INTERPRETATION OF LAB TESTS with a Pharmaceutical Focus

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Rule #1—READ the package insert for suggested testing intervals.. SERIOUSLY? YES, seriously.

- Every drug and every pharmaceutical company has various required or suggested testing intervals—it would be wise to know them and to follow them
- For example:

Rule #1--READ the package insert for suggested testing intervals

- Valproic acid (VPA)—anti-convulsant, mood stabilizer
- CBC for platelets, LFTs, pregnancy test prior to prescribing* (highly teratogenic*)
- LFTs @ 2 weeks, 6 months, then annually; CBC/platelets annually or if S & S
- VPA levels 1 week after dosage change, every 6-12 months after
- *Maternal use of the anti-convulsant/mood stabilizer valproic acid (Depakote, Depakene)—8x greater risk of autism in the child if exposed during the first trimester; 20x greater risk of NTD if exposed during the first 30 days
- Alsdorf R, Wyszynski DF. Teratogenicity of sodium valproate. *Expert Opin Drug Saf. 2005* Mar;4(2):345-53.

Rule #2 (continued) -- *"Never let a negative or (positive) lab test take precedence over your clinical judgment."* M. Goldberg, MD.

- Personal story, not as the HCP taking care of the patient, but as the post-op partial hepatectomy patient with elevated liver enzymes… AST—2,445, ALT – 1,876 😳😳
- *"I feel great…no really, I feel FINE…why don't you re-check the LFT's before having me admitted to the hospital in 10 minutes?"*

RULE #3… Polypharmacy and the "stacking effect"

- Taking a careful and thorough drug history can help reduce this potentially dangerous adverse effect in the world of polypharmacy—cardiologist, rheumatologist, GI, ANP, Urologist…drug, after drug, after drug…let's take a look…
- Spironolactone (Aldactone) is an old, tired "mild" K+ - sparing diuretic that has taken on a new life; It's part of the triad of drugs used to treat of heart failure with a reduced ejection fraction —an ACE inhibitor, a beta-blocker, and spironolactone (more in the HF lecture)
- Spironolactone inhibits aldosterone resulting in sodium and water *excretion* and potassium ***retention;***
- Hyperkalemia is usually not a problem with a single agent…until OTHER drugs are added that also retain potassium and the K+ level can go into the RED ZONE

Spironolactone (Aldactone) and eplerenone (Inspra)

- Recommendations for monitoring serum potassium with aldosterone antagonists include obtaining a serum potassium level at 1 week and 1 month after initiating therapy and then obtain a potassium level at each visit. If potassium is less than 5 mmol/L at 1 month, up-titration will be performed. If potassium is 5.0–5.4 mmol/L, the dose will be maintained; if the level is 5.5–6.0 mmol/L, the dose will be decreased; and if the level is greater than 6.0 mmol/L, the drug will be discontinued.
- Spironolactone—highly protein bound, lots of drug interactions, food can interfere; CHEAP; 9% risk of gynecomastia
- Eplerenone – less than 50% protein bound, few drug interactions, food doesn't interfere, EXPENSIVE; less than 1% risk of gynecomastia
- (Miller AB. Aldosterone antagonism in heart failure. Vasc Health Risk Manag. 2007 Oct;3(5):605-609)

What other drugs?

- Any drug that blocks angiotensin will also block aldosterone down the line…and K+ retention is the final result
- ACE inhibitors—the "PRILS" and Angiotensin receptor blockers (ARBs)("SARTANS") come to mind immediately
- ACE inhibitors or ARBs + spironolactone? Some patients w/HF need additional aldosterone antagonism
- ARNI (angiotensin-receptor neprilysin inhibitor)—sacubitril/valsartan (Entresto) also increases K+ levels

Other K+ retaining drugs—TMP/SMX and hyperkalemia

- Trimethoprim **inhibits** distal tubular reabsorption of Na+ and subsequent K+ secretion, resulting in K+ retention
- This potentially life-threatening side effect was first described in AIDS patients in 1993 while being treated with TMP/SMX for *pneumocystis carinii* (now, *jiroveci*) pneumonia (Allapan, et al. *Annals of Internal Medicine* February 1, 1996)
- Trimethoprim-induced hyperkalemia has subsequently been reported multiple times in both patients with mild renal insufficiency and in otherwise normal patients given TMP-sulfamethoxazole (Bactrim/Septra) combinations for as short a time as **5 days**.

TMP/SMX and hyperkalemia

- Up to 6% of patients on TMP/SMX develop hyperkalemia within the first few days
- Highest risk—older than 65, renal insufficiency, diabetes, HF or those taking other meds that increase K+ (the "stacking effect")
- check K+ after 4 or 5 days of TMP/SMX; or hold the ACE I if possible; If needed, switch antibiotics
- Hospitalizations due to hyperkalemia increase by 7-fold or more when elderly patients take TMP/SMX with any other drug that retains potassium (due to the declining eGFR with aging)
- ~3 per 1000 seniors will have sudden death within 14 days of taking an TMP/SMX with an ACEI or ARB compared with 1 of every 1000 patients taking an ACEI or ARB with amoxicillin
- January 15, 2015 *Prescriber's Letter*

What about Nitrofurantoin instead of TMP/SMX?

