" (FDG = 18-fluorodeoxyglucose). Patients with NHL often have persistent masses seen on CT scan after treatment. These masses usually represent either residual lymphoma or fibrous scar tissue. A mass that does not fully resolve with treatment and is FDG avid would represent persistent disease, while a lack of avidity would represent remission or cure.

NHLs fall broadly into 2 groups: indolent and aggressive (Table 8-7).

Indolent lymphomas have a long clinical course, measured over years. They are seldom cured with conventional chemotherapy, and early treatment has never been shown to improve survival over delayed treatment. Treatment is ordinarily held until symptoms develop—a "watch and wait" strategy. Treatment controls symptoms by placing the lymphoma in a temporary remission or decreasing the overall disease burden.

Aggressive NHLs grow more quickly—often becoming symptomatic early in the disease course. If left untreated, they lead to death within months. These rapidly growing lymphomas respond well to chemotherapy, and, while many ultimately relapse, an increasing number are being cured.

An individual patient's prognosis with NHL depends primarily upon characteristics of the lymphoma: the subtype, the Ann Arbor stage (same as that for Hodgkin disease), and the LDH (a marker for tumor burden). Prognosis is also dependent on characteristics

Table 8-6: REAL / WHO Classification of the Most Common NHLs and Leukemias

Types	Freq %
B-Cell Neoplasms	
Diffuse large B-cell lymphoma	33
Follicular lymphoma	22
Extranodal marginal zone B-cell lymphoma	8
CLL/B-cell SLL	7
Mantle cell lymphoma	6
Burkitt lymphoma	2
Nodal marginal zone B-cell lymphoma	2
Lymphoplasmacytic lymphoma	1
Precursor B-cell neoplasms, B-cell prolymphocytic leukemia, splenic marginal zone B-cell lymphoma, hairy cell leukemia, plasma cell myeloma	< 1% each
T-Cell Neoplasms	
Mature (peripheral) T-cell neoplasms	8
Precursor T-lymphoblastic leukemia/lymphomas	2
Primary systemic anaplastic large cell lymphoma	2

Adapted from Evans LS and Hancock BW. Non-Hodgkin lymphoma. *Lancet.* 2003 Jul 12;362(9378):139–146.

Table 8-7: Types of NHL

Indolent Lymphomas	Aggressive Lymphomas
CLL/SLL	Diffuse large B cell
Follicular lymphoma	Burkitt
Marginal zone (MALT, nodal, splenic)	Precursor T-lymphoblastic
Mycosis fungoides	B-lymphoblastic
	Mantle cell

of the patient: age and performance status at the time of diagnosis.

The International Prognostic Index (IPI) is commonly utilized, and uses the following 5 factors to help predict outcome:

1) Age
2) Serum LDH
3) Ann Arbor stage
4) Performance status
5) Number of extranodal disease sites

More recently, molecular and genetic markers of prognosis have been introduced.

Know that there is growing use of monoclonal antibodies in the treatment of NHL.

Rituximab is a chimeric antibody directed against CD20, a surface marker found on many B-cell lymphomas. The binding of antibody to the neoplastic cell causes cell death by complement-mediated lysis, cellular cytotoxicity, and directly by apoptosis. Rituximab is well tolerated even in elderly patients and can be used alone against indolent lymphomas or in combination with traditional chemotherapy against aggressive disease.

Ofatumumab is a fully human anti-CD20 monoclonal antibody also used in the treatment of refractory CLL.

Alemtuzumab is a monoclonal antibody directed against CD52, a cellular marker often found in CLL. This antibody can control otherwise refractory CLL, although its use comes at the price of immunosuppression because CD52 also is found on normal B and T cells.

INDOLENT NON-HODGKIN LYMPHOMAS

Follicular Lymphoma

Follicular lymphoma is the most common of the indolent non-Hodgkin lymphomas (NHLs). Patients are often elderly and present at a late stage with diffuse adenopathy. Patients are often asymptomatic at presentation. The hallmark is overexpression of the anti-apoptotic protein BCL-2 caused by a t(14;18) translocation. As with other indolent lymphomas, follicular lymphoma is commonly slow growing and incurable (except in very early-stage disease in which it sometimes can be cured with local radiation therapy).

Treatment is not indicated in asymptomatic patients. Younger patients may receive combination therapy with the goal of prolonged (though not permanent) remission. Older patients can be treated with gentler, single-agent therapy, such as rituximab. If in early-stage disease, radiation therapy alone is an option. In relapsed or refractory disease, the radioimmunoconjugates tositumomab and ibritumomab, anti-CD20 monoclonal antibodies bound to radioactive iodine and yttrium-90 respectively, may be used. The role of these agents in 1st line treatment, particularly with rituximab, is still under investigation.

Patients progress over time to develop cytopenias and die from infection or complications of anemia. Approximately 10% of follicular lymphomas undergo a transformation to a more aggressive lymphoma---diffuse large cell lymphoma. Transformed diffuse large cell lymphoma is more resistant to chemotherapy than its *de novo* counterpart, and such a transformation is often a sign of a rapidly fatal outcome.

Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) is an indolent lymphoma that in part develops from chronic antigenic stimulation. It is separated into **mucosa-associated lymphoid tissue** ([**MALT**]; extranodal), **nodal**, and **splenic** marginal zone lymphoma. Unlike many indolent lymphomas, MZLs are often found at an early stage. The most common location is the gastric or intestinal mucosa (referred to as a MALT lymphoma), and the most common antigenic stimulant is chronic *H. pylori* infection. MZL also can occur in bronchial mucosa and salivary glands, and splenic MZL may arise from chronic HCV infection.

When MZL is diagnosed, rule out infectious causes (*H. pylori* and HCV).

Early-stage gastric MALT lymphoma may be treated with antibiotics alone to eradicate *H. pylori* or with added radiation if the initial treatment fails. Early treatment of the other types of MZL with lung lobectomy and splenectomy can result in a prolonged symptom-free remission.

CLL / SLL

CLL/SLL is an indolent disease characterized by the clonal proliferation of mature but poorly functioning B-cell lymphocytes (see Image 8-26 through Image 8-28.)

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are the same B-cell lymphocyte

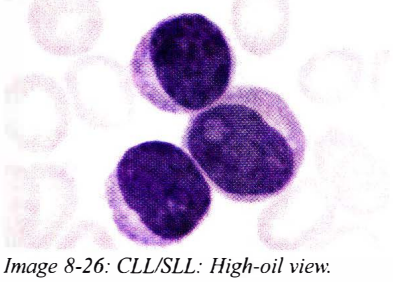

Image 8-26: CLL/SLL: High-oil view. 3 leukemic lymphocytes.

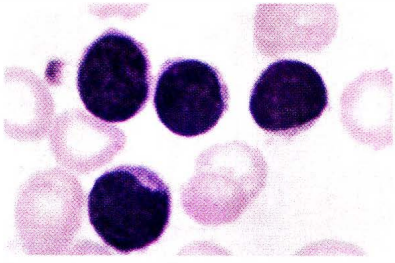

Image 8-27: CLL/SLL: More leukemic lymphocytes.

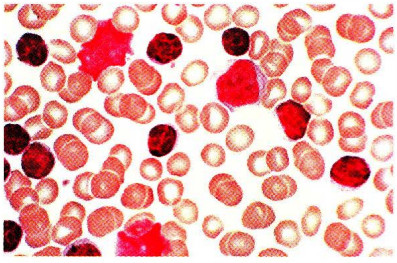

Image 8-28: CLL/SLL: Smudge cells.

Quick Quiz

- NHL prognosis depends on what 2 patient-specific factors?
- What drug is now incorporated into treatment for most cases of NHL—whether indolent or aggressive?
- What is the treatment for asymptomatic follicular lymphoma?
- Marginal zone lymphoma is associated with what chronic infection?
- What is the difference between CLL and SLL?
- What does rapid enlargement of previously stable lymph nodes in a patient with CLL/SLL suggest?
- What is the treatment for CLL/SLL without symptoms?
- What is the clinical presentation of hairy cell leukemia?

disease, with different manifestations depending on where the abnormal cells are found.

Typically, there is an initial leukemic phase (cells in the blood: CLL) that progresses to a lymphoma phase (cells in the lymph nodes: SLL).

Clinically, the majority of patients with CLL/SLL are diagnosed at an asymptomatic stage with a high lymphocyte count found on a routine CBC. Suspect CLL with the appearance of a high lymphocyte count and smudge cells on the peripheral blood smear. Of note, only 5,000 B cells of a monoclonal origin (noted on flow cytometry) are required to diagnose CLL. Characteristic markers on the cell surface can differentiate CLL/SLL from other lymphomas with leukemic components.

Prognosis has largely been based on the Rai staging system. Other favorable prognostic findings:

- Mutated Ig heavy chain variable region
- 13q deletion
- Low ZAP-70 and CD38 levels

Poor prognostic cytogenetics:

- 17p deletion
- 11q deletion

A staging system unique to CLL/SLL, the Rai system, is shown in Table 8-8, along with the Binet system that also is used. Asymptomatic patients with only high WBC are stage 0 and have a near-normal life expectancy.

With disease progression, the lymphoma element begins to dominate, and patients develop symptoms secondary to lymphadenopathy (stage I), hepatosplenomegaly (stage II), anemia (stage III), and thrombocytopenia (stage IV). The cytopenias are due to bone marrow infiltration by leukemic cells, splenic sequestration, and antibody-mediated destruction.

CLL/SLL is characterized by a disordered immune system. Frequent autoantibodies directed against red cells and platelets develop, leading to immune-mediated hemolytic anemia and thrombocytopenia. The resultant cytopenias can be managed with prednisone. Paradoxically, CLL/SLL also is characterized by hypogammaglobulinemia. When patients with CLL/SLL and low immunoglobulin levels develop frequent infections (especially pneumococcus, *Staphylococcus*, *H. influenzae*, and herpes), they can be managed with monthly IVIG infusions.

As with follicular lymphoma, approximately 10% of patients with CLL/SLL transform to diffuse large cell lymphoma ("Richter transformation")—a transformation often heralded by fever, rapid enlargement of previously stable nodal disease, and a rising LDH.

Treatment of CLL/SLL is mainly a "watch and wait" strategy like other indolent lymphomas. Several treatment options are available, however:

- Young patients: multiple agents (fludarabine and rituximab) with the goal of a prolonged remission (risks immunosuppression). Stem cell transplant is under investigation.
- Elderly patients: chlorambucil (gentle, single-agent therapy) and rituximab with goal of symptom palliation. Bendamustine (an alkylating agent) is gaining increased use in both elderly and younger patients.

Hairy Cell Leukemia

Hairy cell leukemia is a rare indolent NHL with components of both lymphoma and leukemia. Patients often present with splenomegaly and complications of

Table 8-8: Staging Systems for B-cell Leukemias

Stage	Clinical Findings	Risk Level	Median Survival (Years)
Rai System			
Stage 0	Lymphocytosis	Low	12
Stage I	Lymphocytosis + adenopathy	Mid	9
Stage II	Lymphocytosis + hepatosplenomegaly	Mid	7
Stage III	Anemia	High	1–2
Stage IV	Thrombocytopenia	High	1–2
Binet System			
A	< 3 sites involved	Low	10
B	> 3 sites involved	Mid	5
C	Anemia and/or thrombocytopenia	High	3

cytopenias. The peripheral smear can show characteristic cytoplasmic "hairy" projections on the lymphocytes' cell surface (see Image 8-29 and Image 8-30).

The disorder responds well to chemotherapy, and remissions can be prolonged. Purine analogs are used with cladribine (2-CDA), which are preferred over pentostatin because of equally good results (> 80% remission)—with less toxicity and only 1 cycle of treatment needed.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia (lymphoplasmacytic lymphoma) is an indolent B-cell lymphoma characterized by the clonal expansion of lymphocytes with plasma cell properties that produce monoclonal IgM. Clinical presentation includes:

- **Hyperviscosity syndrome** (headache, dizziness, vision disturbances) secondary to high levels of IgM (look for "sausage-link veins" on funduscopy, which are tortuous veins caused by the hyperviscosity)
- **Constitutional** symptoms, oozing blood at mucosal surfaces, lymphadenopathy, and/or splenomegaly

Acute hyperviscosity syndrome should be treated with plasmapheresis. Prognosis depends upon age and the presence of anemia. As with other indolent lymphomas, treatment should be initiated only after symptoms develop. Therapy is typically rituximab-based chemotherapy.

Teaching point: Note that hyperviscosity symptoms can occur with polycythemia vera (PV), leukocytosis > 100,000/mL, WM, MM, and cryoglobulinemia. When the hyperviscosity and associated symptoms are due in immunoglobulins (WM, MM, cryoglobulins), it is called "hyperviscosity syndrome." When it is due to WBCs, it is called leukostasis.

AGGRESSIVE NON-HODGKIN LYMPHOMAS

Diffuse Large Cell Lymphoma

This is the most common aggressive lymphoma. It may develop *de novo* or arise from a previously indolent lymphoma. While diffuse large cell lymphoma (DLCL) is predominantly a disease of the lymph nodes, it may also develop in extranodal sites such as the lung or liver. If left untreated, life expectancy is measured in months.

Treat with the standard chemo regimen: R-CHOP (rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone). Localized DLCL can be treated with 3 cycles of R-CHOP, followed by involved field radiotherapy. Advanced disease gets 6–8 cycles of R-CHOP.

Almost all patients respond to this treatment, and 40–50% get long-term disease control. Half of these become refractory—or the lymphoma recurs soon after completing therapy. Treat recurrence in young patients with further chemotherapy and refer for autologous stem cell transplant. Treat older patients with palliative chemotherapy.

Burkitt Lymphoma

Burkitt's is the most aggressive of the NHLs and presents in the context of endemic EBV infection (Africa), sporadic occurrence (U.S. and Europe), and immunodeficiency (especially HIV/AIDS).

The genetic hallmark is translocation of the *C-MYC* oncogene, which results in aggressive cell turnover with rapid growth.

Know that for patients with HIV, the development of a Burkitt lymphoma is an AIDS-defining illness regardless of the CD4 count.

Presentation typically is an enlarging abdominal mass, and the rapid cell turnover may be associated with spontaneous tumor lysis syndrome. Dissemination to the CNS is common, and treatment with intrathecal chemotherapy is standard. Treatment consists of prolonged high-dose chemotherapy as well as treatment or prophylaxis for CNS involvement.

Mantle Cell Lymphoma

Mantle cell is a subtype of NHL that combines the least desirable characteristics of both classes of NHL. Like indolent NHL, it is incurable with standard chemotherapy; and like aggressive NHL, it progresses rapidly with median survival ≤ 3 years. There is typically bone marrow, peripheral blood, and spleen involvement; and patients often present with cytopenias and splenomegaly.

Extranodal involvement is common, especially in the GI tract, and there is often a leukemic component. Hallmark is overexpression of *BCL-1* gene product cyclin D1 due to the t(11;14) translocation. Initiate treatment early with the goal of inducing a temporary remission.

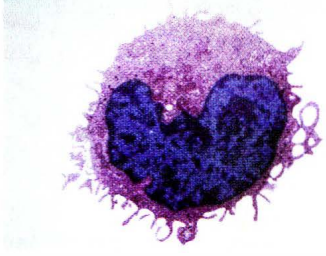

Image 8-29: Hairy cell (electron microscope).

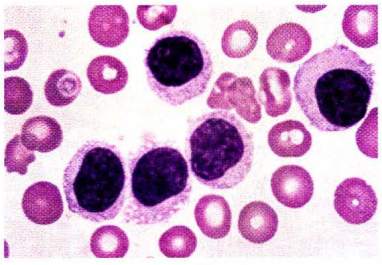

Image 8-30: Hairy cell leukemia.

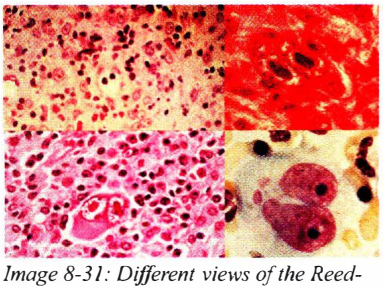

Image 8-31: Different views of the Reed-Sternberg cell as seen in Hodgkin disease.

QuickQuiz

- What is the standard chemo regimen for DLCL?
- Characterize the clinical presentation of Burkitt's. What cytogenetic abnormality is associated?
- What diseases are seen after radiation therapy to the chest during treatment of Hodgkin disease?

T-CELL NON-HODGKIN LYMPHOMAS

T-cell NHLs are classified in a similar fashion as B-cell NHLs: indolent and aggressive.

The peripheral T-cell lymphomas are a group of disorders that includes mycosis fungoides/Sézary syndrome. Early disease is limited to the skin, but later disease develops in lymph nodes. The disorder can be controlled in the early stages with photochemotherapy. As with other indolent lymphomas, the goal of treatment is control rather than cure.

The aggressive forms of T-cell NHL include a T-cell variety of DLCL, which is treated with CHOP (no rituximab as with B-cell DLCL).

HODGKIN DISEASE

Hodgkin disease (HD) is primarily a disease of the young (unlike NHL), with average age of 30 years at time of diagnosis. HD is also a far more curable illness than NHL, with cure rates of 95% in early stages and 65% in advanced stages. Patients with HD often present with an enlarged, painless lymph node.

Diagnosis is made by excisional biopsy (not fine needle aspiration [FNA]). Although the Reed-Sternberg cell (a B cell that resembles "owl's eyes") is the classic and specific histological finding, the diagnosis is aided by immunohistochemical staining. (See Image 8-31.)

In the WHO classification, these lymphomas are categorized as follows:

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classic Hodgkin lymphoma (most common)
  - Nodular sclerosis (most common)
  - Lymphocyte-rich
  - Mixed cellularity
  - Lymphocyte-depleted

These 4 subtypes of classic lymphoma are similar and are typically treated in the same fashion. Accurate staging is critical in HD so as to avoid both undertreatment and overtreatment (Table 8-9).

Staging: H&P; CXR; CT of neck, chest, abdomen, and pelvis; and bone marrow aspiration and biopsy. PET scan is used both for initial staging and to monitor response to treatment. Always restage after treatment.

Treat with **ABVD** (**A**driamycin® [doxorubicin], **b**leomycin, **v**inblastine, and **d**acarbazine:

- Early-stage disease (Ann Arbor stage I or II without bulky disease or B symptoms): 2–4 cycles ABVD + radiation to disease sites.
- Advanced disease (stage III or IV, bulky stage II, or B symptoms): 6–8 cycles ABVD + radiation to any bulky sites.
- Relapsed or refractory disease: high-dose chemotherapy + autologous stem cell transplant.
- Relapsed disease after transplant or multiple lines of chemotherapy: brentuximab vedotin, an anti-CD30 monoclonal antibody-drug conjugate that releases its antimitotic agent upon binding to CD30 positive cells present in HL.

ABVD is less likely than previous treatments to cause sterility (but still may), and it can cause cardiac and pulmonary toxicities from the doxorubicin and bleomycin, respectively.

Radiation to the chest is associated with increased risk of future solid tumors, including lung and breast cancer. Women who receive radiation to the chest should have mammograms starting 10 years after treatment. Also, remember to watch for cardiovascular complications and hypothyroidism.

Table 8-9: Cotswold Modification of Ann Arbor Staging System for Hodgkin Disease

Stage	Definition
I	1 node region or lymphoid structure (e.g., spleen, thymus) or 1 extralymphatic site
II	2 or more lymph node regions on same side of diaphragm (or hilar nodes on both sides)
III	III: Both sides of diaphragm involved III_E: If also contiguous localized involvement of one extranodal site III_S: If involvement of the spleen; if both extranodal and spleen = III_{ES}
IV	Disseminated

The following apply to all stages:
A = Asymptomatic.
B = Symptoms: Fever > 38° C, drenching night sweats, unexplained loss of > 10% body weight within preceding 6 months.
X = Bulky disease (a widening of the mediastinum by more than 1/3 of the size of a nodal mass—this nodal mass having a max dimension > 10 cm).
E = Involvement of a single extranodal site that is contiguous or proximal to the known nodal site. If the extranodal site is the spleen, then S = spleen is used.
The number of anatomic regions involved is also indicated by a subscript.

LYMPHOMA AND IMMUNOSUPPRESSION

Overview

Patients with both congenital and acquired immunodeficient states are at increased risk for lymphoma. In adults, the 2 most common immunodeficient states are HIV/AIDS and iatrogenic immunosuppression after solid organ transplant.

Lymphoma and HIV

The majority of HIV-associated lymphomas are aggressive NHLs, with DLCL and Burkitt's predominating. Whether or not antiretroviral therapy (ART) has impacted the incidence of NHL in HIV/AIDS is unclear. ART seems to have reduced the incidence of lymphoma in patients with CD4 < 50/mm^3, but Burkitt's is increasing in incidence in patients with higher CD4 counts. Patients with HIV also are at increased risk for Hodgkin disease, and control of the infection has not altered this risk.

Primary CNS lymphoma (DLCL limited to the CNS) is universally associated with EBV in patients with HIV/AIDS. Primary effusion lymphoma (PEL) usually presents as ascites or pleural effusion and is associated with HHV-8. HIV/AIDS-associated HD presents more often with extranodal disease and B symptoms.

Treatment is similar to that given to patients without HIV, except that rituximab may not show benefit in HIV-positive patients with DLCL and CD4 counts < 50/mm^3 due to the increased risk of death from infection.

Lymphoma and Post Transplant

Post-transplant lymphoproliferative disorders occur in approximately 5% of patients with solid organ transplants. The risk of lymphoma is highest in the 1st year after transplant. The lymphoma is often composed of nonclonal B cells. Over 90% of early lymphomas are EBV-positive. When disease occurs, it is often at a late stage with extranodal manifestations.

Treatment consists of lowering the degree of immunosuppression—allowing anti-EBV immunity to attack the lymphoma cells. If this is not tolerated, attempt treatment with chemotherapy.

Quick Review

Remember these diseases that are associated with an increased risk of lymphoma:

- Chronic autoimmune thyroiditis (Hashimoto's)
- Sjögren syndrome
- Celiac disease
- Chronic *H. pylori*
- HIV/AIDS

PLASMA CELL DISORDERS

Multiple Myeloma

Multiple myeloma (MM) is a neoplasm of B cells that results in a clonal expansion of plasma cells. These cells produce an M (monoclonal) component, which may be intact immunoglobulin or fragments of heavy or light chains. Any immunoglobulin subclass (IgG, IgA, IgD, IgE, and IgM) may appear as the "M" component. Waldenström macroglobulinemia (page 8-36) is a B-cell lymphoma that secretes monoclonal IgM. It presents differently from MM. These paraproteins, together with the cells producing them, cause many clinical problems.

In MM, bone pain is the most common symptom—often localized in the back or ribs. Tumor cells invade bone and release osteoclast-activating factor, creating punched-out lytic lesions that are seen on radiographs but not on bone scans—because there is no associated new bone formation. Pathologic fractures are common.

Frequent infections result from a diffuse hypogammaglobulinemia. While total immunoglobulin levels are elevated, normal immunoglobulin production is suppressed, and catabolism of immunoglobulin is accelerated.

Renal failure can result through a multitude of mechanisms, including hypercalcemia, amyloid deposition, tubular obstruction, and direct toxic effects of the paraproteins.

Additional clinical symptoms secondary to hypercalcemia, anemia, and neuropathy develop. Plasmacytomas (plasma cell tumors) can cause local symptoms, depending on their location, including spinal cord compression.

Think about myeloma when you see:

- Bone pain
- Symptoms of hyperviscosity
- Recurrent bacterial infections

Plus a combination of the following labs:

- Rouleaux formation on peripheral blood smear
- Hypercalcemia
- Increased creatinine +/– proximal (Type 2) renal tubular acidosis
- Normocytic/normochromic anemia
- Elevated T protein but decreased albumin with decreased anion gap (due to increased positively charged paraprotein)

Diagnose with a serum (SPEP) and urine immunoelectrophoresis (UPEP) to detect the monoclonal protein, but know that the plasmacytoma variant may not have an M spike. Furthermore, myelomas that produce only light chain immunoglobulins do not have an M spike.

Measure serum viscosity if the M-protein concentration is > 5 g/dL (or if the patient has symptoms, such as headache).

QuickQuiz

- Primary CNS lymphoma in patients with HIV/AIDS is associated with which virus?
- Which virus is associated with post-transplant lymphoma?
- What diseases are associated with an increased risk of lymphoma?
- What are the typical symptoms of multiple myeloma? The lab findings?
- Characterize the differences between MGUS, smoldering myeloma, and multiple myeloma.

A skeletal survey helps identify lytic lesions.

Bone marrow biopsy assists with definitive diagnosis (> 10% plasma cells in BM sample).

Measurement of serum β_2-microglobulin helps predict survival and is used in the ISS staging system (see below). β_2-microglobulin is a protein that is associated with MHC class I heavy chains—found on the surface of nucleated cells. An increase in its amount tells you that extra lymphocytes are circulating.

Multiple myeloma must be distinguished from the vastly more common MGUS and from smoldering myeloma. See Table 8-10.

