MEHLMANMEDICAL PHARMACOLOGY ASSESSMENT #1

Pharmacology Assessment #1:

1. A 38-year-old IV drug-user presents with a two-week history of progressive dysphagia, odynophagia, and fever. The most likely cause of this patient's condition is most appropriately treated with an agent that does which of the following?

A) Creation of pores in the ergosterol membrane
B) Inhibition of 14α-demethylase
C) Inhibition of squalene epoxidase
D) Inhibition of microtubules
E) Inhibition of synthesis of 1,3-β-glucan

The answer is B.

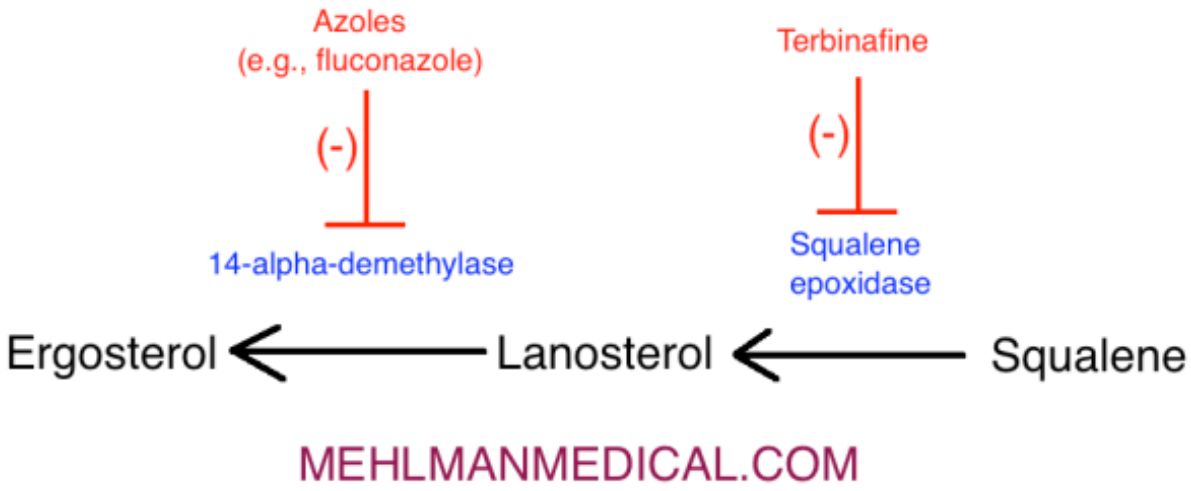
IV drug-use = ↑↑ risk of HIV/AIDS.[1]

The most common cause of infectious esophagitis in HIV/AIDS is **candida.**[2]

The treatment for candidal esophagitis is **oral fluconazole** 200 to 400 mg per day for 14 to 21 days.[3] (You do not need to know doses for the USMLE)

Azole anti-fungals inhibit ergosterol synthesis by inhibiting 14α-demethylase. Ergosterol is the cholesterol equivalent in fungi.[4]

Terbinafine inhibits lanosterol synthesis by inhibiting squalene epoxidase. Lanosterol is the precursor to ergosterol.[5, 6] Topical terbinafine is a first-line treatment for tinea pedis.[7] Oral terbinafine is a first-line treatment for onychomycosis (fungal nail infection).[8]



Creation of pores in the ergosterol membrane refers to nystatin[9] and amphotericin B.[10]

Nystatin, or an azole, may be used in topical suspension (mouthwash) form as first-line treatment for **oropharyngeal candidiasis**[11, 12, 13]**,** however esophageal candidiasis is treated with oral azole.[3]

Amphotericin B is an extremely hard-hitting anti-fungal used in various CNS and disseminated fungal infections.[14] On the USMLE, only choose this drug only if the patient is very sick, often with high fever and chills/rigors (i.e., suggesting fungemia and/or CNS involvement).

Inhibition of microtubules refers to griseofulvin, which may be used orally to treat tinea capitis.[15]

Inhibition of synthesis of 1,3-β-glucan refers to the echinocandins, such as caspofungin, which is used in the treatment of invasive aspergillosis in patients who cannot receive, or who fail, voriconazole therapy.[16, 17]

Bottom line: You must know the mechanisms of action of the anti-fungals to score above the 220s on the USMLE Step 1. Understand the basic uses of each agent as well.

1) https://www.ncbi.nlm.nih.gov/books/NBK218616/

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3980995/

3) https://www.ncbi.nlm.nih.gov/books/NBK537268/#_article-21328_s8_

4) http://www.jbc.org/content/292/16/6728.full

5) https://aac.asm.org/content/aac/40/2/443.full.pdf

6) https://www.ncbi.nlm.nih.gov/pubmed/21229992

7) https://www.ncbi.nlm.nih.gov/books/NBK470421/

8) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6600855/

9) https://www.dovepress.com/efficacy-of-nystatin

10) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3441194/

11) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6441600/

12) https://www.ncbi.nlm.nih.gov/books/NBK545282/

13) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4312689/

14) https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2141.2005.05749.x

15) https://www.ncbi.nlm.nih.gov/books/NBK537323/

16) https://www.ncbi.nlm.nih.gov/books/NBK545140/

17) http://jeccm.amegroups.com/article/view/5315/html

2. A 56-year-old woman comes to the physician for an annual health maintenance examination. BMI is 25 kg/m2. A complete blood count shows no abnormalities. Her serum lipids are as follows:

Fasting total cholesterol: 195 mg/dL
HDL cholesterol: 55 mg/dL
Triglycerides: 520 mg/dL

In addition to lifestyle modification, which of the following agents is most appropriate for this patient?

A) Atorvastatin
B) Fenofibrate
C) Niacin
D) Colesevelam
E) Ezetimibe

The answer is B.

Fibrates, such as fenofibrate and gemfibrozil, are indicated as the primary treatment for triglycerides >500 mg/dL.[1]

Fibrates are known to cause myopathy and hepatotoxicity.[2, 3]

Fenofibrate is the most commonly implicated fibrate in causing liver injury, which can be severe and prolonged with autoimmune features.[2]

Gemfibrozil eclipses fenofibrate for causing myopathy when used in conjunction with statins. Gemfibrozil interferes with statin glucuronidation, whereas fenofibrate does not.[3]

The guidelines for initiating statin therapy are lengthy and vary depending on an individual's risk factors. USMLE Step 1 **will not be** pedantic about exact numerical figures, but Step 2CK does want you to know the following HY points about commencing statins:

- Adults age 40-75 who have **fasting LDL** (not total cholesterol) >190 mg/dL.[4]
- **Diabetics** age 40-75 who have **fasting LDL** >70 mg/dL[4] This is because diabetes mellitus is one of the most acceleratory risk factors for atherosclerosis.[5]

Once again, that is heavily simplified and there are lengthy guidelines, but those above two points are testable on Step 2CK.

