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TITLE: Antifungal Agents

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Slide 1:

Hello, my name is **Xing Tan**. I am an **Infectious Diseases Pharmacotherapy Fellow at the University of Illinois at Chicago**. Welcome to this Pearl of Laboratory Medicine on "**Antifungal Agents**."

Slide 2: Invasive fungal infections including candidiasis and invasive mold infections are responsible for significant morbidity, mortality, and excess healthcare costs. Significant advances in medical therapies has increased the number of patients living with immunocompromising conditions and the duration for which they live, which in turn has increased the prevalence of IFIs. In addition to infecting vulnerable patient populations, IFIs are challenging to manage given the difficulty in recognizing and diagnosing them and subsequently administering timely antifungal therapy.

Slide 3: The most common IFI is invasive candidiasis which most often manifests as a bloodstream infection (candidemia). These infections are most commonly caused by C. albicans although there has been a shift in the epidemiology towards non-albicans Candida species which are often more resistant to azole antifungals, such as C. glabrata and C. auris more recently. Aspergillosis and mucormycosis are the most common invasive mold infections and are caused by species of Aspergillus and Rhizopus most commonly. As discussed, these pathogens most commonly infect immunocompromised patients and those with significant comorbidities and healthcare

exposure. Unfortunately, despite optimal treatment these infections are still associated with significant mortality.

Slide 4: Managing invasive fungal infections is challenging for multiple reasons. The signs and symptoms are nonspecific and fungal colonization versus infection is difficult to differentiate with current diagnostic methodologies. Traditional diagnostic tools, such as culturing and tissue biopsies remain the gold standards but are either insensitive, not timely or feasible, especially in an immunocompromised host. Additional diagnostic methods, such as antigen assays detecting galactomannan and 1-3-beta-d-glucan, are oftentimes used in clinical practice but can be influenced by other factors that may contribute to false positive results or make their clinical interpretation a challenge. Therefore, their role in the diagnosis of IFIs is still controversial and unclear. On the flip side, there are several emerging diagnostic methods, particularly molecular-based assays that are recently developed or are in the pipeline, however, their usage is not fully elucidated since they are new. Finally, advances in whole genome sequencing techniques have improved our understanding of mechanisms of resistance and contributed to the development of novel antifungal agents.

Slide 5: For the remainder of the presentation, I will focus on the pharmacotherapy aspect of IFIs. There are several classes of antifungal agents used in clinical practice, spanning from some of the earliest agents that have been in use for decades such as amphotericin B and flucytosine to the newest triazole antifungal agent isavuconazole. Of note, there are currently five triazole antifungals approved in the U.S., all of them are active against molds with the exception of fluconazole.

Slide 6: Here is the spectrum of activity for azole antifungals. This chart is based solely on the in vitro activity of these agents regardless of their clinical utility for infections caused by these pathogens. For example, although isavuconazole demonstrates in vitro activity against the endemic fungi such as histoplasmosis and blastomycosis, clinical data for the treatment of these infections are extremely limited. Similarly, although

isavuconazole has potent in vitro activity against Candida it did not meet the non-inferiority margin against caspofungin in a phase 3 trial of invasive candidiasis. Conversely, it is one of only two azoles with activity against mucormycosis along with posaconazole.

Slide 7: Here is a similar table for amphotericin B and the echinocandins from which you can see that amphotericin is our most broad spectrum antifungal agent by far with activity against virtually all the yeasts, molds, and dimorphic fungi while the echinocandins are solely active against Candida. While they do have some in vitro activity against Aspergillus, their in vivo activity is not reliable enough to be used clinically for the treatment of aspergillosis. Several small uncontrolled studies have evaluated caspofungin and micafungin for primary therapy for invasive *Aspergillosis* and the results were less than favorable. Therefore, IDSA does not recommend echinocandins as monotherapy for the primary treatment of aspergillosis.

Slide 8: Despite having multiple agents within the same class, the PK properties of some antifungal agents are quite different from one another which impacts which clinical scenarios they are used in and their ability to achieve optimal PK/PD endpoints. For example, amphotericin B deoxycholate concentrates in the urine and therefore can be used for fungal UTIs while the liposomal formulations do not and therefore are not adequate for treatment. Similarly, fluconazole has the highest renal elimination and lowest protein binding of the azoles, necessitating dosage adjustments for patients with renal dysfunction.

Slide 9: Converse to the azole agents, the echinocandins are comparable in their PK properties and have relatively similar dosing schemes and systemic exposure across various patient populations.

Slide 10: Given these differences in PK and variability across patients, it is recommended to perform therapeutic drug monitoring for the azole antifungals in certain clinical scenarios such as to confirm absorption or when clinical failure or toxicities are suspected. Given their linear PK and limited toxicity profile, TDM for fluconazole and isavuconazole is not recommended, although a recent study showed potential value for isavuconazole monitoring during prolonged administration. For the other azoles listed here TDM should be performed after at least a week of therapy to allow these drugs to reach steady state given their long half-lives.

Slide 11: The next handful of slides will go into greater detail about each of these drug classes, beginning with Amphotericin B. Amphotericin acts as a detergent by binding to ergosterol in the fungal cell membrane and causing the intracellular contents of the fungal cell to leak out causing cell death. As discussed, it is the most broad spectrum and therefore has the most clinical indications. The dosing is based on the patient's body weight and the toxicities, mainly nephrotoxicity, infusion related reactions, and electrolyte abnormalities, are primarily associated with the deoxycholate formulation.