Staging for MM includes the Durie-Salmon system (which utilizes level of anemia, hypercalcemia, presence of lytic lesions, and level of paraprotein) and a much simpler International Staging System ([ISS], Table 8-11).

Initiate treatment when symptomatic (i.e., lytic lesions appear) or the M component rises above 5 g/dL.

Table 8-10: Monoclonal Gammopathies

MGUS (monoclonal gammopathy of undetermined significance)	Serum monoclonal protein < 3 g/dL Bone marrow plasma cells < 10% and Absence of end-organ damage
Smoldering myeloma (asymptomatic myeloma)	Monoclonal protein ≥ 3 g/dL or Bone marrow plasma cells ≥ 10% and Absence of end-organ damage
Multiple myeloma	Bone marrow plasma cells > 10% or biopsy-proven plasmacytoma and Presence of monoclonal protein (in urine or serum) and Evidence of end-organ damage (i.e., lytic bone lesions, anemia, hypercalcemia, renal insufficiency attributable to the plasma cell disorder)

There are many effective therapies, including thalidomide and dexamethasone, and newer therapies, including a thalidomide-like agent, lenalidomide (Revlimid®) and the proteosome inhibitor, bortezomib (Velcade®), to induce remission. Stem cell transplant is then used for remission prolongation. Older patients can be managed with alkylating agents (melphalan or cyclophosphamide) plus prednisone. Treat plasmacytomas with local radiation.

Monoclonal Gammopathy of Uncertain Significance

Both MM and monoclonal gammopathy of undetermined significance (MGUS) have an association with previous heavy exposure to pesticides. MGUS is seen in 1% of people age > 50 years and 10% of people age > 75.

Patients with MGUS have:

- a bone marrow plasmacytosis < 10%,
- no bony lesions, and
- M components < 3 g/dL.

Any immunoglobulin subtype may be seen (IgG, A, M, D, E). Urinary light chains are absent. There is no increased risk of infection, renal failure, or anemia.

A risk stratification model including M-spike > 1.5 g/dL, non-IgG subtype, and an abnormal serum free light-chain ratio is useful for predicting progression. Depending upon these 3 things, 5% (no risk factors) to 58% (all 3 risk factors) progress to multiple myeloma at 20 years.

There is no role for preemptive therapy with MGUS.

Follow-up for patients with MGUS includes a repeat SPEP q 6 months x 13 years and, if stable, annually thereafter.

Patients with smoldering myeloma (asymptomatic myeloma) do not require treatment either but should have more involved follow-up, including a CBC, creatinine, calcium, and SPEP/UPEP every 3–6 months along with annual skeletal survey.

Table 8-11: International Staging System for MM

Stage	Definition	Median Survival (Months)
I	β_2MG < 3.5 mg/L Albumin ≥ 3.5 g/dL	62
II	Neither I nor III	44
III	β_2MG ≥ 5.5 mg/L	29

ONCOLOGY

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia due to cancer occurs most frequently in patients with the following malignancies:

- Squamous cell carcinomas arising in the lung or head and neck
- Multiple myeloma
- Breast carcinoma
- T-cell lymphoma
- Renal cell carcinoma

Symptoms include fatigue, constipation, anorexia, nausea, polyuria, polydipsia, and alteration in mental status. Patients often present with profound hypovolemia. Obtundation and dysrhythmias can occur in severe cases. Symptom severity is associated with the rate of rise in calcium and the ionized calcium level.

Causes of hypercalcemia of malignancy:

- Increased osteoclastic activity induced by local bone metastasis
- Ectopic production of a parathyroid-related protein (PTHrP)
- Overproduction of 1,25-$(OH)_2$-D (active form)

PTHrP is the usual cause of malignancy-associated hypercalcemia in patients with squamous cell carcinomas. The receptor-binding area for PTHrP is similar to PTH, which results in increased calcium resorption from the bones and increased calcium resorption in the distal tubules. Given the high incidence of concomitant hyperparathyroidism in patients with malignancy, evaluation should include PTH, PTHrP, and 1,25-$(OH)_2$-D.

Albumin binds calcium and, with hyperalbuminemia, you may have a high total calcium level but a normal free calcium level. When a lab result shows hypercalcemia, first check the albumin level. For any increase in albumin above the normal upper limit, decrease the patient's total calcium lab result by 0.8 x that increase. If the result now falls in the normal range for calcium, the free calcium level is normal. (Same in reverse for hypocalcemia in the setting of hypoalbuminemia.)

ECG changes indicating hypercalcemia are a short QT interval due to a shortened ST interval. With levels > 16 mg/dL, the T wave widens.

Know management: The most important step in the management of hypercalcemia is vigorous hydration with IV normal saline. Once euvolemia is established, furosemide (if volume overload is an issue) can be given to force diuresis and calciuresis. If furosemide is given prior to euvolemia, it may exacerbate the hypercalcemia and hypovolemia. Volume expansion helps treat hypercalcemia but does not maintain calcium levels in the normal reference interval. It is important to administer a bisphosphonate. (Zoledronic acid 4 mg IV over 15 minutes is preferred because of its increased potency and decreased infusion time, but you need to be careful if there is concomitant renal failure.)

Prolonged treatment with pamidronate is associated with sclerosis of glomeruli and nephrotic syndrome.

Osteonecrosis of the jaw (ONJ) is an uncommon adverse effect seen with IV doses and prolonged use of bisphosphonates. ONJ presents as pain, infection, and sometimes fracture of the mandible. There may be exposed bone along the gum line. Patients receiving long-term bisphosphonates should have necessary dental work performed prior to taking the drugs. (Or, if possible, defer the work until the drugs are discontinued.) Counsel such patients that any emergent dental work should be as conservative as possible; e.g., preserve the dental root when possible, in lieu of extraction. X-rays, CT, and MRI can diagnose severe disease but reveal nonspecific findings only in early disease. Treatment of ONJ is still being determined. The bisphosphonate is stopped and a conservative approach with minimal debridement, antibiotic therapy, and oral rinses is usually followed.

Definitive treatment of hypercalcemia of malignancy is treatment of the underlying tumor. See Endocrinology, Book 4, for more on hypercalcemia.

SVC SYNDROME

Superior vena cava (SVC) syndrome occurs most commonly in patients with lung cancer (especially small cell), lymphoma (Hodgkin's and non-Hodgkin's), and mediastinal germ cell tumors.

Classic symptoms:

- Swelling of the face, neck, and arms (typically worse after the patient is supine)
- Cough
- Dyspnea
- Hoarseness (due to laryngeal edema)
- Headaches (due to increasing intracranial pressure)

Physical examination findings:

- Periorbital and upper extremity edema
- Facial plethora
- Elevated jugular venous pressure
- An increased number of collateral veins covering the anterior chest wall
- Abnormal pulmonary exam due to airway compression (i.e., stridor)
- Altered mental status secondary to cerebral edema

Diagnose by CT venogram of the chest, which typically shows a large mediastinal and/or right hilar mass with SVC occlusion.

Although SVC syndrome was previously thought to require emergent treatment, there is often time to establish a diagnosis prior to treatment. A tissue diagnosis prior to therapy is recommended in those without a

Quick Quiz

- Hypercalcemia occurs most commonly in which type of lung cancer?
- How do you initially manage acute hypercalcemia?
- What are the most common causes of SVC syndrome? What is the treatment?
- Name the cancers that commonly metastasize to bone.
- What is the urgent treatment when you suspect spinal cord compression due to bone metastasis?
- What treatment option is available to patients with 3 or fewer small brain mets?

known malignancy. Immediate treatment to shrink the tumor is required for signs of airway compromise and increased intracranial pressure. Radiation therapy, once the mainstay of treatment, is now limited to those tumors that do not respond rapidly to chemotherapy. Chemotherapy is used as initial therapy for most small cell lung cancer, germ cell tumors, and lymphoma. Also, endovascular stents can be used for emergent relief. Use of corticosteroids is controversial, except in cases of a steroid-responsive malignancy (i.e., lymphoma).

BONE METASTASES

Bone metastases are most commonly associated with cancer of the lung, breast, prostate, and kidney—and also with multiple myeloma and non-Hodgkin lymphoma.

Pain is the usual presenting symptom. The large bones with bone marrow: pelvis, vertebral body, sternum, ribs, and femur are most commonly affected.

Confirm the diagnosis by technetium uptake on a bone scan. Note: Lytic only lesions, as commonly seen in multiple myeloma and less commonly in breast and renal cancer, are not evident on the bone scan but can be diagnosed by plain radiographs, CT scan, or MRI.

Radiotherapy is the most common treatment to provide pain relief and prevent fractures. Opiate analgesics along with NSAIDs are often necessary to control symptoms. **Bisphosphonate** therapy may reduce skeletal-related events, as can the RANK ligand inhibitor, denosumab, in solid tumors. Radiopharmaceutical agents such as **samarium** and **strontium** may help palliate painful osteoblastic metastases, which are commonly experienced in prostate cancer. Other developing therapies include radiofrequency ablation (**RFA**), especially in previously irradiated regions, and **vertebroplasty** for vertebral metastasis leading to painful compression fractures. When a lytic lesion occurs in a weight-bearing long bone or the humeri with significant cortical bone destruction, orthopedic intervention is typically indicated to prevent or stabilize a pathologic fracture.

SPINAL CORD COMPRESSION

Spinal cord compression is a dreadful oncologic complication that can lead to paralysis if not recognized promptly and managed effectively. Back pain and localized tenderness are ordinarily the 1st symptoms and may precede neurologic deficits by days to months. The pain is often worse with activity but typically continues with rest. Radiation of pain in a radicular manner is common. Escalating narcotic needs for a patient's baseline pain can be a warning sign of impending cord compression.

All cancer patients with new-onset or worsening back pain should be evaluated promptly with a careful history and neurologic exam looking for paresthesias, paralysis, and pain. The MRI is the diagnostic procedure of choice for the spine. You must conduct a spinal screen of all levels (cervical, thoracic, lumbar, and sacral), since occult, incipient structural problems are often revealed.

As soon as you suspect spinal cord compression due to bone metastases, give dexamethasone at 4–8 mg q 6 h. **Radiotherapy** is the treatment of choice for spinal cord compression due to multiple myeloma or lymphoma. **Surgical** intervention is recommended for most solid tumors, for any patient with progressive neurologic decline, those with no tissue diagnosis, and those who have had previous radiotherapy in the involved region.

BRAIN / LUNG / LIVER METASTATIC DISEASE

Brain metastases can cause significant morbidity. If neurologic abnormalities are present, then treat with intravenous dexamethasone to lessen tumor-associated edema. If the metastatic lesion is solitary and the systemic disease is well controlled, consider neurosurgical resection. Prophylactic antiepileptics are not recommended for patients with no previous seizure history.

Stereotactic radiosurgery is an option for patients with ≤ 3 brain metastases that are all < 3 cm in size. In many patients, the best option is to proceed with whole brain radiotherapy for palliation. Malignancies commonly associated with brain metastasis include lung cancer, breast cancer, renal cell cancer, malignant melanoma, and gastric cancer. On the other hand, malignancies such as prostate cancer and colon cancer are rarely associated with brain metastasis.

The lungs and liver are common sites for metastasis in most malignancies. Surgical resection of liver and lung metastases is reserved for patients with single-organ involvement and low tumor burden. Radiofrequency ablation is a useful modality to palliate painful liver metastasis.

MALIGNANT EFFUSIONS

PLEURAL EFFUSIONS

Malignant pleural effusions have 2 major causes:

1) Exudative reactions due to metastases to major lymphatic structures or pleural surface
2) Chylous effusions due to lymphatic/thoracic duct obstruction

Lung cancer, by far, is the most common cause of exudative malignant effusions. However, as with most sites of metastases, many malignancies can spread to the pleura. Chylous effusions are more commonly seen in patients with non-Hodgkin lymphoma.

Evaluation includes a thoracentesis with appropriate studies to calculate Light criteria (exudative vs. transudative; see Pulmonary Medicine, Book 2, Pleural Effusions), and the fluid should be sent for cytologic evaluation as well. Repeated thoracentesis with cytologic evaluation is worthwhile if the initial cytology is non-diagnostic. You can perform thoracoscopic pleural biopsies in patients when the diagnosis is uncertain.

In patients with symptomatic (dyspnea, chest pain) malignant effusions, drainage is indicated. Most effusions quickly recur if effective treatment of the underlying malignancy with systemic therapy is not achieved. In these patients, consider chest-tube placement with talc pleurodesis or placement of PleurX® catheter with repetitive drainage.

PERICARDIAL EFFUSIONS

Malignant pericardial effusions are caused by either local disease extension into the pericardium or by hematogenous spread to the pericardium. The most commonly associated malignancies are lung cancer, breast cancer, and non-Hodgkin lymphoma.

Closely monitor patients with suspected malignant pericardial effusions for signs and symptoms of tamponade (hypotension with muffled heart sounds, pulsus paradoxus, and JVD; more in Cardiology, Book 3, Pericardial Diseases). Echocardiography is highly recommended. It not only confirms the presence of the effusion, but it gives an immediate determination of degree of hemodynamic compromise. If the effusion presents a risk for tamponade, perform a pericardial window procedure.

ASCITES

Malignant ascites is due to peritoneal seeding of the malignancy. This often presents in patients with ovarian cancer. All gastrointestinal cancers, breast cancers, and non-Hodgkin lymphomas can cause malignant ascites. Paracentesis can be both diagnostic and therapeutic. In refractory cases, peritoneal catheters are placed for palliative therapy.

TUMOR LYSIS SYNDROME

Tumor lysis syndrome is the metabolic derangement caused by release of cellular components into the blood after rapid lysis of malignant cells. It can occur spontaneously in cancers with a high cell turnover (e.g., Burkitt's), in response to cytotoxic therapy or radiation if a large tumor burden is present, or if the cancer is highly sensitive to treatment (e.g., non-Hodgkin lymphomas, ALL, AML).

Lysis results in hyperuricemia +/– acute kidney injury due to uric acid precipitation in renal tubules. Malignant cells have high levels of phosphorous—rapid release of PO_4 stores can cause hyperphosphatemia and hypocalcemia. Calcium phosphate then can precipitate in the kidneys, also contributing to kidney injury. Potassium release causes hyperkalemia. Clinical manifestations of tumor lysis include arrhythmias, acute kidney injury, and seizures—and sometimes death.

In 2008, the American Society of Clinical Oncology (ASCO) published risk-stratification guidelines and recommendations for tumor lysis prophylaxis. For patients who are at high risk for hyperuricemia, add rasburicase to initial supportive management of aggressive hydration. Intermediate-risk patients can be managed with hydration only, with the addition of rasburicase if hyperuricemia develops.

Allopurinol prevents formation of the uric acid but does not decrease pretreatment uric acid levels. It can also increase serum levels of the relatively insoluble purine precursor, xanthine, which can precipitate in the kidneys and cause obstructive uropathy.

Rasburicase (recombinant urate oxidase) oxidizes uric acid to the more soluble allantoin, which decreases pretreatment uric acid levels and avoids the risk of xanthine precipitation seen with allopurinol.

BREAST CANCER

NOTE

Know breast cancer perfectly. It is the most common malignancy in women and the second leading cause of death in women (after lung cancer). 12% of women born today develop breast cancer at some point in their lives. There are ~ 200,000 new cases diagnosed annually; ~ 40,000 women die from breast cancer each year in the U.S. The incidence of breast cancer has been increasing at 2% per year for the past 50 years, and the deaths-per-year index is only just now decreasing slightly—likely due to earlier detection and better treatment.

Quick Quiz

- What malignancies are associated with pericardial metastases?
- Rasburicase is used in the management of what condition?
- List the factors associated with an increased risk for breast cancer.
- What cancers are associated with *BRCA* mutations?

RISK OF BREAST CANCER

Increased risk:

- The most significant risk factors for breast cancer are a personal history of previous breast cancer, female sex, and increased age.
- 1st degree relatives of breast cancer patients—3x normal, especially if the involved member was premenopausal and had bilateral breast cancer.
- Genes: In 1994, the first breast cancer gene was identified (*BRCA1*). It was localized to chromosome 17q21. It is present in 5% of women and is associated with a 50–85% lifetime risk of developing breast cancer, with a 50% chance of occurrence before age 50. This compares to a 12% lifetime risk in the general population. Male breast cancer is rare, but many men with breast cancer carry *BRCA* mutations.
- *BRCA* also is associated with a 40% lifetime risk of developing ovarian cancer—and accounts for most patients with familial ovarian cancer, which compares to a 1.5% lifetime risk in the general population. *BRCA1* also is associated with colorectal and prostate cancer. *BRCA2* (13q12-13) is associated with a similarly high risk of breast cancer and a 10–20% risk of ovarian cancer. *BRCA2* also is associated with melanoma, pancreatic cancer, and prostate cancer. Although only about 5% of breast cancer cases are attributable to a specific genetic abnormality, together, alterations of the *BRCA1* and *BRCA2* genes account for 30–50% of all inherited breast cancer. In patients with a *BRCA* mutation, bilateral mastectomies may decrease the incidence of breast cancer by up to 90%. Bilateral oophorectomies may decrease the risk of ovarian cancer by up to 90% and can decrease the risk of breast cancer for premenopausal women.
- Atypical ductal hyperplasia in breast biopsy samples ---4x normal.
- DCIS or LCIS (ductal/lobular carcinoma *in situ*)—10x normal. LCIS is associated with increased risk of cancer in either breast. LCIS is a marker for invasive carcinoma, while DCIS evolves into invasive carcinoma.
- Also: early menarche, late menopause, late 1st pregnancy or nulliparity, obesity, moderate-to-heavy alcohol ingestion, and mantle field radiation therapy.

In normal postmenopausal women, conjugated estrogens cause a slightly increased risk of breast cancer after 5 years of use. They definitely increase the risk of endometrial cancer if given without progestins.

A trial of combined estrogen plus progestin (the Women's Health Initiative) was stopped early because overall risks, including invasive breast cancer, exceeded benefits.

The oncologic risks of postmenopausal estrogen replacement therapy (ERT) were thought to be offset by the benefits: decreased incidence of hip fractures, sexual dysfunction, and cardiovascular disease; however, the 1998 HERS trial showed that estrogens with progestin are associated with an increased risk of secondary cardiac events in the 1st year of treatment, and it also showed no cardiovascular benefit at 7-year follow-up. Also noted was an increased risk of thromboembolism and biliary tract surgery in those on long-term estrogen/progestin replacement therapy. Due to the results of this trial, this therapy has fallen out of favor. Breast cancer survivors should not be treated with estrogen replacement therapy because data have shown it to be associated with breast cancer recurrence and worsened mortality.

SCREENING FOR BREAST CANCER

Overview

The following paragraphs are summaries of the current breast cancer screening guidelines. Many of these guidelines are at odds with one another. Thus, suggestions on how to handle the discrepancies are provided.

Mammography is less sensitive in women with dense breasts and those who have used estrogen replacement therapy or oral contraceptives (which delay the transition of breast tissue from dense to fatty). Being postmenopausal increases the sensitivity of mammography.

ACS Screening Guidelines

The American Cancer Society (ACS) guidelines recommend yearly mammography starting at age 40 and continuing as long as the woman is in good health. Existing data suggest that digital mammography is superior to film mammography in women younger than age 50 with dense breasts—but digital mammography offers no benefit over film in any other groups of women.

Clinical breast exam (CBE) is recommended every 3 years between ages 20 and 40 and yearly after age 40. Breast self-exam (BSE) is an option for women once they reach age 20.

USPSTF Screening Guidelines

The U.S. Preventative Services Task Force (USPSTF) 2009 guidelines recommend biennial (q 2 years) mammography screening between the ages of 50 and 74. Biennial screening prior to age 50 is an individual decision. There are insufficient data to recommend screening in women > 75 years of age.

There are insufficient data to recommend for or against CBE, digital mammography, or MRI screening. USPSTF recommends against BSE.

ACP Screening Guidelines

The American College of Physicians (ACP) panel had difficulty similar to the USPSTF in making recommendations for women 40–50 years of age. The ultimate ACP guideline recommends that mammography risks and benefits be discussed with the patient.

Putting It Together

The vagueness of the USPSTF and ACP guidelines arise because their recommendations are "data driven" or "evidence based"—not "expert driven," like the ACS guidelines. Thus, if only limited data exist for or against an intervention, then the USPSTF and ACP won't make a definitive recommendation for or against.

Most practicing physicians are recommending BSE and CBE for women > 40 years of age (or earlier in patients with significant family histories). But, again, this is not an evidence-based decision.

But what do you learn for the Boards? We recommend you focus on where the guidelines agree. Guidelines agree in the recommendation to screen women with mammography from ages 50 to 74 (most say yearly, but the USPSTF says every 2 years). There are opposing stances in the guidelines on the use of breast exams (BSE and CBE), so they shouldn't appear on the Boards.

Breast MRI

Breast MRI is being used for screening in select women, usually young women with dense breast tissue at high risk of developing breast cancer. It has a high sensitivity but limited specificity. The procedure requires injection of gadolinium contrast and is significantly more expensive than mammography. The ACS supports breast MRI screening for the following high-risk women only:

- *BRCA1*- or *BRCA2*-positive status
- 1st degree relatives with *BRCA1* or *BRCA2* and the patient untested
- Lifetime risk of breast cancer ≥ 20–25%
- Radiation to the chest between ages 10 and 30 years
- Carrier of, or 1st degree relative with, the TP53 (Li Fraumeni syndrome), *PTEN* mutation (Cowden syndrome), or hereditary diffuse gastric cancer syndrome

PHYSICAL FINDINGS

Patients often find breast cancer, either incidentally or during a self-exam. Over the last 10 years, an increasing proportion has been diagnosed by mammography. Breast cancer may be any shape or size. Typically, it forms a hard, well-defined "**dominant mass**," in contrast to diffuse fibrocystic changes.

Work up **asymmetric eczema** of the nipple in a non-breastfeeding woman for Paget disease of the breast. This is done by a nipple scraping for cytology or a nipple punch biopsy. Note that allergic eczema is a symmetric disease.

Inflammatory breast cancer is very aggressive and can present as a mastitis with **warmth**, **redness**, and **swelling**. There can be a peau d'orange (skin of the orange) appearance and nipple inversion. Mastitis in a non-lactating woman is rare, so initiate a workup for inflammatory breast cancer in non-lactating women with this presentation. Inflammatory breast cancer is very aggressive. Mammograms pick up 63% of minimal breast cancers that are not otherwise detectable.

Nipple discharge that is not milky and bilateral is always considered abnormal. **Bloody** discharge is commonly due to a papilloma but can be a sign of breast cancer. **Greenish** discharge is an indication of a draining cyst. **Clear** discharge may also be caused by breast cancer. Cancer is less likely when the discharge occurs from both breasts.

WORKUP FOR BREAST CANCER

What workup to do for a suspicious breast finding:

1st: mammogram, ultrasound, +/– MRI.

2nd: aspiration (FNA)/biopsy.

3rd: Determine receptor and *HER2/neu* status.

4th: Treat as indicated.

1st: **Mammography** is required for all suspicious breast lesions (e.g., for mastitis not associated with lactation; for eczematous nipple—see Physical Findings above).

Suggestive findings of concern for malignancy on the mammogram:

- Clusters of irregular microcalcifications (most clusters are benign)
- Densities with irregular borders (stellate or spiculated lesions)
- Distorted architecture

Ultrasound the mass to determine whether it is cystic or solid. If the mass is a simple cyst, consider fluid aspiration and analysis. Ultrasound cannot differentiate solid malignant from solid benign tumors—so, if the mass is solid by ultrasound, refer for biopsy.

The impact of a breast MRI during the initial evaluation is evolving. Nearly all invasive breast cancers enhance with

QuickQuiz

- Mammography, either yearly or every 2 years, should definitely be recommended as a screening tool for women at what ages?
- Clinical mastitis in a woman who is not breastfeeding should make you consider what diagnosis?
- What is the sequence of actions used in the workup of a suspicious breast mass? Explain in detail.
- What are the indications for breast-conserving therapy for treatment of DCIS?

gadolinium. MRI also is helpful in evaluating both the ipsilateral and contralateral breasts for occult lesions once malignancy has been established. Finally, MRI is the best modality to assess the breasts for an occult primary tumor in a woman with adenocarcinoma of unknown primary site involving the axillary lymph nodes.

2nd: **Biopsy** to confirm the diagnosis of breast cancer by FNA and core needle biopsy. At this time, the ultrasonographer also looks in the axilla for enlarged lymph nodes.

Also, biopsy any palpable non-cystic masses—even if the mammogram is negative—because the sensitivity of mammography for identifying malignancy is only 75–80%.

3rd: If the biopsy shows invasive cancer, evaluate estrogen and progesterone **receptor status**, *HER2/neu* status, and grading of the cancer.

4th: **Treat** (discussed later). See Table 8-12 for staging and survival rates.

CARCINOMA *IN SITU* (LCIS AND DCIS)

Overview

We now review 2 types of carcinoma *in situ* ([CIS]; noninvasive cancer) and then invasive breast cancer.

2 types: Lobular (**LCIS**) and ductal/intraductal (**DCIS**). Both are associated with risk of breast cancer (10x N). Both types are benign and curable with resection, but both can be associated with multifocal involvement of the involved breast and also bilateral breast involvement. LCIS is frequently bilateral (30%).