Niacin (vitamin B3) increases HDL cholesterol and decreases hepatic export of VLDL.[6]

Bile acid sequestrants, such as colesevelam, prevent enterohepatic reabsorption of bile acids at the terminal ileum. As the intrahepatic bile acid pool diminishes, hepatic CYP7A1 upregulates in order to increase the conversion of cholesterol to bile acids. The number of hepatic LDL receptors then increases secondarily to compensate for the reduction of hepatic cholesterol, which increases the clearance of LDL from the circulation.[7]

Ezetimibe is a selective cholesterol absorption inhibitor in the small bowel.[8] It lowers serum LDL cholesterol by 13-20% in most patients.[1]

Bottom line: Fibrates are the first-line therapy for lowering triglycerides in patients with levels >500 mg/dL. They cause hepatotoxicity and myopathy, the latter notably when combined with statins.

1) https://www.acc.org/latest-in-cardiology/articles/2019/01/11/07/39/

2) https://www.ncbi.nlm.nih.gov/books/NBK548607/

3) https://www.ncbi.nlm.nih.gov/pubmed/16407687

4) https://www.heart.org/-/media/files/health-topics/cholesterol/chlstrmngmntgd_181110

5) https://ahajournals.org/doi/full/10.1161/circulationaha.116.022194

6) https://www.ahajournals.org/doi/pdf/10.1161/ATVBAHA.108.171363

7) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2291317/

8) https://www.ncbi.nlm.nih.gov/pubmed/14620392

3. A 32-year-old woman has a 7-month history of gradually worsening pain and stiffness in her hands, wrists, and ankles. She began taking 800 mg daily of ibuprofen several months ago which had resulted in temporary amelioration of her symptoms but now is ineffective. Serum studies show positivity for rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP). She is started on a short course of prednisone that does not relieve her symptoms. The physician discusses his recommendation for commencing a disease-modifying anti-rheumatic drug (DMARD). Which of the following best describes the mechanism of action of this recommended therapy?

A) Inhibition of soluble TNF-α
B) Inhibition of TNF-α receptor
C) Inhibition of dihydroorotate dehydrogenase
D) Inhibition of dihydrofolate reductase
E) Inhibition of interleukin-6 (IL-6)

The answer is A.

Methotrexate, a competitive and reversible inhibitor of dihydrofolate reductase (DHFR), is the well-established first-line DMARD used to treat rheumatoid arthritis (RA). As soon as a diagnosis of RA is made, it is recommended that DMARD therapy is commenced.[1]

NSAIDs, such as ibuprofen, and glucocorticoids may be used for symptomatic relief only, but they do not halt progression of the disease.[2] Glucocorticoids are generally implemented as a short taper while the initial DMARD is being commenced (or if DMARDs are being switched).[1]

Methotrexate causes **pulmonary fibrosis**[3]**,** hepatotoxicity (↑ ALT, AST)[4], and mucositis (due to agranulocytosis).[5]

Inhibition of soluble TNF-α inhibition refers to **infliximab, adalimumab, etanercept** (a recombinant receptor), golimumab, and certolizumab pegol.[6]

The above three bold TNF-α agents are exceedingly HY for the USMLE. The latter two agents are lower yield but newer. And anything new is fair game.

Inhibition of dihydroorotate dehydrogenase refers to leflunomide.[7]

Inhibition of interleukin-6 (IL-6) refers to tocilizumab.[8]

Treatment of RA:[1]

Early, symptomatic RA

- Methotrexate is first-line DMARD. Commence as soon as diagnosis of RA is made.
- If methotrexate monotherapy is insufficient, add leflunomide or sulfasalazine (i.e., combination DMARD therapy), OR commence TNF-α agent monotherapy.

Established RA

- Methotrexate is first-line DMARD. Commence as soon as diagnosis of RA is made.
- If methotrexate therapy fails, *add* an TNF-α agent.

The USMLE Step 1 and 2CK will **not** make you differentiate between early and established RA. **However they want you to know that methotrexate is used first** and to merely be aware of the other available treatments.

Bottom line: Methotrexate is a competitive, reversible inhibitor of DHFR. It causes pulmonary fibrosis, hepatotoxicity, and mucositis (due to neutropenia). Depending on the severity and progression of RA, anti-TNF-α agents are frequently used as a step-up after methotrexate.

1) https://www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3527878/

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3814259/

4) https://www.ncbi.nlm.nih.gov/books/NBK548219/

5) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4851368/

6) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5877629/

7) https://www.ncbi.nlm.nih.gov/pubmed/7575649

8) https://www.ncbi.nlm.nih.gov/pubmed/30427250

4. A 14-year-old girl is referred to pediatric oncology complaining of ongoing abdominal pain and distention for the past 2 months. Physical examination shows a distended but non-tender abdomen with a painless, immobile, and firm mass, 4×7 cm in diameter, inferior and lateral to the umbilicus on the left. Bone marrow and hematologic examinations are normal. Basic metabolic panel is within normal limits. Abdominal CT confirms a mass surrounding the inferior mesenteric artery. Burkitt lymphoma is diagnosed. CD20 positivity is reported by immunohistochemical examination. Which of the following chemotherapeutic agents may demonstrate efficacy in the management of this patient?

A) Daclizumab
B) Vemurafenib
C) Cetuximab
D) Alemtuzumab
E) Rituximab
F) Eculizumab

The answer is E.

This patient has **Burkitt lymphoma,** a type of non-Hodgkin lymphoma.

Although jaw lesions have been classically described in the literature, intra-abdominal Burkitt lymphoma has been reported to account for more than 50% of cases. Jaw lesions appear to be associated with male gender and young age.[1]

Rituximab is a monoclonal antibody that targets **CD20 on B cells**. It may be used in the treatment of non-Hodgkin lymphoma.[2,3] It may also be used in the treatment of autoimmune disease, such as rheumatoid arthritis and granulomatosis with polyangiitis (formerly known as Wegener).[4] **This agent is exceedingly HY for the USMLE.**

Daclizumab is a monoclonal antibody against CD25, the alpha subunit of **IL-2 receptor** on T cells.[5]

Vemurafenib is an inhibitor of **BRAF serine/threonine-kinase** in the treatment of $BRAF^{V600E}$-mutated late-stage **melanoma.**[6]

Cetuximab is a monoclonal antibody against epidermal growth factor receptor **(EGFR)** in the treatment of EGFR-positive metastatic colorectal cancer.[7]

Alemtuzumab is a monoclonal antibody against **CD52** in the treatment of chronic lymphocytic leukemia (CLL).[8]

Eculizumab is a monoclonal antibody against **complement protein C5** in the treatment of paroxysmal nocturnal hemoglobinuria (PNH).[9]

Bottom line: Rituximab is a monoclonal antibody against CD20 on B cells. This agent is exceedingly HY for the USMLE. The other agents listed are fair game on the USMLE and are not random obscurities. But to pass the USMLE you need to know rituximab.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2574984/

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3915537/

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2844047/

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4993704/

5) https://www.ncbi.nlm.nih.gov/books/NBK548018/

6) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6080616/

7) https://www.ncbi.nlm.nih.gov/pubmed/16117976

8) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2767316/

9) https://www.ncbi.nlm.nih.gov/pubmed/25468487

5. L-asparaginase is an integral component of treatment of acute lymphoblastic leukemia (ALL) in children. It hydrolyzes L-asparagine to L-aspartate in leukemic cells. A researcher who is investigating this enzyme isolates an actinomycetes strain, *Streptomyces* sp. NEAE-82, which produces L-asparaginase. He then carries out kinetic studies of the purified enzyme and presents his findings in a report:

Researcher's report	Km (M)	Vmax ($Uml^{-1}min^{-1}$)
Estimations prior to investigation:	0.02000	95.00
Findings as per kinetic studies:	0.01007	95.08

Which of the following most accurately describes the researcher's findings of L-asparaginase in comparison to his prior estimations?

