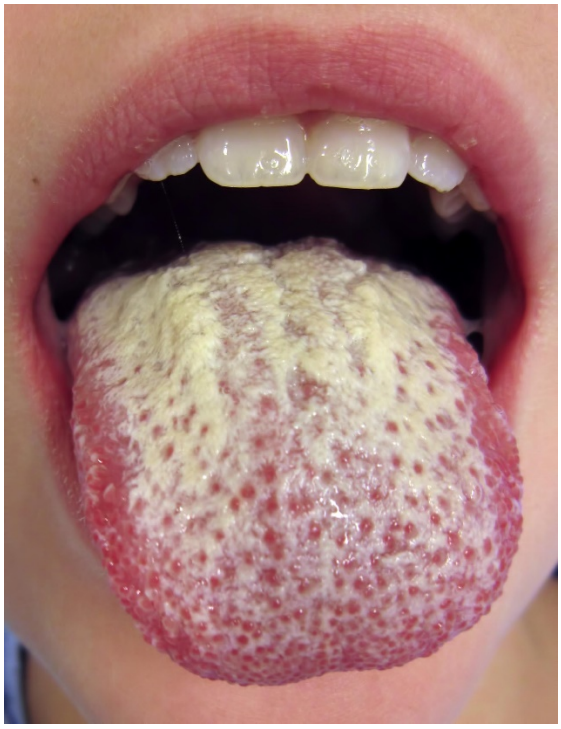
STANDARD DEVIATIONS: O(oh-oh) Candida!

Greetings,

Fungi are everywhere. Every lung-full of breath contains fungal matter. Typically, our immune system is adequate to keep infection from occurring, but we are constantly at risk.

There are over 40 different fungus species known to cause disease in humans. More than 20 types of *Candida* can cause infection with *Candida albicans* being the most common.

In the United States there are approximately *1.4 million doctor office visits every year* for **candidiasis**. About three-quarters of women have at least one yeast infection at some time during their lives. Oral candidiasis is the most common fungal infection of the mouth, and it also represents the most common opportunistic oral infection in humans. About 20% of those receiving chemotherapy for cancer and 20% of those with AIDS also develop the disease. Patients recovering from surgeries and admits to intensive care have an out-sized risk of infection. Infections of the mouth occur in about 6% of babies less than a month old.

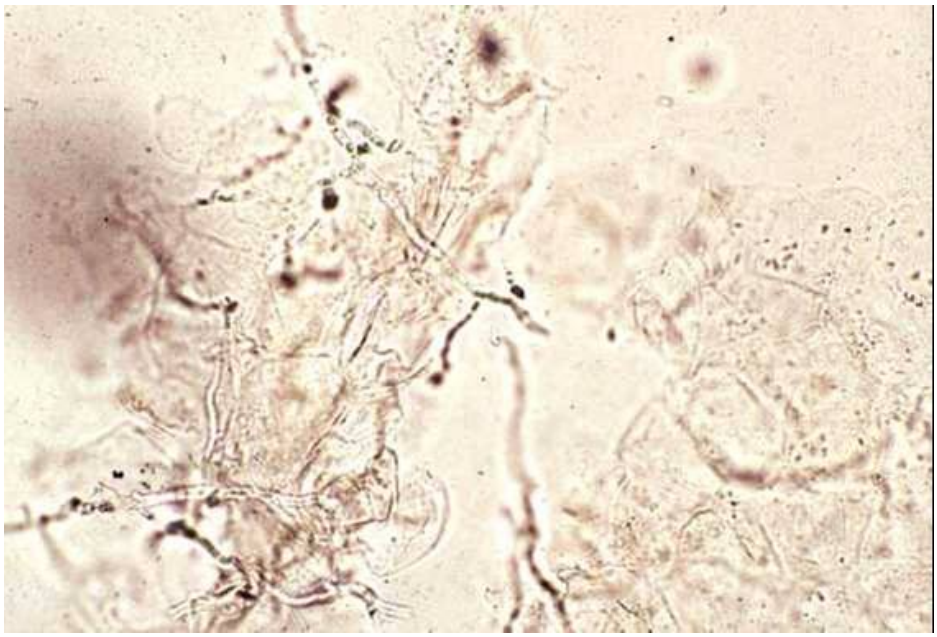


{Say ahh. Oral candidiasis.}

Diagnosis of a yeast infection is done either via microscopic examination or culturing. If you've spent time on the bench, you are probably familiar with the KOH (Potassium Hydroxide) test.