LCIS appears to be a marker indicating that either breast is at risk of developing an invasive carcinoma but, by itself, does not evolve into an invasive carcinoma. Rather, it is an "innocent bystander," seen in about 2–3% of biopsies.

DCIS is more common (20% of all new breast cancers) than LCIS. It is frequently associated with distinct microcalcifications on mammogram, and it is usually confined to a lobule. The calcifications are often clustered and rod-shaped or angulated. DCIS is divided into low-, intermediate-, and high-grade types. The high-grade type is comedocarcinoma, which has a high risk of becoming invasive. DCIS evolves into an invasive carcinoma at the rate of 1% per year.

Treatment of LCIS

LCIS is a benign lesion and more appropriately managed with observation. However, because of the increased risk of breast cancer, and because the disease is frequently multifocal and bilateral, some patients opt for a bilateral mastectomy (occurs less often now). This is an extreme approach, but might be given more consideration in the woman whose mammograms show very dense breast tissue and are thus difficult to evaluate.

In the 1998 NSABP-P1 prevention trial, tamoxifen—an estrogen receptor modulator—was shown to reduce invasive breast cancer in LCIS patients by 56%. However, there are risks with tamoxifen therapy (venous thromboembolism, endometrial cancer), and you should carefully discuss these risks with the patient before beginning such treatment.

Treatment of DCIS

Treat DCIS with surgical excision: either simple mastectomy or (preferably) local excision with adequate margins, also known as breast-conserving therapy (BCT).

The majority of women with DCIS are candidates for BCT as long as certain criteria are met:

- Negative margins should be achieved, with the optimal margin being ≥ 10 mm.

Table 8-12: Breast Cancer Staging and Survival

Breast Cancer — Do not memorize, just review!					
Stage	**Definition**	**TNM Classification**			**10-yr survival**
Stage 0	Carcinoma *in situ*	Tis	N0	M0	Most
Stage I	< 2 cm, no nodes	T1			75%
Stage II	2–5 cm or axillary node positive	T < 4	N0–1		50%
Stage IIIa	> 5 cm or fixed nodes		N2		
Stage IIIb	Ca spread to chest wall or skin or Spread to internal mammary nodes	any with T4 or any with N3			27%
Stage IV	Distant metastases	any T and N		M1	< 10%

- The resection should lend itself to a cosmetically acceptable result. This is dependent on the size and number of lesions in relation to breast size. Multifocal disease often requires a simple mastectomy.

Important prognostic factors include grade of lesion (high-grade lesions, such as comedo subtype, are more likely to recur than low-grade lesions, such as cribriform subtype) and resection margin width.

For patients who elect BCT, local radiation therapy (RT) reduces risk of in-breast recurrence by 50%. However, the addition of RT has not shown any survival benefit.

The NSABP-24 trial examined the role of tamoxifen in patients with DCIS. All patients underwent excision and RT and subsequently were randomized to placebo or tamoxifen. In DCIS, tamoxifen reduced the absolute risk of an ipsilateral breast event by 3.3% at 5 years. However, the addition of tamoxifen has not shown a survival benefit.

INVASIVE BREAST CANCER

Types

Most invasive breast cancer is the invasive ductal type (> 80%). Next is invasive lobular (10%); then medullary (5%).

Prognosis for Localized Invasive Breast Cancer

[Know:] The most important prognostic factor is the presence or absence of lymph node metastases. The more nodes involved, the worse the prognosis. More than 1/2 of breast cancer patients have negative axillary nodes at the time of diagnosis.

More recently, a technique using "sentinel nodes" has been used. Sentinel nodes are the 1st nodes that the tumor drains into, and they are determined by the injection of a radioactive substance around the tumor or into the biopsy cavity. These sentinel nodes then are identified and removed by probe-guided resection. The majority of breast cancers drain to nodes in the axilla. The positive or negative status of the sentinel nodes is 97% accurate in reflecting the positive or negative status of all the axillary nodes. If the sentinel node is negative, no further sampling is required. If the sentinel node is positive, a full axillary dissection must be performed.

The next most important prognostic factor is the size of the primary tumor. If the tumor is < 1 cm and axillary nodes are negative, the 5-year relapse rate is around 10%; if > 2 cm, the 5-year relapse rate is 20%. If axillary nodes are at all positive, 5-year relapse rates rise to 50–80%.

Overexpression of the *HER2/neu* oncogene occurs in ~ 25–30% of breast cancers and is associated with increased likelihood of distant metastases, as well as with a more aggressive cancer. Overexpression of the *HER2/neu* oncogene is predictive of a benefit from adjuvant chemotherapy (now includes 1 year of trastuzumab), but is associated with less benefit from adjuvant hormonal therapy.

Positive estrogen receptors (ER+) and positive progesterone receptors (PR+) are favorable prognostic indicators because they predict a benefit from adjuvant hormonal therapy (tamoxifen or aromatase inhibitor).

Genomic technologies are increasingly being applied to breast cancer specimens to refine prognosis. Oncotype DX® is a RT-PCR testing for 16 gene panels on paraffin-embedded tissue. It has been evaluated retrospectively in node-negative breast cancer patients. In this analysis, gene profiling has been able to risk-stratify patients into groups with low-, intermediate-, and high-risk recurrence scores when treated with endocrine therapy. High-risk patients benefit from adjuvant chemotherapy, while there is no benefit in low-risk patients. It is still unclear which patients in the intermediate-risk group benefit from treatment, and the decision should include patient preferences.

An aggressive histologic grade and the presence of nodal metastases are also poor prognostic factors.

Overall, the most powerful prognostic factor is stage of disease—indicated by lymph node status and size of tumor. The presence of distant metastasis indicates incurable disease.

Initial Treatment of Invasive Breast Cancer

Management of invasive breast cancer is determined by the following:

- Presence or absence of lymph node involvement
- Size of the primary lesion
- *HER2/neu* status
- Hormone receptor status (HR+ or HR–)
- Presence or absence of metastasis
- Whether the patient is pre- or postmenopausal
- Patient preferences

Note that, except for the last 2, these are the same factors used to determine prognosis. Review and learn Table 8-12 on page 8-45 and Table 8-13 on page 8-48.

Primary treatment for invasive breast cancer is broken down into 2 parts:

1) **Local** control: This entails removal of the tumor, whether by modified radical mastectomy or a breast-conserving therapy ([BCT]; lumpectomy). When lumpectomy is performed, it is always followed by radiation therapy to the breast (BCT + RT).
2) **Systemic** control: While lumpectomy and radiation decrease the risk of the cancer returning to the affected breast, they do not prevent the cancer from recurring at distant sites. For this, adjuvant therapy is given. There are 3 types of adjuvant therapy: hormonal, chemotherapy, and biologic therapy.

Quick Quiz

- What is the most important prognostic indicator for localized invasive breast cancer? How important is the size of the tumor?
- What is the significance of *HER2/neu* oncogene overexpression?
- What is the significance of positive estrogen and progesterone receptors?
- What factors influence the type of adjuvant therapy selected for a breast cancer patient?
- Which drugs, when given concomitantly, decrease the efficacy of tamoxifen?
- What are the significant risks of tamoxifen therapy?
- What is the role of aromatase inhibitors in the treatment of breast cancer?

Note on local and systemic control: Local control with a modified radical mastectomy is often the surgery of choice when the tumor is > 4 cm or the breast is comparatively small, because good cosmetic results are difficult to achieve with BCT.

A second and increasingly popular option is to give systemic chemotherapy in the preoperative setting. This neoadjuvant approach addresses the systemic risk of relapse and provides some shrinkage to the primary tumor, thus increasing the chance that local control can be achieved with lumpectomy and RT. To date, this technique has not shown a survival benefit.

Adjuvant Chemo / Hormonal / Biological Therapy Options for Invasive Breast Cancer

Overview

The types of adjuvant therapy used for systemic control depends on the following factors:

- **Size of tumor** and **nodal status**: Chemotherapy is generally reserved for patients with a high risk of relapse. This includes patients with tumors > 1 cm in size or those with positive lymph nodes. Oncotype DX analysis can help distinguish which woman with T1 (< 2-cm) tumors that are node-negative benefit from adjuvant chemotherapy.
- **Hormonal status** of the tumor: Using tissue from the initial core biopsy, the pathologist determines if the tumor expresses receptors for estrogen and progesterone. If the tumor is hormone receptor-positive (HR+), the patient benefits from adjuvant hormone therapy (tamoxifen or aromatase inhibitor).
- **Gene expression**: Women with > 2-cm tumors and/or node-positive disease whose tumors overexpress the *HER2/neu* gene benefit from trastuzumab (Herceptin®).

Chemotherapy

Chemotherapy decreases risk of recurrence in many patients. It is generally given in drug combinations that follow these general rules:

- Each agent is effective.
- Each agent has a different mechanism of action.

Common combinations are:

- **CMF** (**c**yclophosphamide, **m**ethotrexate, **f**luorouracil)
- **TAC** (docetaxel [**T**axotere®], doxorubicin [**A**driamycin®], **c**yclophosphamide)
- **AC** (doxorubicin [**A**driamycin], **c**yclophosphamide)
- **AC + T** (**AC** followed by paclitaxel [**T**axol®])

The most common regimens in use today are:

- AC for node-negative breast cancers, and
- AC + T for node-positive cancers.

The AC + T is often given in a "dose-dense" fashion, meaning the patient receives AC chemotherapy every 2 weeks instead of the more traditional 3-week schedule. The increased efficacy of this schedule is offset by the increased toxicity to the bone marrow, so growth factor support with G-CSF is used.

Hormonal Therapy

Tamoxifen is a selective estrogen receptor modulator. It is effective only in HR+ patients (both pre- and postmenopausal) in which its overall effect is comparable to chemotherapy.

Know that tamoxifen is converted to its active metabolite, endoxifen, by CYP2D6. Enzyme inhibitors (mainly SSRIs) and/or genetic variation can lead to decreased efficacy of tamoxifen. If a patient needs an SSRI (for depression or hot flashes) while on tamoxifen, venlafaxine is considered the best choice because it does not inhibit CYP2D6.

Tamoxifen's principal adverse effects include hot flashes, weight gain, increased risk of thromboembolic events, and a slight increased risk of endometrial cancer.

Recent data suggest that some patients may benefit from treatment longer than 5 years, but the risks of thromboembolic disease and patient tolerance of the drug need to be assessed.

Letrozole, **anastrozole**, and **exemestane** are aromatase inhibitors. These agents markedly suppress estrogen levels in postmenopausal women by inhibiting the enzyme responsible for synthesizing estrogens from androgenic substrates. Aromatase inhibitors cannot be used in premenopausal women since they do not block ovarian estrogen production.

Data from a randomized trial revealed that the addition of an aromatase inhibitor (letrozole) after 2–5 years of adjuvant tamoxifen improved disease-free survival by 6% (93% vs. 87%) at 4 years. Meta-analysis data support a lower rate of recurrence with aromatase inhibitor over

tamoxifen. Women with a contraindication to tamoxifen (history of DVT/PE or endometrial cancer) can be treated with an aromatase inhibitor alone for 5 years.

Aromatase inhibitors are not associated with an increased risk of thromboembolic events or endometrial carcinoma. However, arthralgias, myalgias, and osteoporosis are more common with these agents. Breast cancer survivors who were treated with aromatase inhibitors should be screened with DXA.

Fulvestrant is an estrogen receptor antagonist without any agonist features. It is given as a monthly intramuscular injection.

Biologic Agents

Trastuzumab (Herceptin®) is a newer biologic agent. It is a monoclonal antibody that targets a growth factor receptor on the surface membrane of breast cancer cells. Around 25–30% of breast cancers have an overexpression of the *HER2/neu* gene, which leads to an increase in the amount of growth receptor protein. This, in turn, leads to an increase in cell proliferation. Trastuzumab has been approved for advanced metastatic cancer with evidence of overexpression of the *HER2/neu* gene. Recent trials have shown a 50% decrease in recurrence when the drug is used as an adjuvant for high-risk (> 2-cm or node-positive) tumors.

Let's review treatment again from a slightly different perspective.

Adjuvant Therapy for the Node-Negative Patient

See Table 8-13. If the tumor is < 1 cm, adjuvant chemotherapy is typically unnecessary because the risk of recurrence is < 10%. Exceptions include young women with high-risk Oncotype DX® scores. Women are often placed on hormonal therapy if the tumor is HR+.

If the tumor is > 1 cm, adjuvant chemotherapy with AC is recommended. Give adjuvant hormonal therapy to women with HR+ tumors. Tamoxifen is used for premenopausal women; an aromatase inhibitor can be used alone or sequentially after tamoxifen for postmenopausal women. The use of adjuvant biologic therapy for node-negative tumors < 2 cm is being investigated. In tumors > 2 cm that are *HER2/neu*+, give adjuvant trastuzumab after chemotherapy.

Adjuvant Therapy for the Node-Positive Patient

Chemotherapy is recommended for node-positive patients. The preferred regimen is dose-dense AC + T. If the tumor overexpresses the *HER2/neu* gene, give patient 1 year of trastuzumab therapy. Give premenopausal women with HR+ tumors adjuvant tamoxifen. Aromatase inhibitor can be used alone or sequentially after tamoxifen for postmenopausal women.

Give all patients radiation therapy after lumpectomy. Contraindications include pregnancy and previous radiation therapy to the same breast for prior breast cancer. Relative contraindications include connective tissue disorders affecting the skin, tumors > 5 cm, and women ≥ 35 years with a *BRCA* mutation. Give radiation after chemotherapy is completed and before hormonal therapy is started.

Prophylaxis / Prevention of Breast Cancer

Tamoxifen is FDA-approved for the prevention of breast cancer in both pre- and postmenopausal women. According to the NSABP Breast Cancer Prevention Trial (terminated early in 1998), which followed 13,388 high-risk women for 6 years, 175 on placebo vs. 89 on tamoxifen developed invasive breast cancer, a relative risk reduction of 38%. Tamoxifen prophylaxis for a duration of 5 years is now considered for women at high risk for invasive breast cancer (defined as a 1.67% 5-year risk of developing breast cancer, or the risk present in an average 60-year-old woman). There is an increased risk of endometrial cancer with the use of tamoxifen; it is the same risk as in postmenopausal women taking single-agent estrogen replacement therapy. Also increased is the risk of DVT (about 1.5x N) and pulmonary embolism (about 3x N).

Table 8-13: Treatment of Node-Negative Invasive Breast Cancer

Size of Tumor	< 1 cm	1 cm to < 4 cm	≥ 4 cm
Type of Surgery	BCT + radiotherapy	Modified Radical Mastectomy or BCT + radiotherapy	Modified Radical Mastectomy
Adjuvant Therapy?	No adjuvant chemotherapy	† Adjuvant chemotherapy for all premenopausal and HR– postmenopausal patients also if ... HR+: add tamoxifen x 5 yrs	
What if node-**positive**? Treatment follows the same basic guidelines as above, except the adjuvant therapy (†) is given for all tumor sizes. Also for postmenopausal HR+ women with more than 1 node involved, both chemotherapy and hormonal therapy are often used.			

Quick Quiz

- What is the role of tamoxifen in the prevention of breast cancer? For which women is it considered?
- What are the established risk factors for cervical cancer?
- What patient populations are approved for receipt of the HPV vaccine?
- At what age and with what test results is it appropriate to stop screening for cervical cancer?

Raloxifene is FDA-approved for breast cancer prevention in postmenopausal women and has a lower risk of endometrial cancer and DVT compared to tamoxifen.

Recurrent Breast Cancer

If there is local recurrence of breast cancer, the patient undergoes the diagnostic protocol again and is retreated based on the same criteria, except for the drugs that are used. Many oncologists consider an anthracycline or paclitaxel for recurrences.

Metastatic Breast Cancer

Although there is no curative therapy for metastatic disease, effective palliation and survival extension is possible with the implementation of active agents. There are many newer chemotherapy agents that are effective in metastatic breast cancer.

In patients with HR+ disease, initiating or changing hormonal therapy is often effective. Aromatase inhibitors are more effective than tamoxifen for the initial treatment of metastatic disease in postmenopausal women.

Bisphosphonate therapy can effectively reduce bone pain and fractures due to skeletal metastasis.

Denosumab is a RANK ligand inhibitor that also decreases the risk of skeletal-related events.

Radiation therapy is useful in providing palliation and local control to symptomatic regional disease, brain metastasis, skeletal metastasis, and soft tissue metastasis.

CERVICAL CANCER

INCIDENCE

Since the introduction of the Papanicolaou (Pap) smear in 1947, mortality due to cervical cancer in the U.S. has dropped by 70%. Still, despite effective screening, there will be 10,000 cases of cervical cancer diagnosed in the U.S. this year.

RISK OF CERVICAL CANCER

The major risk factor for cervical carcinoma is HPV (human papillomavirus) infection. Other risk factors reflect the risk of exposure to HPV: early onset of coitus, number of sexual partners, smoking, and history of other sexually transmitted diseases. In addition, patients with chronic immunosuppression are at increased risk of developing HPV infection (e.g., HIV/AIDS is a risk factor).

HPV isolates are found in 85–90% of cervical carcinomas, especially types 16 and 18. HPV is thought to express E7 protein, which binds to the RB (retinoblastoma) protein, inactivating the RB tumor suppressor gene. HPV is the cause of the cervical intraepithelial neoplasia (CIN) dysplasia, and 65% evolve into CIS over a period of 10 years. Without treatment, 30–70% of CIS lesions evolve into an invasive carcinoma over 10–12 years.

A significant medical advancement has been the development of the quadrivalent HPV 6/11/16/18 virus-like particle vaccine (Gardasil®). The safety and efficacy of this vaccine has been established in 4 placebo-controlled randomized trials. The FUTURE II trial revealed the vaccine to be 100% effective in preventing CIN grade 1–3 in HPV-susceptible women. The vaccine is approved for use in both females (to prevent cervical, vulvar, and vaginal cancer) and males (to prevent genital warts), ages 9 to 26 years.

SCREENING AND WORKUP OF CERVICAL CANCER

Pap smears are used as a screening method to find cancerous or precancerous cervical lesions. Because most atypia and cancer form in the transformation zone between the endocervix and exocervix, it is crucial to get a good sample from this area.

The American Congress of Obstetricians and Gynecologists (ACOG) released new guidelines for cervical cancer screening in 2012, which advocate beginning to screen at age 21 and every 3 years thereafter in women ages 21–29. Women 30 and older with 3 consecutive negative screens (and no history of CIN 2 or CIN 3, HIV-negative, no immunocompromise, and no *in utero* DES exposure) can be screened every 5 years if there is co-testing of HPV and cytology, or every 3 years if done with cytology alone.

Liquid-based and conventional methods are both acceptable for screening. Patients who have had a total abdominal hysterectomy for benign conditions can discontinue screening. Stop screening at age 65 if patient has had adequate screening (3 or more negative cytology test results in a row or 2 consecutive negative co-tests in the past 10 years with the most recent within the past 5 years). Whatever the age, continue screening for 20 years after treatment for a high-grade precancerous lesion.

Testing for HPV DNA and cytology is appropriate in women ≥ 30 years of age. Low-risk women 30 and older,

with both negative cytology and HPV testing, can be screened every 3 years. All guidelines apply to women who have received the vaccine.

Remember: The Pap smear is only a screening test; a biopsy is required for diagnosis of CIN or invasive carcinoma.

The Bethesda classification is the most common method to communicate the grade of atypia or dysplasia found on Pap smears. It has 3 categories:

1) ASCUS (atypical squamous cells of undetermined significance)
2) LGSIL (low-grade squamous intraepithelial lesion), which usually reflects CIN 1, but occasionally 2 or 3
3) HGSIL (high-grade squamous intraepithelial lesion), which is due to CIN 2, 3, or invasive carcinoma

ASCUS can be evaluated with colposcopy-guided biopsy or DNA testing for high-risk viruses with colposcopy reserved for cases where viral DNA is identified. A third option is to treat any underlying infection and repeat the Pap smear in 3 months.

Both LGSIL and HGSIL require colposcopic-guided punch biopsies for the diagnosis of CIN or cancer. Colposcopy is also recommended for all visible cervical lesions—even if the Pap smear is normal. If the entire transitional zone cannot be visualized, perform endocervical curettage (ECC).

Biopsy results: The premalignant and malignant lesions of the cervix are termed either:

- cervical intraepithelial neoplasia (CIN), or
- invasive cancer.

CIN is further divided into CIN 1 (slight dysplasia), CIN 2 (moderate dysplasia), and CIN 3 (severe dysplasia). CIN 1 may resolve spontaneously, whereas CIN 2 and 3 require treatment.

TREATMENT OF CERVICAL CANCER

Most CIN is treated with ablative therapy, normally consisting of loop electrosurgical excision procedure (LEEP) or cold-knife conization (CKC). Follow-up after treatment of CIN is reexamination and cytology at 6 months. If the follow-up smear is normal, screening can resume, depending on the patient's age and level of immunosuppression.

Treat local, invasive cancer with various combinations of hysterectomy, pelvic node dissection, and radiation, along with chemotherapy.

OVARIAN CANCER

OVERVIEW

Ovarian cancer is the 4th leading cause of cancer deaths in women. It is the 7th most common malignancy in women; 1 out of 70 women develop this type of cancer. The incidence increases with age, and 1/2 of affected patients are > 65 years of age. Ovarian cancer is the most common cause of an ovarian mass in postmenopausal women.

Most (85%) ovarian cancers are epithelial cell cancers, and most of these are serous and mucinous, but they also may be endometrioid, clear cell, Brenner, or undifferentiated. The next most common cause is germ cell (5%). Most ovarian germ cell tumors are benign, however.

Again, know the following: Epithelial cell (85%) and germ cell (5%), and:

- Epithelial cell tumors are more common among postmenopausal Caucasian patients.
- Germ cell tumors typically occur in young women (10–30 years of age).

Germ cell cancers account for 3% of testicular cancers but only < 5% of ovarian cancers.

RISK OF OVARIAN CANCER

Increased risk:

- Positive family history
- Nulliparity
- *BRCA1* or *BRCA2*-positivity
- Lynch syndrome

Decreased risk:

- Oral contraceptive use
- Tubal ligation
- Breastfeeding
- Early age of 1st pregnancy
- Multiparity (10% decrease in risk with each pregnancy)

BRCA1 (17q21) is associated with a 40% lifetime risk of ovarian cancer. This compares to a 1.5% lifetime risk in the general population. *BRCA1* accounts for most cases of familial ovarian cancer. *BRCA2* (13q12-13) is associated with a 10–20% risk of ovarian cancer. Remember: *BRCA1* and *BRCA2* also are associated with increased risk of breast cancer.

Lynch syndrome (or hereditary nonpolyposis colon cancer) is caused by a germline mutation in a mismatch repair gene and is associated with a 12% lifetime risk of ovarian cancer.

BIOLOGIC MARKERS IN OVARIAN CANCER

CA-125 levels are often increased in ovarian cancer, so include this test when working up possible ovarian cancer. CA-125 also is beneficial in monitoring the effects of therapy.

Recent data show that treatment at a CA-125 relapse does not impact survival. Routine screening for ovarian cancer with either CA-125 or transvaginal ultrasound, or both, is of no benefit and is not recommended.

Quick Quiz

- What is the appropriate procedure to follow up an LGSIL Pap smear result?
- Which type of ovarian cancer is usually benign? In what age group do you typically find these cancers?
- What is the lifetime risk of ovarian cancer in a woman with *BRCA1*? With *BRCA2*?
- What are the risk factors for testicular cancer?
- What biologic markers are used for testicular cancer, and how are they used?
- What is the significance of finding AFP elevation in a patient with a testicular mass?

Alpha fetoprotein (AFP) and hCG are not elevated in epithelial cancers. Both may be elevated in the less common germ cell cancer. Choriocarcinoma, one of the germ cell cancers, produces large amounts of hCG.

STAGING OF OVARIAN CANCER

I. Confined to the ovary

II. Extended to adjacent pelvic structures

III. Spread to peritoneal surfaces, including liver and diaphragmatic surfaces, or to lymph nodes

IV. Distant metastases

Staging is often performed with CT scans of the chest, abdomen, and pelvis. Large intraperitoneal metastases can be seen by CT, but small peritoneal studding may be missed. For this reason, patients are often determined to have a higher than expected stage at the time of laparotomy.

TREATMENT OF OVARIAN CANCER

Treatment for stages I, II, and III consists of surgically removing all visible tumor from the peritoneal surfaces. This debulking or cytoreduction surgery includes a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) and often removal of sections of small bowel, colon, and bladder. The goal is to leave < 1 cm of residual disease. Systemic chemotherapy and, increasingly, intraperitoneal chemotherapy are used in the treatment for stage II and III disease. Optimally, start chemotherapy 4–6 weeks after surgery to allow for adequate post-surgical healing. 5-year survival is 65% for stage II disease and 40% for stage III disease. In stage III disease, optimal cytoreduction is a significant prognostic factor. Also manage Stage IV with chemotherapy (and debulking, in certain situations).

If diagnosed and treated while the cancer is still localized, the 5-year survival rate is 90%, but only 23% are found in this stage. Overall, the 5-year survival rate is 42%.

