# Step-Up to MEDICINE, 4th edition

## Errors/Clarifications/Additions – *[Updated 06.13.2017]*

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Note: This is a collection of factual corrections to the text, as well as extra information (derived from popularly tested concepts in the major Qbanks as well as the Internal Medicine NBME exam itself) you might consider writing into the margins of your book. These notes also include terminology changes of which you should be aware, because the official NBME materials are NOT using the same terms for certain things (i.e. "diastolic heart failure"; "Wegener granulomatosis" that the authors of SUM use). Please e-mail any errors or possible additions to lev0phedmed (at) gmail (dot) com.

## Chapter 1 – Diseases of the Cardiovascular System

**Page 1** – *"4. […] patients with ischemic pain do not have chest wall tenderness..."*

Reproducible chest wall tenderness can suggest musculoskeletal etiology, but does occur in some patients (possibly up to 30%) with acute M.I. Any process involving the pericardium may cause chest wall tenderness reproducible on palpation. [i]

**Page 3** – *"IV adenosine and dipyridamole cause generalized coronary vasodilation. Since diseased coronary arteries are already maximally dilated at rest to increase blood flow, they receive relatively less blood flow when the entire coronary system is pharmacologically vasodilated."*

Nothing technically wrong, but to simplify: the diseased (narrowed or occluded) arteries are dilated BEFORE administration of adenosine or dipyridamole owing to autoregulation. As soon as one of these agents is given, the NON-DISEASED coronary arteries also become dilated, which results in LESS blood flow availability for the diseased arteries. It is important to note that this phenomenon is called "**coronary steal**."

**Page 15** – Addition: Heart failure and its relationship to renal physiology

This is a relatively complex topic that requires advanced knowledge of renal physiology (salt and water balance) to truly understand. The first thing that is crucial to understand (besides the basics of total body water distribution) is the concept of **effective arterial blood volume (EABV), which is the unmeasurable fraction of ECF perfusing portions of the vascular system that regulate ECF volume and blood pressure** (carotid sinus, aortic arch, renal afferent arteriole, and atrial baroreceptors).[ii]

In healthy individuals, an increase in ECF $Na^+$ is accompanied by an increase in ECF volume. To compensate for this ECF volume expansion, there is an increase in renal NaCl excretion (natriuresis). The compensation occurs because aforementioned baroreceptors are distended (in the case of the "high-volume" baroreceptors). These baroreceptors send signals (via the SNS, RAA axis, AVP) which cause an increase in renal NaCl excretion to lower ECF volume. **The crucial thing to note about this situation is that it is increased total ECF volume (specifically, an increased in that part of the total ECF volume causing distention of**

**<u>baroreceptors – aka EABV)</u> which ultimately promotes natriuresis (NOT the ECF concentration of $Na^+$).**

The reason this is important is because there are pathologic situations in which total ECF volume (and $Na^+$ concentration) are increased but the appropriate compensation does not occur. In heart failure, reduced cardiac output fails to "distend" the vascular space (hence there is inadequate baroreceptor stimulation). Put another way, reduced cardiac output causes a decrease in EABV.

In heart failure, endogenous levels of angiotensin II induce efferent arteriolar constriction (which helps maintain GFR).

The majority of heart failure is caused by a decrease in venous compliance due to sympathetic activation (e.g. from a stressor of some kind). In patients with cardiac dysfunction, the shift in volume from the capacitance vessels increases preload. Note that this mechanism has nothing to do with excess intake of fluid or salt, it is purely due to the movement of unstressed volume to stressed volume.

**Page 23** – Addition: Various factoids (*Atrial fibrillation*)

*B. Causes*

**Mitral stenosis** (usually caused by **rheumatic heart disease**) causes atrial dilatation and predisposes patients to atrial fibrillation.

*C. Clinical features*

When atrial fibrillation is due to mitral stenosis, the build-up of left atrial pressure can cause **pulmonary congestion and dyspnea**.

**Page 38** – *"3. NSAIDs are the mainstay of therapy (for pain and other systemic symptoms). Colchicine is also often used."*

Treatment of acute pericarditis should be done with both NSAIDs AND **colchicine** (therefore NSAIDs <u>alone</u> are not the "mainstay" of therapy). For those with acute pericarditis following M.I., treatment should be done with aspirin and colchicine. Colchicine is taken for ~3 months.

Do NOT confuse the treatment of pericarditis with the treatment of myocarditis. Patients with viral myocarditis should generally be instructed to avoid NSAIDs (animal studies have shown increased mortality).[iii]

**Page 61** – Addition: Arteriovenous fistula

Vascular abnormality in which a connection between the arterial and venous systems are formed without an intervening capillary bed. Causes can be congenital (i.e. PDA, angiomas, CNS, or pulmonary AVF) or acquired (i.e. trauma, catheterization, etc.). Hemodynamic changes may result in high-output cardiac failure due to the decrease in stressed volume (SVR) and concomitant increase in venous return. Can cause a constant systolic and diastolic ("to-and-fro") murmur or bruit and palpable thrill at the site of fistulization.[iv] Hemodynamic changes include:

| | |
|---|---|
| **SVR** | ↓ |

| | |
|---|---|
| **Preload** | ↑ |
| **Cardiac output** | ↑ |

# Chapter 2 – Diseases of the Pulmonary System

**Page 91** – *"B. Histiocytosis X"* and text that follows

- Histiocytosis X is no longer the correct nomenclature. The disease is called "**Langerhans cell histiocytosis (LCH)**."
- "Hand-Schüller-Christian disease" (multifocal eosinophilic granulomas) and "Letterer-Siwe disease" are actually different presentations of this same disease (LCH), and these names are no longer being used.

**Page 91** – *"C. Wegener granulomatosis"*

"Wegener granulomatosis" is no longer the correct nomenclature. The disease is called "**granulomatosis with polyangiitis**."

**Page 91** – *"D. Churg-Strauss syndrome"*

"Churg-Strauss syndrome" is no longer the correct nomenclature. The disease is called "**Eosinophilic granulomatosis with polyangiitis**."

**Page 105** – *"$PaO_2$ and $PaCO_2$ are low (the latter due to hyperventilation) […]"*

Hypoxemia is seen in only ~75% of cases of pulmonary embolism. In some cases, a PE may divert pulmonary blood flow to lung areas with a high $\dot{V}/\dot{Q}$ ratio (which could cause $PaO_2$ to INCREASE). Hypoxemia will only occur if there is PBF diversion to lung areas with a low $\dot{V}/\dot{Q}$ ratio (in other words, worsening an existent $\dot{V}/\dot{Q}$ mismatch).

Hypercapnia is an even less sensitive and specific finding on ABG, and tachypnea is only present in approximately 50% of cases.[v]

# Chapter 3 – Diseases of the Gastrointestinal System

**Page 132** – *"1. The liver synthesizes clotting factors I, II, V, VII, IX, X, XII, and XIII, the function of which is reflected by PT."*

Prothrombin time (PT) is used to assess the extrinsic and common pathways – specifically, the activities of factors II (prothrombin), V, VII, and X. Activated partial thromboplastin time (aPTT) is used to assess the activities of the intrinsic pathway – specifically, the activities of factors VIII, IX, XI, and XII.[vi]

**Page 139** – Addition: Carcinoid syndrome (diagnostic test)

Diagnosis of carcinoid syndrome can be made by measuring 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin.

**Page 139** – Addition: Carcinoid-induced niacin deficiency

Niacin (vitamin $B_3$) can be synthesized from tryptophan. In carcinoid syndrome, more and more tryptophan is diverted to form serotonin, which can in rare cases lead to the development of pellagra ("dermatitis, diarrhea, and dementia").