- Nitrofurantoin is also associated with hyperkalemia. If an antibiotic is necessary for a symptomatic urinary tract infection in the elderly use fosfomycin (Monurol) or a fluoroquinolone (ciprofloxacin or levofloxacin)*, or beta-lactams (Amoxicillin/clavulanate [Augmentin], cefaclor, etc.)
- *ugh, don't use a floxacin if *C. diff* is a high risk or if they are on corticosteroids (acute tendonitis; "risk of aortic dissection or aneurysm in certain patients associated with systemic use of these antibiotics" FDA warning MAY 2017)
- (Arnold)(Antoniou)

Just a friendly reminder—Spironolactone is used for other conditions, not just HF…

- **"go to drug" for treatment-resistant HTN (**Resistant BP is defined as BP not controlled on a 3-drug regimen with a diuretic as one of the agents).

"It's a pharmaceutical backbone for resistant hypertension treatment."
(Williams B, et al. Spironolactone vs. placebo, bisoprolol, and doxazosin, to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomized, double-blind, crossover trial. Lancet 2015;386:2059-2068)

- Female pattern hair loss
- Augment breast development in transgender male to female patients
- Cirrhosis of the liver (secondary hyperaldosteronism)
- PCOS for its mild testosterone-inhibiting properties to treat hirsutism and acne

OCs that contain drospirenone (an analog of spironolactone)

- Drospirenone (an analog of spironolactone) and ethinyl estradiol are marketed to treat PCOS
- This combination may be used in young women with PCOS who also might be on an ACE inhibitor because of the associated hypertension and type 2 diabetes with PCOS
- K+ levels should be checked 2 weeks after starting a COC that contains drosperinone and ethinyl estradiol
- Which oral contraceptives? Yaz, Beyaz, Gianvi, Loryna, Ocella, Safyral, Syeda, Yasmin, and Zarah
- Don't forget the increased risk of DVTs in women with drospirenone (3mg)-ethinyl estradiol (0.03 mg) containing COCs (10/10,000 vs. 6/10,000) (FDA Drug Safety Communication: Safety review update on the possible increased risk of blood clots with birth control pills containing drospirenone; 5/31/2011)

We're not finished stacking drugs yet…Other drugs that increase potassium

- NSAIDS vasoconstrict the renal artery and the renal afferent arterioles due to prostaglandin inhibition (ibuprofen, piroxicam (Feldene), and naproxen (Aleve) are the biggest offenders)—resulting in sodium, water and **potassium** retention
- NSAIDS for longer than 2 weeks in young adults & adults; NSAIDS for any length of time in geriatric patients…why?
- The geriatric kidney is more dependent on prostaglandin-induced afferent arteriole vasodilation than the "younger" kidney...NSAIDs inhibit renal prostaglandins and cause vasoconstriction with Na+, **K+,** and water retention

Newest class of oral drugs for diabetes—"FLOZINS"--SGLT2 inhibitors--2013

- Sodium glucose co-transporter 2 inhibitors (SGLT2); lower HbA1c by 1%; Reduce renal glucose reabsorption and increase urinary glucose excretion + natriuresis
- Retain potassium
- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)

(*Medical Letter,* December 21, 2015)

Herbal products that increase K+

- Alfalfa (*Medicago sativa*)
- Dandelion (*Taraxacum officinale) (French –Pissenlit)*
- Horsetail (*Equisetum arvense)*
- Stinging Nettle (*Urtica dioca)*
- *Chan su (*marketed as a topical aphrodisiac)
- Milkweed (Asclepias species)
- Lily of the valley (Convallaria majalis)
- Siberian ginseng (Eleutherococcus senticosus)
- Hawthorn Berry (Crataegus species)

(Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 2004;351:585)

A bit more on ACE inhibitors and ARBs—serum creatinine levels

- Serum creatinine may rise 10% to 30% from baseline within the first two weeks of starting therapy with either class of angiotensin inhibitors/blockers
- Patients with normal renal function starting either class experience a rise of about **0.2 mg/dL** over a two- to three-week period, returning to baseline in the 4th week.
- If the patient has renal insufficiency to begin with, expect a rise in serum creatinine of 0.5 mg/dL over a four-week period.
- Patients with renal artery stenosis, extensive atherosclerotic cardiovascular disease, or dehydration may experience a progressive increase in serum creatinine of 2.0 mg/dL. ***Discontinuing the ACE or the ARB is the appropriate course of action with this significant rise in serum creatinine.***

Drugs that affect platelets

- Quantitative platelet counts—normal? 150,000 to 450,000 range (ranges vary based on the lab measuring the numbers)
- Qualitative platelet dysfunction—platelet numbers are normal, but the platelets don't work—platelet function assay (old test? Bleeding time)
- Platelet-type bleeding with platelet counts lower than 50,000 or qualitative platelet dysfunction—superficial bleeding; petechiae, purpura, nose bleeds, occult blood in stool, hematuria

Platelet-type bleeding

- Acute DIC -- Severe thrombocytopenia due to meningococcemia
- Meningococcus rips the endothelial cells from the blood vessels, exposing collagen—the most potent platelet attractor known to man; platelets aggregate along the walls of the vessels, platelet counts fall dramatically

Platelet type bleeding –thrombocytopenia; chronic DIC

- Secondary to malignancy

Drugs causing thrombocytopenia

- Heparin (HIT)(HITT syndrome), some chemotherapy agents, quinine and quinidine , sulfa drugs, antibiotics (piperacillin, linezolid, rifampin, vancomycin), thiazide diuretics, cimetidine (Tagamet), alcohol
- valproic acid (Depakene, Depakote)—check platelet count and coagulation tests baseline, periodically, and prior to planned surgery