TESTICULAR CANCER

OVERVIEW

Testicular cancer is the most common solid malignancy affecting men 15–35 years of age. Testicular cancer is one of the most curable cancers, with the 5-year survival rates between 90% and 95%.

Patients usually present with a painless mass in the testicle. If a testicular mass is palpated, then a scrotal ultrasound should be obtained to determine if it is solid. If the mass is solid, inguinal orchiectomy is the preferred next step. Needle biopsy should not be performed because of risk of seeding the biopsy tract. 95% of testicular carcinomas are germ cell tumors (GCTs: seminoma and nonseminoma). The remaining 5% consist of sex cord-stromal tumors, adenocarcinoma of rete testis, mesothelioma, carcinoid, lymphoma, and gonadoblastoma. Testicular cancer also can occur in extragonadal primary sites (retroperitoneum and mediastinum).

Risk factors for testicular GCTs include cryptorchidism (undescended testes), a personal or family history of testicular cancer, infertility, and HIV infection (relative risk for seminoma is 21!). Cryptorchidism increases the risk of testicular cancer in both the undescended and normal testes. The risk increases with delayed orchiopexy. Isochromosome 12p is present in 70–80% of testicular GCTs; however, its role in familial GCTs is unknown. Klinefelter syndrome is a risk factor for primary mediastinal germ cell tumors.

Management of testicular cancer is determined by the type of germ cell tumor. Nonseminoma is the more aggressive type, so when there are elements of both types, follow management of nonseminoma.

BIOLOGIC MARKERS IN TESTICULAR CANCER

Biologic markers include α-fetoprotein (AFP) and hCG. Tumor markers have several important functions:

- Staging and prognosis
- Monitoring for disease relapse
- Monitoring for efficacy of therapy

These markers should be checked prior to surgery, after surgery, and during follow-up. See Figure 8-5 on page 8-52.

AFP is never produced by seminomas. If morphology from a specimen suggests a pure seminoma but the AFP is elevated, the testicular cancer is classified as a nonseminoma. AFP is secreted by all yolk sac tumors and less frequently by embryonal cell carcinoma. The half-life of AFP is 5 days. AFP is also produced by hepatocellular carcinoma, other GI tract tumors, and is elevated in chronic liver disease.

hCG is secreted by all choriocarcinomas, many embryonal cell carcinomas, and 15% of seminomas.

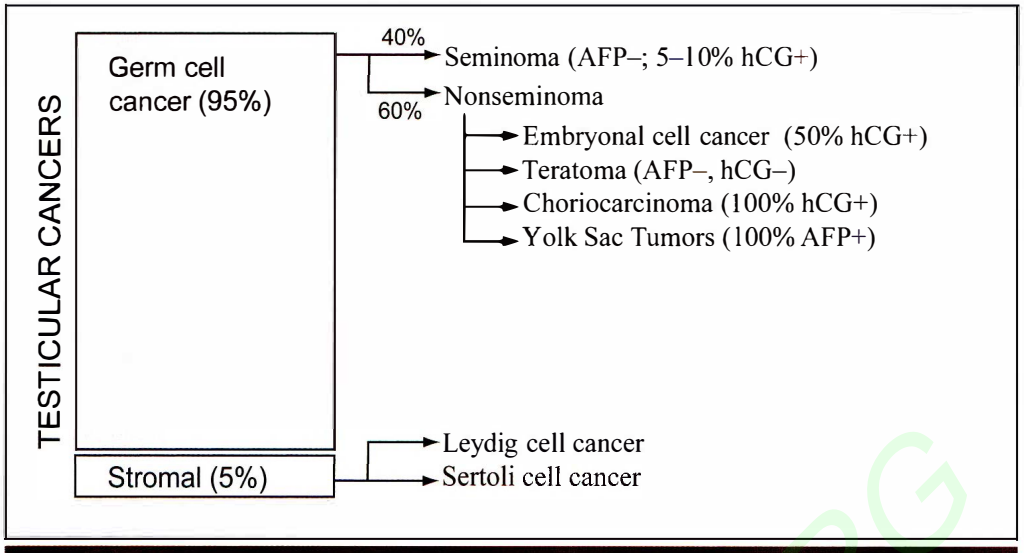

Figure 8-5: Testicular Cancers and the Associated Biologic Markers

Syncytiotrophoblast cells produce hCG in pure seminomas; thus, it is possible to have a pure seminoma with an elevated hCG. False-positive hCG values can occur in hypogonadal states and with marijuana use. The half-life of hCG is 18–36 hours.

STAGING OF TESTICULAR CANCER

Testicular cancer follows a predictable course of metastasis. Stage I disease is limited to the testicle. Stage II disease involves the retroperitoneal nodes, and stage III disease includes more distant metastatic disease—often to the lung. Note that there is no stage IV classification for testicular cancer.

The staging process includes CT of the abdomen and pelvis, as well as tumor markers and LDH. See Table 8-14 for the TNM classification of germ cell tumors.

TREATMENT OF TESTICULAR CANCER

Seminomas are highly radiosensitive. Standard therapy includes orchiectomy followed by radiation to the retroperitoneal lymph nodes, chemotherapy, or surveillance. Radiation can be used on nodes up to 5 cm in size. If nodes are > 5 cm, or there is metastatic disease elsewhere, chemotherapy is used. In small, good-risk tumors, surveillance is an option. Note that there is no poor-risk seminoma, so even metastatic disease is curable.

Table 8-14: TNM Classification of Germ Cell Tumors

I	Confined to testes with normal or abnormal serum tumor markers
II	Lymph node involvement with LDH < 1.5 x N, β-hCG < 5,000, and AFP < 1,000
	IIA: Lymph node or lymph node mass < 2 cm IIB: Lymph node or lymph node mass 2–5 cm IIC: Lymph node or lymph node mass > 5 cm
III	Distant metastases or lymph node metastasis with tumor markers above levels listed for stage II

Treatment of **nonseminomas** is complicated, and only a general approach is reviewed here. The initial management always includes inguinal orchiectomy. Patients with disease limited to testes (negative abd/pelvic CT for adenopathy and negative tumor markers post-orchiectomy) can be managed with observation (20% relapse rate but salvage chemotherapy 90% successful), or with nerve-sparing retroperitoneal lymph node dissection (RPLND). A short course of adjuvant chemotherapy also is an option, especially when the poor prognostic feature of lymphovascular invasion is present. Patients with persistently elevated tumor markers after orchiectomy should always be treated with chemotherapy.

Stage II disease can be treated with either chemotherapy or RPLND. Adjuvant chemotherapy is used after RPLND, when bulky nodes are removed. Stage III disease is treated with chemotherapy. Patients sometimes have residual masses in the chest or the abdomen with normal tumor markers after chemotherapy. These masses often are mature teratomas and should be surgically excised since local growth and malignant transformation is possible.

PROSTATE CANCER

OVERVIEW

Prostate cancer is the most common cancer and the 2nd leading cause of cancer death (after lung cancer) in men in the U.S. Prostate cancers have been detected more frequently due to the availability of the prostate specific antigen (PSA).

Quick Quiz

- What is the association between benign prostatic hypertrophy and prostate cancer?
- What is the normal level of PSA in men 60–64 years of age?

95% of prostate cancers are adenocarcinomas. The major risk factors for prostate cancer are increased age, race (African-Americans > Caucasians > Asians) and family history. Diet (increased risk with fats) and high testosterone levels may also pose a significant risk.

Benign prostatic hypertrophy (BPH) is not a risk factor for prostate cancer.

SCREENING

Screening remains controversial. A European study (ERSPC) showed a 20% decrease in prostate cancer mortality in the PSA screening group. However, 1,410 men needed to be screened to prevent 1 death over 9 years. A U.S. study (PLCO) showed no decrease in mortality with screening, but in that study, more than 50% of the patients in the control group had at least 1 PSA during the study.

The American Cancer Society recommends that men have a discussion with their physician about the risks and benefits of screening. PSA and DRE should be done in those men older than 50 who chose to be screened if they have a life expectancy > 10 years.

The USPSTF guidelines released in 2012 recommend against screening for prostate cancer regardless of age, suggesting that harm outweighs benefit. They do qualify this statement by saying the use of PSA for screening is outside the scope of the USPSTF.

The American Urologic Association (AUA) released new guidelines in 2013 recommending against screening men < 40 years of age and recommended against routine screening for average-risk men between the ages of 40 and 54, men older than 70, or those with a life expectancy < 10 years.

Some primary care physicians and oncologists chose to screen African-American men who are outside the recommendation ranges of the ACS or AUA, given that the risk of prostate cancer is higher in this population. Men with multiple 1st degree relatives with prostate cancer also fall into this category.

The normal level of PSA varies with age. One study revealed that normal PSA levels were:

- 3.7 ng/mL for men 50–54 years of age
- 4.0 ng/mL for 55–59 years of age
- 5.4 ng/mL for 60–64 years of age
- 6.2 ng/mL for 65–69 years of age
- 6.6 ng/mL for men 70–74 years of age

If the rectal exam is suggestive, and/or the PSA is > 4 ng/mL (or > age-specific normal values), transrectal ultrasound-guided needle biopsies (12 cores) are performed for diagnosis.

STAGING OF PROSTATE CANCER

The TNM staging system (Table 8-15) is the most widely utilized. The TNM system is able to distinguish disease confined to the prostate (T1–T2) from disease that extends outside the gland (T3–T4). A limitation of the TNM system is its failure to predict organ-confined disease in patients diagnosed with prostate cancer due to an elevated PSA with clinical T1 or T2 disease.

A combination of pretreatment tumor stage, PSA level, and tumor grade (better known as the Gleason grade) can predict pathologic stage and risk of prostate cancer

Table 8-15: TNM Staging of Prostate Cancer

Tumor Stage	Substage
T1 Clinically inapparent tumor neither palpable nor visible by imaging	T1a: tumor incidental histologic finding in 5% or less of tissue resected
	T1b: tumor incidental histologic finding in more than 5% of tissue resected
	T1c: tumor identified by needle biopsy (e.g., because of elevated PSA)
T2 Tumor confined within the prostate	T2a: tumor involves 1/2 of lobe or less
	T2b: tumor involves more than 1/2 of lobe but not both lobes
	T2c: tumor involves both lobes
T3 Tumor extends through the prostate capsule	T3a: extracapsular extension (uni- or bilateral)
	T3b: tumor invades the seminal vesicles(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall	
N Regional lymph nodes assessed	NX: not assessed
	N0: no regional lymph node
	N1: metastasis in regional lymph node
M Distant metastases	M0: no distant mets
	M1: distant mets present
	M1a: non-regional lymph nodes
	M1b: bone(s)
	M1c: other site(s) with or without bone disease

Adapted from AJCC Cancer Staging Manual, Sixth Edition (2002).

recurrence after radical prostatectomy. The Gleason grade is an additive scoring system between 2 (least aggressive) and 10 (most aggressive) used to describe the 2 most prevalent histologic patterns of the prostate cancer.

Pretreatment staging of prostate cancer includes a bone scan and CT scan of the pelvis because the bone and lymph nodes are by far the most likely sites of metastasis. In patients who elect surgery, lymph nodes are often sampled at the time of surgery.

TREATMENT OF PROSTATE CANCER

All treatments for prostate cancer can have serious side effects (such as impotence and urinary incontinence). For this reason, active surveillance (PSA q 6 months; digital rectal exam q 12 months; repeat prostate biopsy q 12 months) is often appropriate for older patients and patients with early-stage, low-risk disease. Patients with asymptomatic metastatic disease or PSA elevation after primary therapy also can be observed, with therapy (androgen deprivation) delayed until rapid PSA doubling time or symptom development.

Radical prostatectomy (RP) is reserved for patients with clinical T1–T2cN0M0 disease with a life expectancy of > 10 years. Radiation therapy (RT) can be offered to patients with clinical T1–T3bN0M0 with an acceptable life expectancy. Data support the use of androgen deprivation therapy along with radiation in patients with Gleason 7–10 disease.

Also remember that pretreatment PSA, tumor stage, and Gleason grade are helpful in predicting extracapsular spread. For example, patients with T1–T2 lesions with a high pretreatment PSA (> 10–20 ng/mL) or high Gleason grade (8–10) are less likely to have organ-confined disease and are more suitable for RT.

Hormonal therapy consists of androgen deprivation. This is achieved by a LHRH agonist (leuprolide, goserelin) combined with an androgen receptor antagonist (flutamide, bicalutamide) or orchiectomy. Hormonal therapy was once thought of as benign treatment, but there are significant adverse effects: weight gain, osteoporosis, gynecomastia, loss of muscle mass, anemia, sexual dysfunction, hot flashes, and an increased risk of diabetes. In retrospective analysis, hormonal therapy has been associated with a 5–8% increased risk of cardiac mortality. Hormonal therapy can be appropriately offered to several categories of prostate cancer patients:

- Those with metastatic disease (best reserved for symptomatic patients or patients with a rapidly rising PSA)
- Those with a PSA-only recurrence after primary therapy with a short PSA doubling time (< 6–10 months)
- Those with N+ disease discovered after RP: adjuvant therapy for 36 months
- Those undergoing RT (adjuvant therapy for 4–24 months in those with Gleason 7–10 disease)

Eventually, most patients with metastatic disease become refractory to hormonal therapy. This is referred to as androgen-independent prostate cancer (AIPC).

Treatment options for AIPC include:

- Alternative hormonal therapy: corticosteroids, ketoconazole, estrogens, and abiraterone (inhibits the enzyme CYP17, which is required for the formation of the testosterone precursors DHEA and androstenedione).
- Immunotherapy with sipuleucel-T for patients with little to no symptoms from metastasis has been shown to prolong overall survival. In this therapy, autologous antigen-presenting cells from the patient are collected, activated with GM-CSF and prostate acid phosphatase, and then reinfused.
- Chemotherapy: taxanes (specifically docetaxel and the semi-synthetic taxanes cabazitaxel because each has shown survival benefit), mitoxantrone, estramustine.
- Palliative RT to painful bone disease.
- Radiopharmaceuticals.

Bisphosphonates are useful in decreasing bone pain from metastases and decreasing osteoporosis associated with hormonal therapy. Once again, denosumab is available to prevent skeletal-related events.

PROSTATE CANCER PREVENTION

Based on a recent randomized trial, ASCO recommends having a discussion with patients regarding the potential 25% decreased risk of prostate cancer with use of finasteride, a 5-α-reductase inhibitor, for 7 years. Since patients in the treatment arm had a higher percentage of high-grade prostate cancers, patients need to be warned about that potential risk.

HEAD & NECK CANCER

Head and neck cancer: 90% of patients are smokers and 75% abuse alcohol; thus, most are preventable. There is increased head and neck cancer with smoking, alcohol, chewing tobacco, and HPV 16/18 infections. 95% of head and neck cancers are squamous/epidermoid.

If a suspicious cervical node is present, diagnose with FNA, and, if positive for squamous cell carcinoma with unknown primary, most recommend doing CT and/or MRI staging of the head/neck. This is commonly followed by panendoscopy.

In early stage disease, there is a real potential for cure with surgery and/or radiation therapy. Effort should be made to preserve function. Recent clinical trials have demonstrated that the addition of chemotherapy or biologic therapy (cetuximab, an EGFR inhibitor) with RT as primary therapy improves outcomes in head and neck cancer. If the disease is metastatic, treatment is palliative,

Quick Quiz

- Where are the likely sites of metastases in patients with prostate cancer?
- Name the side effects of androgen-deprivation treatment.
- What drug has been shown to actually decrease the risk of prostate cancer when used long-term?

ordinarily with cisplatin, 5FU, taxanes, or cetuximab. Patients who have HPV-positive tumors respond better to treatment.

CANCER OF UNKNOWN PRIMARY

These account for 4–5% of all invasive cancers. In all cases, immunohistochemistry and imaging with CT and/or PET scan may be helpful. Classification by histologic group determines further workup and treatment:

- Adenocarcinoma: accounts for 70% of cases. In a woman with isolated axillary nodes, consider breast MRI and treat as stage II breast cancer. Often, occult primary tumors may be found at mastectomy. In a woman with peritoneal carcinomatosis or ascites, treat as a stage III ovarian cancer. Men with blastic bone metastases or an elevated PSA may respond to treatment for prostate cancer.
- Poorly differentiated carcinoma: accounts for 20% of cases. Consider germ cell tumors. Elevated LDH, AFP, and/or β-hCG may suggest extragonadal germ cell tumor, especially if retroperitoneal or mediastinal site of disease, and should be treated as a stage III germ cell tumor.
- Neuroendocrine tumors: high-grade neuroendocrine tumors are aggressive and typically respond to chemotherapy, although the response is usually short-lived. Determining the primary site is not commonly of great importance because all forms of aggressive neuroendocrine cancer are treated with the same chemotherapy regimens (treated like small cell lung cancer with a platinum agent and etoposide).

MISCELLANEOUS

For cancers of the colon, lung, kidney, endocrine system, and CNS, see, respectively: Gastroenterology, Book 1; Pulmonary Medicine, Book 2; Nephrology, Book 2; Endocrinology, Book 4; Neurology, Book 5.

One quick note to remember: An isolated supraclavicular node has a high risk of malignancy, and its primary depends on which side it arises. If it's on the left—look for an abdominal tumor (GI, GU); on the right—suspect mediastinum, lungs, or esophagus.

CARCINOID

Carcinoids are neuroendocrine tumors that generally occur in the appendix (50%), small bowel, or rectum. These tumors are usually asymptomatic—especially the rectal carcinoids—until they have metastasized to the liver or lungs. Carcinoids are seen in MEN1. Hormone-secreting carcinoids produce serotonin, bradykinins, GH, ACTH, calcitonin, and prostaglandins, resulting in the "carcinoid syndrome."

Carcinoid syndrome consists of a triad:

1) Flushing
2) Valvular heart disease
3) Diarrhea

These symptoms are especially prominent in hormone-secreting carcinoids. Initial evaluation should include a urinary 5-hydroxyindoleacetic acid (5-HIAA) level and a serum chromogranin A level.

Treatment: Surgical resection is done for localized disease (< 1 cm rarely has metastases). There is an 80% cure rate for localized carcinoid. If the carcinoid has metastasized, the treatment is typically symptomatic. Even metastatic carcinoid is a slowly progressive and fairly benign disease, and often can be managed with symptomatic therapy for many years with little difficulty (e.g., using an antidiarrhea medication, avoiding offending foods and alcohol). The somatostatin analog, octreotide (Sandostatin®), can help control symptoms and is now available as a monthly injection.

CARCINOGENS

Agents and processes that can cause cancer, and what they typically affect:

Tobacco: lung, bladder, head and neck, and esophagus. Tobacco is related to 30% of U.S. cancer-related deaths.

Alcohol: liver, head and neck, and esophagus.

Tobacco + alcohol: synergistic effect on the development of head and neck and esophageal cancers.

Asbestos: lung, mesothelioma of the pleura, and abdominal peritoneum (much increased risk if combined with tobacco use).

Estrogens: uterine, vaginal, and breast cancers. Both birth control pills and postmenopausal estrogens appear to have a slight increase in risk after 5 years of use; however, the NCI is currently conducting a national study to evaluate this risk.

Nitrites: stomach.

Animal fat: colon, breast, and prostate.

Ionizing radiation: leukemia and thyroid. There is a slightly increased risk of breast cancer in Hodgkin patients who received radiation therapy. Generalized, high-dose exposure to radiation (e.g., nuclear bomb) is associated with an increased risk of all malignancies except CLL.

Ultraviolet radiation: skin (basal cell, squamous cell, and melanoma).

Radon gas: lung.

Viruses:

- HHV 8 (human herpesvirus 8): Kaposi sarcoma, primary effusion lymphoma
- Hepatitis B and C: liver cancer
- HPV (human papillomavirus): cervical, anal, and oropharyngeal cancers
- EBV: Burkitt lymphoma, nasopharyngeal carcinoma, and 30–50% of AIDS-related lymphomas (and 100% of AIDS-related primary CNS lymphoma)
- HIV: Kaposi sarcoma, non-Hodgkin lymphoma
- HTLV-1: adult T-cell leukemia

CHEMOTHERAPY AND BIOLOGIC THERAPY

NOTE

See Table 8-16 and Table 8-17 on the following pages. The main things to know are the major toxicities of the drug or drug classes.

CHEMOTHERAPY DRUG HIGHLIGHTS

Capecitabine (Xeloda®) is an oral chemotherapeutic agent approved for the treatment of colon cancer and advanced breast cancer. It is activated/converted by the malignant cell into 5-fluorouracil. Diarrhea can lead to life-threatening volume loss. Affects warfarin metabolism leading to labile INRs and bleeding risk.

Rituximab (Rituxan®) is a chimeric monoclonal antibody with significant activity in low-grade lymphomas. The antibody is directed against the CD20 antigen, which is found on the surface of almost all B lymphocytes of the low-grade lymphomas and normal, circulating B lymphocytes. CD20 is important because it regulates early steps in the activation process for cell-cycle initiation and differentiation. Rituximab is approved as 1st line therapy for low-grade and high-grade B-cell lymphomas in combination with chemotherapy. Ofatumumab is another anti-CD20 monoclonal antibody used for refractory CLL.

Brentuximab is an anti-CD30 monoclonal antibody bound to an antimitotic drug conjugate. Binding to CD30 internalizes the molecule and activates the drug conjugate. It is used in refractory Hodgkin lymphoma and other CD30+ lymphomas.

Denileukin diftitox (Ontak®) is a unique compound that binds to the IL-2 receptor (CD25) on T cells. After binding, the diphtheria toxin is introduced into the cell, which then inhibits protein synthesis. It is used in patients with cutaneous T-cell lymphomas. It is associated with hypersensitivity reactions.

Imatinib mesylate (Gleevec®) binds to tyrosine kinase and prevents downstream signaling for cellular proliferation. It is approved for use in CML and gastrointestinal stromal tumors (GIST). Also approved for CML are 2 additional tyrosine kinase inhibitors, **dasatinib** and **nilotinib**.

Trastuzumab (Herceptin®) is a monoclonal antibody directed at the receptor on the surface of the breast cancer cell. It is exciting because its development was based on our knowledge of the molecular biology of the breast cancer cell. *HER2/neu* is an oncogene, which is overexpressed in some breast cancers. This drug is approved for patients with tumors known to be associated with overexpression of *HER2/neu*. Cardiotoxicity is the main side effect. It causes a usually reversible cardiomyopathy that may be asymptomatic or present as heart failure.

Interferon-alpha is effective against Kaposi sarcoma in AIDS patients if the CD4 count is > 200/mL. There is evidence that adjuvant therapy with high-dose interferon in high-risk melanoma delays recurrence.

Interleukin-2 has been approved for the treatment of renal cell carcinoma. IL-2 occasionally produces complete remissions in these patients! It also may be of benefit in malignant melanoma.

IL-2 and GM-CSF can cause capillary leak syndrome. This syndrome occurs when there is increased capillary permeability, leading to extravasation of the intravascular fluid, which then leads to hypotension, decreased organ perfusion, organ failure (such as liver or kidney failure), cardiac arrest, and intestinal perforation.

Ipilimumab is an anti-CTLA4 monoclonal antibody that enhances T-cell activation and proliferation approved for metastatic melanoma. It carries a significant side effect profile, including hypophysitis and colitis due to its immune effects.

Retinoids are differentiating agents. There have not been many uses found. Two uses are cis-retinoic acid for cutaneous T-cell lymphoma and all-trans-retinoic acid (ATRA) for acute promyelocytic leukemia.

Carboplatin, like cisplatin, is used for ovarian, testicular, and lung cancer (and may be used for head and neck cancer). Dosing requires calculations that take into account the patient's creatinine clearance.

Compared to cisplatin, it has less nausea and vomiting and less nephrotoxicity. Carboplatin has a stronger myelosuppressive effect; its main toxicity is thrombocytopenia, which is dose-related; a nomogram is available that shows dose vs. expected platelet level. Hypersensitivity may develop after multiple doses.

Oxaliplatin is another platinum agent. It has superior activity in colorectal cancer when combined with 5-fluorouracil. Similar to carboplatin, it produces less

Quick Quiz

- Which cancers are associated with a history of radiation therapy?
- Know these unique chemotherapy drugs: rituximab, imatinib, trastuzumab, ATRA, paclitaxel, and lenalidomide. (Also, tamoxifen from the breast cancer section.)
- Know the following associations:
  - Cyclophosphamide and hemorrhagic cystitis
  - Platinum compounds and ototoxicity
  - Doxorubicin and cardiomyopathy
  - 5-FU and sun sensitivity
  - Hydroxyurea and leg ulcerations
  - Rituximab and infusion reactions, including bronchospasm
  - α-interferon and flu-like illness
- What is the dose-limiting toxicity of vinblastine? Vincristine?
- Which agent causes magnesium wasting?

nephrotoxicity, nausea, and vomiting than cisplatin. However, it is associated with peripheral neuropathy that is exacerbated by exposure to cold temperatures. Additionally, hypersensitivity may develop after multiple doses.

Idarubicin is an anthracycline analog that is used for acute myeloid leukemia (AML).