**Page 151** – Addition: Differentiating major causes of esophageal dysmotility

- **Diffuse esophageal spasm**: episodes of dysphagia and chest pain attributable to abnormal esophageal contractions with normal LES relaxation.
    - Manometry: intermittent normal and absent peristaltic waves.
    - Symptoms: esophageal chest pain closely mimics angina pectoris. **Can be relieved by nitroglycerin**.
- **Achalasia**: primary esophageal motility disorder characterized by the absence of esophageal peristalsis.
    - Manometry: **hypertensive LES** which fails to relax appropriately in response to swallowing.
- **Systemic sclerosis (scleroderma)**: systemic autoimmune disease that commonly involves the lower esophagus.
    - Manometry: **hypotensive LES**, can progress to complete loss of peristalsis.[vii]

**Page 158** – *"Treatment depends on the stage of the disease and the presence of complications. Options include surgical resection, radiation, and chemotherapy."*

There are a handful of primary GI non-Hodgkin lymphomas, but the most relevant one for the Medicine NBME and Step II CK seems to be gastric extranodal marginal B cell (MALT) lymphoma. The initial step in the management of this particular condition is to test for the presence of *H. pylori*. In patients with *H. pylori*-positive lymphoma, the initial treatment is *H. pylori*-eradicating antibiotic regimens (*see SUM page 156*). Most of the time, this is the only treatment required, and if the lymphoma is in fact eradicated, then the patient should undergo periodic endoscopy for surveillance purposes.

Patients with *H. pylori*-negative lymphomas as well as non-responding *H. pylori*-positive lymphomas receive different treatment, but that is a more nuanced discussion for Heme/Onc

fellows. What should be mentioned is that the presence of the t(11;18) translocation portends a much lower possibility that antibiotic treatment will result in complete histologic remission.[viii,ix]

**Page 158** – Addition: Hyperplastic gastropathies: Ménétrier disease and Zollinger-Ellison syndrome (gastrinoma)

**Ménétrier disease**

Acquired premalignant gastric disease characterized by massive gastric folds, excessive mucous production with protein-losing enteropathy, and minimal to absent acid production. It is associated with excess secretion of **transforming growth factor-α (TGF-α)**.

Characteristics include:

- Diffuse hyperplasia of the foveolar epithelium of the body and fundus.
- **Hypoproteinemia** due to protein-losing enteropathy.
- Common symptoms include epigastric pain, anorexia, weight loss, vomiting, and peripheral edema.[x]
- Increased risk of gastric adenocarcinoma (in adults).

Note: Ménétrier disease in children is similar to adults however pediatric disease is usually self-limited and often follows a respiratory infection.

**Zollinger-Ellison syndrome (gastrinoma)**

Disorder characterized by hypersecretion of gastric acid, resulting in peptic ulcer disease and diarrhea. It is caused by gastrin-secreting neuroendocrine tumors (gastrinomas) of the pancreas or duodenum. Most cases are sporadic, but ~25% are associated with **multiple endocrine neoplasia type I (MEN-1)***. It should be suspected in a patient with **multiple duodenal ulcers** and chronic diarrhea.

*MEN-1 is characterized by increased risk for:

- Parathyroid adenoma
- Pancreatic tumor(s) (i.e. Zollinger-Ellison syndrome)
- Pituitary adenoma (most common is prolactinoma)

**Page 163** – Addition: Dermatitis herpetiformis

Cutaneous manifestation of celiac disease. Bilateral, symmetrically-arranged "herptiform" erythematous papules, vesicles, and bullae which occur on the extensor surfaces, elbows, knees, back, and buttocks. Treatment (in addition to gluten-free diet) is with dapsone.

**Page 166** – Addition: Atypical colitides

These diseases have completely normal appearance on endoscopy. The main symptom for both is chronic watery diarrhea.

- **Collagenous colitis (microscopic colitis)**:
    - Mostly affects females (9:1 ratio) and usually presents around 60-80 years of age.

    - Risk factors: Smoking, aspirin or NSAID usage, PPI usage, history of autoimmune disease.
    - Main histologic feature: Increased subepithelial collagen.
- **Lymphocytic colitis**:
    - Affects males and females about equally and usually presents around 60-80 years of age.
    - Risk factors: Sertraline (SSRI).
        - Sizeable overlap with Celiac disease (perhaps up to ~25% of patients with lymphocytic colitis also have Celiac disease).
            - All those with this disease require Celiac testing.
    - Main histologic feature: Increased intraepithelial lymphocytes.[xi]

**Page 166** – Addition: Dumping syndrome

Occurs when postgastric bypass patients consume meals consisting primarily of simple carbohydrates:

- **Early dumping syndrome** occurs within 15 minutes of eating, and is caused by the rapid delivery of a hyperosmolar load into the small bowel. This results in rapid fluid shifts from the plasma to the bowel lumen. Symptoms include colicky abdominal pain, diarrhea, tachycardia, and nausea. Patients may become hypotensive.
- **Late dumping syndrome** occurs within 2-3 hours of eating, and is caused by hyperglycemia provoked by the consumed high glucose load, which in turn causes a reactive hyperinsulinemia and hypoglycemia. Symptoms include dizziness, diaphoresis, and fatigue/weakness.[xii]

Treatment:

- Avoid meals consisting of simple carbohydrates.
- Eat meals consisting of complex carbohydrates, high fiber, and high protein.

**Page 166** – Addition: Postcholecystectomy syndrome

- Persistent abdominal pain or dyspepsia in the months to years following cholecystectomy.
- Possible etiologies include retained common bile duct, cystic duct stone, pancreatitis, peptic ulcer disease, inflammatory bowel disease, psychosomatic disorder.
- RUQ ultrasound may show dilated common bile duct, elevated alkaline phosphatase, mildly elevated serum aminotransferases.
- Further testing requires ERCP/MRCP.

**Page 166** – Addition: Step-wise treatment of ascites

1. $Na^+$ and $H_2O$ restriction
2. Spironolactone
3. Diuresis with loop diuretic (i.e. furosemide) (~1 L/day)
4. Periodic paracentesis (2-4 L/day) - only if renal function is adequate

**Page 166** – Addition: Vanishing bile duct syndrome

Rare disorder characterized by progressive destruction of intrahepatic bile ducts. Histology reveals “ductopenia” (shares this feature with primary biliary cirrhosis).

# Chapter 4 – Endocrine and Metabolic Diseases

**Page 167** – Addition: Physiologic thyroid changes in pregnancy[xiii]

| **TBG** ↑ | **Total $T_4$** ↑ | **Free $T_4$** ~No Δ | **Total $T_3$** ↑ | **TSH** ↓ |
|---|---|---|---|---|
| Estrogen increases hepatic glycosylation of TBG (prolonging its metabolic clearance rate). | Due to increased TBG. | | Due to increased TBG. | Due to maternal hCG agonism of the TSH receptor, which suppresses TSH release. |

**Page 168** – Addition: Untreated hyperthyroidism

Untreated hyperthyroidism also causes:

- Increases bone resorption (serum alkaline phosphatase may be increased, indicating increase bone turnover).
- Dyslipidemia - specifically, low serum total cholesterol and low serum HDL.
- Impaired glucose tolerance (increased insulin secretion as well as peripheral insulin resistance).[xiv]

**Page 169** – *For pregnant patients with Graves disease*
*a. Endocrinology consult is indicated before starting treatment.*
*b. PTU is preferred.*

This is incorrect. Propylthiouracil (PTU) is preferred only in the first trimester. At the beginning of the second trimester (13 weeks' gestation), patients on PTU should be switched to the equivalent dosage of methimazole (MMI). The reason for this is that after the first trimester, PTU-associated hepatotoxicity is more likely to occur than MMI-associated teratogenic effects (which, if they do exist, are probably confined only to the period of organogenesis).

**Page 170** – Addition: Bile acid sequestrants in thyroid storm treatment

Bile acid sequestrants (i.e. cholestyramine) should be used to reduce enterohepatic recycling of thyroid hormone.[xv]

**Page 171** – Hypothyroid-associated galactorrhea[xvi]

A reduction in thyroid hormone leads to an increase in thyrotropin-releasing hormone (TRH) from the hypothalamus. In addition to binding thyrotropes in the pituitary gland (causing an increase in TSH secretion), TRH also binds lactotropes (which causes an increase in prolactin secretion). The result is that hypothyroidism can lead to a hyperprolactinemic state severe enough to cause galactorrhea.

**Page 171** – *"5. Other laboratory value abnormalities that may be present:*
*a. Elevated LDL and decreased HDL levels."*

Abnormal lab findings in hypothyroidism may include increased cholesterol and triglycerides, increased creatine phosphokinase (CPK), and a possible normocytic or macrocytic anemia.