ASA , NSAIDS and clopidogrel (Plavix), pasugrel (Effient) cause qualitative platelet dysfunction

- numbers are normal, platelet function assay is abnormal--prolonged
- ASA and NSAIDs inhibit the enzyme cyclooxygenase (COX), which in turn prevents the formation of thromboxane A2 and prostaglandins—ASA is an irreversible inhibition (7 days) vs. ibuprofen is reversible (24 hours)
- Exception in the NSAID class: celecoxib (Celebrex) does not affect platelets
- Clopidogrel (Plavix) and pasugrel (Effient) block platelet aggregation by blocking the $P2Y_{12}$ receptor (pasugrel is more effective, but causes more bleeding)
- Ticagrelor (Brilinta) – $P2Y_{12}$ inhibitor; more effective than clopidogrel with similar risk of bleeding; only take with low-dose aspirin; faster onset and elimination; also binds platelets irreversibly

The stacking effect: Case study

- 28 y.o. female presented to ER with petechiae, purpura, nose bleeds, blood in urine, blood in stool, bleeding from her "snuff box" and around her hairline, but she felt "fine" 😳
- Hematology MD called STAT to the ER…asked her about any drugs she was on and she said just a "baby aspirin" a day. Ordered a battery of tests, PT, aPTT, thrombin time, fibrinogen, platelet counts, platelet aggregation assay, lactate (early sepsis? DIC?)
- Upon further questioning—the G's, ibuprofen, SJW, vitamin E, red wine…

Alternative therapies and platelet aggregation

- If it starts with a G it inhibits platelet aggregation—gingko, garlic, glucosamine, ginseng, ginger, grapeseed extract
- SJW (St. John's Wort)
- feverfew (used for migraines)
- Fish oil (greater than 3 grams/day) can decrease the ability of platelets to aggregate especially if the patient is taking other G's + ASA and/or NSAIDS and/or Plavix
- Vitamin E (over 800 IU per day)

When to stop prior to surgery

- Aspirin—7 days prior to surgery
- Clopidogrel (Plavix) and prasugrel (Effient) — stop 5-7 days prior to surgery
- more effective than Plavix; BUT, more bleeding; 5-7days prior to surgery
- ticagrelor (Brilinta)—BID; stop 5 – 7 days before going to the OR
- Ibuprofen – 24 hours prior to surgery
- Celcoxib – doesn't have to be stopped as it doesn't inhibit platelet aggregation
- Have your patients d/c feverfew, garlic, ginger, and ginseng 7 days prior to surgery; gingko 36 hours prior to surgery; SJW at least 5 days prior, some say 2 weeks

Warfarin (Coumadin) and the INR

- Inhibits vitamin K-dependent activation of Factors II, **VII**, IX, X, all of which are formed in the liver
- When adding or subtracting a drug, check the INR within 72-96 hours
- International Normalized Ratio (The INR is 0.9-1.1 in those of us not taking warfarin and with normal liver protein synthesis)
- Standard therapeutic range for patients on warfarin is 2-3 with a goal of 2.5; mechanical heart valves? 3.5
- A review of 2,460 patients from 2000-2003 found that 83% of major bleeding events occurred in patients with an INR > 3.0 (*Am J Cardiol*. 2005;96(4):595-98)

While we're talking about warfarin

- Bad news? We've always known that there are lots of drug interactions making warfarin either MORE effective (bleeding) or less effective (clotting)
- One to mention in the geriatric world—Monistat for vaginal yeast infections— *"Well, I have this little 'itch' down there…"*
- …OTC intravaginal Monistat can double the INR

Anti-coagulant therapy—no monitoring is necessary

NOACs or DOACs (Novel or Direct Oral Anticoagulants)

- rivaroxaban/Xarelto, apixaban/Eliquis, edoxaban/Savaysa (Factor Xa inhibitors—the "abans"
- dabigatran/Pradaxa (direct thrombin inhibitor)
- Follow up every 6 months; stop 1-2 days before surgery; start up about 24 hours after surgery; short half-lives and quick acting

A few notes on anti-coagulants

- Up to 15% of patients on an anticoagulant will have a GI bleed.
- Mounting evidence suggests that restarting anticoagulation is usually worth the extra bleeding risk. However, greater than 25% won't restart—so here are a few notes:
- Atrial fib patients are more likely to **die from a stroke** than a GI bleed
- Which anticoagulant? Warfarin or the DOAC, apixaban (Eliquis)?…less GI bleeding with apixaban and **no monitoring is necessary**
- more gastrointestinal bleeding with both **dabigatran** (at least with the 150 mg twice-daily dose) and **rivaroxaban** than with **warfarin**, particularly in the elderly.
- Patel MR, Mahaffey KW, Garg J, et al. (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med **365**(10):883–891.