{KOH dissolves our cells but not yeast.}

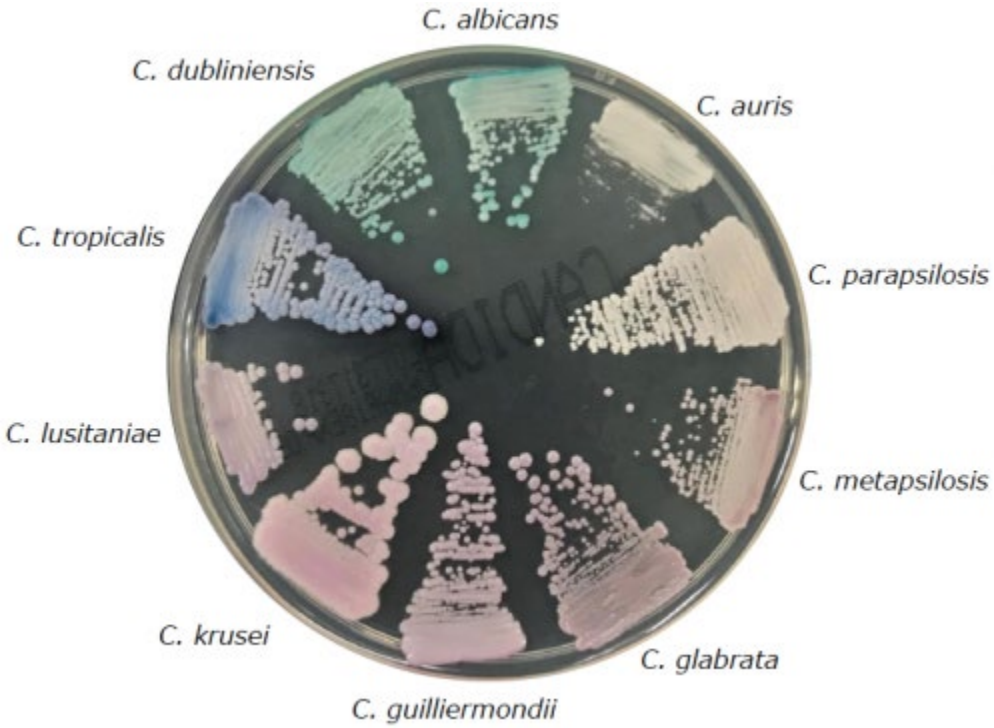
A drop added to a specimen allows visualization of pseudo-hyphae and budding yeast cells typical of many *Candida* species.



{Slide view of KOH prep.}

Culturing enables us to differentiate and speciate the organism. Any surface can be swabbed and streaked to growth media and incubated (37°C) where the morphology and/or color can be used for identification.

The Chromagar (Hardy) media made differentiating species quick and simple:



{Proprietary enzymatic chromogens release different colored degradation products. Chloramphenicol inhibits bacterial contamination.}

And now, MALDI-TOF allows us to rapidly and accurately describe our culture findings.

{The magic of MALDI, in a little box.}

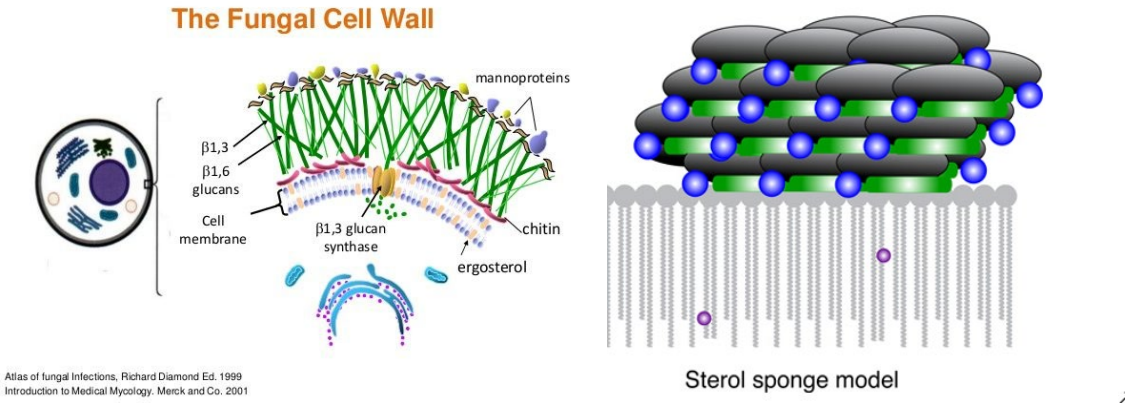
Until recently, antifungal drugs have been able to thwart thrush and the fungal conditions that afflicted us. But life finds a way, and fungi are fighters; resistance is emerging and the landscape of fungal therapy, and disease, is changing.

Drugs used as antifungals target nucleic acids and cell function and synthesis pathways. Some drugs are just killers; they affect all cells. Drugs that inhibit DNA/RN synthesis (flucytosine), microtubule function (griseofulvin), or mitochondria (naphthoquinone) are cidal for everyone and are the ones we use topically (because of the risk to our own cells).