**Page 171** – Addition: Amiodarone-induced thyroid abnormalities[xvii]

The class III antiarrhythmic **amiodarone** has a high iodine content and is directly thyrotoxic. Its hepatic metabolism results in an estimated release of 6mg of inorganic iodine per 200mg dose. It can cause hypo- or hyperthyroidism.

**Page 171** - Addition: Sick euthyroid syndrome

A condition in which a severe acute illness, fasting, or starvation results in a decrease in total and free $T_3$ levels with normal $T_4$ and TSH levels.

It is thought that the fall in active $T_3$ is an adaptive response to limit catabolism in severely ill or starving individuals.

**Page 173** – *Figure 4-2*

The **initial** workup of a solitary thyroid nodule (whether found on physical exam or CT/MRI done for some other reason) does NOT involve FNA.

The initial workup of ALL thyroid nodules (after H&P) requires two things:

- Serum TSH measurement
- Ultrasound

If serum TSH is low, the nodule is possibly hyperfunctional, and thus thyroid scintigraphy should be performed next. If serum TSH is normal or high, and ultrasound shows that the nodule meets certain criteria, then FNA should be performed.

**Page 174** – *"a. Thyroid scan plays a supplemental role. It is performed if the FNA biopsy is indeterminate."*

Incorrect. The "thyroid scan" (scintigraphy or radionuclide scan) is done if serum TSH is low (to evaluate a possibly hyperfunctional nodule). FNA is done if serum TSH is normal or high, but only after ultrasound.

**Page 171** – *"A. Subacute (viral) thyroiditis"* and *"B. Subacute lymphocytic thyroiditis"*

"Subacute (viral) thyroiditis) also goes by the names "deQuervain's thyroiditis," "subacute nonsuppurative thyroiditis," "giant cell thyroiditis," or "painful thyroiditis." (I think the textbook authors made up "subacute viral thyroiditis" as their own special new term for a disease that didn't need any more names).

To avoid confusion, and keep notes in-line with likely test terminology, simply use the correct term for this condition which is **subacute granulomatous thyroiditis**.

"Subacute lymphocytic thyroiditis" is simply **painless thyroiditis**, and it is a separate condition from subacute granulomatous thyroiditis. Painless thyroiditis is a special variant of Hashimoto's thyroiditis, and these patients will have a **positive thyroid peroxidase antibody**.

**Postpartum thyroiditis** is simply the exact same thing as painless thyroiditis, only that it occurs within one year post-delivery, abortion, or miscarriage.

**Page 172** – *Addition: Painless thyroiditis vs. subacute granulomatous thyroiditis*

| | |
|---|---|
| **Painless thyroiditis** | • Brief, mild hyperthyroid phase<br>• No pain, spontaneous recovery<br>• Positive thyroid peroxidase antibody (variant of Hashimoto's thyroiditis) |
| **Subacute granulomatous thyroiditis** | • Hyperthyroid picture<br>• Painful<br>• Possibly a postviral process<br>• Elevated ESR and cRP |
| **Both** | • Low radioactive iodine uptake |

**Page 181** – Addition: Hypocalcemia symptoms, workup, and treatment[xviii,xix]

Severe hypocalcemia causes tetany, seizures, laryngospasm, and QT prolongation. These severe features are often preceded by paresthesias of the fingers, toes, and circumoral regions.

- If exam points to hypocalcemia as problem:
  - Obvious causes should be excluded:
    - **Tissue breakdown** (i.e. tumor lysis syndrome, crush injury)
      - Due to hyperphosphatemia.*
    - **Postsurgical hypoparathyroidism**
    - **Acute pancreatitis**
      - Due to dystrophic calcification (saponification).
      - Normally associated with a high PTH level.
    - **Massive blood transfusion****
  - Initial tests should include complete metabolic panel (for total $Ca^{2+}$, albumin, creatinine, and BUN), serum phosphate level, serum magnesium level, ionized $Ca^{2+}$ level, and serum PTH level.
    - If there is a low total $Ca^{2+}$ level and normal ionized $Ca^{2+}$ level, it might be due to **low serum albumin levels**. Calculate the corrected total calcium using the serum albumin, and if normal, this is **pseudohypocalcemia**. Corrected total calcium can be calculated as follows:

$$Corrected\ Total\ Ca^{2+} = 0.80 \times (4 - [ALBUMIN_{LAB\ VALUE}]) + Ca^{2+}_{LAB\ VALUE}$$

    - If there is a low total $Ca^{2+}$, inappropriately low PTH, high phosphate, and normal magnesium level, this is **primary hypoparathyroidism**.

- Most often due to **destruction or damage of parathyroid glands during surgery** (i.e. from total thyroidectomy); or autoimmuine damage (i.e. **polyglandular autoimmune syndrome type 1**)
- If there is a low magnesium level, the cause may be **hypomagnesemia** (causes hypocalcemia by inducing PTH resistance and decreasing PTH secretion).

▪ If there is low total $Ca^{2+}$ and high PTH, this is **secondary hypoparathyroidism**.

- Vitamin D axis* should next be assessed by taking a serum 25-hydroxycholecalciferol level.
  - If 25-hydroxycholecalciferol level is low, the cause is **nutritional or malabsorptive vitamin D deficiency** and/or **reduced UV light exposure**.
  - If 25-hydroxycholecalciferol level is high, take serum 1,25-$(OH)_2D_3$ levels.
    - If low, the cause is likely **renal insufficiency**.
    - If normal or high, the cause is likely **hereditary vitamin D-resistant rickets (HVDRR)**.

* Review: Of the total body calcium, less than 1% is present in the ECF. Of the total ECF calcium, only the ionized $Ca^{2+}$ fraction is metabolically active and regulated. The ionized fraction comprises about 50% of ECF calcium. The other 50% is complexed to albumin (~40% total ECF calcium) and other anions (~10% total ECF calcium), most importantly phosphate and citrate. Increases in serum concentrations of $PO_4^{3-}$ or citrate therefore reduce the ionized $Ca^{2+}$ fraction. For example, in tumor lysis syndrome, intracellular phosphates are spilled into ECF from dying malignant cells and cause a large reduction in ionized calcium. Massive blood transfusion can cause a similar result by introducing large amounts of citrate into ECF (blood products are anticoagulated with sodium citrate and citric acid).

** Review: Vitamin $D_3$ is converted in the liver to 25-hydroxycholecalciferol (calcidiol), which is in turn converted in the proximal convoluted tubule (by 1α-hydroxylase) to the active 1,25-dihydroxycholecalciferol (calcitriol or 1,25-$(OH)_2D_3$).

*** Serum 25-hydroxycholecalciferol (25-hydroxyvitamin D) level is the correct lab test when screening for vitamin D deficiency, despite it not being the active form of vitamin D.

Treatment of hypocalcemia:

- Acute, severe, symptomatic: IV calcium gluconate.
- Chronic (2° to hypoparathyroidism): Vitamin $D_2$, vitamin $D_3$, or calcitriol (renal insufficiency).

**Page 181** – Addition: Hypercalcemia (primary hyperparathyroidism vs. hypercalcemia of malignancy)

Over 90% of patients with hypercalcemia have either **primary hyperparathyroidism** or **hypercalcemia of malignancy**. Hypercalcemia of malignancy is usually quite severe compared to primary hyperparathyroidism (where serum total $Ca^{2+}$ is rarely exceeds 13 mg/dL).

**Page 184** – Addition: Cushing syndrome mimics

Elevated 24-hour urine free cortisol greater than 3x normal may be due to so-called **pseudo-Cushing syndrome**. Causes include acute illness (i.e. infection), renal failure, malnutrition, severe obesity, intense exercise, psychological stress (particularly major depression), and chronic alcoholism.