A) ↓ enzyme affinity for substrate; ↑ efficacy
B) ↓ enzyme affinity for substrate; ↓ efficacy
C) ↑ enzyme affinity for substrate; ↑ efficacy
D) ↑ enzyme affinity for substrate; ↓ efficacy

The answer is C.

Vmax

- Reaction velocity (rate of reaction) when the enzyme is fully saturated by substrate, indicating that all the binding sites are being constantly reoccupied.[1]
- Reflective of enzyme efficacy (i.e., maximum rate of reaction).[2]
- **In other words, ↑ Vmax = ↑ efficacy; ↓ Vmax = ↓ efficacy**

Km

- The substrate concentration at 1/2 Vmax[3]
- Inversely reflective of affinity (i.e., if the enzyme binds more strongly to the substrate, then you need less substrate to achieve 1/2 Vmax).[3]
- **In other words, ↑ Km = ↓ affinity; ↓ Km = ↑ affinity**

The true finding for Km was less than the researcher's prior estimate, meaning the enzyme has greater affinity for substrate than predicted.

The true finding for Vmax was greater than the researcher's prior estimate, meaning the enzyme achieves greater efficacy than predicted.

(By the way, the researcher's true findings are actually the real Km and Vmax for L-asparaginase.[4])

Bottom line: Km = substrate concentration at 1/2 Vmax. ↑ Km = ↓ affinity; ↓ Km = ↑ affinity. ↑ Vmax = ↑ efficacy; ↓ Vmax = ↓ efficacy

1) https://www.sciencedirect.com/science/article/pii/B9780123971760000017

2) https://books.google.co.jp/books?id=9-xeDwAAQBAJ&pg

3) https://books.google.co.jp/books?id=MgqI-pfk45QC&pg

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5015098/

6. A 63-year-old male with a medical history of type II diabetes mellitus, COPD, hepatitis C, and remote IV drug-use presents to emergency with debilitating headaches, progressive gait instability, weakness when standing, and 15 kg weight loss over the past two months. He works at a plastics factory and spends his lunch breaks at a local park where there is a large pigeon population. Serum Cryptococcal antigen of 1:64 is reported. Which of the following should be initiated in this patient?

A) Amphotericin B
B) Flucytosine
C) Amphotericin B + Flucytosine
D) Amphotericin B + Fluconazole
E) Fluconazole + Flucytosine
F) Fluconazole

The answer is C.

This patient has Cryptococcus neoformans meningitis.

Treatment[1]

Give amphotericin B + flucytosine together initially, then do a fluconazole taper.

Once again, you do **not** need to know doses for the USMLE, but in case you're curious:

Week 1: Amphotericin B + flucytosine

Week 2: Fluconazole 1200 mg daily

Weeks 3-10: Fluconazole 800 mg daily

Week 11-onward (minimum 1 year of treatment): Fluconazole 200 mg daily

Immunocompromised patients with exposure to pigeon populations carry a high risk of infection.[2, 3]

Diagnosis

Made first-line via **latex agglutination or lateral-flow assay** for CNS cryptococcal antigen.[4] This is more sensitive and specific than **India ink prep.** On the USMLE, if latex agglutination or lateral flow assay is listed, choose that over India ink.

Mucicarmine staining (red in color) has also been used for diagnosis.[5] It is not first-line, but rarely it shows up in USMLE questions.

Bottom line: Cryptococcal meningitis is treated with amphotericin B + flucytosine, followed by a lengthy fluconazole taper. Diagnosis is made first-line with latex agglutination or lateral-flow assay. Be aware of India ink prep and mucicarmine staining for the USMLE, but these are not first-line for diagnosis.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6544127/

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3719228/

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714070/

4) https://www.sciencedirect.com/science/article/pii/S0325754119300616

5) https://www.ncbi.nlm.nih.gov/pubmed/7678937

7. A 54-year-old man comes to emergency 90 minutes after attending a party in his friend's cellar. He complains of severe stomach cramping and worsening visual disturbance. He appears acutely intoxicated. Serum laboratory studies show:

$HCO3^-$: 12 mEq/L
Na^+: 142 mEq/L
Cl^-: 100 mEq/L
pH: 7.14
pCO_2: 23 mm Hg
PO_2: 110 mm Hg

Which of the following is the most appropriate first-line treatment for this patient?

A) Ethylene glycol
B) Ethanol
C) Fenoldopam
D) Fomepizole
E) Pralidoxime

The answer is D.

This patient has **acute methanol intoxication.**

Intoxication is classically associated with consumption of home-distilled alcohol.[1] Individuals typically seek medical attention within 12-48 hours because of abdominal pain, encephalopathy, and/or blurred vision.[2]

High-anion gap metabolic acidosis is characteristic.[3] Toxicity is due to metabolism to formaldehyde, followed by formic acid, with the latter being more toxic.[2]

First-line treatment is with **fomepizole, a potent inhibitor of alcohol dehydrogenase.** This is also the first-line treatment for **ethylene glycol (antifreeze) poisoning.**[3] The use of ethanol in the treatment of methanol and ethylene glycol poisoning is also considered effective, but fomepizole is first-line if available.[3,4]

Ethanol works via competitive saturation of alcohol dehydrogenase, thereby allowing increased time for unmetabolized renal clearance of methanol and ethylene glycol.[5]

Fenoldopam is a dopamine 1 (D1) agonist used sometimes in hypertensive emergencies. The D1 agonism acts to maintain renal blood flow, since significantly lowering one's blood pressure in the acute setting may otherwise inadvertently decrease renal perfusion.[6]

Pralidoxime is used after atropine in the treatment of organophosphate poisoning. It functions to regenerate functional acetylcholinesterase.[7]

Bottom line: Fomepizole is the first-line treatment for methanol and ethylene glycol intoxication. It is a potent alcohol dehydrogenase inhibitor. Ethanol is also an effective treatment but fomepizole is the correct answer on the USMLE if listed.

1) https://onlinelibrary.wiley.com/doi/pdf/10.1046/j.1442-2026.1999.00067.x

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4436753/

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4806829/#__sec7title

4) https://www.ncbi.nlm.nih.gov/pubmed/26109326

5) https://www.sciencedirect.com/science/article/pii/B008045044X001243

6) https://www.ncbi.nlm.nih.gov/books/NBK526058/

7) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2493390/

8. A previously healthy 64-year-old male arrives at emergency after a 2-hour history of chest tightness and burning. Blood pressure is 162/93 mm Hg. Heart rate is 92/min. There is jugular venous distension and crackles auscultated in the lung fields bilaterally. ECG shows ST-segment elevations in leads II, III, and aVF. Which of the following is the most appropriate initial pharmacotherapy?