The true antifungals are more specific. Fungal cell wall structure and function are primary targets; they make the cells too porous or unstable. They act on the sterol in the membrane or enzymatic pathways, and cell wall structure. We generally talk about these antifungals in three categories:

- **Polyenes**
- **Azoles**
- **Echinocandins**.

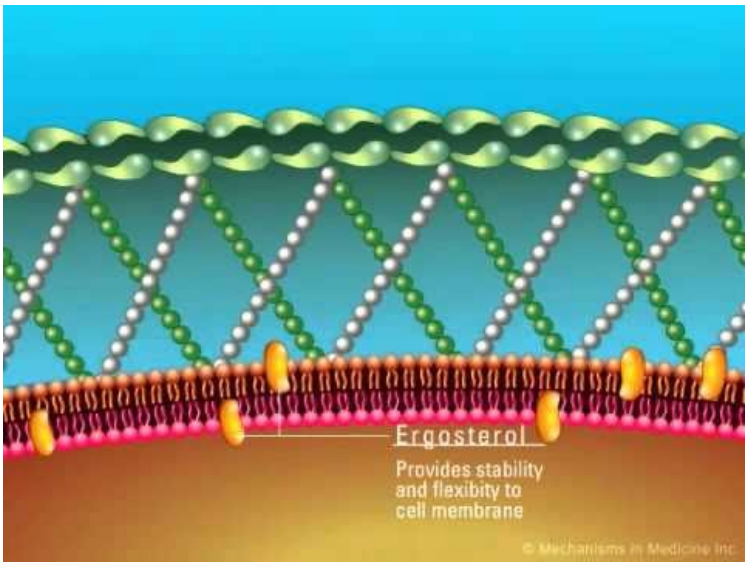
Polyenes (Amphotericin B, nystatin, and natamycin are examples) bind and compromise ergosterol in the membrane, destroying ion-channel capability and causing leakage and cell death. Fungi use ergosterol instead of cholesterol in the lipid bilayer of the membrane. These drugs love ergosterol and pull it from the membrane. The consequence of this binding is a disruption of the osmotic integrity of the membrane, with leakage of intracellular potassium and magnesium (also the disruption of oxidative enzymes).

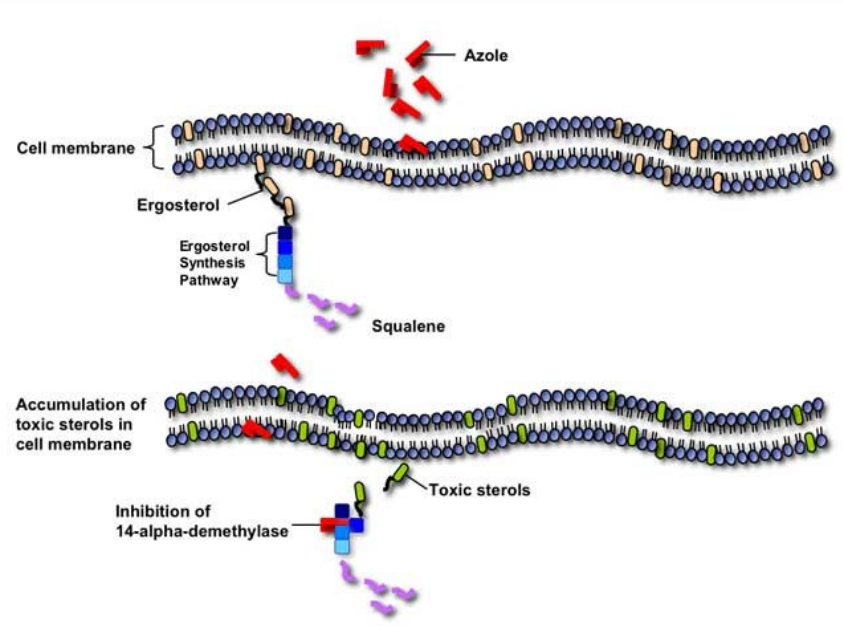


{Polyenes are huge molecules that bind and purge the membrane of ergosterol, soaking it up like a sponge.}

The main problems associated with the use of polyenes are due to its poor aqueous solubility and toxicity rather than antifungal resistance. Resistance is rare and poorly understood. Mutations in ergosterol genes are changing the molecule and these mutants tend to be selected for, leading to resistant strains surviving.