**Page 194** - Addition: Drugs to include with current list (*Table 4-6*)[xx,xxi,xxii]

| Medication | Mechanism | Site of action | Advantages | Side effects |
|---|---|---|---|---|
| **SGLT2 Inhibitors** (e.g. canagliflozin, dapagliflozin, empagliflozin) | Block the sodium-glucose transporter 2 (SGLT2) in the proximal tubule (responsible for 90% of glucose reabsorption), which lowers the plasma glucose threshold for glycosuria. | Kidney | Can reduce $Hb_{A1c}$ by ~0.5 to 1.0%<br><br>Can cause modest weight loss of ~4.5-10lbs | **Genitourinary infections**<br><br>Osmotic diuresis (leading to intravascular volume contraction, hypotension)<br><br>Canagliflozin and empagliflozin may cause modest LDL cholesterol increase<br><br>Dapagliflozin may be associated with increased risk of breast and/or bladder cancer |
| **Dipeptidyl peptidase-4 (DPP-4) inhibitors** (e.g. anagliptin, linagliptin, saxagliptin, sitagliptin) | Prolongs action of endogenous GLP-1 by inhibiting its degradation by DPP-4 (*see GLP-1 mechanism in box below*) | Multiple cell types | Can reduce $Hb_{A1c}$ by ~0.2 to 0.8%<br><br>Do not cause hypoglycemia | **Increase risk of nasopharyngitis and URIs**<br><br>Possible increased risk of ACE-inhibitor-associated angioedema |
| **Glucagon-like peptide (GLP-1) receptor agonists** (e.g. exenatide, liraglutide, albiglutide, dulaglutide) | Stimulate glucose-dependent insulin release from pancreatic islet cells, slow gastric emptying, inhibit excessive post-meal glucagon release, and appetite suppression. | GLP-1 receptors (pancreatic β-cells and ducts, gastric mucosa, kidney, heart, skin, immune cells, hypothalamus, among others) | Can reduce $Hb_{A1c}$ by ~0.2 to 1.5%<br><br>**Can cause modest weight loss of ~3.0-6.5lbs (very common)**<br><br>Do not cause hypoglycemia | **Nausea and vomiting** (common)<br><br>Immunogenicity (formation of autoantibodies to injected agents which may attenuate glycemic response)<br><br>Inject site reactions (cellulitis, abscess, etc.)<br><br>Possible increased risk of acute pancreatitis (unconfirmed at this time)<br><br>Possible increased risk of AKI with exenatide |

**Page 203** – *"Bariatric surgery should only be attempted in patients with a BMI of 40 kg/m$^2$ or greater…"*

Indications for bariatric surgery:

- BMI ≥40 kg/m$^2$ with failed diet, exercise, and a trial of drug therapy.

- BMI >35 kg/$m^2$ with obesity-related comorbidities (hypertension, sleep apnea, dyslipidemia, impaired glucose tolerance, diabetes mellitus) who have failed diet, exercise, and a trial of drug therapy.

**Page 204** – Addition: β-blockers ("*Hypoglycemic Unawareness*" *Quick Hit* box)

The β-blockers (metoprolol, propranolol, atenolol, carvedilol, etc.) blunt the sympathetic response to hypoglycemia, and are a highly testable cause of a diabetic being unaware of falling blood glucose levels.

**Page 206** – Addition: Miscellaneous conditions

**Fibrous Dysplasia**

Disorder characterized by replacement of healthy bone with one (monostotic) or more (polyostotic) **expanding fibrous connective tissue lesions and poorly-formed trabecular bone**. It is a dysplastic (not neoplastic) condition caused by a mutation in the guanine nucleotide stimulatory protein (*GNAS1*) gene.[xxiii]

**McCune-Albright Syndrome**:[xxiv]

- **Polyostotic fibrous dysplasia** coupled with **café au lait spots** and **peripheral (ovarian) precocious puberty**.
    - Girls may begin menstruation at very young age.
- Other abnormalities (hyperthyroidism, Cushing syndrome, acromegaly, hyperparathyroidism, hypophosphatemic hyperphosphaturic rickets) may also be present.
- High incidence of both **pathologic fractures** and **orthopedic deformities 2° bone cysts**, and possible hearing impairment due to temporal area thickening.
- In McCune-Albright Syndrome, there may be **café au lait spots with rough borders** ("coast of Maine"). Do not confuse with the café au lait lesions of neurofibromatosis that have smooth borders ("coast of California").

# Chapter 5 – Diseases of the Central and Peripheral Nervous Systems

**Page 219** – *"B. Clinical Features [..]*
*a. Early stages – mild forgetfulness, impaired ability to learn new material [..]"*

This description is partially inaccurate and also quite vague. In Alzheimer disease, **declarative episodic memory** is the earliest affected (hippocampus and medial temporal lobe). Specifically, the patient's **memory for recent events is impaired**. Immediate memory (sensory association cortex, prefrontal cortex) and long-term consolidated memory are spared early-on. The disease is exceptionally rare in non-Trisomy 21 individuals under the age of 60.

**Page 225** – *"The following increase the chances of severe disability [..]"*

All of these factors are likely false. In particular, age of onset and the type of early symptoms experienced (i.e. sensory vs. pyramidal vs. cerebellar, etc.) cannot be reliably used in determining prognosis.[xxv]

**Page 225** – Addition: Plasma exchange (*Treatment*)

Patients with severe deficits that are refractory to glucocorticoid treatment should receive **therapeutic plasmapheresis** (plasma exchange).

**Page 226** – Addition: MG vs. LES (location of defect)

In myasthenia gravis, the defect occurs at the **neuromuscular junction** (autoantibodies vs. **postsynaptic nicotinic ACh receptors**).

In Lambert-Eaton syndrome, the defect occurs at the **presynaptic membrane** (autoantibodies vs. presynaptic voltage-gated $Ca^{2+}$-channel), which interferes with the $Ca^{2+}$ influx required for ACh release.

**Page 230** – Addition: Rabies

Devastating neurologic disease caused by infection with an *ss*(-)RNA rhabdovirus.

Virus has a wide-range of hosts which includes all warm-blooded animals. Dogs and cats typically become clinically ill within 10 days of becoming contagious (**dogs or cats who bite humans should be quarantined for 10-days to see if they develop the illness**). Most infected animals die, but certain bats can survive. Bats are a major vector in the United States, because they can carry and excrete the virus for long periods without becoming ill.[xxvi]

Virus enters the CNS via retrograde microtubule-dependent axonal transport from the site of inoculation. Viral replication causes progressive neurologic dysfunction which leads rapidly to death in virtually all cases.[xxvii]

Symptoms can be varied, but classically include **paresthesias at the bite site, followed by anxiety, muscle spasm, drooling, hydrophobia, delirium**. Pharyngeal spasm, coma, and death soon follow.

Treatment (must be administered before onset of clinical disease):

- Thorough cleansing of wounds with soap and water

- **Rabies immune globulin**
- **Rabies vaccine**

**Page 231** – Addition: Benign positional vertigo (BPV) and Ménière's disease pathophysiology, drug-induced ototoxicity (*Types of peripheral vertigo*)

BPV: Due to **canaliths (crystalline deposits) in the semicircular canals** that disrupt the normal flow of fluid in the vestibular system.

Ménière's disease: Due to the **accumulation of endolymph** within the inner ear.

**Gentamicin** (aminoglycoside) is one of the more common agents implicated in drug-induced ototoxicity.

**Page 231** – Addition: Sustained vertigo[xxviii,xxix]

Sustained vertigo lasts longer than a brief period (several days), and usually requires patient to remain immobile to avoid symptoms.

| Condition | Symptoms | Typical Patient Characteristics |
|---|---|---|
| Vestibular neuritis | • Rapid-onset sustained vertigo<br>• Nausea, vomiting, gait instability<br>• **Positive head impulse test**<br>• NO auditory symptoms | Frequently young adults with **antecedent URI** |
| Labyrinthitis | • Above symptoms PLUS unilateral hearing loss | |
| Brainstem/cerebellar stroke | • Rapid-onset sustained vertigo<br>• **Usually multiple other neurologic deficits**<br>• Usually NO auditory symptoms | Usually older adults with vascular risk factors |

**Page 234** – Addition: Importance of syncope workup

All patients presenting with a syncopal episode require (at the very least) an **EKG**. This **includes children and seemingly healthy young people**. Many diseases that cause syncope also cause sudden death in children. As many as 25% of children who die suddenly have a history of at least one prior syncopal event.[xxx]

Some myocardial electrical problems that can present with syncope:

- Brugada syndrome
- Long QT syndrome
- Wolff-Parkinson-White syndrome

Page 236 – Addition: Psychogenic nonepileptic seizures ("pseudoseizure")

A type of conversion disorder characterized by convulsion attacks that are not caused by abnormally hypersynchronous electroneuronal activity in the cerebral cortex.

Pseudoseizures may have side-to side head, arm or leg movements with eyes closed. If the eyes are open, the eye movements are normal as opposed to deviated. A bicycling movement of the legs is highly suggestive of pseudoseizure. Failure to recognize psychiatric issues may promote the persistence of conversion symptoms and deny the patient needed psychiatric interventions. **A history of recurrent medical evaluations for psychosomatic illnesses** (i.e. fibromyalgia, irritable bowel syndrome, etc.) may coexist. **Patients with pseudoseizures are rarely malingering**.

**Page 238** – Addition: Aphasia (lesion localization)

- Wernicke (receptive) aphasia: Involves the **dominant TEMPORAL** lobe.
- Broca (expressive or motor) aphasia: Involves the **dominant FRONTAL** lobe.

**Page 243** – Addition: Neuroimaging in neuropsychiatric disorders

| **Disorder** | **Neuroanatomical Changes** |
|---|---|
| Autism | Increased total brain volume |
| Obsessive-Compulsive Disorder (OCD) | Abnormalities in the anterior cingulate cortex, striatum, and orbitofrontal cortex |
| Panic disorder | Reduced amygdala volume |
| PTSD | Reduced hippocampal volume |
| Schizophrenia | Enlargement of cerebral ventricles |

# Chapter 6 – Connective Tissue and Joint Diseases

**Page 243** – Addition (*Table 6-1*)

RF (Rheumatoid Factor) is positive in ~25% of patients with Sjögren's syndrome.[xxxi]

**Page 262** – Addition: Ultrasound (*Polymyalgia Rheumatica – C. Diagnosis*)

Elevated ESR, CRP, or both are present in only 90% of PMR cases, and by themselves are neither sensitive nor specific hallmarks since both ESR and CRP are elevated in a wide-range of conditions. Lately, there has been research looking at other diagnostic modalities that can be used to support a diagnosis of PMR. A June 2016 systematic review in JAMA examined studies where ultrasound was used with very good sensitivity to aid in diagnosis. Subdeltoid bursitis, biceps tenosynovitis, and glenohumeral/hip synovitis are very commonly found on sonographic examination of patients with PMR. **Ultrasound identification of subdeltoid bursitis** in particular can help support a diagnosis of PMR.[xxxii]

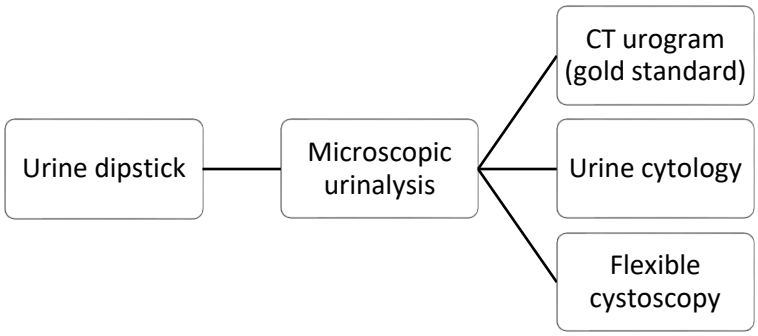
**Page 266** – Addition: Ultrasound/MRI diagnosis (*Temporal/Giant Cell Arteritis – C. Diagnosis*)

Temporal artery biopsy is the standard test for definitive diagnosis of cranial GCA, but both ultrasound and MRI are reliable, non-invasive diagnostic modalities that may be utilized more in the near future. On ultrasound, a characteristic finding is the so-called **"halo sign" – a hypoechoic ring around the arterial lumen representing inflammation-induced edematous thickening of the arterial wall**. Contrast-enhanced MRI findings in GCA may demonstrate **arterial wall thickening with mural and periadeventitial contrast enhancement**.[xxviii]

# Chapter 7 – Diseases of the Renal and Genitourinary System

**Page 283** – Addition: Appropriate work-up of hematuria

The specificity of urine dipstick to detect hematuria is as low as 65%. A positive finding for blood on dipstick requires follow-up testing with **microscopic urinalysis**. Confirmation with microscopic urinalysis can then be followed with the gold-standard test, the **CT urogram** (basically, abdominopelvic CT with noncontrast, contrast, and excretory phases). **Urine cytology** or **flexible cystoscopy** are other options for determining the source of hematuria. These three tests first require confirmation with microscopic urinalysis.[xxxiii]




**Page 295** – *"2. Imaging*
*a. Plain radiograph of the kidneys, ureter, and bladder (KUB)*
*• Initial imaging test for detecting stones"*

The tests of choice are ultrasound or noncontrast helical (spiral) CT scan. KUB may be used as follow-up imaging of known lesions.

**Page 295** – *"• Cystine and uric acid stones are not visible on plain films"*

Cystine stones are visible on X-ray, assuming they are large enough. Uric acid stones are not visible on X-ray (they are radiolucent).

**Page 295** – *"• All stones, even radiolucent ones such as uric acid stones and cystine stones are visible on the CT scan."*

Cystine stones are not radiolucent. Compared to calcium oxalate stones, however, they are less radiopaque.

# Chapter 8 – Fluids, Electrolytes, and Acid-Base Disorders

**Page 304** – *"4. Lactated Ringer solution - [..] Do not use if hyperkalemia is a concern (contains potassium)."*

LR contains very little $K^+$ (4-5 mEq/L). In normal patients requiring volume resuscitation, $K^+$ usually needs to be supplemented with LR.

**Page 308** – *"Urine $Na^+$ concentration <40 mmol/L is consistent with [..] SIADH."*

The correct statement is, "urine $Na^+$ concentration GREATER THAN 40 mmol/L" etc. (text statement reads 'LESS THAN').

Remember that 1 mmol/L $Na^+$ = 1 mEq/L $Na^+$ (test is more likely to use mEq/L).

**Page 311** – (*See: "**Page 181** – Addition: Hypocalcemia symptoms, workup, and treatment"*)

**Page 312** – *"a. Sarcoidosis – increased GI absorption of calcium."*

Not technically incorrect, but incomplete. In certain granulomatous diseases such as sarcoidosis, there is a **PTH-independent production of 1,25-dihydroxycholecalciferol** (aka calcitriol, aka activated vitamin D) by activated mononuclear cells (e.g. macrophages).[xxxiv]

**Page 314** – Addition: Low serum $K^+$ and digoxin (*Quick Hit* box)

Digoxin works by **inhibiting the active transport of $Na^+$ and $K^+$ across the cell membrane during repolarization by binding to the membrane $Na^+/K^+$-ATPase**. This results in an increase in cytosolic $Na^+$, which reduces the $Na^+$ transmembrane gradient. The $Na^+/Ca^{2+}$ antiporter is powered by this gradient. Therefore, $Na^+/K^+$-ATPase inhibition reduces $Ca^{2+}$ extrusion from the cell. This increase in intracellular $Ca^{2+}$ enhances $Ca^{2+}$-induced-$Ca^2$+ release from the sarcoplasmic reticulum during systole, increasing the force of contraction.

Low serum $K^+$ also inhibits the activity of the $Na^+/K^+$-ATPase, and therefore potentiates (increases toxicity) of digoxin.[xxxv]

**Page 313 –** Addition: Promotion of intracellular $K^+$ transfer (*Potassium Metabolism*)

Insulin, aldosterone, and β-agonists (epinephrine, albuterol) promote $K^+$ transfer from ECF to ICF.[xxxvi] Albuterol is sometimes used in severe hyperkalemia (with acute EKG changes) to temporarily shift $K^+$ intracellularly.

**Page 316** – *"a. Kayexalate – GI potassium exchange resin"*

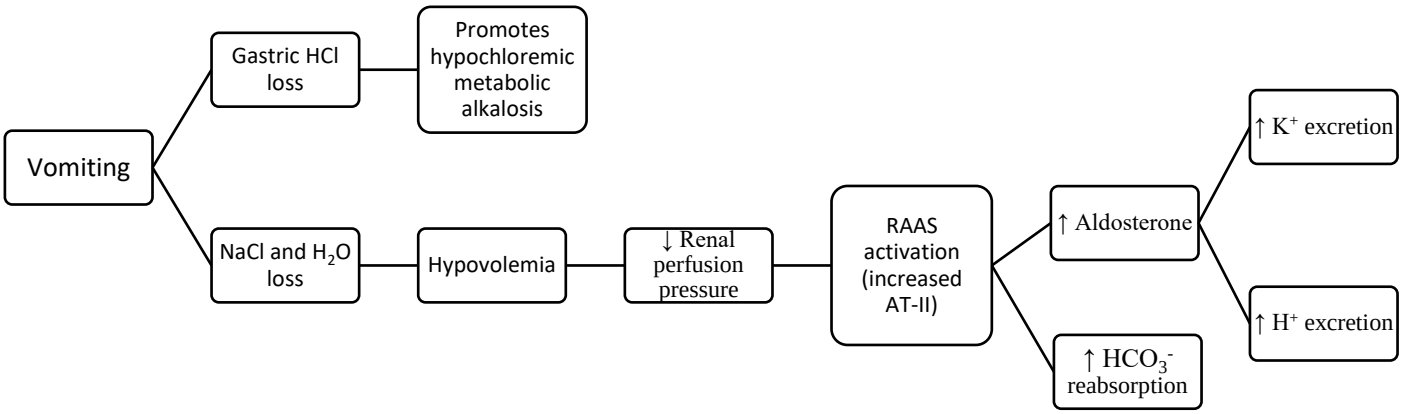
Despite widespread use, sodium polystyrene sulfonate (Kayexalate®) is a poor if not completely worthless method of lowering serum $K^+$:

- It is not a "potassium exchange resin," it is in fact a cation-exchange resin which is not specific for potassium.
- It requires multiple doses over several days to exert any effect (**cannot be used emergently to treat hyperkalemia**), if it has a beneficial effect at all.
    - It was approved in 1958, before manufacturers were required to prove the effectiveness and safety of their drugs prior to FDA approval.

- Modern studies have repeatedly failed to demonstrate that its use increases fecal potassium losses.[xxxvii]
- Multiple studies have shown that it can cause **colonic necrosis**, an often fatal complication.[xxxviii]

**Page 323** – Addition: "Contraction alkalosis" vs. chloride-depletion alkalosis

Here is the traditional paradigm of "contraction alkalosis":




As r/delasmontanas on the medical school reddit pointed out, "contraction alkalosis" is actually a myth:

- Contraction alkalosis is a misnomer and the phenomenon is more appropriately termed "chloride depletion alkalosis".
- The pathophysiology involves a more recently identified renal transporter named pendrin.
- Pendrin is a chloride-bicarbonate exchanger located in the cortical collecting duct. Rather than volume depletion, chloride deficiency leading to insufficient/inappropriate bicarbonate excretion is now thought to be responsible for the maintenance of alkalosis.
- Evidence for the concept of chloride depletion alkalosis over the old paradigm of contraction alkalosis include studies that showed:
    - Chloride repletion alone even in the presence of depleted volume was shown to result in rapid correction of alkalosis
    - Volume, $Na^+$, and $K^+$ repletion in the absence of chloride repletion resulted only in continued maintenance of the metabolic alkalosis.

For more information, see this paper:

Luke RG, Galla JH. It Is Chloride Depletion Alkalosis, Not Contraction Alkalosis. *Journal of the American Society of Nephrology*. 2012;23(2):204-207. doi:10.1681/asn.2011070720.

**Page 324** – Addition: Assessing acid-base disturbance compensation

The follow equations are used to determine if the degree of renal or respiratory compensation is complete. The four "1-4-2-5 Rule" equations deal with a primary respiratory disturbance, while the other two deal with a primary metabolic disturbance. If the actual and expected values for $HCO_3^-$ or $P_aCO_2$ differ, then there is likely a mixed acid-base disturbance.

| Condition | $HCO_3^-$ | $P_aCO_2$ | Equation |
|---|---|---|---|
| Acute respiratory acidosis (<48 hours duration) | ↑ 1.0mmol/L | for every 10mmHg | $Expected\ HCO_3^- = 24 + \left[\frac{(PaCO_2 - 40)}{10}\right]$ |
| Chronic respiratory acidosis (>48 hours duration) | ↑ 4.0mmol/L | for every 10mmHg | $Expected\ HCO_3^- = 24 + \left[4\times\frac{(PaCO_2 - 40)}{10}\right]$ |
| Acute respiratory alkalosis (<48 hours duration) | ↓ 2.0mmol/L | for every 10mmHg | $Expected\ HCO_3^- = 24 + \left[2\times\frac{(PaCO_2 - 40)}{10}\right]$ |
| Chronic respiratory alkalosis (>48 hours duration) | ↓ 5.0mmol/L | for every 10mmHg | $Expected\ HCO_3^- = 24 + \left[5\times\frac{(PaCO_2 - 40)}{10}\right]$ |
| Metabolic acidosis | | | $*Expected\ P_aCO_2 = (1.5\times[HCO_3^-]) + 8 \pm 2$ |
| Metabolic alkalosis | | | $Expected\ P_aCO_2 = (0.7\times[HCO_3^-]) + 20 \pm 5$ |

** This equation is known as Winters' formula, after Yale-educated pediatrician R.W. Winters.*

The highest yield of these is Winter's formula, followed by the rule for metabolic alkalosis (there is a major QBank question which requires knowledge of the latter).

**Page 324** – Addition: Osmolality and Osmolal Gap

Serum Osmolality

$$OSM_{MANUALLY\ CALCULATED\ VALUE} = (2\times[Na^+]) + \left({}^{BUN}/_{2.8}\right) + \left({}^{GLUCOSE}/_{18}\right)$$

*Where, $[Na^+]$ is in mmol/L, BUN is in mg/dL, and GLUCOSE is in mg/dL*

Osmolal Gap

$$Osmolal\ Gap = OSM_{LAB\ VALUE} - OSM_{MANUALLY\ CALCULATED\ VALUE}$$

*Normal value: LESS than 10 mOsm/kg*

Causes of an elevated osmolal gap: Ingestion of ethanol, methanol, ethylene glycol (in anti-freeze solutions), propylene glycol (vehicle for some drugs, i.e. lorazepam), or propylene glycol.

# Chapter 9 – Hematologic Diseases and Neoplasms

**Page 326** – *Clinical PEARL: Transfusion Pearls* and text that follows

Fresh frozen plasma (FFP) will likely be the answer to any question about reversing warfarin-related anticoagulation when vitamin K alone will not suffice (i.e. extremely high PT/INR, liver failure). In real-life, FFP is the cheapest option for this purpose, but not the most efficient. Prothrombin-complex concentrates (PCC) can normalize INR faster (within minutes) than both FFP and vitamin K.[xxxix]

Cryoprecipitate is essentially thawed-out FFP. It contains factor VIII, factor XIII, fibrinogen, fibronectin, and von Willebrand factor (vWF).

- It can be used to reverse anticoagulation (decrease INR) in patients taking warfarin (but isn't used anymore, because FFP and PCC are available)
- It can be used to treat von Willebrand disease (but isn't used anymore, because desmopressin is available).
- It can be used to treat to hemophilia A (but isn't used anymore, because factor VIII concentrate is available).