A) Aspirin
B) Clopidogrel
C) Aspirin + Prasugrel
D) Heparin
E) Aspirin + Heparin
F) Heparin + Clopidogrel

The answer is C.

Anti-platelet therapy has been shown to improve the prognosis of patients with acute coronary syndrome (ACS) with ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation ACS (NSTE).[1]

Dual anti-platelet therapy with aspirin + an ADP2Y12 blocker (i.e., clopidogrel, prasugrel, ticagrelor) is superior to aspirin alone, and is recommended for all patients with ACS for 12 months regardless of the initial revascularization strategy. Prasugrel and ticagrelor lead to a more rapid and effective inhibition of platelet aggregation and improved outcomes compared with clopidogrel, however prasugrel carries significantly greater bleeding risk.[1, 2, 3]

The treatment algorithm for the use of other agents, such as anticoagulants, morphine, oxygen, nitrates, beta-blockers, etc., is a complex and lengthy discussion, but the administration of dual anti-platelet therapy is recommended for all patients.[2]

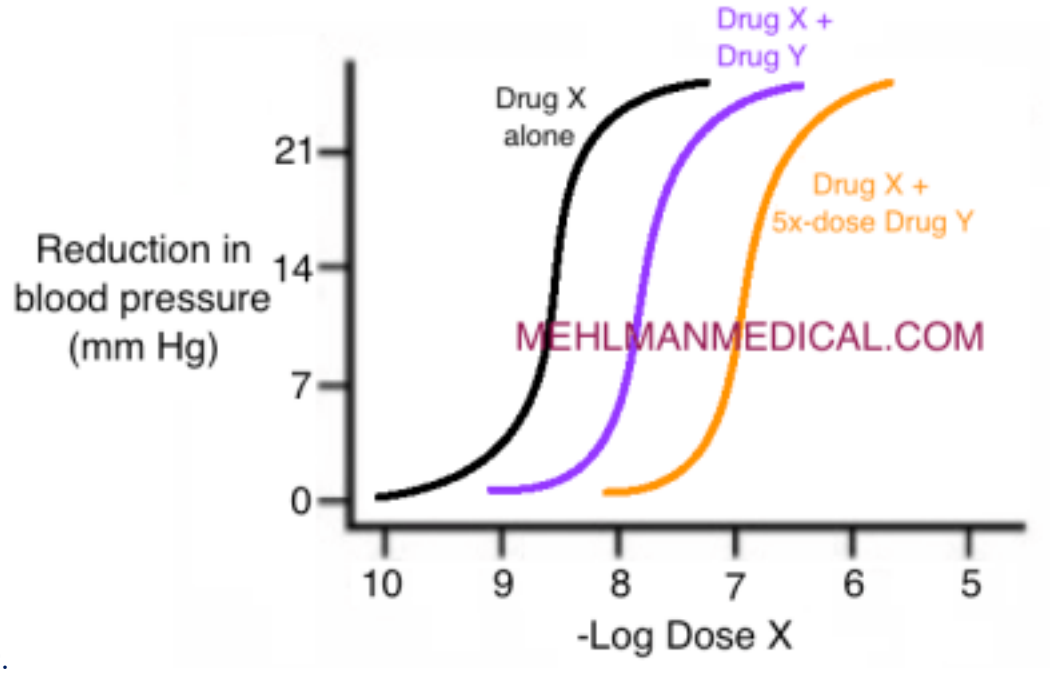
Bottom line: The combination of aspirin + an ADP2Y12 blocker (i.e., dual anti-platelet therapy) is superior to aspirin alone in the management of ACS. Prasugrel and ticagrelor are superior to clopidogrel for improving outcome in ACS. Prasugrel carries increased risk of bleeding compared to clopidogrel.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1994022/

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5866121/

3) https://www.ncbi.nlm.nih.gov/pubmed/19717846

9.



Regarding the above findings, which of the following is true?

A) Drug Y is a non-competitive antagonist of Drug X
B) Drug X is a non-competitive antagonist of Drug Y
C) Drug Y is a competitive antagonist of Drug X
D) Drug X is a competitive antagonist of Drug Y
E) Drug Y is a partial agonist of Drug X
F) Drug X is a partial agonist of Drug Y

The answer is C.

The main point to observe is that the presence of Drug Y does not decrease the ability of Drug X to achieve its maximum potential effect, even if more Drug X is required to achieve just such.

This means Drug X and Drug Y **are competing** for the same receptor(s) – i.e., as long as you keep increasing the dose of Drug X, you can eventually overcome and drown out the impact of Drug Y.

Important examples of competitive inhibitors for the USMLE are **methotrexate** (on dihydrofolate reductase)[1], **statins** (on HMG-CoA reductase)[2], and **almost all α1-blockers** (i.e., tamsulosin[3], terazosin[4], phentolamine[5], etc.).

If Drug Y were to cause a ↓ in the ability of Drug X to achieve its maximum effect (i.e., a downward shift of the curve), even as the dose of Drug X is continually increased, Drug Y would therefore **not be competing** for the same receptor as Drug X. This could be due to a negative allosteric effect on Drug X, or it could mean Drug Y binds to Drug X's receptor at a distinct location and prevents Drug X from binding, while simultaneously not inhibiting or potentiating the receptor itself. In other words, with non-competitive inhibition, no matter how much the dose of Drug X is increased, the impact of Drug Y can never be overcome.

The super-HY non-competitive antagonist you need to know for the USMLE is **phenoxybenzamine** at α1 receptors.[6]

Bottom line: Competitive antagonism = Right-shifted curve. Non-competitive antagonism = Down-shifted curve. Methotrexate, statins, and almost all α1-blockers are competitive inhibitors. Phenoxybenzamine is non-competitive.

1) https://www.ncbi.nlm.nih.gov/pubmed/3122764

2) https://www.ncbi.nlm.nih.gov/pubmed/27313057

3) https://www.ncbi.nlm.nih.gov/pubmed/9117115

4) https://www.ncbi.nlm.nih.gov/pubmed/2457715

5) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1282628/

6) https://www.sciencedirect.com/science/article/pii/B9780323481106000144

10. A 44-year-old man with advanced hemochromatosis has progressive confusion over the past four days. Physical exam shows asterixis. Lactulose is administered, which rapidly improves his mental status. Which of the following best explains this effect?

A) Alkalinization; ↑ Ammonium absorption in the bowel
B) Alkalinization; ↓ Ammonium absorption in the bowel
C) Alkalinization; ↑ Ammonia absorption in the bowel
D) Alkalinization; ↓ Ammonia absorption in the bowel
E) Alkalinization; ↑ Ammonium reabsorption in the kidney
F) Alkalinization; ↓ Ammonium reabsorption in the kidney
G) Alkalinization; ↑ Ammonia reabsorption in the kidney
H) Alkalinization; ↓ Ammonia reabsorption in the kidney
I) Acidification; ↑ Ammonium absorption in the bowel
J) Acidification; ↓ Ammonium absorption in the bowel
K) Acidification; ↑ Ammonia absorption in the bowel
L) Acidification; ↓ Ammonia absorption in the bowel
M) Acidification; ↑ Ammonium reabsorption in the kidney
N) Acidification; ↓ Ammonium reabsorption in the kidney
O) Acidification; ↑ Ammonia reabsorption in the kidney
P) Acidification; ↓ Ammonia reabsorption in the kidney

The answer is J.