Paclitaxel (Taxol®) is derived from the bark of the Western yew tree. It is approved for use in ovarian, breast, and lung cancer. It can cause anaphylactic infusion reaction.

Docetaxel (Taxotere®) is a synthetic taxane approved for treatment of breast, prostate, and lung cancers.

Irinotecan (Camptosar®) is an inhibitor of topoisomerase I, an enzyme involved in DNA replication. It is approved for the treatment of metastatic colon cancer. Severe diarrhea can result.

BCG bladder installation improves disease-free survival in superficial bladder cancer.

2-CDA (2-chlorodeoxyadenosine; cladrabine) is an extremely interesting drug used in hairy cell leukemia, CLL, and low-grade lymphomas. It induces apoptosis, the normal programmed death of cells. Cells in such diseases as hairy cell leukemia, CLL, and low-grade lymphomas are thought to "lose" their programming for maturation and to stay young and immortal while still dividing. 2-CDA essentially re-programs that portion of the cell's gene to function normally and to go on to die naturally. 2-CDA is sometimes curative for hairy cell leukemia.

Fludarabine and **pentostatin** are other drugs that appear to work similarly to 2-CDA. They are used to treat low-grade lymphomas and CLL.

Vinorelbine is an agent with activity in breast cancer and lung cancer.

Pemetrexed (Alimta®) is an antimetabolite used in combination or as a single agent for the treatment of adenocarcinoma of the lung. It is ineffective in the squamous cell subtype of non-small cell lung cancer. It also is approved for the treatment of mesothelioma. Vitamin B_{12} and folate replacement are necessary to avoid excess toxicity.

Bendamustine is a nitrogen mustard derivative alkylating agent that also has a purine ring. It is used in indolent lymphomas, particularly CLL and follicular lymphoma, as either single agent therapy or in combination with rituximab.

Cetuximab (Erbitux®) is a monoclonal antibody against the epidermal growth factor receptor (EGFR) that is FDA-approved for refractory colon cancer and head and neck cancer. It is likely to have activity in other cancers that express EGFR. It can cause an acne-like rash.

Erlotinib (Tarceva®) is an oral agent that also binds to the EGFR. It is used in lung cancers that express a mutation in the EGFR and in refractory lung cancer. It can cause an acne-like rash.

Bevacizumab (Avastin®) is a monoclonal antibody directed against the vascular endothelial growth factor (VEGF) receptor, preventing tumor-associated angiogenesis. It is FDA-approved for use in metastatic colon cancer, glioblastoma, non-squamous non-small cell lung cancer, and metastatic renal cell cancer.

Thalidomide (Thalomid®) is a unique agent with a unique history. It is an agent that is associated with severe birth defects and was removed from circulation several decades ago. Thalidomide has significant activity in multiple myeloma, but its mechanism of action is not understood. Nevertheless, it has regained FDA approval for multiple myeloma. It can still cause severe birth defects, so patients need to undergo a comprehensive education program before the drug is prescribed. It also is associated with peripheral neuropathy.

Lenalidomide (Revlimid®) is an antineoplastic agent with similarities to thalidomide. It is approved for the treatment of multiple myeloma and the 5q- myelodysplastic syndrome. Lenalidomide also can cause birth defects similar to thalidomide.

Bortezomib (Velcade®) is part of a new class of agents: proteasome inhibitors. Inhibition of proteasomes prevents targeted proteolysis that affects intracellular signaling cascades. This agent also is used for multiple myeloma and mantle cell NHL.

Sorafenib (Nexavar®) and **sunitinib** (Sutent®) are biologic agents that target intracellular signaling pathways. Both have proven activity in renal cell cancer.

Table 8-16: Common Chemotherapy Agents (Table 1 of 2)

CLASS / ACTION	Agents	Major Dose-Limiting Side Effects	Other Side Effects
ALKYLATING AGENTS Interfere with cross-linking of DNA Class side effects: • Dose-limiting myelosuppression • Azoospermia, which may be permanent • Amenorrhea • Secondary leukemias	Cyclophosphamide	Myelosuppression, hemorrhagic cystitis	Amenorrhea and male sterility
	Ifosfamide	Less myelosuppressive but more hemorrhagic cystitis than cyclophosphamide	
	Melphalan	Myelosuppression (esp. platelets)	Most secondary leukemia Amenorrhea and male sterility No hemorrhagic cystitis
	Busulfan	Strong myelosuppression	Interstitial pneumonitis Progressive pulmonary fibrosis
	Mechlorethamine (nitrogen mustard)	Myelosuppression	Amenorrhea and male sterility Phlebitis N/V
	Chlorambucil	Myelosuppression (usually mild)	Amenorrhea and male sterility
	Nitrosoureas (the CNUs: BCNU and CCNU)	Myelosuppression	Pulmonary fibrosis, N/V
	Platinum compounds: Cisplatin Carboplatin Oxaliplatin	Neurotoxicity, including ototoxicity Nephrotoxicity	Myelosuppression, N/V Alopecia
TOPOISOMERASE INHIBITORS Interfere with topoisomerase I or II, causing distortion of DNA cross-linkage	Topotecan (topo-I) Irinotecan (topo-I)	Neutropenia	Anemia, dyspnea, fever, neutropenia, thrombocytopenia
	Etoposide (topo-II) Teniposide (topo-II)	Leukopenia	Fever, hypotension, bronchospasm
	Anthracyclines (topo-II): Doxorubicin (Adriamycin®) Daunorubicin (Doxil®) Idarubicin	Myelosuppression Mucositis Cardiomyopathy	Alopecia, N/V

Sorafenib also is approved for hepatocellular carcinoma. Patients have a significant chance of developing arterial thrombolic events (ATEs) and hypertension.

Vemurafenib (Zelboraf®) targets the BRAF intracellular pathway. It is approved for metastatic melanoma.

Temsirolimus is a mammalian target of rapamycin (mTor) inhibitor approved for renal cell cancer.

Abiraterone (Zytiga●) was approved in 2011 for castrate-resistant prostate cancer and is a 17-alpha hydroxylase inhibitor. Its major side effects include edema, hypertriglyceridemia, and transaminitis.

Cabazitaxel (Jevtana●) is approved to treat metastatic prostate cancer, and its major toxicities include significant myelosuppression along with diarrhea.

MAIN SIDE EFFECTS OF CHEMOTHERAPEUTIC AGENTS

Know all the following:

Alkylating agents and procarbazine are very toxic to the germinal cells of the testes; MOPP (mechlorethamine, vincristine, procarbazine, prednisone), a previously used treatment for Hodgkin lymphoma, caused permanent sterility in > 90% of males > age 25.

Alkylating agents are leukemogenic.

Bleomycin can cause irreversible pulmonary fibrosis.

Vinblastine: Myelosuppression is dose limiting.

Vincristine: Neurotoxicity is dose limiting. Virtually all patients lose deep tendon reflexes, develop paresthesias of the digits, and, over time, develop

Table 8-17: Common Chemotherapy Agents (Table 2 of 2)

CLASS / ACTION	Agents	Major Dose-Limiting Side Effects	Other Side Effects
ANTIMETABOLITES Serve as false substrates for biochemical reactions or interfere with enzymes involved with these reactions	Pyrimidine-analog agents: Fluorouracil (5-FU) Cytarabine (Ara-C) Gemcitabine	Mucositis, some myelosuppression 5-FU: plus cerebellar ataxia	Alopecia, N/V 5-FU: plus sun sensitivity
	Purine-analog agents: Fludarabine (Ara-A) Cladribine (2-CDA) Pentostatin 6-mercaptopurine (6-MP) 6-thioguanine (6-TG)	Myelosuppression	N/V Opportunistic infections Hemolytic anemia
	Other: Hydroxyurea	Moderate leukopenia	N/V Hyperpigmentation Leg ulcers
	Other: Methotrexate	Myelosuppression, mucositis, neurotoxicity	Alopecia Liver and lung damage Diarrhea
ALKALOIDS Derived from plants	Vinca Alkaloids: Vincristine Vinblastine Vinorelbine	Neurotoxicity Myelosuppression	Vincristine: muscle weakness; SIADH in kids; more neurotoxic than myelosuppressive Vinblastine and vinorelbine: bone pain; more myelosuppressive than neurotoxic
	Taxanes: Paclitaxel (Taxol®) Docetaxel (Taxotere®)	Myelosuppression, esp. neutropenia	Hypersensitivity reactions (esp. with paclitaxel) Fluid retention (docetaxel) Alopecia (both)
BIOLOGICALS	Monoclonal antibodies: Trastuzumab (Herceptin®) Rituximab (Rituxan®)		Trastuzumab: infusion reaction, CHF Rituximab: infusion reaction, hypersensitivity reaction (including bronchospasm)
	Interferon-alpha		Flu-like syndrome, N/V, skin rash, diarrhea, myelosuppression
	Interleukin-2 (IL-2)		Capillary leak syndrome contributing to liver or kidney failure, cardiac arrest, intestinal perforation

muscle weakness—especially of the quadriceps in adults. Children develop footdrop. Taxanes, cisplatin, oxaliplatin, bortezomib, and thalidomide also commonly cause peripheral neuropathy.

Cisplatin causes magnesium wasting, neurotoxicity, nephrotoxicity, and also is one of the most emetogenic chemotherapy agents.

Anthracyclines are associated with dose-dependent cardiomyopathy. **Trastuzumab** also causes cardiomyopathy.

Taxanes, **monoclonal antibodies**, and **carboplatin** are most frequently associated with significant infusion-related hypersensitivity reactions.

Anthracyclines, **mitomycin**, and **nitrogen mustards** are vesicants. Extravasation can lead to severe skin and tissue damage that may require surgical intervention. Consider central intravenous access in these agents.

EGFR inhibitors (cetuximab, erlotinib) commonly cause an acne-like skin rash.

Many targeted **biologic agents** (e.g., bevacizumab, sorafenib, sunitinib) are associated with an increased risk of vascular events and hypertension.

USE OF GROWTH FACTORS

Erythropoietin has 2 forms: epoetin (Epogen®) and darbepoetin, a long-acting form. Remember to keep iron stores > 100 with oral iron, as needed.

Erythropoietin is indicated for the treatment of the following:

- Chemotherapy-induced anemia with Hgb < 10. Remember that there is a risk of thrombosis, especially if given when hemoglobin > 12 g/dL.
- Anemia of chronic renal failure.
- Anemia in HIV patients taking zidovudine (AZT).

Erythropoietin is not for use in anemia due to cancer, because it may worsen survival, especially in head and neck and breast cancers.

Thrombopoietin agonists (romiplostim and eltrombopag) are approved for the treatment of chronic ITP that have an insufficient response to corticosteroids or IV IgG.

Table 8-18: Uses of Bone Marrow Transplant (BMT)

		Disorders	Effectiveness / Notes
Malignant Diseases		AML	40–70% cure if done during 1st complete remission.
		ALL	Normally no benefit over chemo but useful in 1st remission of Ph+ ALL. Also done in 2nd remission if 1st remission is short.
		CML	Treatment of choice for CML in accelerated phase, blast phase, or imatinib failure.
		Myelodysplastic synd.	Useful in certain cases.
	†	CLL	Autologous and allogeneic BMTs have been used in young patients with CLL. Short-term follow-up reveals 50% disease-free.
	†	Non-Hodgkin lymphoma	May be used as primary Tx in some patients (60–90% disease-free survival at 2–3 yrs). Autologous.
	†	Hodgkin lymphoma	Not the normal therapy but shows promise! Autologous appears better than allogeneic. One trial: 90% disease-free survival at 3 years.
	†	Multiple myeloma	Autologous BMT has a much lower mortality rate than allogeneic BMT. Moderately successful.
	†	Breast cancer	Awaiting treatment recommendations for breast cancer.
	†	Testicular cancer	Disease-free survival in 10–20% with severe disease suggests much better results if done earlier.
Nonmalignant Diseases		Thalassemia	75% 1-year disease-free survival.
		Sickle cell anemia	Potentially curable with BMT.
		Aplastic anemia	> 50% disease-free survival after BMT for severe aplastic anemia.
		Genetic disorders	Most genetic immunologic or hematopoietic disorders are potentially curable.

Note: All BMTs require an HLA-identical donor.

† Autologous BMTs. All others are allogeneic.

Granulocyte colony-stimulating factor (G-CSF) is indicated for the treatment of the following:

- Neutrophil recovery after treatment for AML or post-bone marrow transplant
- Mobilization of stem cells for use in stem cell transplantation
- Neutrophil recovery after myelosuppressive chemotherapy regimens (does not improve survival, but does decrease the number of days of hospitalization due to febrile neutropenia)
- Severe chronic neutropenia (cyclic, congenital, or idiopathic).

There are 2 forms of G-CSF: filgrastim (Neupogen®) and pegfilgrastim (Neulasta®), which is longer-acting.

BONE MARROW TRANSPLANTATION

Table 8-18 reviews the indications for bone marrow transplantation.

Allogeneic bone marrow transplantation is from one person to another. If these people are identical twins, it is more specifically called a syngeneic transplantation.

Autologous BM transplantation is the use of the patient's own bone marrow.

For information on post-transplant infection risks, see Solid Organ Transplantation in Infectious Disease, Book 1.

FOR FURTHER READING

HEMATOLOGY AND HEMATOLOGIC MALIGNANCIES

[Guidelines in blue]

ANEMIA

Annibale B, Lahner E, et al. Diagnosis and management of pernicious anemia. *Curr Gastroenterol Rep.* 2011 Dec;13(6):518–524.

Bieber E. Erythropoietin, the biology of erythropoiesis and epoetin alfa. An overview. *J Reprod Med.* 2001 May;46(5 Suppl):521–530.

Calabrich A, Katz A. Management of anemia in cancer patients. *Future Oncol.* 2011 Apr;7(4):507–517.

Cunningham MJ. Update on thalassemia: clinical care and complications. *Hematol Oncol Clin North Am.* 2010 Feb;24(1):215–227.

Da Costa L, Galimand J, et al. Hereditary spherocytosis, elliptocytosis, and other red cell membrane disorders. *Blood Rev.* 2013 Jul;27(4):167–178.

Dezern AE, Brodsky RA. Clinical management of aplastic anemia. *Expert Rev Hematol.* 2011 Apr;4(2):221–230.

Gangat N, Wolanskyj AP. Anemia of chronic disease. *Semin Hematol.* 2013 Jul;50(3):232–238.

Gabrilove J. Overview: erythropoiesis, anemia, and the impact of erythropoietin. *Semin Hematol.* 2000 Oct;37(4 Suppl 6):1–3.

Garratty G. Immune hemolytic anemia associated with drug therapy. *Blood Rev.* 2010 Jul-Sep;24(4-5):143–150.

Gonzalez-Casas R, Jones EA, et al. Spectrum of anemia associated with chronic liver disease. *World J Gastroenterol.* 2009 Oct 7;15(37):4653–4658.

Guillaud C, Loustau V, et al. Hemolytic anemia in adults: main causes and diagnostic procedures. *Expert Rev Hematol.* 2012 Apr;5(2):229–241.

Lankhorst CE, Wish JB. Anemia in renal disease: diagnosis and management. *Blood Rev.* 2010 Jan;24(1):39–47.

Michel M. Classification and therapeutic approaches in autoimmune hemolytic anemia: an update. *Expert Rev Hematol.* 2011 Dec;4(6):607–618.

Parker CJ. Paroxysmal nocturnal hemoglobinuria. *Curr Opin Hematol.* 2012 May;19(3):141–148.

Soderquist C, Bagg A. Hereditary elliptocytosis. *Blood.* 2013 Apr 18;121(16):3066.

Steinberg MH. In the clinic. Sickle cell disease. *Ann Intern Med.* 2011 Sep 6;155(5):ITC31–15.

Rizzo JD, Somerfield MR, et al. Use of Epoetin and Darbepoetin in Patients With Cancer: 2007 American Society of Clinical Oncology/American Society of Hematology Clinical Practice Guideline Update. *Journal of Clinical* Oncology. 2008 Jan 1;26(1):132–149. http://jco.ascopubs.org/content/26/1/132

Erythropoiesis-Stimulating Agents (ESAs) in Chronic Kidney Disease: Drug Safety Communication—Modified Dosing Recommendations, U.S. Food and Drug Administration. 2011. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm260641.htm

Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int* Suppl. 2012 Aug;2(4):279–335.

Adamson JW, Bailie GR, et al. Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. National Kidney Foundation. 2006. http://www.kidney.org/professionals/kdoqi/guidelines_anemia/index.htm

Rizzo JD, Brouwers M, et al. American Society of Hematology and the American Society of Clinical Oncology Practice Guideline Update Committee. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood.* 2010 Nov 18;116(20):4045–4059.

MISCELLANEOUS DISORDERS THAT AFFECT RBCs

Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. *Blood.* 2012 Nov 29;120(23):4496–4504.

Cortazzo JA, Lichtman AD. Methemoglobinemia: A Review and Recommendations for Management. *J Cardiothorac Vasc Anesth.* 2013 Aug 13. pii: S1053–0770(13)00043–8. doi: 10.1053/j.jvca.2013.02.005.

Skold A, Cosco DL, et al. Methemoglobinemia: pathogenesis, diagnosis, and management. *South Med J.* 2011 Nov;104(11):757–761.

Bacon BR, Adams PC, et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011 Jul;54(1):328–343.

Qaseem A, Aronson M, et al. Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Screening for hereditary hemochromatosis: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2005 Oct 4;143(7):517–521. Erratum in: *Ann Intern Med*. 2006 Mar 7;144(5):380.

U.S. Preventive Services Task Force. Screening for hemochromatosis: recommendation statement. *Ann Intern Med*. 2006 Aug 1;145(3):204–208.

HEMOSTASIS

Abildgaard U, Heimdal K. Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review. *Eur J Obstet Gynecol Reprod Biol*. 2013 Feb;166(2):117–123.

Alfirević Z, Alfirević I. Hypercoagulable state, pathophysiology, classification and epidemiology. *Clin Chem Lab Med*. 2010 Dec;48 Suppl 1:S15–26.

Andrews RK, Berndt MC. Bernard-soulier syndrome: an update. *Semin Thromb Hemost*. 2013 Sep;39(6):656–662.

Aster RH, Curtis BR, et al. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. *J Thromb Haemost*. 2009 Jun;7(6):911–918.

Ayesh MH, Alawneh K, et al. Adult primary and secondary immune thrombocytopenic purpura: a comparative analysis of characteristics and clinical course. *Clin Appl Thromb Hemost*. 2013 Jun;19(3):327–330.

Bergman GE. Progress in the treatment of bleeding disorders. *Thromb Res*. 2011 Jan;127 Suppl 1:S3–5.

Blaisdell FW. Causes, prevention, and treatment of intravascular coagulation and disseminated intravascular coagulation. *J Trauma Acute Care Surg*. 2012 Jun;72(6):1719–1722.

Brenner B, Kuperman AA, et al. Vitamin K-dependent coagulation factors deficiency. *Semin Thromb Hemost*. 2009 Jun;35(4):439–446.

Broos K, Feys HB, et al. Platelets at work in primary hemostasis. *Blood Rev*. 2011 Jul;25(4):155–167. doi:10.1016/j.blre.2011.03.002.

Coppola A, Favaloro EJ, et al. Acquired inhibitors of coagulation factors: part I-acquired hemophilia A. *Semin Thromb Hemost*. 2012 Jul;38(5):433–446.

Duga S, Salomon O. Factor XI Deficiency. *Semin Thromb Hemost*. 2009 Jun;35(4):416–425.

Favaloro EJ, Lippi G. Coagulation update: what's new in hemostasis testing? *Thromb Res*. 2011 Jan;127 Suppl 2:S13–16.

Franchini M, Lippi G, et al. Acquired inhibitors of coagulation factors: part II. *Semin Thromb Hemost*. 2012 Jul;38(5):447–453.

Franchini M, Mannucci PM. Inhibitors of propagation of coagulation (factors VIII, IX and XI): a review of current therapeutic practice. *Br J Clin Pharmacol*. 2011 Oct;72(4):553–562.

Gale AJ. Continuing education course #2: current understanding of hemostasis. *Toxicol Pathol*. 2011 Jan;39(1):273–280.

George JN, Al-Nouri ZL. Diagnostic and therapeutic challenges in the thrombotic thrombocytopenic purpura and hemolytic uremic syndromes. *Hematology Am Soc Hematol Educ Program*. 2012:604–609.

Hsieh L, Nugent D. Rare factor deficiencies. *Curr Opin Hematol*. 2012 Sep;19(5):380–384.

Israels SJ, El-Ekiaby M, et al. Inherited disorders of platelet function and challenges to diagnosis of mucocutaneous bleeding. *Haemophilia*. 2010 Jul;16 Suppl 5:152–159.

James PD, Lillicrap D. von Willebrand disease: clinical and laboratory lessons learned from the large von Willebrand disease studies. *Am J Hematol*. 2012 May;87 Suppl 1:S4–11.

Johnson NV, Khor B, et al. Advances in laboratory testing for thrombophilia. *Am J Hematol*. 2012 May;87 Suppl 1:S108–112.

Karimi M, Bereczky Z, et al. Factor XIII Deficiency. *Semin Thromb Hemost*. 2009 Jun;35(4):426–438.

Karpman D, Sartz L, et al. Pathophysiology of typical hemolytic uremic syndrome. *Semin Thromb Hemost*. 2010 Sep;36(6):575–585.

ten Kate MK, van der Meer J. Protein S deficiency: a clinical perspective. *Haemophilia*. 2008 Nov;14(6):1222–1228.

Lim W. Antiphospholipid antibody syndrome. *Hematology Am Soc Hematol Educ Program*. 2009:233–239.

Lippi G, Favaloro EJ, et al. Inherited and acquired factor V deficiency. *Blood Coagul Fibrinolysis*. 2011 Apr;22(3):160–166.

Lippi G, Franchini M, et al. Inherited disorders of blood coagulation. *Ann Med*. 2012 Aug;44(5):405–418.

Lippi G, Mattiuzzi C, et al. Novel and emerging therapies: thrombus-targeted fibrinolysis. *Semin Thromb Hemost*. 2013 Feb;39(1):48–58.

Reddy S, Shen YM; American College of Chest Physicians; International Society of Angiology. Prevention and treatment of surgical thrombosis and thromboembolism. *Surg Technol Int*. 2008;17:39–47.

Rydz N, James PD. Approach to the diagnosis and management of common bleeding disorders. *Semin Thromb Hemost*. 2012 Oct;38(7):711–719.

Stasi R. How to approach thrombocytopenia. *Hematology Am Soc Hematol Educ Program*. 2012;2012:191–197.

Stavrou E, Schmaier AH. Factor XII: what does it contribute to our understanding of the physiology and pathophysiology of hemostasis & thrombosis. *Thromb Res*. 2010 Mar;125(3):210–215.

Todd T, Perry DJ. A review of long-term prophylaxis in the rare inherited coagulation factor deficiencies. *Haemophilia*. 2010 Jul 1;16(4):569–583.

Varga EA, Kujovich JL. Management of inherited thrombophilia: guide for genetics professionals. *Clin Genet*. 2012 Jan;81(1):7–17.

Qaseem A, Snow V, et al. Current diagnosis of venous thromboembolism in primary care: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians. Annals of Internal Medicine. 2007. http://annals.org/article.aspx?articleid=733705

Bates SM, Greer IA, et al. American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012 Feb;141(2 Suppl):e691S–736S.

Carson JL, Grossman BJ, et al. Clinical Transfusion Medicine Committee of the AABB. Red blood cell transfusion: a clinical practice guideline from the AABB*. *Ann Intern Med.* 2012 Jul 3;157(1):49–58.

Huth-Kühne A, Baudo F, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica.* 2009 Apr;94(4):566–575.

JCS Joint Working Group. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009). *Circ J.* 2011;75(5):1258–1281.

Linkins LA, Dans AL, et al. American College of Chest Physicians. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012 Feb;141(2 Suppl):e495S–530S.

Lockwood C, Wendel G; Committee on Practice Bulletins—Obstetrics. Practice bulletin no. 124: inherited thrombophilias in pregnancy. *Obstet Gynecol.* 2011 Sep;118(3):730–740.

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association, 2011. http://circ.ahajournals.org/content/123/16/1788.full.pdf

Neunert C, Lim W, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood.* 2011 Apr 21;117(16):4190–4207.

Nichols WL, Hultin MB, et al. von Willebrand disease (vWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia.* 2008 Mar;14(2):171–232.

Nichols WL, Rick ME, et al. Clinical and laboratory diagnosis of von Willebrand disease: a synopsis of the 2008 NHLBI/NIH guidelines. *Am J Hematol.* 2009 Jun;84(6):366–370.

Provan D, Stasi R, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood.* 2010 Jan 14;115(2):168–186.

Roback JD, Caldwell S, et al. American Association for the Study of Liver; American Academy of Pediatrics; United States Army; American Society of Anesthesiology; American Society of Hematology. Evidence-based practice guidelines for plasma transfusion. *Transfusion.* 2010 Jun;50(6):1227–1239.

Warkentin TE, Greinacher A, et al. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008 Jun;133(6 Suppl):340S–380S. Erratum in: *Chest.* 2011 May;139(5):1261.