**Page 326** – Addition: Pre-transfusion blood product treatments

| Specialized treatment | Purpose |
|---|---|
| Washing | • Prevent anaphylaxis in IgA-deficient recipients |
| Leukoreduction | • Prevent febrile nonhemolytic transfusion reaction<br>• Reduce risk of HLA alloimmunization and CMV transmission |
| Gamma irradiation | • Prevent transfusion associated graft-versus host disease in susceptible recipients* |

*Transfusion associated graft-versus-host disease is a highly fatal condition occurring within 30 days following blood transfusion. It is characterized by **donor lymphocyte-mediated attack against the recipient's antigen presenting tissues**. It does not usually occur in immunocompetent patients, because donor lymphocytes are destroyed by the recipient's immune system before they are allowed to attack host tissues. It does occur if the recipient is immunocompromised/deficient (i.e. hematopoietic cell transplant recipient) OR if there is a specific type of partial HLA matching between donor and recipient (i.e. if the donor and recipient are genetically related).[xl]

**Page 328** – *Iron Deficiency Anemia* and text that follows

Low serum ferritin concentration (less than 40 ng/mL) and high total iron binding capacity (TIBC) is diagnostic of iron deficiency anemia. Some other important information:

- In mild iron deficiency, the serum iron may actually be normal. For this reason, serum iron should essentially be ignored.
- Coexisting anemia due to chronic inflammation (anemia of chronic disease) can also cause an increase in serum ferritin concentration. For this reason, **mixed** anemias due to both iron deficiency and ACD can present with normal serum ferritin.

**Page 331** – *Anemia of Chronic Disease* and text that follows, including, *"It may be difficult to differentiate from iron deficiency anemia."*

It is only difficult to differentiate between the two when they coexist (which they often do). Important points:

- In pure ACD, there is typically a **high serum ferritin, low TIBC, and a normal or low MCV (usually normal)**.
- In pure IDA, there is typically a **low serum ferritin, high TIBC, and a low MCV**.
- Serum iron may be low in a pure ACD or pure IDA, and should not be relied upon to make the diagnosis.

**Page 331** – Addition: Other microcytic anemias

Sideroblastic anemia, anemia due to lead poisoning, and the thalassemias are the more common microcytic anemias confused with IDA.

- The thalassemias are a group of autosomal recessive disorders characterized by decreased synthesis of either the α-globin or β-globin genes that comprise adult hemoglobin, HbA ($\alpha_2\beta_2$).
    - The α-thalassemias are more common in South Asian and West African populations.
    - The β-thalassemias are more common in Mediterranean populations.
        - β-thalassemia minor is an especially common cause of microcytosis among certain populations.

**Page 341** – Addition: Drug-induced megaloblastic anemia[xli]

Many agents can precipitate megaloblastic anemia, but here are just a few important ones (grouped by condition drugs used to treat):

- Seizure
    - **Phenytoin**: Mechanism is thought it to involve a disruption in folate metabolism.
    - **Valproic acid**: Mechanism is unknown.
- Infection
    - **Penicillins** (including ampicillin), **tetracyclines** (e.g. doxycycline), **erythromycin**, chloramphenicol: Cause reduced folate absorption.
- GERD
    - **$H_2$-receptor antagonists** (e.g. cimetidine, famotidine) and **proton pump inhibitors** (e.g. omeprazole, pantoprazole): Cause reduced vitamin $B_{12}$ absorption.
- Other (popularly-tested) agents which cause hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency:
    - Dapsone

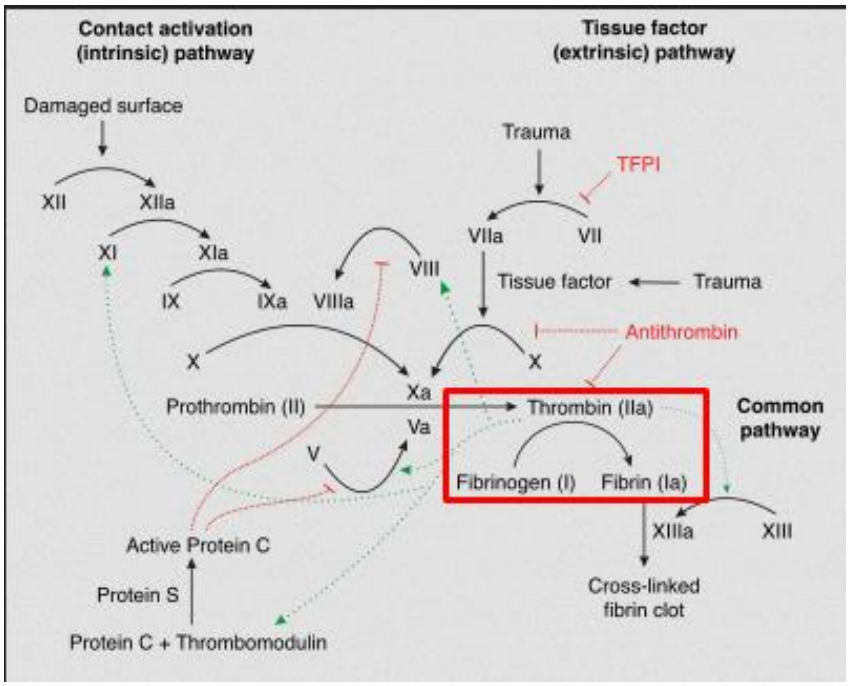
- Primaquine
- Nitrofurantoin
- Methylene blue

**Page 346** – Addition: Abruptio placentae-induced DIC

Abruptio placentae (placental abruption) is an important cause of DIC. Make note of the fact that it occurs as a result of tissue factor release by decidual cells lining the placental vascular bed.

**Page 347** – Addition: Fibrinogen (importance/rationale for measurement)

Fibrinogen is converted to fibrin in the process of secondary hemostasis. As such, a decreased serum fibrinogen level indicates that systemic coagulation is occurring (that thrombin is catalyzing the conversion of fibrinogen → fibrin).




**Page 355** – Addition: Serum protein "gap"

- Total serum protein normal value: 6.0-7.8 g/dL
- Serum Albumin normal value: 3.5-5.5 g/dL

Anytime the total serum protein is 4 g/dL or higher than serum albumin, there is an excess of nonalbumin proteins present. Such proteins may include monoclonal proteins (**multiple myeloma** or **Waldenström's macroglobulinemia**).

# Chapter 10 – Infectious Diseases

**Page 365** – Addition: Pneuomococcal vaccines

- Pneumococcal polysaccharide vaccine (PPSV23; PNEUMOVAX®)
  - Contains capsular polysaccharides from 23 disease-causing types.
    - Since it consists solely of polysaccharide antigens, it generates a **T cell independent B cell response** (polysaccharides alone cannot be presented to T cells).
    - **Not used in young children** (polysaccharides in general are poorly immunogenic in infants and toddlers).
- Pneumococcal conjugate vaccine (PCV13; PREVNAR 13®)
  - Contains capsular polysaccharides from 13 most common disease-causing types covalently linked to a nontoxic protein similar in structure to diphtheria toxin.
    - Generates a **T cell dependent memory B cell response**.
- Indications[xlii]
  - All healthy adults ≥65 years of age should initially receive **PCV13, followed by PPSV23 at least 1 year later**.
  - All adults 19-64 years of age with intermediate risk of pneumococcal disease (i.e. COPD, diabetes mellitus, alcoholism, cigarette smokers, etc.) should receive **PPSV23 alone**.
  - All adults 19 years of age and older with high risk of pneumococcal disease (i.e. immunocompromised, functional/anatomic asplenia, CSF leak, advanced renal disease, etc.) should receive **PSV13 followed by PPSV23 at least 8 weeks later**.

**Page 369** – Addition: Agents with activity vs. *Pseudomonas*

Drugs with activity vs. *Pseudomonas*

- Extended-spectrum β-lactams
  - Piperacillin/tazobactam (Zosyn™)
  - Ticarcillin/clavulanic acid (Timentin™)
  - Cefoperazone (3rd-generation cephalosporin)
  - Ceftazidime (3rd-generation cephalosporin)
  - Cefepime (4th-generation cephalosporin)
- Carbapenems (i.e. imipenem, meropenem)
- Monobactams (i.e. aztreonam)
- Fluoroquinolones
- Aminoglycosides
- For multidrug-resistant strains: polymyxin B, polymyxin E

**Page 385** – Addition: Chlamydia/Gonorrhea NAAT and treatment

The nucleic acid amplification test is a highly sensitive and specific test for diagnosing these diseases. If a patient tests positive for chlamydia on the NAAT, but negative for gonorrhea, there is no reason to treat for both diseases. In this case, the sole treatment is azithromycin.