Hemochromatosis (iron overload) is a known cause of hepatic cirrhosis.[1]

Asterixis is a neurologic sign of "flapping hands" with outstretched arms seen classically in liver failure, but may also be seen in renal and respiratory failure, as well as with the use of some drugs, e.g., benzodiazepines, anticonvulsants.[2]

Hepatic encephalopathy (confusion in the setting of liver failure) is due to the inability of the failing liver to process ammonia, leading to hyperammonemia and deleterious effects on CNS function.[3]

Lactulose is a non-absorbable synthetic disaccharide comprising galactose and fructose.[4] It is a treatment for hepatic encephalopathy. It is metabolized by gut bacteria into monosaccharides, and then volatile fatty acids, hydrogen, and methane, with the net effect being a reduction in gut pH. This causes increased conversion of intraluminal ammonia (NH_3) into ammonium (NH_4^+), which cannot be absorbed the same way ammonia can. This leads to a decrease in ammonia levels in the blood, thereby mitigating the hepatic encephalopathy.[5]

Bottom line: Lactulose is a treatment for hepatic encephalopathy. Gut bacteria metabolize it into acidic end-products that result in the trapping of intraluminal NH_3 as NH_4^+, which in turn is excreted due to non-absorption.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2657669/

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4944342/

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4442852/

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1553161/

5) https://www.ncbi.nlm.nih.gov/books/NBK536930/

11. A 64-year-old man with a history of atrial fibrillation being managed with warfarin experiences right-sided arm weakness and facial droop for the past 12 hours. Recent pharmacologic treatment for which of the following conditions might explain these findings?

A) Community-acquired pneumonia
B) Peptic ulcer
C) Urinary tract infection
D) Ventricular tachycardia (i.e., secondary arrhythmia)
E) Scalp infection

The answer is E.

This type of question is exceedingly HY for the USMLE Step 1.

The presumption is that this patient has experienced a stroke secondary to an **induction**-based P-450 interaction, with increased rate of metabolism of his warfarin.

If his warfarin levels were inadvertently reduced in this fashion, that would have permitted the formation of a left atrial thrombus, which in this case resulted in subsequent embolization to the left middle cerebral artery and contralateral upper-limb and facial weakness.

Griseofulvin, the first-line treatment for tinea capitis (fungal infection of the scalp), is a known P-450 **inducer.**[1, 2]

Azithromycin, which is often first-line empiric treatment for community-acquired pneumonia, does **not** affect P-450. This is in contrast to other macrolides (i.e., clarithromycin, erythromycin), which **inhibit** P-450.[3, 4] If this patient received an inhibitor, he would have experienced bleeding diathesis (increased bleeding) rather than a mural thrombus + stroke.

Proton pump inhibitors (PPIs; e.g., omeprazole, lansoprazole) and cimetidine (H2 antagonist) may be used in the management of peptic ulcers. They are known inhibitors of P-450.[5, 6]

Sulfa drugs (e.g., sulfamethoxazole) are known P-450 inhibitors and frequently used to treat urinary tract infections (i.e., trimethoprim-sulfamethoxazole).[7, 8]

Amiodarone, a known P-450 inhibitor, may be used to treat ventricular tachycardia.[9]

Bottom line: Griseofulvin is a high-yield P-450 inducer. Macrolides (not azithromycin), PPIs, H2-blockers, sulfa drugs, and amiodarone are HY P-450 inhibitors.

1) https://www.karger.com/Article/Fulltext/495909

2) https://www.ncbi.nlm.nih.gov/pubmed/10607315

3) https://www.aafp.org/afp/2006/0201/p442.html

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2015000/

5) https://www.ncbi.nlm.nih.gov/pubmed/22648560

6) https://www.ncbi.nlm.nih.gov/pubmed/8689952

7) https://www.ncbi.nlm.nih.gov/pubmed/12019187

8) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3216436/

9) https://www.ncbi.nlm.nih.gov/books/NBK482154/

12. A 65-year-old man with congestive heart failure has worsening dyspnea the past few hours and peripheral edema up to his knees. He has history of sulfa allergy. Which of the following is the most appropriate pharmacologic agent to improve his symptoms?

A) Ethacrynic acid
B) Furosemide
C) Hydrochlorothiazide (HCTZ)
D) Amiloride
E) Mannitol
F) Spironolactone

The answer is A.

Loop diuretics are the first-line treatment for fluid-unloading a patient with symptomatic heart failure.[1, 2, 3]

Furosemide, the standard go-to loop diuretic, is a sulfa drug, and cannot be used in patients with sulfa allergy. **Ethacrynic acid** is a non-sulfa alternative to furosemide that may be used in the setting of heart failure.[4]

It is HY for the USMLE to know that loop diuretics such as furosemide and ethacrynic acid notably cause reversible **ototoxicity.**[5]

HCTZ, amiloride, and spironolactone may also be used to fluid-unload in heart failure, however loop diuretics are more effective.[6]

Mannitol, an osmotic diuretic, is contraindicated in congestive heart failure because it increases circulatory volume, thereby increasing preload and oxygen demand on the heart, in addition to exacerbating pulmonary edema.[7]

Bottom line: Loop diuretics are used first-line in the treatment of symptomatic heart failure requiring fluid-unloading. Furosemide is the standard go-to agent, however it is a sulfa drug and must be avoided in patients with sulfa allergy. Ethacrynic acid is a non-sulfa alternative to furosemide. Loop diuretics can cause ototoxicity.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5811193/

2) https://www.ncbi.nlm.nih.gov/pubmed/18158482

3) https://www.ncbi.nlm.nih.gov/books/NBK546656/

4) https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/214879

5) https://www.ncbi.nlm.nih.gov/pubmed/29937824

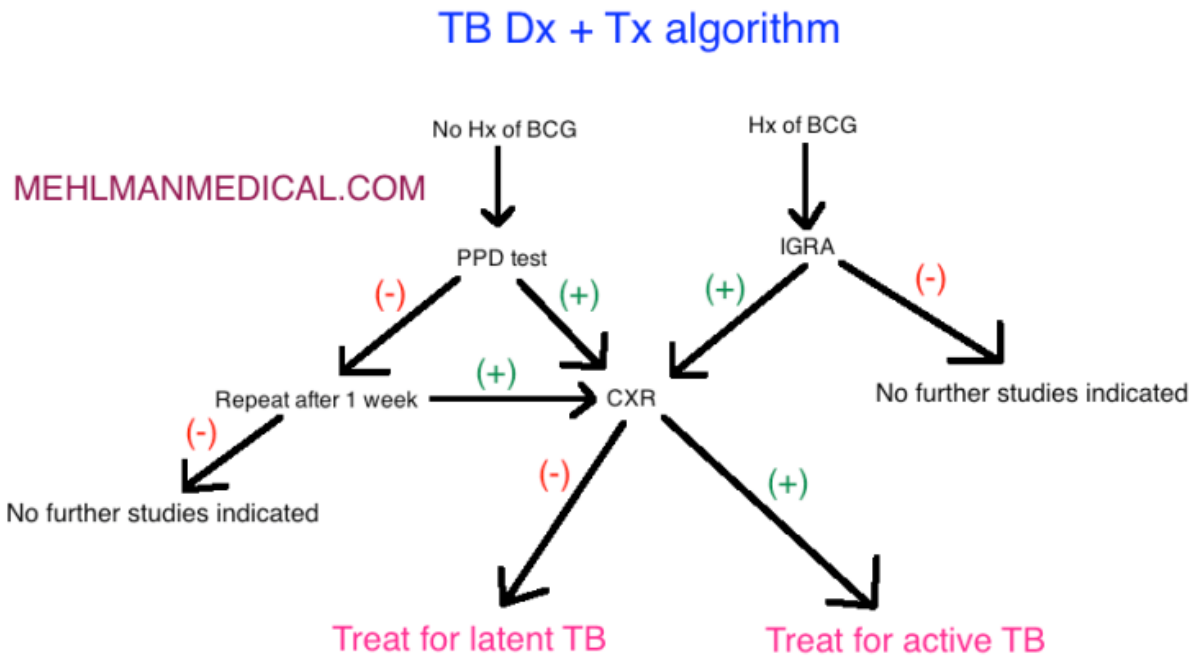
6) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6159465/

7) https://www.sciencedirect.com/science/article/pii/B9780702040849000665

13. A 29-year-old from Indonesia has a PPD test as part of a standard immigration health check for TB. An induration of 11 mm is observed. A chest x-ray is ordered and is unremarkable. Which of the following is the next best step in pharmacologic management?

A) Repeat PPD in 2 weeks
B) Repeat PPD in 6 weeks
C) Isoniazid (INH) for 4 months
D) INH for 9 months
E) Rifampin, isoniazid, pyrazinamide, ethambutol (RIPE) for 6 months
F) RIPE for 2 months, then RI alone for 4 more months
G) INH + rifampin for 4 months
H) INH + pyridoxine for 9 months

The answer is H.



Algorithm information from source:[1]

This man has latent tuberculosis (i.e., positive PPD test but negative CXR). The correct answer (as discussed below), must include B6 in the regimen.

TB diagnosis[2]

PPD skin test is performed first diagnostically. If history of BCG vaccine, do interferon-gamma release assay (IGRA) instead. **Do not do IGRA in addition to PPD.**

If PPD is negative, repeat after one week. If negative again, no further studies indicated. Repeats performed within 1 week may cause a false (+) secondary to a "booster reaction."[2]

If IGRA is negative, no further studies indicated.

If PPD or IGRA is positive, do CXR. **Do not repeat positive PPD tests.**

If CXR is negative, treat for latent TB / give TB prophylaxis. On the USMLE, "treatment for latent TB" and "administer TB prophylaxis" mean the same thing.

If CXR is positive, treat for active TB.

Positive PPD test[3]

Measure induration only. **Erythema does not count.**[4]

5+ mm

- Recent contact with people with active TB
- HIV + status
- Organ transplant recipients
- Chronic prednisone use (>15mg/day for >1 month); anti-TNF-α agent use
- Findings consistent with TB on CXR

10+ mm

- **Immigrant status** (Western countries not included)
- IV drug users
- Healthcare workers; prison workers; homeless shelter personnel
- TB laboratory personnel
- Children under 4 years of age

15+ mm

- Everyone

Tx of Latent TB[5]

- **9 months INH + pyridoxine (vitamin B6) – The USMLE Steps 1 and 2CK assess this as the answer.**
- 4 months rifampin
- 3 months INH + rifapentine + pyridoxine
- Vitamin B6 must be given with INH to prevent vitamin B6 deficiency.[6]

Tx of active TB[7]

- **Rifampin, INH, pyrazinamide, ethambutol (RIPE) for 2 months, followed by RI alone for 4 more months (6 months total)**
- And of course add pyridoxine (annoying that it sounds similar to pyrazinamide)

Bottom line: Know the diagnostic algorithm + latent/active treatments for TB. Always give vitamin B6 with INH use. **This is all exceedingly HY for the USMLE.**

1) https://www.cdc.gov/tb/

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481914/

3) https://www.cdc.gov/tb/topic/treatment/decideltbi.htm

4) https://www.cdc.gov/tb/publications/posters/images/Mantoux_wallchart.pdf

5) https://www.cdc.gov/tb/topic/treatment/ltbi.htm

6) https://www.ncbi.nlm.nih.gov/pubmed/6269259

7) https://www.cdc.gov/tb/topic/treatment/tbdisease.htm

14. A 26-year-old man from the Philippines has a positive interferon-gamma release assay (IGRA) and chest x-ray (CXR) for tuberculosis. Treatment is initiated. He develops orange bodily secretions, including his sweat and tears. The agent responsible inhibits which of the following?

A) Mycolic acid synthesis
B) DNA-dependent RNA polymerase
C) RNA-dependent DNA polymerase
D) Arabinosyl transferase
E) Fatty acid synthase I

The answer is B.

This man is being treated with rifampin, isoniazid (INH), pyrazinamide, and ethambutol for active TB.

Rifampin is a DNA-dependent RNA polymerase inhibitor.[1]

It is known to cause orange bodily secretions. This may worry patients but is a benign finding.[2]

INH is a mycolic acid synthesis inhibitor.[3]

Pyrazinamide inhibits fatty acid synthase I.[4]

Ethambutol inhibits arabinosyl transferase.[5]

Bottom line: Rifampin is a DNA-dependent RNA polymerase inhibitor. It causes orange bodily secretions. This is a benign finding. **The mechanisms of action of the TB drugs are exceedingly HY on the USMLE Step 1.**

1) https://www.ncbi.nlm.nih.gov/pubmed/781514

2) https://www.mayoclinic.org/drugs-supplements/rifampin-oral-route/precautions/drg-20065839

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC284282/

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC134955/

5) https://books.google.co.jp/books?id=qLJ6Bs1Qml4C&pg

15. A man who has been to hospital many times over the years for Wolf-Parkinson-White syndrome is treated with an agent that successfully produces a complete anterograde block in the accessory pathway. This is not the first time he has received this therapy. Several weeks later he develops joint pain in his hands, sharp pain when breathing, purpura on his trunk, and redness of his shins. Which of the following agents is most likely responsible for his condition?

A Dofetilide
B) Amiodarone
C) Mexiletine
D) Procainamide
E) Nebivolol

The answer is D.

Wolf-Parkinson-White (WPW) syndrome is caused by the presence of an accessory conduction pathway in the heart that frequently results in paroxysmal supraventricular tachycardia.[1]

WPW is classically associated with a delta-wave on ECG, which is colloquially referred to as a "slurred upstroke" of the PR-segment.[2]

Procainamide, a type-Ia anti-arrhythmic (sodium channel blocker) may be used to produce an effective block of the accessory pathway in WPW.[3]

Procainamide is classically associated with drug-induced lupus erythematosis (DILE).[4]

DILE and systemic lupus erythematosis (SLE; idiopathic autoimmune lupus) are distinct conditions.

Arthralgia is often the first symptom and presents in up to 90% of patients in both DILE and SLE.

CNS and renal involvement are very rare in DILE. Photosensitivity, purpura, and erythema nodosum are more frequent in DILE.

Malar rash, alopecia, discoid lesions, and mucosal ulcers are **less common in DILE** than in SLE.[4]

Pleurisy (pleuritis; inflammation of the pleura, resulting in sharp pain when breathing) is seen in both DILE and SLE, however it is notably associated with procainamide.[5]

Drugs classically associated with DILE are[4]: "**M**om is **HIPP** "
→ **M**inocycline, **H**ydralazine, **I**soniazid, **P**rocainamide, **P**enicillamine

DILE is associated with anti-histone antibodies.[4]

Bottom line: Know the "**M**om is **HIPP**" drugs as precipitators of DILE. Anti-histone antibodies are characteristic. Renal involvement and malar rash are rare in DILE compared to SLE. Purpura and erythema nodosum are seen more in DILE. Both DILE and SLE present with arthralgia as the most common initial presentation. Pleurisy is seen in both, however is notably associated with procainamide DILE. **This type of question is exceedingly HY for the USMLE.**

1) https://www.ncbi.nlm.nih.gov/pubmed/2229769

2) https://emj.bmj.com/content/20/5/491

3) https://www.ncbi.nlm.nih.gov/pubmed/7137035

4) https://www.ncbi.nlm.nih.gov/books/NBK441889/

5) https://www.ncbi.nlm.nih.gov/pubmed/1729083

16. A 23-year-old primigravid woman at 28 weeks gestation presents to emergency with headache and the general feeling of severe discomfort. Her blood pressure is found to be markedly elevated and she is treated with an agent that is also known to improve mortality in heart failure when combined with nitrates. Her blood pressure proceeds to decrease appropriately. Which of the following is the most likely mechanism of the agent she was treated with?

A) Inhibition of phosphodiesterase-3 (PDE-3)
B) Inhibition of phosphodiesterase-5 (PDE-5)
C) Beta-receptor blockade
D) Alpha-receptor blockade
E) Inhibition of aldosterone receptors
F) Inhibition of angiotensin-converting enzyme
G) Alteration of intracellular calcium signaling

The answer is G.

Hydralazine may be used as one of the first-line treatments for severe hypertension in pregnancy.[1]

It notably **decreases afterload** on the heart.[2]

The combination of hydralazine and nitrates in the management of heart failure is well-known to decrease mortality.[3]

This reduction in mortality in heart failure is especially pronounced among African-Americans, as cited by a major New England Journal of Medicine study.[4]

Hydralazine's mechanism is best described as:

- "Direct relaxation of arteriolar smooth muscle, probably by alteration in **intracellular calcium signaling."**[5]
- "The mechanism is not fully known but is theorized to be due to an **interference of calcium movement in the vascular smooth muscle** which is responsible for vasoconstriction."[6]
- "Hydralazine, by **altering cellular calcium metabolism, interferes with the calcium movements within the vascular smooth muscle** that are responsible for initiating or maintaining the contractile state."[7]
- "Hydralazine (control, cGMP**-independent** vasodilator)"[8] (meaning independent of the actions of phosphodiesterase-5)

Hydralazine has been mentioned in the past in various USMLE resources as a phosphodiesterase inhibitor. However the literature does not support this.

Sildenafil (Viagra) is a HY phosphodiesterase-5 inhibitor for the USMLE. It prevents the breakdown of cGMP.[8]

Cilostazol, both an anti-platelet agent, as well as a vasodilator used in the treatment of intermittent claudication, is a specific and strong PDE-3 inhibitor. It prevents breakdown of cAMP.[9]

Dipyridamole, both an anti-platelet agent, as well as a vasodilator used sometimes in cardiac stress testing, is both a PDE- 3 and PDE-5 inhibitor, preventing breakdown of cAMP and cGMP, respectively.[9]

Bottom line: Hydralazine is often used as a first-line agent to treat severe hypertension in pregnancy by decreasing afterload. It also improves mortality in heart failure when combined with nitrates. It acts by interfering with the signaling and/or movement of calcium in vascular smooth muscle. The literature does not support the conclusion that hydralazine is a phosphodiesterase inhibitor.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC259162/

2) https://www.ncbi.nlm.nih.gov/pubmed/459526

3) https://www.ncbi.nlm.nih.gov/pubmed/31119890

4) https://www.nejm.org/doi/full/10.1056/NEJMoa042934

5) https://www.ncbi.nlm.nih.gov/books/NBK548580/

6) https://www.ncbi.nlm.nih.gov/books/NBK470296/

7) https://www.accessdata.fda.gov/drugsatfda_docs/label/1996/008303s068lbl

8) https://www.ncbi.nlm.nih.gov/pubmed/23382484

9) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3195739/

17. A 62-year-old man presents with a 3-month history of dry cough and a burning sensation in his throat that is particularly worse when lying down after meals. He has a 20-pack-year history of smoking and drinks 4 beers/day. He has type II diabetes mellitus managed with insulin. Pinpoint discrimination is impaired up to his knees. If pharmacologic treatment is attempted for this patient's esophageal symptoms, which of the following may be most appropriate?

A) Cimetidine
B) Omeprazole
C) Metoclopramide
D) Ondansetron
E) Sucralfate

The answer is C.

This is a USMLE-favorite question!

This man presents with symptoms of new-onset gastroesophageal reflux disease (GERD), however he has a history of advanced diabetes mellitus, as evidenced by his peripheral neuropathy up to his knees.

This means **diabetic gastroparesis** is the most likely diagnosis, **not** GERD.

Metoclopramide, a D2-antagonist, is a prokinetic agent that is used first-line in the treatment of diabetic gastroparesis.[1]

H2-antagonists, such as cimetidine, and proton-pump inhibitors (PPIs), such as omeprazole, may be used in the treatment of GERD.[2]

PPIs are superior to H2-antagonists in the treatment of GERD.[2] If the vignette does give you a genuine GERD (not diabetic gastroparesis) presentation, **choose the PPI over the H2-blocker.**

Ondansetron is a highly potent and selective serotonin 5-HT_3 receptor antagonist. It is an anti-emetic classically used in patients with severe nausea and vomiting secondary to radio- or chemotherapy.[3]

Sucralfate is used to slow the progression of peptic ulcers by forming a protective coating over them.[4]

Bottom line: Metoclopramide is a prokinetic D2-antagonist used as the first-line pharmacologic therapy for symptomatic diabetic gastroparesis. The USMLE question will present as a guy with "GERD" who also happens to have advanced diabetes. Don't fall for the PPI trap. If however the vignette is genuinely a presentation of GERD, choose the PPI over the H2-blocker.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3027056/

2) https://www.ncbi.nlm.nih.gov/pubmed/9305486

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3077311/

4) https://www.mayoclinic.org/drugs-supplements/sucralfate-oral-route/description/drg-20066120

18. A 54-year-old man with a history of chronic renal disease secondary to granulomatosis with polyangiitis presents with a large, painful, ulcerated tophus located on the first metatarsophalangeal joint. He has a 36-pack-year history of smoking. Which of the following is the most appropriate initial pharmacologic therapy for this patient?