WBC and differential

- Neutrophils (polys, PMN, segs)(57-63%) of the total white count; acute inflammation, acute bacterial infections, acute necrosis (1.51-7.07)

  Bands (0-4%) (0.00-.51)—precursor to the neutrophil
- Neutropenia (usually preceded by two words— "life threatening…")
- Absolute neutrophil count (ANC)? Segs + bands as a % of the total WBC

The differential, continued…

- Lymphocytes (30%)-first responder to viruses; cells of the immune system (0.65-2.8)
- Monocytes (4%)—macrophages in tissues; cells of chronic inflammation; antigen processing cell (APC) (0.00-0.51); *(Listeria monocytogenes)*
- Eosinophils (3%)—cells that respond to parasites (Carlotta) and allergies (0.00-0.42) (including drug allergies)
- Basophils (less than 1%)—who cares? Contain histamine (0.00-0.16) (basophilia—CML, PV)
- *all the cells with the last name "phil" are collectively called granulocytes—hence, the term agranulocytosis theoretically means a decrease of all three; but in clinical practice agranulocytosis means neutropenia

The Absolute Neutrophil Count (ANC)

- Neutropenia is defined as an absolute neutrophil count (ANC) <500/mm^3 or an ANC of <1,000/mm^3 with an expected decline.
- % segs + % bands x total WBC
- 57% segs + 3% bands x 5000 = ANC = 3,000
- 20% segs + 0% bands x 2000 = ANC = 400
- Serious bacterial infection risk increases directly with the following: (1) severity of neutropenia (ANC < 100 cells/mm^3 imposes a greater risk than ANC < 500 cells/mm^3), (2) rate of ANC decline (rapidly falling rate imposes a greater risk than chronic neutropenia or aplastic anemia), and (3) duration of neutropenia

Drugs and neutropenia

- Chemotherapy (all patients)—but not all chemotherapy
- Clozapine (Clozaril)—ANC weekly x 6 months; every 2 weeks in months 6-12; then monthly; Cimetidine (Tagamet), ranitidine (Zantac)
- Captopril (Capoten), enalapril (Vasotec), propranolol
- amiodarone, quinidine
- NSAIDs, except celecoxib (Celebrex)
- Zidovudine (Retrovir)
- Antibiotics including metronidazole (Flagyl),gentamicin, clindamycin, imipenem, PCNs, tetracyclines, vancomycin, TMP/SMX, dapsone, cephalosporin
- Azothiaprine (Imuran)
- Anti-thyroid drugs--PTU and methimazole
- Carbamazepine (Tegretol); phenytoin, valproate

- (**Up-to-Date** accessed January 26, 2020)

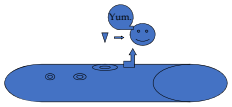
Levamisole used to cut cocaine (70% of cocaine in U.S. is cut with levamisole—life-threatening leukopenia, neutropenia and vasculitis

A few notes on specific drugs and neutropenia

- Methimazole--neutropenia occurs in ~0.1 to 0.4% of patients, generally within the first 3 months of Rx. But, it can occur anytime; Dose-response with methimazole; doses over 30 mg daily have highest risk
- PTU—any dose can cause a neutropenic reaction
- Discontinue drug and have a WBC drawn if a fever or other evidence of infection develops (Brent GA and Med Letter 2009/August)
- Carbamazepine (Tegretol)—baseline, monthly for 2 or 3 months, then at least every-other-year

NEUTROPHILs…normal function

- Margination (flow along the margins), pavementing (stuck to the walls), migration (move into tissues), engulfment, and degranulation



Glucocorticoids (such as Prednisone) inhibit the ability of the neutrophil to function

- Prednisone inhibits migration and degranulation of neutrophils, hence its anti-inflammatory properties
- However, initially it recruits the pavementing cells into circulating and the total WBC increases—looks like an infectious response but isn't—stabilizes within 24-48 hours
- Elderly with decreased migration of neutrophils, increases infection susceptibility
- Fever ***increases*** the migration of neutrophils—is fever good for you? YES!

Glucocorticoids (such as Prednisone) and blood glucose

- Prednisone also increases blood sugar by stimulating glycogenolysis (breakdown of stored glycogen) in the liver—can cause a drug-induced diabetes
- Diabetes– Blood glucose greater than 180 mg/dL (9.99 mmol/L) inhibits neutrophil migration
- *use metformin to block glycogenolysis with HD-Prednisone

Other WBCs and drugs

- Eosinophilia – elevated eosinophils usually means allergies, an allergic reaction to a drug, or parasitic disease (Carlotta)
- Certain drugs can also elevate eosinophils (penicillin, dapsone, cephalosporins, tetracycline, nitrofurantoin, carbamazepine, PPIs, ACE inhibitors) as a part of an allergic phenomenon to the drug; drug allergies can also trigger a fever and maculopapular rash
- Steroids DECREASE eosinophils

Let's talk about the statin drugs for cardiovascular disease

- ***Fasting*** lipid measurements are no longer necessary
- Routine monitoring is not necessary
- Evidence supports using moderate, fixed-dose statin therapy to lower risk for early all-cause death and adverse CV events
- (Downs JR and O'Malleg PG. *Ann Intern Med* 2015 Jun 23)

Muscle aches and pains with statins

- About 1/20 patients experiences muscle pain or weakness; minor aches and pains are common but most likely benign—when in doubt, **check the CK level**
- Solution? Switch drugs (to rosuvastatin if they're on another statin), lower dose, or every other day dosing
- Consider other causes of muscle aches and pains in the age group of patients taking statins…vitamin D deficiency, hyperthyroidism, hypothyroidism*, exercise, and the ED drugs (tadalafil is the major culprit)
- Treating hypothyroidism may relieve or decrease statin-related myalgia (Dr. J. Garber, Harvard Special Report, *Thyroid Disease*, available at www.health.harvard.edu/TD)

Hypothyroidism and muscle aches and pains.