DISORDERS OF THE BONE MARROW

Bennett JM, Orazi A. Diagnostic criteria to distinguish hypocellular acute myeloid leukemia from hypocellular myelodysplastic syndromes and aplastic anemia: recommendations for a standardized approach. *Haematologica.* 2009 Feb;94(2):264–268.

Borthakur G, Estey EE. Therapy of acute myelogenous leukemia in adults. *Cancer Treat Res.* 2010;145:257–271.

Dezern AE, Brodsky RA. Clinical management of aplastic anemia. *Expert Rev Hematol.* 2011 Apr;4(2):221–230.

Kasner MT, Luger SM. Update on the therapy for myelodysplastic syndrome. *Am J Hematol.* 2009 Mar;84(3):177–186.

Li J. Myelodysplastic syndrome hematopoietic stem cell. *Int J Cancer.* 2013 Aug 1;133(3):525–533.

Ribera JM. Advances in acute lymphoblastic leukemia in adults. *Curr Opin Oncol.* 2011 Nov;23(6):692–699.

Scheinberg P. Aplastic anemia: therapeutic updates in immunosuppression and transplantation. *Hematology Am Soc Hematol Educ Program.* 2012:292–300.

Shah MV, Barochia A, et al. Impact of genetic targets on cancer therapy in acute myelogenous leukemia. *Adv Exp Med Biol.* 2013;779:405–437.

Tefferi A. Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2012 Mar;87(3):285–293.

Tefferi A. Primary myelofibrosis: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2011 Dec;86(12):1017–1026.

Torgerson SR, Haddad RY, et al. Chronic myelogenous leukemia for primary care physicians. *Dis Mon.* 2012 Apr;58(4):168–176.

Vasekar M, Allen JE, et al. Emerging molecular therapies for the treatment of acute lymphoblastic leukemia. *Adv Exp Med Biol.* 2013;779:341–358.

O'Brien S, Abboud CN, et al. National Comprehensive Cancer Network. Chronic myelogenous leukemia. *J Natl Compr Canc Netw.* 2012 Jan;10(1):64–110.

LYMPHOPROLIFERATIVE DISORDERS

Betancourt-García RD, García-Pallas MV, et al. Diffuse large-cell lymphoma. Part I: clinical features, histology and prognosis. *P R Health Sci J.* 2009 Mar;28(1):5–11.

Buske C, Leblond V. How to manage Waldenström's macroglobulinemia. *Leukemia.* 2013 Apr;27(4):762–772.

Cabanillas F. New developments in the field of diffuse large cell lymphoma. *Hematology.* 2012 Apr;17 Suppl 1:S98–100.

Freedman A. Follicular lymphoma: 2012 update on diagnosis and management. *Am J Hematol.* 2012 Oct;87(10):988–995.

García-Pallas MV, Betancourt-García RD, et al. Diffuse large-cell lymphoma. Part II: management. *P R Health Sci J.* 2009 Mar;28(1):12–17.

Gertz MA. Waldenström macroglobulinemia: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2012 May;87(5):503–510.

Gobbi PG, Ferreri AJ, et al. Hodgkin lymphoma. *Crit Rev Oncol Hematol.* 2013 Feb;85(2):216–237.

Harel S, Delarue R, et al. Treatment of younger patients with mantle cell lymphoma. *Semin Hematol.* 2011 Jul;48(3): 194–207.

Heise W. GI-lymphomas in immunosuppressed patients (organ transplantation; HIV). *Best Pract Res Clin Gastroenterol.* 2010 Feb;24(1):57–69.

Kaplan LD. HIV-associated lymphoma. *Best Pract Res Clin Haematol.* 2012 Mar;25(1):101–117.

Kluin-Nelemans HC, Doorduijn JK. Treatment of elderly patients with mantle cell lymphoma. *Semin Hematol.* 2011 Jul;48(3):208–213.

Kreitman RJ. Hairy Cell Leukemia-New Genes, New Targets. *Curr Hematol Malig Rep.* 2013 Sep;8(3):184–195.

Linch DC. Burkitt lymphoma in adults. *Br J Haematol.* 2012 Mar;156(6):693–703.

Naderi N, Yang DT. Lymphoplasmacytic lymphoma and Waldenström macroglobulinemia. *Arch Pathol Lab Med.* 2013 Apr;137(4):580–585.

Rodríguez-Vicente AE, Diaz MG, et al. Chronic lymphocytic leukemia: a clinical and molecular heterogenous disease. *Cancer Genet.* 2013 Mar;206(3):49–62.

Roschewski M, Wilson WH. EBV-associated lymphomas in adults. *Best Pract Res Clin Haematol.* 2012 Mar;25(1):75–89.

Shankland KR, Armitage JO, et al. Non-Hodgkin lymphoma. *Lancet.* 2012 Sep 1;380(9844):848–857.

Thomas BR, Whittaker S. A practical approach to accurate classification and staging of mycosis fungoides and Sézary syndrome. *Skin Therapy Lett.* 2012 Dec;17(10):5–9.

Vose JM. Mantle cell lymphoma: 2012 update on diagnosis, risk-stratification, and clinical management. *Am J Hematol.* 2012 Jun;87(6):604–609.

Zinzani PL. The many faces of marginal zone lymphoma. *Hematology Am Soc Hematol Educ Program.* 2012;2012: 426–432.

Anderson KC, Alsina M, et al. National Comprehensive Cancer Network. Multiple myeloma. *J Natl Compr Canc Netw.* 2011 Oct;9(10):1146–1183. Erratum in: *J Natl Compr Canc Netw.* 2011 Dec 1;9(12):xxv.

Anderson KC, Alsina M, et al. NCCN (National Comprehensive Cancer Network). Waldenström's macroglobulinemia/ lymphoplasmacytic lymphoma, version 2.2013. *J Natl Compr Canc Netw.* 2012 Oct 1;10(10):1211–1219.

Hoppe RT, Advani RH, et al. National Comprehensive Cancer Network. Hodgkin lymphoma, version 2.2012 featured updates to the NCCN guidelines. *J Natl Compr Canc Netw.* 2012 May;10(5):589–597.

Mikhael JR, Dingli D, et al. Mayo Clinic. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc. 2013 Apr;88(4):360–376.

Zelenetz AD, Abramson JS, et al. NCCN Clinical Practice Guidelines in Oncology: non-Hodgkin's lymphomas. *J Natl Compr Canc Netw.* 2010 Mar;8(3):288–334.

ONCOLOGY

[Guidelines in blue]

HYPERCALCEMIA OF MALIGNANCY

Rosner MH, Dalkin AC. Onco-nephrology: the pathophysiology and treatment of malignancy-associated hypercalcemia. *Clin J Am Soc Nephrol.* 2012 Oct;7(10):1722–1779.

SVC SYNDROME

McCurdy MT, Shanholtz CB. Oncologic emergencies. *Crit Care Med.* 2012 Jul;40(7):2212–2222.

Wan JF, Bezjak A. Superior vena cava syndrome. *Emerg Med Clin North Am.* 2009 May;27(2):243–255.

BONE METASTASES

Body JJ. New developments for treatment and prevention of bone metastases. *Curr Opin Oncol.* 2011 Jul;23(4):338–342.

Rades D, Schild SE, et al. Treatment of painful bone metastases. *Nat Rev Clin Oncol.* 2010 Apr;7(4):220–229.

Lutz S, Berk L, et al. American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys.* 2011 Mar 15;79(4):965–976.

SPINAL CORD COMPRESSION

Bhatt AD, Schuler JC, et al. Current and emerging concepts in non-invasive and minimally invasive management of spine metastasis. *Cancer Treat Rev.* 2013 Apr;39(2):142–152.

Mahnken AH, Pereira PL, et al. Interventional oncologic approaches to liver metastases. *Radiology.* 2013 Feb;266(2): 407–430.

Bhangoo SS, Linskey ME, et al; American Association of Neurologic Surgeons (AANS); Congress of Neurologic Surgeons (CNS). Evidence-based guidelines for the management of brain metastases. *Neurosurg Clin N Am.* 2011 Jan;22(1): 97–104, viii.

MALIGNANT EFFUSIONS

Barni S, Cabiddu M, et al. A novel perspective for an orphan problem: old and new drugs for the medical management of malignant ascites. *Crit Rev Oncol Hematol.* 2011 Aug;79(2):144–153.

Imazio M, Mayosi BM, et al. Triage and management of pericardial effusion. *J Cardiovasc Med* (Hagerstown). 2010 Dec;11(12):928–935.

McBride A, Westervelt P. Recognizing and managing the expanded risk of tumor lysis syndrome in hematologic and solid malignancies. *J Hematol Oncol.* 2012 Dec 13;5:75.

Quinn T, Alam N, et al. Decision making and algorithm for the management of pleural effusions. *Thorac Surg Clin.* 2013 Feb;23(1):11–6, v.

American Thoracic Society. Management of malignant pleural effusions. *Am J Respir Crit Care Med.* 2000 Nov;162(5): 1987–2001.

BREAST CANCER

Al-Allak A, Lewis PD, et al. Decision-making tools to assist prognosis and treatment choices in early breast cancer: a review. *Expert Rev Anticancer Ther.* 2012 Aug;12(8): 1033–1043.

Scoggins M, Krishnamurthy S, et al. Lobular carcinoma *in situ* of the breast: clinical, radiological, and pathological correlation. *Acad Radiol.* 2013 Apr;20(4):463–470. Erratum in: *Acad Radiol.* 2013 Jun;20(6):790.

Siziopikou KP. Ductal carcinoma in situ of the breast: current concepts and future directions. *Arch Pathol Lab Med.* 2013 Apr;137(4):462–466.

American College of Obstetricians and Gynecologists; ACOG Committee on Practice Bulletins--Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol.* 2009 Apr;113(4): 957–966.

American College of Obstetricians-Gynecologists. Practice bulletin no. 122: Breast cancer screening. *Obstet Gynecol.* 2011 Aug;118(2 Pt 1):372–382.

Breast Cancer Guidelines. American Society of Clinical Oncology. 2014. http://www.asco.org/guidelines/breast-cancer

Bevers TB, Anderson BO, et al. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. *J Natl Compr Canc Netw.* 2009 Nov;7(10):1060–1096. Erratum in: *J Natl Compr Canc Netw.* 2010 Feb;8(2):xxxvii.

Bevers TB, Armstrong DK, et al. Breast cancer risk reduction. *J Natl Compr Canc Netw.* 2010 Oct;8(10):1112–1146.

Burstein HJ, Griggs, JJ, et al. American Society of Clinical Oncology. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol.* 2010 Aug 10;28(23):3784–3796.

Carlson RW, Allred DC, et al. Breast cancer: noninvasive and special situations. *J Natl Compr Canc Netw.* 2010 Oct;8(10):1182–1207.

Carlson RW, Allred DC, et al; National Comprehensive Cancer Network. Invasive breast cancer. *J Natl Compr Canc Netw.* 2011 Feb;9(2):136–222.

Carlson RW, Allred DC, et al; National Comprehensive Cancer Network. Metastatic breast cancer, version 1.2012: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw.* 2012 Jul 1;10(7):821–829.

Khatcheressian JL, Hurley P, et al. American Society of Clinical Oncology. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2013 Mar 1;31(7):961–965.

Levin B, Lieberman DA, et al. American Cancer Society. Guidelines for the Early Detection of Cancer. 2013. http://www.cancer.org/healthy/findcancerearly/cancerscreening-guidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer

NCCN Guidelines. National Comprehensive Cancer Network. http://www.nccn.org/clinical.asp

Qaseem A, Snow V, et al. American College of Physicians Clinical Practice Guidelines. Breast Cancer Screening. *Annals of Internal Medicine.* 2007. http://www.acponline.org/clinical_information/guidelines/guidelines/

Screening for Breast Cancer. U.S. Preventative Services Task Force. 2009. http://www.uspreventiveservicestaskforce.org/uspstf/uspsbrca.htm

Van Poznak CH, Von Roenn JH, et al. American Society of Clinical Oncology. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. *J Clin Oncol.* 2011 Mar 20;29(9):1221–1227. Erratum in: *J Clin Oncol.* 2011 Jun 1;29(16):2293.

Visvanathan K, Chelebowski RT, et al. American Society of Clinical Oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. *Gynecol Oncol.* 2009 Oct;115(1):132–134. Erratum in: *Gynecol Oncol.* 2010 Mar;116(3):592.

CERVICAL CANCER

FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med.* 2007 May 10;356(19):1915–1927.

American College of Obstetricians and Gynecologists Committee on Adolescent Health Care. ACOG Committee Opinion #300: Cervical cancer screening in adolescents. *Obstet Gynecol.* 2004 Oct;104(4):885–889.

Association of Women's Health, Obstetric and Neonatal Nursing. HPV vaccination for the prevention of cervical cancer. *Nurs Womens Health.* 2010 Feb;14(1):81–82.

Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin Number 131: Screening for cervical cancer. *Obstet Gynecol.* 2012 Nov;120(5):1222–1238.

Gaffney DK, Erickson-Wittmann BA, et al. ACR Appropriateness Criteria® on Advanced Cervical Cancer Expert Panel on Radiation Oncology-Gynecology. *Int J Radiat Oncol Biol Phys.* 2011 Nov 1;81(3):609–614.

Koh WJ, Greer BE, et al. National Comprehensive Cancer Network. Cervical cancer. *J Natl Compr Canc Netw.* 2013 Mar 1;11(3):320–343.

Massad LS, Einstein MH, et al. 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol.* 2013 Apr;121(4): 829–846.

Partridge EE, Abu-Rustum NR, et al. National Comprehensive Cancer Networks. Cervical cancer screening. *J Natl Compr Canc Netw.* 2010 Dec;8(12):1358–1386.

Saslow D, Soloman D, et al. ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin.* 2012 May-Jun;62(3):147–172.

Wolfson AH, Varia MA, et al. American College of Radiology (ACR). ACR Appropriateness Criteria® role of adjuvant therapy in the management of early stage cervical cancer. *Gynecol Oncol.* 2012 Apr;125(1):256–262.

OVARIAN CANCER

Kobayashi E, Ueda Y, et al. Biomarkers for screening, diagnosis, and monitoring of ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2012 Nov;21(11):1902–1912.

American College of Obstetricians and Gynecologists; ACOG Committee on Practice Bulletins–Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol*. 2009 Apr;113(4): 957–966.

American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. Committee Opinion No. 477: the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer *Obstet Gynecol*. 2011 Mar;117(3):742–746.

Levy DE, Garber JE, et al. Guidelines for genetic risk assessment of hereditary breast and ovarian cancer: early disagreements and low utilization. *J Gen Intern Med*. 2009 Jul;24(7):822–828.

Morgan RJ Jr, Alvarez RD, et al. National Comprehensive Cancer Network. Epithelial ovarian cancer. *J Natl Compr Canc Netw*. 2011 Jan;9(1):82–113.

Morgan RJ Jr, Alvarez RD, et al. National Comprehensive Cancer Network. Ovarian cancer, version 3.2012. *J Natl Compr Canc Netw*. 2012 Nov 1;10(11):1339–1349.

TESTICULAR CANCER

Ehrlich Y, Beck SD, et al. Serum tumor markers in testicular cancer. *Urol Oncol*. 2013 Jan;31(1):17–23.

Motzer RJ, Agarwal N, et al. National Comprehensive Cancer Network. Testicular cancer. *J Natl Compr Canc Netw*. 2012 Apr;10(4):502–535.

U.S. Preventive Services Task Force. Screening for testicular cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med*. 2011 Apr 5;154(7):483–486.

PROSTATE CANCER

Cheng L, Montironi R, et al. Staging of prostate cancer. *Histopathology*. 2012 Jan;60(1):87–117.

Kollmeier MA, Zelefsky MJ. How to select the optimal therapy for early-stage prostate cancer. *Crit Rev Oncol Hematol*. 2012 Aug;83(2):225–234.

Ciezki JP, Hsu IC, et al. American College of Radiology Appropriateness Criteria. American College of Radiology Appropriateness Criteria–locally advanced (high-risk) prostate cancer. *Clin Oncol (R Coll Radiol)*. 2012 Feb;24(1):43–51.

Kawachi MH, Bahnson RR, et al. NCCN clinical practice guidelines in oncology: prostate cancer early detection. *J Natl Compr Canc Netw*. 2010 Feb;8(2):240–262.

Kramer BS, Hagerty KL, et al. American Society of Clinical Oncology Health Services Committee; American Urological Association Practice Guidelines Committee. Use of 5-alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. *J Clin Oncol*. 2009 Mar 20;27(9):1502–1516. Review. Erratum in: *J Clin Oncol*. 2009 Jun 1;27(16):2742.

Loblaw DA, Virgo KS, et al. American Society of Clinical Oncology. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol*. 2007 Apr 20;25(12):1596–1605.

Mohler JL, Armstrong AJ, et al. Prostate cancer, Version 3.2012: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw*. 2012 Sep;10(9):1081–1087.

Moyer VA; U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012 Jul 17;157(2):120–134.

Qaseem A, Barry MJ, et al. Clinical Guidelines Committee of the American College of Physicians. Screening for prostate cancer: a guidance statement from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med*. 2013 May 21;158(10):761–769.

Rosenthal SA, Bittner NH, et al. American Society for Radiation Oncology; American College of Radiology. American Society for Radiation Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys*. 2011 Feb 1;79(2):335–341.

Thompson I, Thrasher JB, et al. AUA Prostate Cancer Clinical Guideline Update Panel. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol*. 2007 Jun;177(6):2106–2131.

Wolf AM, Wender RC, et al. American Cancer Society Prostate Cancer Advisory Committee. American Cancer Society guideline for the early detection of prostate cancer update 2010. *CA Cancer J Clin*. 2010 Mar-Apr;60(2):70–98.

HEAD & NECK CANCER

Mehanna H, Paleri V, et al. Head and neck cancer—Part 1: Epidemiology, presentation, and prevention. *BMJ*. 2010 Sep 20;341:c4684. doi: 10.1136/bmj.c4684.

Mehanna H, West CM, et al. Head and neck cancer—Part 2: Treatment and prognostic factors. *BMJ*. 2010 Sep 28;341:c4690. doi: 10.1136/bmj.c4690.

Saloura V, Langerman A, et al. Multidisciplinary care of the patient with head and neck cancer. *Surg Oncol Clin N Am*. 2013 Apr;22(2):179–215.

CARCINOID

Bergsland EK. The evolving landscape of neuroendocrine tumors. *Semin Oncol*. 2013 Feb;40(1):4–22. Erratum in: *Semin Oncol*. 2013 Apr;40(2):239.

Doherty G. Surgical treatment of neuroendocrine tumors (including carcinoid). *Curr Opin Endocrinol Diabetes Obes*. 2013 Feb;20(1):32–36.

Leung D, Schwartz L. Imaging of neuroendocrine tumors. *Semin Oncol*. 2013 Feb;40(1):109–119.

CHEMOTHERAPY AND BIOLOGIC THERAPY

Dicato M, Plawny L. Erythropoietin in cancer patients: pros and cons. *Curr Opin Oncol*. 2010 Jul;22(4):307–311.

Li J, Chen F, et al. A review on various targeted anticancer therapies. *Target Oncol*. 2012 Mar;7(1):69–85.

Molineux G. Granulocyte colony-stimulating factors. *Cancer Treat Res*. 2011;157:33–53.

Puhalla S, Bhattacharya S, et al. Hematopoietic growth factors: personalization of risks and benefits. *Mol Oncol*. 2012 Apr;6(2):237–241.

Stasi R, Bosworth J, et al. Thrombopoietic agents. *Blood Rev*. 2010 Jul-Sep;24(4-5):179–190.

Crawford J, Allen J, et al. National Comprehensive Cancer Network. Myeloid growth factors. *J Natl Compr Canc Netw*. 2011 Aug 1;9(8):914–932.

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THE IMMUNE SYSTEM

OVERVIEW

The Innate Immune System

The innate immune system is rapid-acting, nonspecific, and has no memory. It has many components, which include complement, macrophages, and natural killer (NK) cells. It is the first line of defense after the skin.

The Adaptive Immune System

The adaptive immune system is much slower than the innate to get started, but is very specific and has memory.

It consists of T and B cells, as well as immune globulins (Igs), and is a second line of defense that is activated by the innate immune system.

The adaptive immune system can be divided into humoral and cell-mediated components:

- **Humoral**: B cells, plasma cells, and immunoglobulins
- **Cell-mediated**: T cells, activated macrophages, and activated NK cells

Innate vs. Adaptive Immunity

The innate immune system is the foundation on which the more sophisticated adaptive immune system rests. The innate system not only protects the body while the adaptive immune system gears up, but it also helps direct the response. The innate immune system, in general, needs messages to prevent it from killing, while the adaptive immune system needs messages (usually from the innate immune system) to allow it to kill.

The key difference between the 2 systems can be found in their respective receptors:

- **Innate** immune system receptors are generic, germline-encoded receptors (e.g., Toll-like receptors). They allow a quick but non-specific response—one that is very rapid but recognizes only a limited number of microbial patterns rather than a large variety of specific pathogens. Think of the innate immune system as the "first responders" to a new attack.
- **Adaptive** immune system receptors are highly specific receptors (T-cell receptors [TCRs], B-cell receptors [BCRs], and immunoglobulins [Igs]), which are refined to be as precise as possible for the pathogen. This system has the ability to recognize a seemingly infinite variety of pathogens. Once these highly specific receptors have served their purpose, the body keeps a few of them around in case it needs them again in the future—so it can react much more quickly next time (memory).

Innate and Adaptive Overlap

It is important to understand that there is significant overlap between the innate and adaptive immune systems. For example, macrophages and NK cells initially function as part of the innate system. However, after being activated by T cells, they then act as part of the adaptive immune system. Similarly, the "classical pathway" of the complement system uses antibody (Ig) to initiate its activity. Antibody involvement in the complement system is an example of how the adaptive immune system provides memory.

Overlap is again demonstrated by a group of innate-like cells of the adaptive immune system that are more rapid acting and less specific.These innate-like immune cells include:

- γ:δ T cells and natural killer T cells
- B-1 cells (an innate-like version of B cells)

CELLS OF THE IMMUNE SYSTEM

Cells in the immune system are divided into 2 categories: lymphoid and myeloid cells. We'll outline the types here and discuss the need-to-know points.

Lymphoid cells:

- Lymphocytes (B and T cells):
  - B cells:
    - B-1 cells (innate-like)
    - B-2 cells (what we typically call "B" cells)
    - Marginal B cells (innate-like)
  - T cells:
    - α:β T cells: consist of CD4 and CD8 T cells
    - γ:δ T cells (innate-like)
    - Natural killer T (NKT) cells
- Natural killer cells (different from the similarly named NKT cells!)

Myeloid cells:

- Granulocytes:
  - Neutrophils
  - Eosinophils
  - Basophils
- Professional antigen-presenting cells:
  - Monocytes/Macrophages
  - Dendritic cells
- Other:
  - Mast cells
  - Erythrocytes
  - Platelets

HLA ANTIGENS

The major histocompatibility molecules are required by the body to differentiate self vs. non-self material. The major histocompatibility complex (MHC) of genes is located on chromosome 6. The human MHC is called human leukocyte antigen (HLA). There are 3 classes of HLA antigens (I, II, and III).

Class I HLA antigens (HLA-A, -B, and -C) are on most nucleated cells. They present non-self material to CD8+ T cells and play a role in transplant rejection, neoplasms, and viral infections.

Class II HLA antigens (HLA-DP, -DQ, and -DR) are on antigen-presenting cells, which include monocytes/macrophages, Langerhans cells, dendritic cells, and B cells (so these cells have both class I and class II HLA antigens). They mediate the reaction between macrophages, T cells, and B cells. The CD4+ T cells recognize material presented only by the class II antigens.

Class III HLA antigens consist of a few cytokines, like TNF and lymphotoxin, and several complement component structures.

LYMPHOID CELLS

LYMPHOCYTES

T Cells

Overview

Review: "Clusters of differentiation" (CD) markers are like "name tags" and allow one to "differentiate" one immune cell from another. For example:

T cells are CD2+ and CD3+. T cells also usually have either a CD4 or CD8 protein on their surface (more on this below).

Mature B cells are CD19+ and CD20+. Natural killer cells are CD16+ and CD56+.

Functions of T cells:

- Destroy intracellular and other bacteria (especially gram-negative), viruses, fungi, parasites, and mycobacteria
- Regulate antibody production by B cells

All T cells have receptors (T-cell receptor = TCR), which are antigen-specific binding sites composed of 2 subunits (the majority being alpha and beta and a minority being the innate-like gamma and delta). The TCR is always associated with a CD3 complex, which allows for intracellular signaling.

Again: T cells recognize antigen only if it is presented in the context of an MHC molecule. This is the key concept of MHC restriction! CD8+ T cells recognize antigen only if it is presented with a class I HLA antigen, whereas CD4+ T cells recognize antigen only if it is presented with a class II HLA antigen. (A nice way to remember this: CD8 x MHCI = 8, CD4 x MHCII = 8.)