A) Indomethacin
B) Allopurinol
C) Febuxostat
D) Corticosteroids
E) Probenecid
F) Colchicine

The answer is D.

This is a classic USMLE "trick" question.

Indomethacin, colchicine, and corticosteroids are all acceptable and comparably effective first-line treatments for acute gout.[1, 2]

In the United States, **indomethacin,** an NSAID, is the standard choice for **acute** gout attacks.[1]

On the USMLE, most questions on acute gout will have indomethacin as the answer.

However this patient has a history of renal insufficiency, making NSAIDs and colchicine inferior selections compared to steroids.

Stages of renal failure[3]:

- **Stage 1** with normal or high GFR (GFR > 90 mL/min)
- **Stage 2** Mild CKD (GFR = 60-89 mL/min)
- **Stage 3A** Moderate CKD (GFR = 45-59 mL/min)
- **Stage 3B** Moderate CKD (GFR = 30-44 mL/min)
- **Stage 4** Severe CKD (GFR = 15-29 mL/min)
- **Stage 5** End Stage CKD (GFR <15 mL/min)

Regarding NSAIDs (e.g., indomethacin) for acute gout:[4]

- **CrCl 30 to 59 mL/min:** avoid or use with caution depending on the kidney disease
- **CrCl <30 mL/min:** relatively contraindicated

Regarding colchicine for acute gout:[4]

- **CrCl ≥30 mL/min:** dosage adjustment not required
- **CrCl <30 mL/min:** consider dosage reduction

Regarding steroids for acute gout:[4]

- **Dosage adjustment for CKD not required**

What the USMLE wants

- If the patient has no apparent contraindications to any medications and indomethacin, steroids, and colchicine are all listed, choose indomethacin.
- If indomethacin and steroids are not listed, colchicine will be the answer they want for acute attacks.
- If the patient has renal insufficiency, choose corticosteroids.

Allopurinol and febuxostat are xanthine oxidase inhibitors used in the treatment of **chronic gout,** not acute flares.[5]

Probenecid is a uricosuric (i.e., increases urinary excretion of uric acid) used in the treatment of **chronic gout,** not acute flares.[5]

Bottom line: Indomethacin, corticosteroids, and colchicine are all acceptable and comparably effective first-line treatments for acute gout. On the USMLE, indomethacin is usually the answer, however if the patient has renal insufficiency, choose corticosteroids. Colchicine will be the answer if indomethacin and corticosteroids are not listed.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3539261/

2) https://annals.org/aim/fullarticle/2578528/

3) https://www.davita.com/education/kidney-disease/stages

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5572666/

5) https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858

19. A 2-year-old girl with sickle cell disease is administered an agent that increases her fraction of fetal hemoglobin (HbF) and decreases her frequency of vaso-occlusive crises. This agent is best described as which of the following?

A) Prevents addition of a hydroxyl group to the deoxyribose ring of deoxynucleotide diphosphates
B) Inhibits conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP)
C) Inhibits conversion of ribonucleotides to acetylated nucleotides
D) Prevents removal of a hydroxyl group from the ribose ring of nucleotide diphosphates
E) Inhibits conversion of 5-phosphoribosyl-1-pyrophosphate (PRPP) to 5-phosphoribosyl-1-amine (PRA)

The answer is D.

Hydroxyurea is a **ribonucleotide reductase inhibitor** used in the treatment of sickle cell. It increases fetal hemoglobin (HbF) and decreases frequency of vaso-occlusive crises.[1]

Ribonucleotide reductase acts by removing a hydroxyl group from the ribose ring of nucleotide diphosphates (NTPs) in order to make deoxynucleotide diphosphates (dNTPs). Hydroxyurea inhibits this step.[2]

- NTPs have a 2′-hydroxyl (-OH) group = oxidized
- dNTPs don't have a 2′-hydroxyl group = reduced
- So NTPs → dNTPs = reduction reaction (catalyzed by ribonucleotide **reductase**)
- Hydroxyurea inhibits this step / enzyme (ribonucleotide reductase inhibitor)

"Inhibits conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP)" refers to 5-fluorouracil (5-FU), which inhibits thymidylate synthase.[3]

"Inhibits conversion of 5-phosphoribosyl-1-pyrophosphate (PRPP) to 5-phosphoribosyl-1-amine (PRA)" refers to 6-mercaptopurine (6-MP) or azathioprine. 6-MP inhibits PRPP-amidotransferase. Azathioprine is metabolized into 6-MP.[4]

Bottom line: Hydroxyurea is a ribonucleotide reductase inhibitor used in the treatment of sickle cell disease. It increases HbF and decreases vaso-occlusive crises.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4022916/

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009431/

3) http://theoncologist.alphamedpress.org/content/4/6/478.full

4) https://dm5migu4zj3pb.cloudfront.net/manuscripts/105000/

20. A 52-year-old woman is brought to the emergency department for mental status changes and respiratory distress. Her history is significant for severe mitral stenosis secondary to childhood rheumatic fever that was treated with a prosthetic valve placed two years ago. She is on warfarin. A 3/6 holosystolic murmur is auscultated at the 4th intercostal space, left mid-clavicular line. She is febrile with a temperature of 103.2F, HR 108 bpm, and RR 25/min. Three tubes of blood are drawn and sent for cultures. Which of the following is the most appropriate empiric antibiotic therapy?

A) Vancomycin
B) Vancomycin + Ceftriaxone
C) Ceftriaxone + Gentamicin
D) Gentamicin + Vancomycin
E) Ampicillin + Gentamicin
F) Gentamicin + Vancomycin + Rifampin

The answer is F.

This patient most likely has bacterial endocarditis.

On the USMLE, new onset murmur + fever = endocarditis until proven otherwise.

Empiric treatment means that which is given **before the culture results are known.** It is based on educated guessing. The word empiric comes from the Greek word *empeiria,* which in direct translation means experience.[1]

Empiric treatment for endocarditis[2,3]

- Vancomycin or ampicillin/sulbactam, PLUS an aminoglycoside (e.g., gentamicin)
- **Add rifampin in patients with prosthetic valves**

This means in most patients treatment is vancomycin + gentamicin, OR Ampicillin/sulbactam + gentamicin.

Because this patient has a prosthetic valve, rifampin must be added.

Bottom line: Empiric treatment for endocarditis is vancomycin or ampicillin/sulbactam, PLUS an aminoglycoside (e.g., gentamicin). For patients with prosthetic valves, add rifampin.

1) http://esgap.escmid.org/?page_id=389

2) https://www.aafp.org/afp/2012/0515/p981.html

3) https://www.ncbi.nlm.nih.gov/pubmed/19713420

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