- An elevated creatine kinase (CK) can be due to hypothyroid-induced myopathy.
- The AST (aspartate transaminase) and LDH (lactic dehydrogenase) can also be elevated due to the myopathy.
- A CK level of greater than 16,000 is associated with acute renal failure—hypothyroidism doesn't fall into that category.
- Drug-induced myopathy CAN fall into that category, so if the CK is higher than 16,000 U/L look for a drug, if an obvious cause (crush injury) is not found. ((Foster LA. Clinical Challenge. Clinical Advisor. Feb 2016.p73-79.)

Lipid notes

- Patient with triglycerides above 250 mg/dL (2.81 mmol/L) and an HDL less than 40 mg/dL (1.04 mmol/L)—THINK either …

1) Type 2 Diabetes (check the fasting blood sugar or Hemoglobin A1C), OR…
2) Hypothyroidism (TSH) (0.4-4.5 µU/mL or mU/L) for 21-54 y.o.; 0.5-8.9 µU/mL or mU/L for 55-87);

As an FYI…

- Seventy percent of hypothyroid patients have elevated cholesterol levels (low metabolism—can't clear cholesterol from the blood)
- One in seven people with high cholesterol has underlying hypothyroidism
- Check the TSH

Should you consider testing for hypothyroidism before starting a statin?

- No clear evidence, BUT…knowing who's at risk for hypothyroidism may persuade you to think about a quick TSH test...
- Family history of hypothyroidism (or hyperthyroidism)—thyroid problems run in families
- Gender—women are 5-8 x more likely to have thyroid problems
- Age—over 60
- Race—C greater than AA or Hispanic Americans
- Health history—other autoimmune diseases—type 1 DM, Addison's disease, pernicious anemia, RA, premature gray hair, radiation Rx to head and neck, vitiligo

Recommendations to Healthcare Professionals Regarding the Muscle and Statin Safety

- Whenever muscle symptoms or an increased CK level is encountered in a patient receiving statin therapy, health professionals should attempt to rule out other etiologies—increased accidents, prolonged tonic/clonic seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, ketamine (Ketalar)*, methadone, methamphetamine and PCP (McKenney JM)
- Vitamin D deficiency causes muscle aches and pains
- ED drugs cause muscle aches and pains
- Exercise causes muscle aches and pains

Rhabdomyolysis

- Patients on statins who are at highest risk? Concomitant use of gemfibrozil (Lopid)(rarely used anymore), over age 80, hypothyroidism, renal impairment, higher doses)
- Overall risk of myopathy with monotherapy statin use is 4- 10 per 100,000 person-years of follow-up, with the risk of rhabdomyolysis about one-third of this (3 to 4 per 100,000 person-years)(Armitage)
- Renal failure develops in up to 50% of patients with rhabdomyolysis (Naughton)
- Check serum creatinine and BUN

Amiodarone and simvastatin

- Amiodarone inhibits the metabolism of simvastatin—the higher the dose of simvastatin the greater the retention of the drug
- Very high risk of rhabdomyolysis and subsequent acute renal failure with doses of simvastatin over 10 mg combined with amiodarone
- (Foster LA. Clinical Challenge. *Clinical Advisor*. Feb 2016.p73-79)

Statins and diabetes

- Taking high doses of statins increases the risk of T2DM…BUT for every new case of DM, a higher statin dose prevented 3 cardiovascular events, including ACS in diabetics. Benefits outweigh the risks.
- Statin users should keep taking drugs but be screened for DM periodically. (*JAMA* June 22-29, 2011)

Speaking of diabetes-- LDL particle size

- Size of the LDL particles…small and dense (Pattern A) vs. large and loose (Pattern B)
- Diabetics have small and dense particles due to high triglycerides
- Statins change particle size to Pattern B
- **(Gondek, K. LDL particle number and size. ADVANCE for NPs and PAs. January 2012)**

Non-statin drugs that influence LDL-cholesterol

- Increase LDLs: Progestins, androgens, cyclosporine, tacrolimus, thiazide diuretics
- Atypical antipsychotics (clozapine, olanzapine, quetiapine, paliperidone, risperidone)—increase LDL and total cholesterol; check lipids at 12 weeks and at 1 year, then every 5 years if normal (The Carlat Report: Psychiatry, Nov/Dec 2015)
- Drugs that decrease LDLs: estrogen/estradiol

ANEMIAS--Healthy Kidneys…

- Erythropoietin production and hypoxia
- Renal failure and anemia (one of the first signs of early renal failure is mild normocytic anemia)
- 50% of patients in stage 3a CKD have anemia
- Epoetin alfa (1989)(Procrit, Epogen, Eprex) and darbopoetin alfa--Aranesp) (2001)

Overcorrecting anemia in CKD

- fully restoring hemoglobin to greater than 12-14 g/dL in patients with CKD increases their risk of all-cause mortality, poorly controlled BP, strokes, and AV access thrombosis…so partial restoration of hemoglobin is advised.
- Target hemoglobin of 10-12 g/dL
- Monitor hemoglobin at least monthly when on ESAs

Healthy thyroid-- Hypothyroidism…low metabolic rate

- Decreased metabolism decreases the production of red blood cells
- Normocytic anemia (MCV normal)
- Check TSH

Iron for RBC production

- FACT: you need iron to produce RBCs
- You need extra iron to grow vertically, not…

Iron deficiency anemia

- Iron deficiencies are common in kids—usually due to dietary deficiencies
- celiac disease—decreased absorption in the duodenum; as long as the duodenum is not absorbing, these patients will be resistant to iron replacement
- Iron deficiencies are more common in women due to 20% less blood volume combined with menstruation

You lose iron when you bleed

- Women have 20% less blood than men and premenopausal women lose blood once a month—1 tampon = 5 ml (normal periods = 1 to 7 tampons; 9-12 is excessive) hence, lower iron stores
- Post-menopausal women no longer lose iron—iron stores start to increase so we can't blame iron deficiency on periods—where else is she bleeding?

You lose iron when you bleed

- GI bleeding
- GU bleeding
- "Can you think of anything that might have caused your rectal bleeding?"
- NSAIDs
- NOACs (Novel oral anticoagulants)
- Warfarin

Geriatrics and iron

- Elderly and iron absorption
- Decreased acid in stomach decreases iron absorption
- PPIs for GERD?
- Long-term PPIs can lead to iron-deficiency anemia
- If iron supplements are necessary, use vitamin C (orange juice) or coca cola classic with iron supplements to help absorb the iron
- PMF—??iron supplements?
- Not unless you're symptomatic with iron deficiency

Treating iron deficiency anemia

- Feosol Carbonyl Iron tablets or Feosol Ferrous Sulfate Tablets
- Hemoglobin concentration usually increases by 1.0 g/dL weekly; continue treatment until anemia is corrected and the serum ferritin concentration is greater than 50 ng/mL. What's normal?
  M = 20-250 ng/mL or mcg/L
  F = 10-120 ng/mL or mcg/L
- Microcytosis, if present, typically resolves several months after iron stores are replenished. Completion of therapy in patients without continuing blood loss typically requires several months
- **Oral iron therapy often fails in patients who take antacids, H2 Blockers, PPIs, or calcium supplements or who have celiac disease as a cause of their iron deficiency**

Speaking of PPIs*—rare but important

- Clinically significant low magnesium levels
- tubulointerstitial nephritis with PPIs—increased serum creatinine and BUN; eosinophilia and eosinophils in urine; maybe rash and fever; polyuria + polydipsia and nocturia; specific gravity less than 1.010 (inability to concentrate urine)—first morning specimen should be 1.025 (highly concentrated) but not with interstitial disease of the kidney
- (specifically omeprazole, pantoprazole and lansoprazole and the H2 blocker ranitidine/Zantac)

PPIs and B12 deficiency

- Proton Pump Inhibitors—inhibit the pump that pumps HCL acid AND Intrinsic factor (IF);
- Normally intrinsic factor (IF) binds B12 and takes it to the ileum for absorption—no IF? No B12 absorption
- (*Am J Clini Nutr* (2007);86:1384)
- The effect is dose-dependent with B12 deficiency more likely among patients taking PPIs for greater than 2 years and in patients taking greater than 1.5 PPIs per day. (Lam)

Metformin and B12 deficiency

- How many patients are on metformin AND a PPI?
- ~ 22% of the patients on metformin will develop a B12 deficiency (check levels after 4 years)

- *DeJager J, Kooy A, Lehert P, et al. Long-term treatment with metformin in patients with type2 diabetes mellitus and risk of vitamin B12 deficiency: randomized placebo controlled trial. BMJ 2010;340:c2181Sando KR, Barbora J, Willis C et al. Recent diabetes issues affecting the primary care clinician. Southern Med J 2011;104(6):456-61)

B12 … a few more notes

- Normal B12 levels-- range is 200-1100 pg/mL
- MMA test (methylmalonic acid test)--Use the methylmalonic acid test (MMA) which increases with B-12 deficiency)(*Am J Clin Nutr* 2007; 86:1384.
- 2,000 to 5,000 mcg of B12 is stored in the liver for 5-7 years;
- We use a very small amount, ~**2.4** mcg per day for making RBCs, keeping the myelin in our central and peripheral nervous system healthy, stimulating RBC maturation in the bone marrow, and producing serotonin to make us happy
- Takes 5-7 years of no B12 intake to deplete

MMA testing for vitamin B12 deficiency

- Impaired activity of the vitamin B12 dependent enzyme methyl-malonyl coenzyme A mutase leads to a high level of serum methylmalonic acid, which is useful for the diagnosis of B12 deficiency. Low serum B12 status is defined as a serum MMA of greater than 210 nmol/L
- (Am J Clin Nutr 2007; 86:1384)

Clinical conditions associated with B12 deficiency

- Big, immature RBCs—megaloblastic anemia (MCV is greater than 120)
- Cognitive dysfunction—#1 cause of nutritional dementia
- Peripheral neuropathy (one of three top causes in elderly)
- Depression (B12 and folic acid are a co-factors in the production of serotonin)
- So you have NO energy, you're demented, can't feel your feet and depressed…JEEZZZZ…how important is B12?