**Page 390** – Addition/Correction: Opportunistic infection prophylaxis in HIV patients

| Organism | $CD4^+$ count | Prophylactic agent |
|---|---|---|
| *Pneumocystis* | ≤200 cells/μL | Trimethoprim-sulfamethoxazole |
| *Histoplasma* | ≤150 cells/μL (***only in patients who live in endemic areas, i.e. Ohio/Mississippi River valley***) | Itraconazole |
| *Toxoplasma* | ≤100 cells/μL | Trimethoprim-sulfamethoxazole |
| *Mycobacterium avium complex (MAC)* | ≤50 cells/μL | Azithromycin |

**Page 394** – Addition: Syphilis diagnostic testing

| VDRL or RPR | FTA-ABS | Interpretation |
|---|---|---|
| + | + | Indicates active treponemal infection |
| + | - | Likely false positive |
| - | + | Successfully treated syphilis |
| - | - | Syphilis unlikely, although:<br>1. Patients with syphilis who also have AIDS may be seronegative.<br>2. Patients recently infected may not have developed an immune response. |

**Page 395** – Addition: STD screening indications[xliii]

- **Screening tests of choice**
  - HIV
    - HIV-1/2/p24 antibody/antigen assay [4th-generation assay preferred]

- If positive → HIV-1/HIV-2 antibody differentiation immunoassay
- If negative or indeterminate → HIV-1 NAAT

- Hepatitis A
  - Hepatitis A IgM antibody (anti-HAV IgM)
    [Anti-HAV IgM should be positive from the time of symptom onset to three to six months later. The presence of anti-HAV IgG indicates past infection or vaccination.]
- Hepatitis B
  - Hepatitis B surface antigen (HBsAg)
  - Hepatitis B surface antibody (HBsAb)
  - Hepatitis B core antibody (HBcAb)
    - If HBsAg and HBcAb both positive (with IgM HBcAb and HBsAb both negative) → Hepatitis B quantitative DNA and hepatitis B e antigen (HBeAg)
- Hepatitis C
  - Hepatitis C antibody
  - +/- Hepatitis C quantitative RNA PCR
    [Send alongside Hep C antibody in immunocompromised patients at increased risk for false-negatives]
- Human papillomavirus
  - Cytology with Pap test
- Genital chlamydia and gonorrhea (women)
  - NAAT on self-collected vaginal swabs
    [Not acceptable for testing women with symptomatic cervicitis or high-risk women undergoing Pap test, who require NAAT of examiner-collected endocervical or vaginal swabs]
- Genital chlamydia, gonorrhea, and *C. trachomatis* (high-risk women)
  - NAAT on examiner-collected endocervical swab from Pap test
    OR
  - NAAT on patient-collected vaginal swabs
- Genital chlamydia and gonorrhea (men)
  - NAAT on clean-catch urine
- Rectal chlamydia and gonorrhea (men)
  - NAAT on rectal swab
- Pharyngeal gonorrhea (men)
  - NAAT on oropharyngeal swab

- Syphilis
  - Rapid plasma reagin (RPR)
    - If positive → Fluorescent treponemal antibody absorption (FTA-ABS)

STD Screening Test Indications

| Gender | Population | Screening Tests | Frequency | Notes |
|---|---|---|---|---|
| **Females** | Age <25 years | Genital chlamydia and gonorrhea<br>HIV | Every year | Syphilis, trichomoniasis, HBV, and HCV if at increased risk |
| | Age ≥25 years | HIV | At least once | Gonorrhea, chlamydia, syphilis, trichomoniasis, HBV, HCV if at increased risk |
| | Born 1945-1965 | Hepatitis C | Once | If not previously screened |
| | HIV-positive | Hepatitis B<br>Hepatitis C | Initial visit | |
| | | Genital chlamydia and gonorrhea<br>Genital trichomoniasis<br>Syphilis | Every year | |
| **Males** | Age 13-65 years, heterosexual, HIV-negative | HIV | At least once | Gonorrhea, chlamydia, syphilis, HBV, HCV if at increased risk |
| | Born 1945-1965 | Hepatitis C | Once | If not previously screened |
| | Men who have sex with men (MSM), HIV-negative | Genital chlamydia and gonorrhea<br>Rectal chlamydia and gonorrhea<br>Pharyngeal gonorrhea<br>Syphilis<br>HIV | Every year | May require more frequent screening (e.g. 3-6 months) if additional risk factors present |
| | | Hepatitis C | At least once | |

| | | | | |
|---|---|---|---|---|
| | | Hepatitis A<br>Hepatitis B | Initial visit | |
| | Men who have sex with women (MSW), HIV-positive | Genital chlamydia and gonorrhea<br>Syphilis | Every year | |
| | | Hepatitis B<br>Hepatitis C | Initial visit | |
| | Men who have sex with men (MSM), HIV-positive | Genital chlamydia and gonorrhea<br>Rectal chlamydia and gonorrhea<br>Pharyngeal gonorrhea<br>Syphilis<br>Hepatitis C | At least every year | |
| | | Hepatitis A<br>Hepatitis B | First visit | |

**Page 403** – Addition: Travel medicine: malaria prophylaxis

| Location | Major Species of Concern | Agents |
|---|---|---|
| • Sub-Saharan Africa<br>• Southern Asia (India, Pakistan, Afghanistan, etc.)<br>• Southeast Asia (Cambodia, Laos, Vietnam, etc.) | Chloroquine-resistant *P. falciparum* | • Atovaquone-proguanil<br>• Doxycycline<br>• Mefloquine (pregnancy-preferred) |
| • South America<br>• Mexico<br>• North/South Korea | *P. vivax* | Primaquine |
| Most other places with malaria | Chloroquine-sensitive *P. falciparum* | Chloroquine, hydroxychloroquine |

**Page 407** – Addition: SIRS and Sepsis (definitions)

- **Systemic Inflammatory Response Syndrome (SIRS)**: A disordered physiologic state defined by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) in 1992. The criteria consists of an arbitrary set of vital signs/lab results used to "identify" patients exhibiting a systemic response to a stressor (which may be infection, trauma, ischemia, inflammation, or a combination of insults). The criteria include 2 or more of the following:
    - Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F).
    - Heart rate of more than 90 beats per minute.
    - Respiratory rate of more than 20 bpm or $PaCO_2$ of less than 32 mmHg.
    - Abnormal white blood cell count (>12,000/µL or <4,000/µL or >10% immature [band] forms).
- **Sepsis** or **septicemia**: Classically very difficult to define. The modern definition is basically the exact same as for SIRS with the added feature of a known or suspected source of infection.
- **Severe sepsis**: Sepsis-induced organ dysfunction or tissue hypoperfusion resulting hypotension, liver dysfunction, changes in mental status, and elevated lactate.
- **Septic shock**: Hypotension (despite fluid loading) plus hypoperfusion.

**Page 412** – Addition: Drugs that cause agranulocytosis

(►*Mnemonic: Cause Pretty Major Collapse To Defense Cells*)

- Carbamazepine
- Propylthiouracil and Methimazole

- Colchicine
- Ticlopidine
- Dapsone
- Clozapine

## Chapter 11 – Diseases of the Skin and Hypersensitivity Disorders

**Page 425** – Addition: *Tinea cruris* vs. *Candida* intertrigo in males (*Table 11-1: Important Dermatophyte Infections*)

Unlike *Candida*, *Tinea cruris* rarely involves the scrotum and penis.[xliv]

# Chapter 12 – Ambulatory Medicine

**Page 450** – Addition: Nonallergic (vasomotor) rhinitis

- Chronic rhinitis in the absence of identifiable immunologic, infectious, pharmacologic, etc. triggers.
- Predominant symptoms include nasal blockage and postnasal drip.
    - Unlike allergic rhinitis, there is an **absence of prominent ocular symptoms**, sneezing, and rhinorrhea.
- Not responsive to oral antihistamines used to treat allergic rhinitis (i.e. loratadine).
- Treatment includes **topical antihistamine sprays (i.e. azelastine) or intranasal glucocorticoids**.[xlv]

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[i] Simon A. Chest Pain. In: Tintinalli JE, Stapczynski J, Ma O, Yealy DM, Meckler GD, Cline DM. eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8e.* New York, NY: McGraw-Hill; 2016.
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