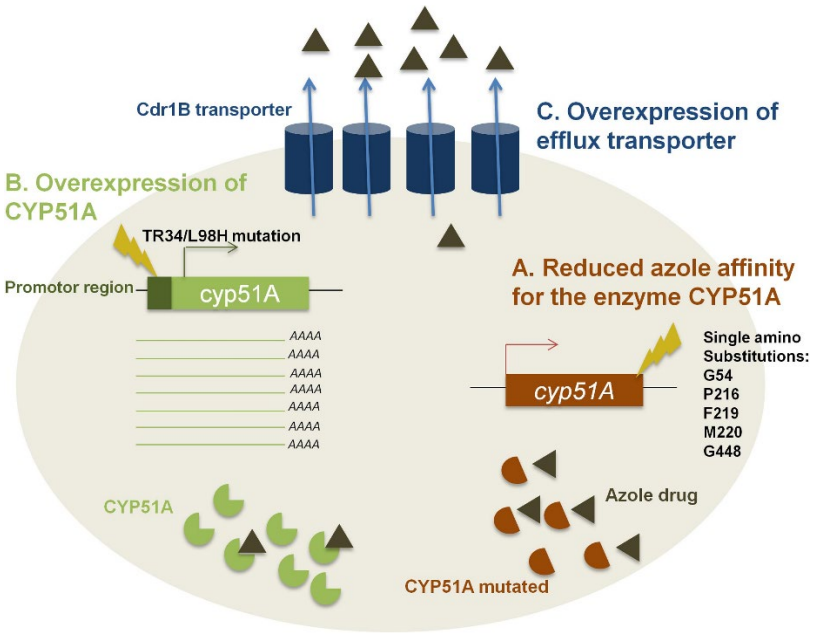
Azoles (imidazoles and triazoles) inhibit cytochrome P450 enzymes. They disrupt the ergosterol production pathway so that less of the functioning sterol makes it to the membrane and the products that do make it are poor substitutes.





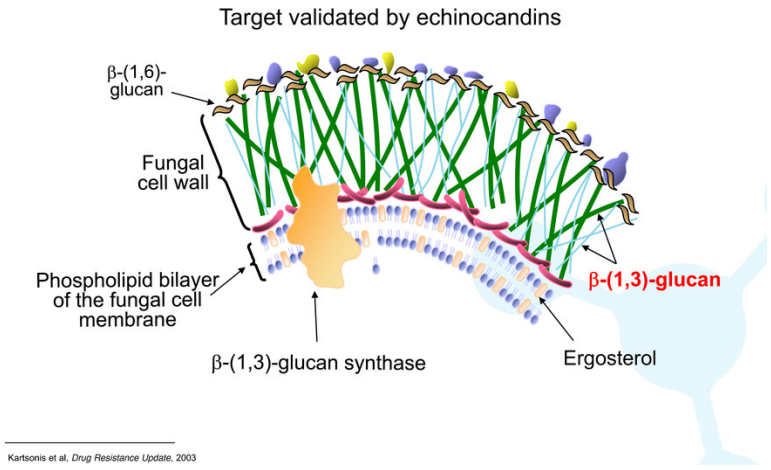
{Azoles inhibit proper membrane sterol formation.}

Resistance to azoles occurs in a couple ways. Either the enzyme path is strengthened/altered or the azoles are pumped out (efflux). Overexpression of the target enzyme can offset drug effect, the enzyme changes in its affinity to the azole, or the efflux pumps are overexpressed, transporting the azole out of the cell. More efflux means more resistance.



{Azole resistance mechanisms. Bugs with higher efflux pump numbers can flush more drug.}

Echinocandins (caspofungin, micafungin, anidulafungin, etc.) act on a different fungal character, the glucans of the cell wall. Echinocandins inhibit beta-1,3-D-glucan synthase enzyme complex to disturb fungal cell glucan synthesis. Beta-glucan destruction prevents resistance against osmotic forces, which leads to cell lysis.



{The cell wall integrity is compromised.}

Echinocandin resistance is rare among *Candida* spp. Changes in the synthase complex, overexpression of efflux pumps (again) and species that have increased chitin (the tough polysaccharide exoskeleton) allow resistance.

Antifungals are effective against a wide swath of fungi, **and humans**. Toxicity is a serious concern and limits the amount of drug we can safely prescribe and the ways they can be used. Because we have cell membranes and enzymes and polysaccharides, these drugs work on our cells too. But, right now, these are the tools we have; and that's a problem.

The problem with our fight against candidiasis is common to the world's resistance emergency; another bug, bad and bold, is moving in and out-competing the fungus we can treat.

Candida auris is a species that until recently has not been on our radar but is threatening to change the landscape of fungal disease. Next week, the newsletter will look at the problem that is mushrooming in hospitals around the world and moving relentlessly toward a ward near you.

Have a great week and be safe,

Bryan

p.s. Here is a quick graphic look at the three major antifungal mechanisms together: