Treatment for Fungal and Protozoal CNS Infections

See antifungal and antiprotozoal agents lectures for further details

Most common causes of fungal and protozoal meningitis

Naegleria fowleri (causes Primary Amebic Meningoencephalitis or PAM)

Balamuthis mandrillaris

Acanthamoeba species

Treatment: Combination therapy using amphotericin B, miltefosine, rifampicin, fluconazole, azithromycin

Why? Though amphotericin B is an effective anti-fungal (binds to ergosterol and forms a transmembrane channel that permeabilizes the fungal cell wall and plasma membrane), many protozoal sp. also synthesize ergosterol, making them responsive to amphotericin as well.

Amphotericin B (deoxycholate salt): Permeabilization is bad for the cell SE: note renal tox (decreased with IV saline), N/V, CV effects at high dose

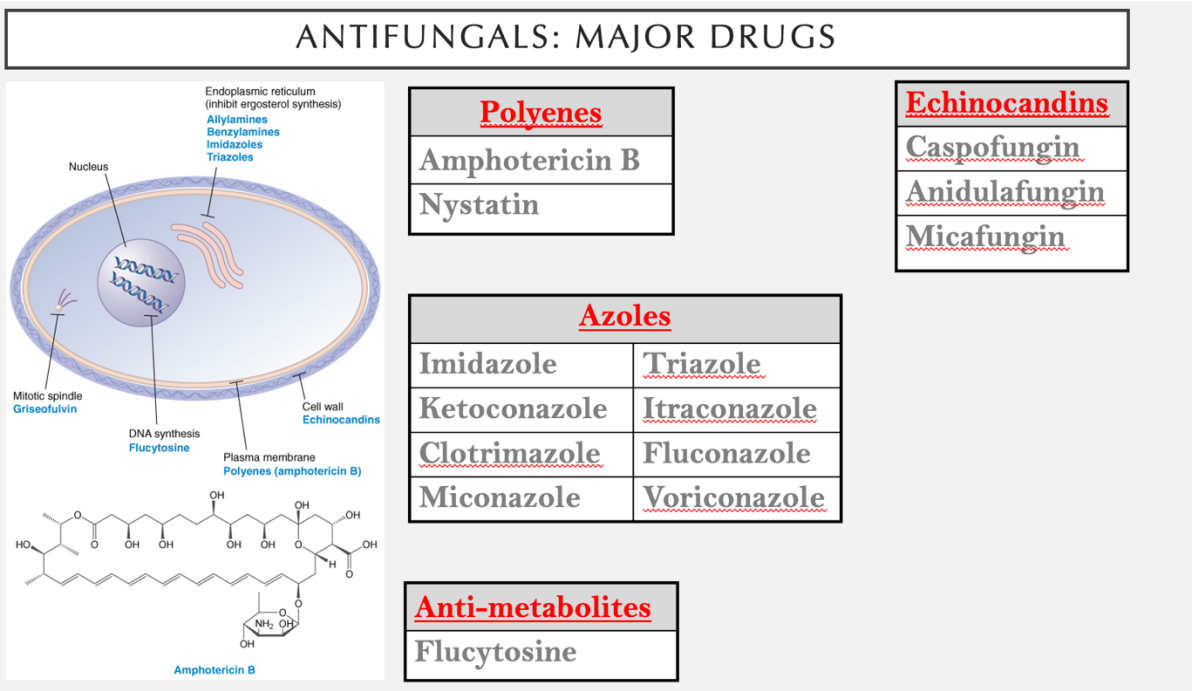
Miltefosine: anti-leishmanial drug that triggers mitochondrial-dependent apoptosis (this is one proposed mechanism; others may also exist).

Rifampicin: targets bacterial and protozoal RNA polymerase. SE: N/V

Fluconazole: targets ergosterol biosynthesis. SE: CYP interactions (3A4, 2C19, 2C9), hepatotoxicity

Azithromycin: macrolide protein synthesis inhibitor; targets 50 ribosome. SE: note macrolide ototoxicity.

Contraindications: miltefosine is teratogenic in humans; C/I in pregnancy, contraception required during treatment and 5 mo following.

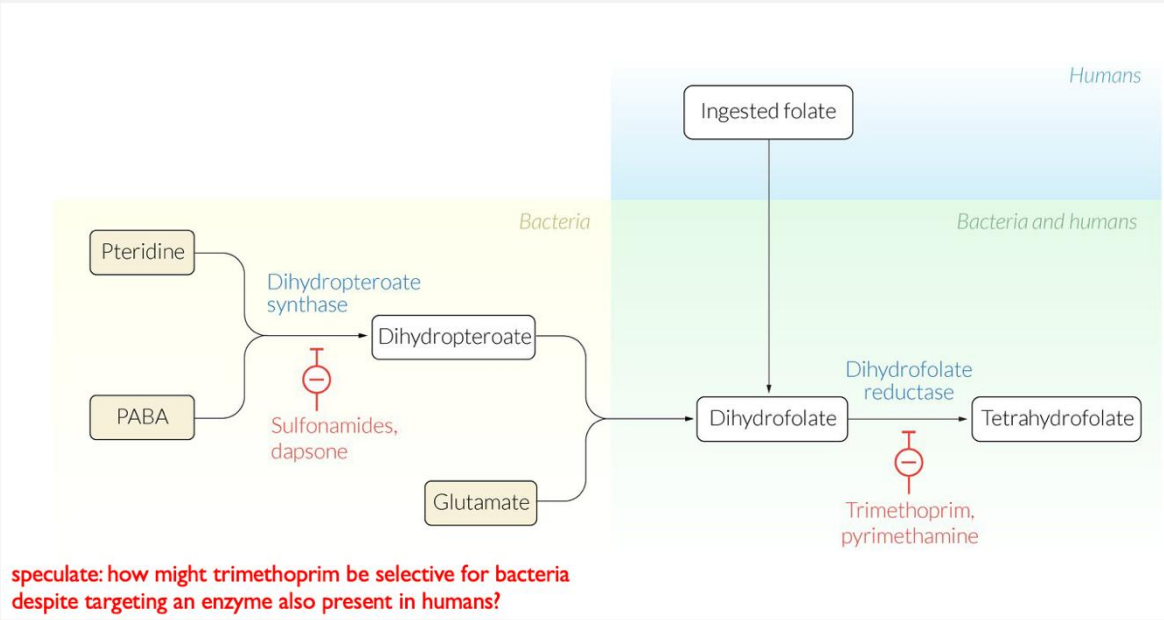


Toxoplasmosis gondii

Treatment: Pyrimethamine + sulfadizine plus folinic acid (as a supplement)

Why? DNA-targeting antibiotics include anti-folates and DNA gyrase inhibitors. (While antibiotics are mainly used to treat bacterial infections), these activities are also effective against protozoa.

Pyrimethamine inhibits protozoal DHFR, decreasing tetrahydrofolate production.
In contrast to trimethoprim which is an anti-folate that inhibits bacterial dihydrofolate reductase), **Sulfa** drugs are analogs of PABA, inhibit dihydropteroate synthase, decreasing dihydrofolate production. (note prevalence of PABA and sulfa allergies)
Combined use of both pyrimethamine and a sulfa drug is synergistic due to dual actions on the same folate pathway,
Major side effects of anti-folates are hematological toxicity (due to inhibition of DNA), and sulfa drug hypersensitivity (most severe form is Stevens-Johnson syndrome, SJS).



Cryptococcus and Coccidioides (consider in ddx of "aseptic" meningitis, esp in areas where these organisms are endemic). Most cryptococcal meningitis (meningoencephalitis) occurs in immunocompromised pt.
Treatment: Cryptococcus: amphotericin B + flucytosine (alt adjunct: fluconazole). Coccidioides: fluconazole or itraconazole (fluconazole preferred)
Why? Flucytosine enhances fungicidal efficacy of amphotericin B, allowing lower doses and lower mortality. Itraconazole has more drug-drug interactions than fluconazole
Major side effects: see above