Stack the other risk factors for B12 deficiency

- Over 55
- Lack of intrinsic factor (IF); autoimmune gastritis; gastrectomy patients
- No animal protein in the diet; vegetarians; Tea and Toasters; alcoholics
- Liver failure
- Malabsorption—Crohn's disease gastric by-pass surgery

B12 replacement

- How can we replace B12? 5 ways…how much?
- With B12 dementia—B12 injections 1000 mcg every other day for 2 weeks, then once a week for 6 weeks, then monthly (various regimens)
- With peripheral neuropathy—B12 injections
- Oral, nasal, or sublingual B12 in all others—1000 micrograms/day
- 5 S's…shoot it, swallow it, spray it, snort it or suck it…
- Can you overdose on B12?
- No, the one dreaded side effect however is:

RBC indices…(morphology)

- **MCV (mean cell volume**) – 90 (83-97) fL; microcytic, normocytic, macrocytic

- How do we define anemias? **Based on morphology, the MCV is the most important test…**

Macrocytic anemia

- RBC 3,000,000
- MCV greater than 100 fL
- MCV between 100 and 120—think booze
- MCV greater than 120—think B12 or Folic acid deficiency

Drugs that cause megaloblastic anemia

- Acyclovir (anti-herpes drug)
- ASA
- Anticonvulsants
- Azathioprine (Imuran)
- Colchicine (gout)
- INH (TB)
- MTX (methotrexate)

And TWO DRUGS that are VERY popular in Type 2 Diabetes

- Proton Pump inhibitors
- Metformin (Glucophage, Glumetza, Fortamet)—type 2 diabetes, PCOS)

Check the eGFR before starting metformin…not using serum creatinine to start metformin

eGFR (mL/min)	Maximun daily dose	Recommended monitoring
≥60	2550 mg	Monitor renal function annually
45-59	2000 mg	Monitor renal function every 3 to 6 months
30-44	1000 mg	2-4 fold risk of lactic acidosis~10/100,000
<30	Do not use	6-7 fold risk of lactic acidosis in this group

Liver function tests (LFTs)

- Hepatocellular integrity -- AST, ALT
- Hepatobiliary integrity--Bile formation and flow (bilirubin, GGT, alkaline phosphatase)
- Hepatosynthesis—albumin levels, INR (clotting factors)
- If a "healthy" person demonstrates an elevated ALT, a thorough history is warranted with special questions such as hepatitis exposure, hepatotoxin exposure, and ***drug*** effects
- Hundreds, if not thousands, of drugs can elevate liver enzymes and cause drug-induced-liver-injury
- If enzymes are not terribly elevated (less than 2x normal—(some hepatologists say up to 3x normal), have the patient stop all OTC drugs/herbal products that are NOT necessary and recheck the enzyme levels in 2 weeks before embarking on a multi-million dollar work-up

herbal and dietary supplements and acute liver injury

- The role of herbal and dietary supplements in causing acute liver injury is a growing and perplexing problem. In studies from the United States, the proportions of cases of liver injury caused by herbal or dietary supplements increased from 7 to 9% in 2004–2007 to 19 to 20% in 2010–2014.
- This change probably reflects the increasing use of herbal products and dietary supplements, as well as the lack of rigorous regulatory oversight in the preparation and marketing of these products.

Herbal products and acute liver injury

- Unexplained liver enzyme elevations with S & S of liver injury **(**anorexia, nausea, generalized pruritis, dull RUQ pain).
- Consider herbal toxicity—kava (dose-related), shark cartilage, germander, chaparral, black cohosh, conjugated linoleic acid (CLA), noni, gotu kola, echinacea, senna, mistletoe, skullcap, comfey, Jin Bu Huan tea, green tea, and other herbal teas (usually as a part of weight loss regimens—especially green tea products), and sodium usniate (usnic acid)*
- *21 reports (FDA) of hepatotoxicity in consumers who ingested dietary supplements containing UA or sodium usniate for weight loss
- Most cases are idiosyncratic- LipoKinetix* (3,5-diiodothyronin, norephedrine HCl, yohimbine, caffeine, usnic acid from plant algae)—weight loss product (Syntrax, Cape Girardeau MO)
- Favreau JT, et al. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. Ann Intern Med 2002 Apr 16;136(8):590-5.

Liver enzyme elevations and vitamins

- Consider high doses of niacin (Vitamin B3) in adolescents and young adults
- Consider high doses of niacin in adults as OTC products to lower cholesterol
- Red Bull, MONSTER, 5-hour energy drink, Relentless all contain high amounts of niacin
- Niacin has been touted on the Internet as an aid to help pass urine drug tests--there is no evidence to support this practice.
- Vitamin A in amounts exceeding 20,000 u/d can also cause liver damage.
- J. M. Backes, R. J. Padley, and P. M. Moriarty, “Important considerations for treatment with dietary supplement versus prescription niacin products,” *Postgraduate Medicine*, vol. 123, no. 2, pp. 70–83, 2011.

Pediatric cases of acute liver failure

- Approximately 20% of pediatric cases of ALF are drug induced with the vast majority of these cases being a result of ingestion of acetaminophen. However, in our case we describe significant liver damage caused by ingestion of an unknown amount of over-the-counter niacin. Niacin, vitamin B3, is a readily available supplement typically utilized for treating dyslipidemia and niacin deficiency. Niacin toxicity has been associated with serious multisystem organ damage and fulminant hepatic failure requiring liver transplantation. The slow release preparation is associated with the highest risk of liver toxicity
- A. M. Daul and M. C. Beuhler, "Niacin toxicity resulting from urine drug test evasion," *Journal of Emergency Medicine*, vol. 41, no. 3, pp. e65–e68, 2011.

How about prescription drugs and acute liver injury?