CD4+ T Cells

CD4+ T cells are the primary defense against exogenous antigens. The CD4+ T cells are divided into several subsets:

1) **TH1**—activates CD8+ T cells and leads to cell-mediated immunity.
2) **TH2**—activates B cells to produce antibody and leads to humoral immunity.
3) **TH17**—plays a role in immunity against fungi and bacteria, and in autoimmune disorders (including RA, MS, and IBD).

Again: Class II antigens appear only on professional antigen-presenting cells such as monocytes/macrophages, Langerhans cells, dendritic cells, and B cells.

How does CD4+ T cell activity get induced? An antigen-presenting cell such as a macrophage ingests a foreign particle or microorganism. The foreign particle is processed and presented along with the class II HLA antigen to CD4+ T cells. These T cells, after being activated, induce B cells to convert to plasma cells and produce specific antibodies against that foreign particle.

HIV targets all CD4+ cells, including CD4+ T cells and other cells that express CD4, such as macrophages, monocytes, and microglial cells. By targeting and attacking CD4+ cells, HIV weakens the immune system, allowing opportunistic infections to occur.

CD8+ T Cells

The CD8+ cells are cytotoxic T cells. They are important in the defense against viruses and neoplastic cells. They are activated by neoplastic antigens and other antigens presented in association with class I HLA antigens. So most cell types can present antigen to CD8+ T cells!

T Regulatory Cells

T regulatory cells are a specialized subpopulation of T cells that modulate the activity of the immune system. This can be a confusing group of cells since it is made up of several different types of T cells (usually CD4+ but also CD8+ and others). The expression of the transcription factor FOXP3 controls the development and function of T regulatory cells. These cells regulate the immune response by secreting immunosuppressive cytokines like IL-10 and TGF-β. T regulatory cells help maintain tolerance to self-antigens, and genetic mutations in FOXP3 leads to overwhelming systemic autoimmunity.

NKT Cells

(Name alert! Don't confuse with "natural killer cells"—the innate lymphoid cells with a very similar name!)

Natural killer T cells have a twist on the concept of MHC restriction. They are restricted to a type of MHC-like molecules called CD1, which recognizes primarily lipids and glycolipids. They are so named because they share several features with natural killer cells, such as granzyme production and CD16 and CD56 expression.

B Cells

Some B cells, upon stimulation, become plasma cells (antibody-producing cells). B cells are surface membrane immunoglobulin positive (SmIg+); i.e., they have IgM and IgD on their surfaces, which distinguish them from T cells, B-cell precursors, and plasma cells. B cells are the most specific antigen-presenting cells. Mature B cells are CD19+ and CD20+.

Quick Quiz

- Explain the differences between innate and adaptive immunity.
- What are class II HLA antigens, and where are they located?
- What are the different functions between CD4+ and CD8+ T lymphocytes?
- What immunoglobulins are present on the surface of mature B cells?
- Characterize the various immunoglobulins: G, A, M, E, and D.

B cells can be stimulated to convert to plasma cells by either antigen alone or activated CD4+ T cells. Plasma cells produce specific antibodies. The specific antibodies can coat the surface of a foreign organism. The coating either identifies it as edible to the macrophages (opsonization) or initiates the complement cascade (complement activation). Specific antibodies can also neutralize bacterial toxins and viruses.

B cells, like monocytes/macrophages, have class II HLA antigens on their surfaces, so they also can present foreign antigens to CD4+ (helper) T cells. The activated T cells can then induce other B cells to convert to plasma cells and produce antibody.

NATURAL KILLER CELLS

(Name alert! Don't confuse with "natural killer T cells"—the similarly-named innate-like CD4+ T cells).

Natural killer (NK) cells are lymphoid cells that play a major role in the immune system response to tumors and viruses. They express CD16 and CD56 but not TCR or its associated CD3 molecules (an important difference between them and natural killer T cells!).

They are called natural killers because they are always in kill mode, and the cells they encounter must present themselves appropriately in order to not be killed. For example, all cells (except mature RBCs) must display class I HLA-E antigens on their cell surface in order to not be killed by natural killer cells.

Natural killer cells are an important component of the immune system because some viruses have evolved to reduce class I HLA expression on the host cell, protecting them from recognition and destruction by T cells. With natural killer cells, it is precisely this absence or reduction of class I HLA expression that causes the natural killer cell to kill (usually by inducing apoptosis) the infected cell.

In comparison, natural killer T cells, like all other T cells, require the antigen to be presented in association with an HLA antigen before they can become activated to kill.

MYELOID CELLS

Granulocytes: white blood cells with identifiable granules in their cytoplasm.

Neutrophils = polys = PMNs = segs (mature) and bands (immature). PMNs phagocytize microorganisms, especially those coated with antibodies. If PMNs are absent, patients get overwhelming pyogenic infections.

Eosinophils: involved in the pathology of allergic reactions but also in the immunologic defense against parasites.

Basophils are discussed under Immediate Hypersensitivity Reactions (page 9-6).

Professional antigen-presenting cells: Cells expressing both MHCI and MHCII. This is an exclusive group of cells consisting of 3 cell types:

1) B cells are the most specific, antigen-presenting cells.
2) Monocytes/macrophages eat opsonized microorganisms, process and present antigens, and secrete interleukin-1 (IL-1), which stimulates T cells.
3) Dendritic cells are scavengers that, when they ingest a pathogen, change conformation, travel to a lymph node, and activate lymphocytes.

Other:

- Mast cells are discussed under Immediate Hypersensitivity Reactions (page 9-6).
- Erythrocytes are covered in Hematology, Book 4.
- Megakaryocytes/platelets also are discussed in Hematology, Book 4.

ANTIBODIES

All antibodies (immunoglobulins) have the same basic structure (Figure 9-1 on page 9-4). Each monomer is composed of 2 heavy and 2 light chains that are held together by disulfide bonds. There are 5 immunoglobulin isotypes: G, A, M, E, and D. These isotypes are determined by differences in the structure of the constant regions of the heavy chains. All antibodies have 1 of 2 types of light chains, kappa or lambda.

Remember the following:

IgG is the main antibody in serum, and it is the major antibody in the immune response. It readily crosses the placenta. It has 4 subclasses (IgG1, IgG2, IgG3, and IgG4). IgG can activate complement.

IgA is the main Ig in secretions and is usually a dimer (2 immunoglobulins) with the J chain and a secretory component, which is actually just a piece of the epithelial or liver cell receptor attached to locally produced IgA. It is the main Ig secreted in breast milk. IgA does not activate complement.

IgM is the 1st Ig subtype produced in an infection. It is a monomer on the cell surface but is secreted as a pentamer (5 immunoglobulins), in which each monomer is

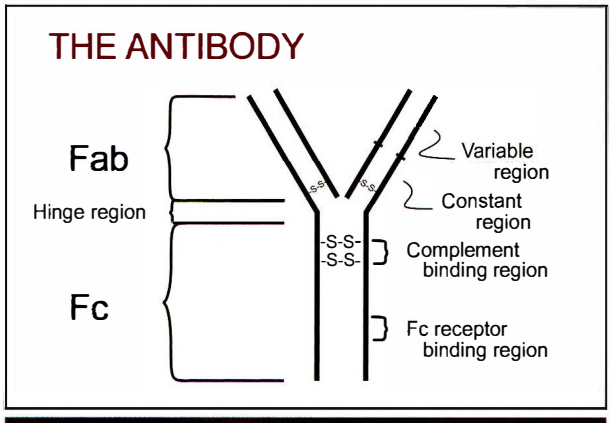

Figure 9-1: Antibody Structure

connected by a J chain. IgM is useful in diagnosis of a recent illness and can help distinguish acute vs. chronic infection. Because IgM is a pentamer, it is the best antibody for complement activation.

IgE is the Ig with the lowest concentration in normal serum but is a major factor in many allergic conditions, including asthma, allergic rhinitis, atopic dermatitis, and food allergies.

IgD is found in trace amounts on adult B cells, and its function is as yet undefined.

The variability in antibody specificity is due to the rearrangement of several regions within the antibody gene. Most of the variability is located in the complementarity determining regions (CDRs), also known as hypervariable regions.

Immunoglobulins (antibodies) bind specific antigens in the Fab region and then activate either cells or complement (discussed next), by means of the Fc region, to destroy the antigen-bearing material.

COMPLEMENT CASCADE

OVERVIEW

The 3 Complement Pathways

First, a brief review of the complement system. See Figure 9-2.

The complement system is a group of about 30 known plasma factors important in host defense and destruction of microorganisms. It is now known to have 3 main pathways: classical, lectin, and alternative. Through different mechanisms, they all perform the same function-—opsonizing target cells with C3b and then forming the "membrane attack complex."

Classical Pathway

The immunoglobulins (usually IgG and IgM) activate the classical pathway. The C1 complex (with q, r, and s subunits) initiates the response when a C1q subunit attaches to antibody in an antigen-antibody complex.

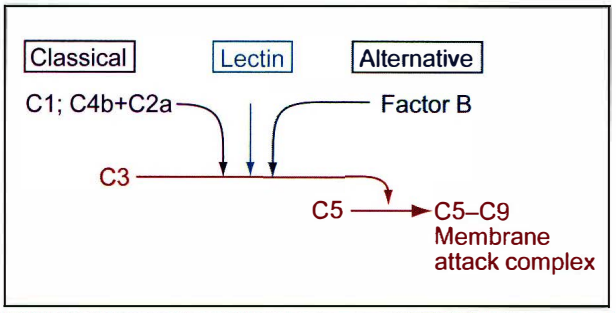

Figure 9-2: Summary of the Complement Cascade

C1q binds to the Fc portion of at least 2 IgGs (or 1 IgM pentamer), or it binds to the surface of the pathogen itself. Binding changes the conformation of the C1q. This activated C1 cleaves many C2 and C4, subcomponents of which (C2a and C4b) combine and form C4b2a ("C3 convertase"), which in turn activates many C3s.

Again: 1 IgM pentamer can initiate the classical pathway, but it generally takes at least 2 IgGs.

Lectin (or Mannose-Binding) Pathway

Lectins (mannose-binding lectin [MBL]; also called mannose- or mannan-binding proteins) bind mannose on the surface of pathogens. Then associated proteases cleave C2 and C4, and further steps are similar to the classical pathway. These MBLs are produced by an acute-phase response and are fairly nonspecific.

Alternative Pathway

C3 also is activated by the alternative pathway. C3 combines with a factor "B." This complex then activates more C3 and factor B, causing a cascade, which is normally kept under control by the inhibitory regulatory proteins "H" and "I." Both gram-positive and gram-negative cell walls directly activate the alternative pathway by spontaneous cleavage of C3.

A C3b-coated circulating bacterium is recognized, removed, and destroyed by Kupffer cells in the liver.

Common Terminal Pathway — Membrane Attack Complex

C3, when combined with either C4b2a or factor B, activates C5, which causes the formation of a C5-6-7-8-9 membrane attack complex (MAC). The MAC can poke holes in bacterial cell membranes and cause the bacteria to lyse.

HEREDITARY COMPLEMENT DEFICIENCIES

Hereditary Angioedema

Hereditary angioedema (HAE) is an autosomal dominant disorder caused by a decrease in C1 inhibitor (C1-INH) function. C1-INH normally inhibits the activity of the

QuickQuiz

- What is the cause of hereditary angioedema? What is the clinical presentation?
- Terminal complement deficiency is associated with which infection?
- What does the CH50 assay measure, and when is it used?

Cl complex (classical pathway) and MBL complex (lectin pathway). Lack of C1-INH function allows for increased complement activation resulting in a secondarily decreased C4 (because of ongoing consumption). Patients can have either a decreased C1 inhibitor enzyme level (85%, Type I) or a non-functioning C1 inhibitor enzyme (15%, Type II). Bradykinin is thought to be the key mediator in the angioedema attacks.

Patients have recurrent nonpitting edema with each episode, lasting 1–3 days. Unlike angioedema/urticaria caused by immediate hypersensitivity reactions, hereditary angioedema does not cause urticaria or itching.

Even minor trauma from dental procedures can precipitate attacks! Attacks may include laryngeal obstruction and very often affect the GI tract, causing severe abdominal pain.

Diagnosis: Screen by checking C4 levels (low). Then, check a C1-INH functional assay:

- If the C1-INH level also is low, then it is **Type I HAE**.
- If the C1-INH level is normal, it is due to a nonfunctioning C1-INH enzyme, and it is **Type II HAE**.

Treatment: Epinephrine is not effective. Fresh frozen plasma can be helpful when given before trauma, such as dental surgery. Androgens (danazol) increase C1-INH levels and decrease swelling episodes. Until recently, this was the only available preventive medication. New available therapies include plasma-derived C1-INH to prevent and treat attacks. A kallikrein inhibitor (ecallantide) and a bradykinin receptor antagonist (icatibant) are available for acute attacks.

C1, C2, and C4 Deficiencies

C1, C2, or C4 deficiency causes decreased activation of complement via the classical pathway. Most of the complement proteins are inherited as autosomal recessive genes. Although the alternative pathway takes up some of the slack, these patients still have recurrent sinopulmonary infections (and ear infections when young) with encapsulated bacteria. In patients with 1 abnormal gene, complement blood levels are about 1/2 normal. In these patients, there is an increased incidence of rheumatoid diseases—especially SLE!

C2 deficiency is the most common complement deficiency in North American Caucasians; thus, consider it in patients with early-onset SLE. This is because complement proteins are either important in removing immune complexes, or their genes are physically associated with genes that control the immune response.

C3 Deficiency

C3 deficiency (complete absence) results in severe pyogenic (bacterial) infections.

C5–C9 Deficiency

C5–C9 MAC deficiency is also called terminal complement deficiency. It results in increased *Neisseria* meningococcal/gonococcal infections (especially meningitis or septicemia). Screen for terminal complement deficiency with CH50. Specific diagnosis is made by assay of these complement components.

CH50

The CH50 assay measures the total complement hemolytic activity of the classical pathway. A normal test shows that all factors of the classical pathway (C1–C9) are present. Know that a CH50 assay still can be normal even if C3 or C4 are significantly lower than normal because normal levels of C3 and C4 are far higher than required. CH50, C3, and C4 are sometimes used to follow disease activity of SLE. The CH50 is a good screen for complement deficiencies. If the CH50 is very low, check individual complement components (C1 through C9 levels) for specific deficiencies.

IMMUNE COMPLEXES

Immune complexes ([ICs]; i.e., antigen-antibody complexes) form during normal, day-to-day immune surveillance, and then are removed from the serum. As they form, complement usually is activated and a C3 component (C3b) attaches to the complex.

This C3b-IC entity is recognized by, and attaches to, the complement receptor. The main complement receptor is CR1, which is found in abundance on RBCs.

The immune complexes are scrubbed off the RBCs by the Kupffer cells in the liver. (Remember that Kupffer cells also remove and destroy C3-coated gram-positive and gram-negative bacteria—see above.) If there are any defects in this elimination process, immune complexes increase in the serum, as in the following conditions:

- **Hepatic vein thrombosis** (Budd-Chiari syndrome) and cirrhosis result in decreased clearance.
- **Paroxysmal nocturnal hemoglobinuria** (PNH) results in decreased binding.
- **SLE** results in a decreased amount of CR1 on the RBCs.

So, each of these disorders causes increased immune complexes in the serum.

Immune complexes activate complement to form C3b, which attaches to the Fc portion of the IgG. This

maintains the solubility of the complexes in the serum and prevents them from cross-connecting and precipitating. IgA does not activate the classical complement pathway and, therefore, may be more susceptible to precipitation; this causes immune complexes to deposit in small blood vessels and tissues when high levels build up.

More under Immune Complex Hypersensitivity (page 9-8).

HYPERSENSITIVITY REACTIONS

OVERVIEW

Hypersensitivity reactions reflect immune-mediated tissue injury, resulting in a variety of outcomes: allergies, autoimmune disease, and other inflammatory diseases.

There are 4 types of hypersensitivity reactions (per Gell and Coombs):

Type I: IgE-mediated—immediate (anaphylactic, atopic)

Type II: IgG- or IgM-mediated---cytotoxic

Type III: Immune complex (antibody-antigen) mediated

Type IV: Cell-mediated—delayed type

TYPE I: IMMEDIATE HYPERSENSITIVITY REACTION

Allergies

The "classic" allergies are Type I hypersensitivity reactions. Examples: hives/urticaria, allergic rhinitis, allergic asthma, reaction to insect stings, drugs (PCN, etc.), and foods (peanuts, eggs, shellfish, etc.).

Type I: Acute Response

The acute phase of immediate hypersensitivity reactions occurs within 1 hour after exposure—usually within minutes. Mast cell degranulation (especially producing histamine) is the cause of the symptoms. This reaction is IgE-mediated. These IgE antibodies are antigen-specific and occur only in response to previous exposure to the same allergen.

The base (Fc portion) of IgE antibodies binds to a receptor on mast cells. This receptor is not specific, so there are many IgEs (each with its own antigen specificity) bound to a mast cell. No reaction occurs when IgE binds to the mast cell.

So what really happens in Type I allergic reactions? An allergen interacts with the allergen-specific receptor on the Fab portion of IgE, and, when the same antigen reacts with more than 1 IgE—thereby interlinking the 2—the mast cell is stimulated to degranulate and release histamine and also begin synthesizing and secreting other mediators (leukotriene C_4, PGD_2, and cytokines). Histamine is responsible for most of the acute symptoms. Mast cells also release other products that have chemotactic effects, and some of them are enzymes (chymase and tryptase). We measure tryptase levels to confirm anaphylactic reactions, and diagnose mast cell disorders. See Mastocytosis on page 9-11.

Review: Histamine interacts with 4 receptors—H_1, H_2, H_3, and H_4.

- **H_1** receptor activation causes the wheal and flare, bronchoconstriction, and pruritus.
- **H_2** receptor activation results in increased gastric acid secretion.
- **H_3** activation causes decreased histamine synthesis and release (negative feedback).
- **H_4** has immunomodulatory effects and affects eosinophil and mast cell recruitment.

Type I: Late-Phase Response

The late-phase response (LPR) occurs 3–12 hours after the acute response and can last hours to days. The LPR is caused by the initial, immediate IgE reaction stimulating the synthesis of cytokines and the subsequent cellular recruitment of eosinophils and basophils. This results in an eosinophilic inflammatory infiltrate. The probability of a LPR increases with the severity of the acute reaction.

In the skin, there is induration that is erythematous, burning, and occasionally pruritic. In the airways, the LPR is one of the causes of nonspecific airway hypersensitivity seen in asthmatic patients.

Type I: Anaphylaxis

Anaphylaxis is usually an extreme IgE-mediated form of immediate hypersensitivity reaction, but it also can be caused by the by-products of activated C3, 4, and 5 (anaphylatoxins), which, like IgE, cause the release of the cytoplasmic granules from mast cells (+/– basophils). The released cytoplasmic granules cause an immediate hypersensitivity reaction.

ASA/NSAIDs, physical stress, and certain chemicals (sulfites that cause asthma, opiates) are causes of non-IgE–mediated anaphylaxis.

The most common causes of IgE-mediated anaphylaxis are drugs, foods, and insect stings. Persons with asthma or heart disease are at greater risk for fatal anaphylaxis. Penicillin allergy is a common cause of drug-related anaphylaxis. Peanuts, tree nuts, and shellfish are common causes of food anaphylaxis. Bees, wasps, and yellow jackets are common culprits of insect sting anaphylaxis. Any insect sting can occasionally cause a large local reaction. This does not increase the risk of anaphylaxis, and further workup is not necessary. However, systemic reactions (generalized hives or anaphylaxis) from insect stings do require further evaluation with venom skin testing and serum venom specific-IgE.

Remember that hypotension is not always required for the diagnosis of anaphylaxis! See Table 9-1.

Quick Quiz

- What mediates immediate hypersensitivity reactions?
- When does the late phase of Type I hypersensitivity reaction occur? Why does it occur?
- Know the causes of and how to treat anaphylaxis—both mild and severe.
- Which antihypertensive medication is relatively contraindicated in someone at risk for anaphylaxis? Why?

Note that ASA-induced anaphylaxis is a separate syndrome from ASA-induced urticaria, and both of these are separate from ASA-induced asthma, which is often associated with rhinosinusitis and nasal polyps due to cyclooxygenase inhibition and leukotriene production.

Type I: Treatment

Treatment for immediate hypersensitivity diseases: **a**voidance of the allergen, and give **a**ntihistamines (occasionally steroids) and **a**llergen-specific immunotherapy (3 **A**s). The immunotherapy may take up to 6 months to show an effect. Patients at high risk for anaphylaxis, such as beekeepers, should get an epinephrine auto-injection kit. Effective immunotherapy causes an increase in T regulatory cell secretion of IL-10 and blocking antibodies of the IgG isotype, among many other effects. Only reactions that are IgE-mediated benefit from immunotherapy treatment.

Treatment for anaphylaxis:

- Give epinephrine (1:1,000) 0.2–0.5 cc IM (maximum dosage 0.5 mg, 0.5 cc of 1:1,000 = 0.5 mg; do not give IV); repeat every 10–20 minutes as needed. If the cause is antigenic material injected into an extremity (e.g., bee sting), place a tourniquet proximal to the site.
- H_1 and H_2 antagonists (usually diphenhydramine and cimetidine, respectively) also may be given.
- Inhaled albuterol may be given if bronchospasm develops.
- Steroids may help prevent the delayed (late-phase) reactions.
- For significant hypotension, give epinephrine (1:10,000) 5 cc IV q 5–10 min (5 cc of 1:10,000 = 0.5 mg), a normal saline bolus, and (lastly) dopamine as needed.
- IV steroids are not effective for acute cases but may abort or decrease the delayed response.

Epinephrine is 1st line treatment for all causes of anaphylaxis! The failure to recognize the symptoms of anaphylaxis, and to administer epinephrine promptly, has led to preventable fatalities.

Table 9-1: Anaphylaxis Diagnosis

Anaphylaxis is diagnosed when any 1 of the following 3 criteria is fulfilled.

1) Sudden onset with involvement of the skin/mucosal tissue and either:
   - Sudden respiratory symptoms, or
   - Hypotension
2) 2 or more of the following that occur suddenly after exposure to a likely allergen:
   - Skin/mucosal tissue involvement
   - Respiratory involvement
   - Hypotension
   - GI symptoms
3) Hypotension after exposure to known allergen

Epinephrine affects the alpha and beta adrenergic systems, resulting in bronchial relaxation, vasoconstriction, and decreased vascular permeability. The effect of epinephrine is blunted in patients on beta-blockers, so these are relatively contraindicated in patients at risk for anaphylactic reactions. Glucagon or vasopressin injections may be used in patients with anaphylaxis on beta-blockers after epinephrine has already been administered. Again: Epinephrine is always 1st line!

TYPE II: CYTOTOXIC HYPERSENSITIVITY

Type II reactions occur when an IgG or IgM antibody binds to a fixed tissue antigen or cell receptor. These are autoantibodies.

Binding of the antibody results in target cell destruction by various means:

- Complement activation may cause cells to be lysed by the membrane attack complex (MAC, discussed on page 9-4).
- Complement activation may result in opsonization from the production of C3b. Phagocytes have a receptor for C3b.
- Phagocytes also have a receptor for the Fc portion of the antibodies and therefore may attack antibody-coated cells.

Examples of target cell receptors:

Target Cell	Disease
Platelets	Thrombocytopenia
RBCs	Autoimmune hemolytic anemia
WBCs	Leukopenia

Examples of target fixed tissue antigens:

Target Antigen	Disease
Component of the basement membrane (kidney and lung)	Goodpasture's
ACh receptor on muscle cells	Myasthenia gravis

TYPE III: IMMUNE COMPLEX HYPERSENSITIVITY

Anytime you see a vasculitis, think of Type III hypersensitivity reaction. Type III reactions are also seen in Ig autoimmune diseases and reactions to drugs. Immune complexes (ICs) form when antibodies combine with an antigen (self or foreign). A hypersensitivity reaction occurs when antibody (usually IgG) reacts with a target antigen to form ICs, which precipitate and activate complement with subsequent small vessel inflammation and necrosis.

Remember: Just because an antibody reaction occurs and ICs are formed, it does not necessarily mean there is precipitation. Significant precipitation occurs only when there is slight antigen excess in relation to the antibody.

When the antibody response initiates, there is a huge excess of antigens compared to antibodies (Ag:Ab >> 1). The ICs that are formed are small, soluble, and quickly cleared.

Within 1–2 weeks, as exceedingly more antibodies are produced, a point is reached when there is only slight antigen excess, and the ICs interlace and become bigger and less soluble. These precipitate in the small vessels and activate complement, which starts a cascade causing the release of more cytokines and the gathering of more inflammatory cells. This process ultimately results in necrosis of the small vessels. The pathologic hallmark skin sign is leukocytoclastic vasculitis (hemorrhagic, indurated lesions).

As the antigen is cleared, there comes a point when there is antibody excess. The formed ICs are large and quickly cleared by circulating phagocytes (macrophages).

There are 2 animal models for what happens clinically:

1) Serum sickness (a systemic reaction): A large amount of antigen is injected into a nonimmunized animal, and within 1–2 weeks, you see a necrotic vasculitis similar to the one just discussed.
2) Arthus reaction (a local reaction): The animal is first hyperimmunized, so there are many circulating IgG antibodies, and then given a small intradermal injection of the target antigen. All reaction occurs at the injection site, where there are many ICs made—inducing the complement cascade and inflammation. Within 4–12 hours, a painful indurated lesion appears and may progress to a sterile abscess.