- Children are more prone to DILI w/ salicylates and valproic acid
- Obesity increases the risk of liver injury due to halothane and methotrexate (Rheumatrex dose pack, Trexall)
- Women are more likely to experience DILI caused by diclofenac (Voltaren), isoniazid, or nitrofurantoin
- azathioprine (Azasan, Imuran) is a more likely cause in men
- The incidence of liver injury varies among the NSAIDs and appears to be the most common with diclofenac (Voltaren) (1-5 cases per 100,000) and sulindac (Clinoril)
- Acetaminophen-induced liver injury is more likely in persons who are fasting or malnourished, as well as those who chronically abuse ETOH (more than 3 adult beverages per day)

Lest we forget…Acetaminophen (Tylenol) and the liver

- Acetaminophen is in over 600 OTC products advertised for drippy, coughy, hacky, sneezy, wheezy, headachy, achy, sleepy, ouchy symptoms

Prescription products—acetaminophen and hydrocodone—brand names: Anexsia, Dolorex Forte, Hycet, Liquicet, Lorcet, Lortab, Maxidone, Norco, Polygesic, Stagesic,, Xodol, Zamicet, Zydone, Vicodin (325/mg per tab to reduce toxicity)—

…acetaminophen (Tylenol#3 [30/300] + caffeine)

Acetaminophen overdose

- Acetaminophen overdose (most often inadvertent) is the most frequent cause of acute liver failure in the U.S. population, accounting for 39% of cases (Ostapowicz)
- The minimum toxic single dose in healthy adults is between 7.5 and 10 grams and ≥ 150 mg/kg in children.
- Variability among patients re: toxic dose is most likely due to a genetic variation

If the AST/ALT ratio is greater than 1…

- Consider ETOH…
- AST is especially sensitive to alcohol
- If alcohol damages liver cells, the AST will increase higher than the ALT
- Ratio in alcohol- induced hepatitis is usually 3:1 to 8:1*

*It is rare for the AST level to be more than 8 times the normal value in patients with alcohol abuse

AST/ALT ratio of less than 1

- If less than 1 consider DRUGS
- fatty liver disease (enzymes may be perfectly normal with NAFLD), viruses, autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency
- Always check the TSH—may see mild increase in liver enzymes with hypothyroidism
- Eating lots of fast foods can also increase liver enzymes
- RED BULL and niacin-containing energy drinks as previously mentioned

Drugs that cause NAFLD

- Drugs—prednisone, MTX, synthetic estrogens, amiodarone (Cordarone, Pacerone), tamoxifen, nifedipine, and diltiazem

Extremely high levels of hepatocellular enzymes

- Marked elevation of ALT and AST is typical of severe acute viral hepatitis, herbal or drug-induced hepatic necrosis , and shock or ischemia to the liver
- The finding of extremely high levels (greater than 2000 to 3000 U/L) should always raise concern for acetaminophen OD, use of excessive therapeutic doses of acetaminophen by an alcoholic patient, or shock and/or ischemia to the liver

Alkaline Phosphatase (ALP, or AP)

- 42-136 U/L
- Drugs that increase ALP—IV albumin, antibiotics (PCN, tetracycline, lincomycin, oxacillin, penicillin), and more, more, more…
- PMF estrogen can increase ALP via cholestasis

Drugs and acute pancreatitis (partial list)—increased amylase and lipase levels

- Sulfasalazine (Azulfidine) and other sulfa-containing drugs
- Furosemide, Thiazides
- Azathioprine (Imuran)
- Gliptins—sitagliptin, saxagliptin, linagliptin
- Exanatide (Byetta) **and liraglutide (Victoza)**
- Chemotherapy—L- asparaginase
- HAART drugs
- Sulindac (Clinoril)
- Acetaminophen
- Alpha-methyldopa
- Benazapril
- Bezafibrate
- Cannabis
- Cimetidine
- Clozapine
- Codeine
- Corticosteroids

Creatine Kinase—Total CK—55-170 units/L (male); 30-135 units/L (female)

- Found in high-energy tissues including:
- Isoenzymes for specific tissues—1 (BB),2 (MB), 3 (MM)
- Skeletal muscle (98% CK-3, CK-MM; 2% is CK-MB)
- Cardiac muscle (40% CK-2, CK-MB; 60% CK-MM)
- Brain (CK-1, CK-BB) (also large intestine, CK-BB)

Rhabdo “skeletal” myo “muscle” lysis

- Rhabdomyolysis is usually diagnosed when the CK concentration is greater than 40 times the ULN or there is evidence of end organ damage – most often acute renal failure or worsened renal function with elevated BUN and creatinine

Rhabdomyolysis

- Statins get all of the press, but in reality over 150 drugs and toxins (including alcohol, cocaine and heroin, ecstasy, LSD)
- Sunitinib, imatinib (tyrosine kinase inhibitors)
- Leflunomide
- Daptomycin
- propofol
- cyclosporine.
- erythromycin.
- colchicine (low-dose colchicine is being used to reduce inflammation post MI today—be aware of elevated CK)(*NEJM* 2019 Nov 16)
- amphetamines.
- Drugs and alcohol are causative factors in up to 81 percent of the cases of rhabdomyolysis
- (Curr Opin Pharmacol. 2012 Jun; 12(3): 335–339)

Thanks.

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- At the 2013 American Society of Hypertension Meeting, a speaker was asked if he still prescribed clonidine for hypertension. He answered, *"Yes, for patients I don't like."*

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