Type III reaction plays a part in the following conditions—autoimmune diseases (and associated antigen[s]):

- SLE (nuclear materials such as dsDNA, Smith antigen, and many others)
- Hashimoto thyroiditis (thyroglobulin)
- Pernicious anemia (intrinsic factor)
- Rheumatoid arthritis (rheumatoid factor)

External antigens:

- Hepatitis-antigen–associated serum sickness
- Tetanus and diphtheria immunization
- Local insulin reactions

Serum sickness and Arthus Type III hypersensitivity reactions are generally self-limited, and patients usually recover fully. Occasionally, corticosteroids are given.

Treatment of autoimmune diseases is covered in other sections, particularly Rheumatology, Book 3.

Treat external antigen reaction by stopping the exposure to the antigen.

TYPE IV: CELL-MEDIATED HYPERSENSITIVITY

Previously sensitized T cells interact with an antigen, causing an inflammatory reaction. The reaction peaks in 24–72 hours—hence the common name: delayed-type hypersensitivity.

Tuberculin sensitivity and contact dermatitis caused by poison ivy are examples of delayed-type IV hypersensitivity reactions. Don't confuse "delayed-type" IV hypersensitivity reaction with the "late phase" of Type I!

TYPE V: AUTOIMMUNE STIMULATORY HYPERSENSITIVITY

The term Type V hypersensitivity reaction is used by some to indicate when the autoimmune IgG has a stimulatory effect on a receptor (as distinguished from Type II, which is destructive). It is not part of the Gell and Coombs classification. An example is Graves disease, where an IgG stimulates the TSH receptor.

OTHER URTICARIA

There are also several non-allergen–mediated causes of urticaria:

- **Acquired cold urticaria** is usually mediated by either cryoglobulins or IgE. Shock may occur if the patient is immersed in cold water! Test with a 5-minute skin ice-cube challenge.
- **Familial cold urticaria** is an autosomal dominant, inherited inflammatory disease characterized by urticaria, myalgias, fever, and joint pain after cold exposure.
- **Cholinergic urticaria** is precipitated by heat (e.g., hot shower, hot day, exercise). Usually presents as punctate lesions that are very pruritic.
- **Immediate pressure urticaria** is seen with severe dermatographism and may develop around the waistline.
- **Delayed pressure urticaria** typically causes swelling and burning (not itching) of palms and soles several hours after carrying a load for a while or walking long distances.

Quick Quiz

- Which diseases are mediated by Type III immune complex hypersensitivity reactions?
- A tuberculin test is an example of which type of hypersensitivity reaction?
- What is the difference between a Type II and a Type V hypersensitivity reaction?
- What causes cholinergic urticaria?
- Distinguish between chronic urticaria and urticarial vasculitis.
- What is rhinitis medicamentosa? How is it treated?
- What is atrophic rhinitis? How is it treated?
- Why is it important to avoid 1st generation antihistamines in the elderly?
- Which class of medication should be avoided for the treatment of allergic rhinitis in pregnancy?

- **Autoimmune urticaria** occurs when autoantibodies to the IgE receptor on mast cells link the receptors and cause degranulation.
- **Chronic urticaria** occurs when hives last > 6 weeks. Most often the underlying cause is unknown. In some patients, thyroid disease can cause chronic urticaria, so remember to check for thyroid function and thyroid autoantibodies.
- **Urticarial vasculitis** can clinically resemble chronic urticaria. However, patients report hives lasting ≥ 24 hours in a fixed location (in contrast to acute urticaria, which resolves in minutes to hours or migrates to other areas). Other red flags include residual ecchymosis, purpura, or petechiae. Diagnose with skin biopsy.

RHINITIS

Allergic rhinitis—may be:

- seasonal, provoked by seasonally present pollens, or
- perennial, usually provoked by dust mites, molds, or animal dander.

Once initiated, patients have nonspecific hypersensitivity to many irritant stimuli. Eosinophils appear on nasal smear only if the patient is symptomatic. Patients with perennial (year-round) allergic rhinitis have a high eosinophil count in secretions year-round!

NARES: **n**on-**a**llergic **r**hinitis with **e**osinophilia **s**yndrome typically occurs in the middle-aged. Symptoms are similar to allergic rhinitis, including rhinorrhea, sneezing, and occasionally loss of smell. Nasal eosinophilia is also found in secretions. However, patients do not demonstrate sensitization to allergen, either by skin prick test or RAST test (See Skin Testing vs. RAST on page 9-11).

Vasomotor rhinitis: This is an interesting reaction to neurogenic/vagal stimuli. Patients have sneezing attacks, followed by nasal congestion on exposure to cold, sunlight, food, or various other stimuli.

Rhinitis medicamentosa is rebound congestion caused by prolonged use of vasoconstricting nasal drops (phenylephrine or oxymetazoline). Treat by stopping the drug.

Atrophic rhinitis is characterized by (you guessed it!) atrophy of the nasal mucosa, crusting, dryness, fetor, and loss of smell. Patients are typically younger and from warmer climates. Some are colonized with *Klebsiella ozaenae*. Secondary causes include excessive nasal/sinus surgery, granulomatous disease, and exposure to radiation. Treat with nasal saline lavage.

Other possible causes of chronic nasal congestion include deviated septum, foreign body, tumors, and drug reactions (especially with propranolol and alpha-methyldopa). Persistent nasal symptoms may accompany pregnancy, hypothyroidism, or testosterone deficiency (hormonal rhinitis).

Treatment: H_1 antihistamines are 1st line therapy for allergic rhinitis. However, intranasal steroid sprays are the most effective medicine for allergic rhinitis. Intranasal steroid sprays are effective in all types of rhinitis; cromolyn only in the allergic type.

Early-generation antihistamines (diphenhydramine, chlorpheniramine, and hydroxyzine) have the major side effect of sedation. This is due to the ability of these drugs to cross the blood-brain barrier and interact with dopamine, serotonin, and acetylcholine receptors in the brain. The interaction with acetylcholine receptors also results in blurry vision, dry mouth, and urinary retention. Therefore, 1st generation antihistamines should be avoided in the elderly. 2nd generation antihistamines (cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine) do not cross the blood-brain barrier as much and cause less sedation.

Considerations in pregnancy: [Know!] For pregnant patients, use chlorpheniramine, tripelennamine, or diphenhydramine. If sedation is an issue, use 2nd generation antihistamines such as loratadine and cetirizine (pregnancy category B).

Cromolyn and montelukast are considered safe in pregnancy. If an intranasal steroid spray is needed, budesonide is preferred (pregnancy category B). Allergy shots are not started during pregnancy, but if a woman who is already on allergy shots becomes pregnant, she can continue without dose escalation.

Avoid oral decongestants in pregnancy! May cause congenital malformations such as gastroschisis and atresia of the small intestine.

ASTHMA

The etiology of exercise-induced asthma is uncertain. The early response may be due to mast cell degranulation in the airways or excessive cooling. The late response causes a dramatic increase in inflammatory cells (often eosinophils) in the airways.

Sulfites can exacerbate or precipitate symptoms in susceptible patients.

In the 2007 guidelines, the 2 major components to assess for asthma control are impairment (symptoms) and risk (exacerbations).

Apply one of the following categories of control at each visit:

1) Controlled
2) Not well controlled
3) Very poorly controlled

To simplify and summarize the important points briefly: Monitor and follow control using the rule of **2**s!

Step-up therapy for any of the following:
- Asthma symptoms during the day > **2**x/week
- Night time awakenings > **2**x/month
- ED visits/admissions for asthma > **2**x/year

If patients are not controlled, intensify treatment. This can include treating contributory comorbid conditions like rhinitis and gastroesophageal reflux. Reevaluate new patients and those requiring step-up in therapy in 2–6 weeks. Follow stable patients at longer intervals.

Asthma is also covered in Pulmonary Medicine, Book 2.

DRUG ALLERGY

OVERVIEW

See Hypersensitivity Reactions on page 9-6.

The timing and type of reaction provide clues to which type of reaction is elicited. If a drug is given intravenously and an immediate reaction with urticaria develops within minutes to an hour, a Type I immediate IgE-mediated reaction has occurred.

If a reaction is delayed up to 24–72 hours, a delayed hypersensitivity reaction is likely. An exanthematous (maculopapular or morbilliform) eruption also suggests a delayed hypersensitivity reaction.

More severe skin manifestations include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS syndrome (more on this later). These manifestations usually appear > 72 hours after exposure to the drug.

Besides skin manifestations, other problems can occur, including fever, arthritis, and vasculitis, as well as GI, neurologic, and pulmonary findings. Prior exposure to the drug is necessary for an immunologic reaction to occur.

Laboratory testing is generally not helpful. Peripheral blood eosinophilia is suggestive but not conclusive of a drug allergy. Penicillin skin testing may be helpful if you suspect an IgE-mediated mechanism (i.e., Type I hypersensitivity reaction).

BETA-LACTAM ANTIBIOTICS

Beta-lactam antibiotics are the most common cause of drug allergy. Penicillin is composed of benzylpenicillin, which is 95% of the tissue-bound penicillin. Benzylpenicillin is known as the major determinant of penicillin. The minor determinants (benzylpenicilloate and benzylpenicilloic acid) are responsible for most of the anaphylaxis due to penicillin allergy. Therefore, it is important to include both the major and minor determinants for penicillin-allergy testing. Also note, a negative allergy test does not rule out a delayed (non-IgE mediated) hypersensitivity reaction. Remember: Allergy skin testing (PCN testing included) checks only for IgE-mediated reactions!

Treatment: For any drug causing an allergic reaction, the key is to stop the drug. If anaphylaxis is occurring, use epinephrine, antihistamines, and corticosteroids if necessary. See treatment for anaphylaxis on page 9-7.

Know about PCN cross-reactivity: Penicillin cross-reacts with cephalosporins at a rate of 1–3%. Cross-reactivity between beta-lactams and carbapenems is very low. Aztreonam does not cross-react with other beta-lactams except for ceftazidime (both share a common R group side chain).

DRUG DESENSITIZATION

Also known as induction of tolerance, drug desensitization allows for a temporary state of tolerance to the drug as long as the person continues to take the specific drug.

Know: Desensitization is necessary if the drug is the only clinically effective therapy. Otherwise, use alternative drugs if available.

Desensitization is likely to be effective only if the drug reaction is due to an immediate hypersensitivity mechanism (i.e., IgE-mediated). Desensitization is contraindicated for serious non-IgE–mediated reactions such as SJS, TEN, or DRESS.

Scenarios:
- A pregnant woman with syphilis who has a penicillin allergy
- A person with neurosyphilis who has a penicillin allergy

Both require penicillin, so both require desensitization. In these two cases, penicillin is the only effective therapy and there are no alternatives. Also, remember that desensitization works only for that particular episode, and future administrations require repeat desensitization.

Quick Quiz

- What are the 2 major components to assess for asthma control?
- When is drug desensitization indicated? Give two examples of when penicillin desensitization is required.
- What is DRESS syndrome? Name a few drugs commonly associated with this reaction.
- Describe the difference between Stevens-Johnson syndrome and toxic epidermal necrolysis.
- What does a RAST test measure?
- What physical finding is pathognomonic for urticaria pigmentosa?

DRESS SYNDROME

DRESS syndrome: **d**rug **r**ash with **e**osinophilia and **s**ystemic **s**ymptoms. Patients typically develop (you guessed it!) a nonspecific drug rash, peripheral eosinophilia, and systemic symptoms, including fever, lymphadenopathy, and multi-organ involvement (liver, kidney, cardiac, etc.). Usually occurs 2–8 weeks after exposure to the offending drug, typically with aromatic anticonvulsants, minocycline, and allopurinol. Reactivation of human herpesvirus 6 has been implicated. Treat by stopping the drug. Paradoxically, symptoms may worsen or persist even after stopping the drug. Glucocorticosteroids and IVIG are beneficial.

STEVENS-JOHNSON SYNDROME (SJS) & TOXIC EPIDERMAL NECROLYSIS (TEN)

SJS and TEN are part of a single disease spectrum. Mortality is high. Diagnosis depends on the extent of epidermal detachment according to body surface area (BSA):

- SJS = epidermal detachment < 10% BSA
- Overlap syndrome = 10–30% BSA
- TEN = epidermal detachment > 30% BSA

There is severe sloughing away of the skin, equivalent to a 3rd degree burn! Mucosal involvement of the eyes, mouth, and lips almost always occurs. Nikolsky sign refers to removal of the epidermis with slight tangential pressure. Treat with supportive care in a burn unit. Of course, the offending drug is stopped. IVIG may be beneficial. Glucocorticosteroids are contraindicated.

PNEUMONITIS & ABPA

Hypersensitivity pneumonitis is immune complex-mediated and cell-mediated (Types III and IV). **Acute bronchopulmonary aspergillosis (ABPA)** is IgE- and immune complex-mediated (Types I and III).

Both respond to glucocorticoids.

In neither one of these would you give allergy injections. Why? Because:

- Hypersensitivity pneumonitis is not IgE-mediated.
- ABPA can be worsened by allergy injections—they could induce production of more *Aspergillus*-immune complexes.

Both are discussed in more detail in Pulmonary Medicine, Book 2.

SKIN TESTING vs. RAST

In vitro tests for antigen-specific IgE in serum include radioallergosorbent test (RAST) and fluorenzyme immunoassay (CAP-FEIA). Skin testing is quicker, more sensitive, and more cost effective, so use blood testing only if skin testing cannot be done, as when the patient has:

- extensive skin disease,
- dermatographism,
- anaphylactic sensitivity to the allergen, or
- ongoing antihistamine use (these depress the skin test response), which cannot be withheld for 1–2 weeks.

MASTOCYTOSIS

Mastocytosis is a rare disorder characterized by abnormal mast cell proliferation and accumulation in various organs. The degree of involvement determines the extent of the disease.

There are cutaneous, systemic, and malignant types of mastocytosis:

- **Cutaneous mastocytosis** results from increased mast cells only in the dermis. There are characteristic brownish macules called urticaria pigmentosa. Formation of a wheal upon gentle stroking of the macule (Darier sign) is pathognomonic.
- **Systemic mastocytosis** is caused by increased mast cells in tissues, organs, and skin. So patients have generalized symptoms, depending on the degree of involvement, in addition to urticaria pigmentosa.
- **Malignant mastocytosis** causes severe systemic symptoms, but often no skin changes. Signs include hepatosplenomegaly and lymphadenopathy.

Diagnosis: Positive screen is with elevated tryptase > 20. Remember mast cells secrete tryptase. So if you have a lot of mast cells, the tryptase levels are high. Diagnose with biopsy.

Treatment: Stay away from cold, heat, alcohol, ASA, and opiates. Oral cromolyn may help for GI symptoms. Various chemotherapy regimens have been used in the treatment of systemic and malignant mastocytosis. Unfortunately, chemotherapy has not been particularly successful.

HLA DISEASES

There are many diseases associated with certain HLA antigens. This makes sense because the HLA complex is the backbone of immune surveillance. Autoimmune disease arises when there is immune dysfunction. Many rheumatic disorders are associated with HLA-B27, especially ankylosing spondylitis, acute anterior uveitis, reactive arthritis, psoriatic spondyloarthropathy, and juvenile rheumatoid arthritis—but not adult rheumatoid arthritis. (RA is associated with the DR4 and DR2 antigens—see Rheumatology, Book 3.)

CONGENITAL IMMUNODEFICIENCY

IMMUNOGLOBULIN DEFICIENCIES

See also Hereditary Complement Deficiencies on page 9-4.

Congenital agammaglobulinemia (= "Bruton" = "X-linked" = XLA): Patients have increased susceptibility to pyogenic and encapsulated organisms (*Staphylococcus*, *Streptococcus*, meningococcus, *Haemophilus*). Hence, they have recurrent sinopulmonary and ear infections. They usually have normal resistance to fungi, gram-negative organisms, and viruses. The only exception is that XLA patients are susceptible to enteroviral infections and *Giardia*.

Diagnosis: Ig assay shows very low or no immunoglobulins at all (no Igs). There also are no B cells (i.e., no SmIg+ cells or CD19+ cells).

Prognosis is good if the condition is caught early. Check all of the patient's brothers and male cousins on the mother's side.

Treat by replacing immunoglobulins with exogenous IVIG or SQIG. Prophylactic antibiotics may be required for some patients.

Common variable immunodeficiency (CVID): deficiency of IgG +/– IgA, and/or IgM. Like XLA, patients have increased susceptibility to encapsulated organisms (*S. pneumoniae*, *H. influenzae*). They have recurrent sinopulmonary infections and bronchiectasis. They also tend to get giardiasis and enterovirus. They usually have normal resistance to fungi, gram-negative organisms, and viruses.

Unlike XLA, there is an increased incidence of autoimmune disease and malignancy.

Diagnosis: Ig assay shows low IgG +/– low IgA, and/or IgM. Unlike XLA, CVID patients have mature B cells present (CD19+).

Treat by replacing immunoglobulins with exogenous IVIG or SQIG. Monitor for signs of disease-associated autoimmune complications and malignancy.

IgA deficiency: the most common Ig deficiency. Its incidence is as high as 1/300! Fortunately, most patients are asymptomatic. There is only a slightly increased incidence of associated autoimmune disease. Some patients with IgA deficiency have recurrent sinopulmonary infections, recurrent giardiasis, and an association with multiple autoimmune diseases, such as celiac disease and Hashimoto thyroiditis. Most, however, have no symptoms.

For these patients with recurrent infection, treat with prophylactic antibiotics. (This is discussed more in Infectious Disease, Book 1.)

Wiskott-Aldrich syndrome: low IgM and elevated IgA and IgE. The triad of findings is **e**czema, **i**mmunodeficiency, and **t**hrombocytopenia. Remembering that it is **X**-linked makes for a nice mnemonic ("Wisk through the **EXIT**"). You can treat successfully with bone marrow transplantation.

CELL-MEDIATED DEFICIENCY

DiGeorge syndrome (congenital thymic hypoplasia) is a T-cell deficiency due to an early intrauterine malformation of the embryo that can affect several tissues, including the thymus, parathyroids, heart and great vessels, and face. Infants may present with hypocalcemic tetany! A mnemonic for these findings is "DiGeorge **CATCH-22**" (**c**ardiac, **a**bnormal facies, **t**hymic hypoplasia, **c**left lip, **h**ypocalcemia, chromosome **22**).

There is a wide range of symptoms and variable decrease in T-cell function related to the variable decrease in thymic tissue. In many patients, a microdeletion in 22q11 can be demonstrated. For the most severely affected infants (with no thymus or T cells!), treating with thymus transplantation is under investigation.

COMBINED DEFICIENCIES

Severe, combined immunodeficiency: a deficiency in numbers or function of both T and B cells; either autosomal recessive or X-linked; always fatal unless treated. Treat with bone marrow transplantation.

Ataxia-telangiectasia is an autosomal recessive disorder causing both cellular and Ig deficiency. This results in recurrent sinopulmonary infections, bronchiectasis, and progressive telangiectasias. These patients also have a progressive neurologic deterioration of uncertain etiology, characterized by cerebellar ataxia and progressive mental deterioration.

QuickQuiz

- Which rheumatologic disorders are associated with HLA-B27?
- Which immune deficiency has no mature B cells? What are its symptoms?
- What is the most common immunoglobulin deficiency? What are its symptoms?
- What is Wiskott-Aldrich syndrome?
- For which types of cancer is interleukin-2 approved to treat?

CANCER IMMUNOTHERAPY

Know the following:

- **Interferons**, in general, are cytostatic (not 'cidal) and often cause symptoms similar to a severe viral syndrome. Alpha-interferon has been effectively used in hepatitis C and hairy cell leukemia.
- **Tumor necrosis factor** is produced by activated macrophages. It attracts PMNs and causes vasodilation.
- **Monoclonal antibodies** are antibodies from cells originating from one clone and are therefore monospecific. They can be used to carry chemotherapy agents or isotopes to the tumor.
- **Interleukin-2** is a lymphokine that activates the natural killer T cells; it is approved for treating melanoma and renal cell cancer.

FOR FURTHER READING

[Guidelines in blue]

THE IMMUNE SYSTEM

Adkinson NF, Bochner BS, et al. *Middleton's Allergy: Principles and Practice*, 7th Ed. Mosby-Elsevier, 2009.

Bonilla FA, Oettgen HC. Adaptive immunity. *J Allergy Clin Immunol*. 2010 Feb;125(2 Suppl 2):S33–S40.

Chaplin DD. Overview of the immune response. *J Allergy Clin Immunol*. 2010 Feb;125(2 Suppl 2):S3–S23.

Murphy K, Travers P, et al. *Janeway's Immunobiology*, 8th Ed. Garland Publishing, 2011.

Turvey SE, Broide DH. Innate immunity. *J Allergy Clin Immunol*. 2010 Feb;125(2 Suppl 2):S24–S32.

ANTIBODIES

Schroeder HW Jr, Cavacini L. Structure and function of immunoglobulins. *J Allergy Clin Immunol*. 2010 Feb;125(2 Suppl 2):S41–S52.

COMPLEMENT CASCADE

Botto M, Kirschfink M, et al. Complement in human diseases: lessons from complement deficiencies. *Mol Immunol*. 2009 Sep;46(14):2774–2783.

Zuraw BL, Bernstein JA, et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2013 Jun;131(6):1491–1493.

HYPERSENSITIVITY REACTIONS

Bernstein IL, Li JT, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008 Mar;100(3 Suppl 3):S1–S148.

Burks AW, Calderon MA, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol*. 2013;131:1288–1296.

Cox L, Nelson H, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011 Jan;127(1 Suppl):S1–S55.

Cox L, Williams B, et al. Pearls and pitfalls of allergy diagnostic testing: report from the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology Specific IgE Test Task Force. *Ann Allergy Asthma Immunol*. 2008 Dec;101(6):580–592.

Hamilton RG. Clinical laboratory assessment of immediate-type hypersensitivity. *J Allergy Clin*. 2010 Feb;125(2 Suppl 2):S284–S296.

Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology, et al. Allergen immunotherapy: a practice parameter second update. *J Allergy Clin Immunol*. 2007 Sep;120(3 Suppl):S25–S85.

Jones SM, Burks AW. The changing CARE for patients with food allergy. *J Allergy Clin Immunol*. 2013 Jan;131(1):3–11.

Lieberman P, Nicklas RA, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010 Sep;126:477–480.

Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol*. 2010 Feb;125(2 Suppl 2):S116–S125.

Simons FE. Anaphylaxis. *J Allergy Clin Immunol*. 2010 Feb;125(2 Suppl 2):S161–S181.

NIAID-Sponsored Expert Panel Boyce JA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010 Dec;126(6 Suppl):S1–S58.

Simons FE, Ardusso LR, et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol*. 2011 Mar;127(3):587–593.

OTHER URTICARIA

Schaefer P. Urticaria: evaluation and treatment. *Am Fam Physician*. 2011 May 1;83(9):1078–1084.

RHINITIS

Hamilos DL. Chronic rhinosinusitis: epidemiology and medical management. *J Allergy Clin Immunol*. 2011;128:693–707.

Schroer B, Pien LC. Nonallergic rhinitis: common problem, chronic symptoms. *Cleve Clin J Med*. 2012 Apr:79(4):285–293.

Wallace DV, Dykewicz MS, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. 2008 Aug;122:S1–S84.

Brozek JL, Bousquet J, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466–476.

ASTHMA

Thomas A, Lemanske RF Jr, et al. Approaches to stepping up and stepping down care in asthmatic patients. *J Allergy Clin Immunol*. 2011 Nov;128:915–924.

National Asthma Education and Prevention Program. Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol*. 2007 Nov;120(5 Suppl):S94–S138.

DRUG ALLERGY

Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010 Feb;125(2 Suppl 2):S126–S137.

Solensky R, Khan DA, et al. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010 Oct;105(4):259–273.

PNEUMONITIS AND ABPA

Girard M, Cormier Y. Hypersensitivity pneumonitis. *Curr Opin Allergy Clin Immunol*. 2010 Apr;10(2):99–103.

CONGENITAL IMMUNODEFICIENCY

Bonilla FA, Bernstein IL, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol*. 2005 May;94(5 Suppl 1):S1–S63.

Durandy A, Kracker S, et al. Primary antibody deficiencies. *Nat Rev Immunol*. 2013 Jul;13(7);519–533.

Geha RS, Notarangelo LD, et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. *J Allergy Clin Immunol*. 2007;120:776–794.

Notarangelo LD. Primary immunodeficiencies. *J Allergy Clin Immunol*. 2010 Feb;125(2 Suppl 2):S182–S194.

Oliveira J, Fleisher TA. Laboratory evaluation of primary immunodeficiencies. *J Allergy Clin Immunol*. 2010 Feb;125:S297–S305.

CANCER IMMUNOTHERAPY

Topalian SL, Weiner GJ, et al. Cancer immunotherapy comes of age. *J Clin Oncol*. 2011 Dec 20;29(36):4828–4836.