Slide 12: The main take-home points for the clinical use of amphotericin are shown here. Importantly, although the liposomal formulations of amphotericin B can cause nephrotoxicity, the drug is not eliminated by the kidneys. That means that the dose of LAMB should not be decreased if the patient experiences kidney injury from the drug, which is a common mistake seen in clinical practice. On a similar note, the drug only concentrates significantly in organs in the reticuloendothelial system but sites such as the brain or CSF. Therefore, the dose of LAMB should not be increased over 5 mg/kg in an attempt to achieve higher concentrations at extravascular sites, which is another common mistake.

Slide 13: All of the azole antifungals work via inhibiting ergosterol synthesis, and fluconazole is primarily used clinically for invasive candidiasis and cryptococcus given that it does not have activity against molds. The most commonly used doses are 400-

800 mg/day although it is very well tolerated such that the doses can be pushed multiple fold higher than this if needed for the treatment of a less susceptible organism or based on patient-specific factors (i.e. weight-based dosing up to 12 mg/kg daily for susceptible *C. glabrata* infections or deep-seated infections).

Slide 14: Itraconazole is used almost exclusively for the treatment of Histoplasmosis and Blastomycosis. Its oral bioavailability is high dependent on the formulation, with the solution form being 30% more bioavailable than capsules. Capsules require an acidic environment for optimized absorption. Itraconazole displays non-linear PK and has significantly more toxicities than fluconazole including a black box warning against use in patients with heart failure since it is a negative inotrope and can prolong the QTc interval and lead to cardiac arrythmias.

Slide 15: Voriconazole is the most widely used out of the mold-active triazoles given its place in therapy as the drug of choice for the treatment of invasive aspergillosis. Despite this pervasive use, it is challenging to tolerate given the many toxicities including hallucinations, photopsia (seeing spots), and liver toxicity, along with difficulties achieving therapeutic serum concentrations due to its non-linear PK.

Slide 16: Posaconazole is used primarily for prophylaxis against IFIs in cancer patients with AML, MDS, or GVHD and for the treatment of mucormycosis. Prior to 2014, only the suspension formulation was available which was problematic as the absorption was highly dependent on being taken with a high fat meal which most cancer patients cannot do. Since then the delayed release tablet formulation has been developed which is not affected by food or gastric acid suppressing medications such as PPIs.

Slide 17: Isavuconazole is the newest triazole agent with indications for the treatment of aspergillosis and mucormycosis, although it is also commonly used off-label for prophylaxis as well. Since its approval, isavuconazole has quickly become arguably the most attractive azole agent given its linear PK profile, limited toxicities, and few drug-

drug interactions compared to the other drugs in its class. Specifically, isavuconazole is a moderate 3A4 inhibitor and has its advantages over strong 3A4 inhibitors posaconazole and voriconazole, as their use can be contraindicated with certain therapies. However, isavuconazole was not able to prove noninferiority compared to echinocandins against invasive candidiasis and its use in prophylaxis among patients with high risk hematologic malignancies may experience more breakthrough infections.

Slide 18: To summarize the main points of the azole class, itraconazole absorption is highly dependent on the formulation with the suspension needing to be taken with food and the capsules on an empty stomach while neither can be taken with a PPI. In addition to the side effects of voriconazole, its non-linear PK and significant variability within and between patients makes it challenging to optimize in clinical practice. Additionally, it is a substrate and inhibitor of CYP3A4 and CYP2C19 and therefore has many drug interactions and is affected by genetic polymorphisms in these enzymes. Finally, posaconazole is the drug of choice for prophylaxis while isavuconazole is the most well tolerated mold active triazole agent and can be used in select circumstances when standard therapy is contraindicated.

Slide 19: Echinocandins consists of three agents, all of which work via interfering with 1,3-beta-D-glucan synthase and inhibiting fungal cell membrane formation and are only available as injection form only. Echinocandins are only active against yeasts and therefore are mostly utilized in candidemia and in both invasive and esophageal candidiasis. The echinocandins are particularly attractive clinically as they are extremely well tolerated and have virtually no appreciable toxicities.

Slide 20: As mentioned although they demonstrate some in vitro activity against aspergillus spp., the echinocandins should not be used for the treatment of aspergillosis in the clinic. Additionally, they have demonstrated improved outcomes over the azoles in the treatment of candidiasis and candidemia, most recently with caspofungin over isavuconazole. This improved efficacy along with their lack of toxicity and the increases

in azole resistance among Candida species had made them the mainstay of therapy for invasive candidiasis. The IDSA recommends echinocandins as initial therapy for candidiasis/candidemia.

Slide 21: The last antifungal in this presentation is flucytosine. It is used only in combination with amphotericin B as induction therapy in cryptococcal meningitis. It should never be used as monotherapy due to emergence of resistance. It is excreted renally, so dosage adjustments need to be made in patients with a GFR less than or equal to 40 mL/min. Of all the antifungals in this presentation, flucytosine is the only agent where routine TDM is done. TDM is done to minimize hematologic toxicities. A peak concentration greater than 100 mcg/mL is associated with increased hematologic toxicities, which should be obtained 2 hours post dose administration. There is also evidence that states that serum concentrations less than <25 mcg/mL have been associated with the emergence of resistance but in clinical practice, routine TDM is performed for mitigating toxicities.

Slide 22:

- IFIs contribute to morbidity, mortality, and excess healthcare costs
- Prevalence of infections due to non-albicans *Candida* continue to increase, and are more azole resistant
- Amphotericin B is most broad-spectrum antifungal
    - Liposomal formulation less toxic
- Azole antifungals each have unique pharmacologic properties, clinical indications, and adverse effects
- Isavuconazole is the newest mold-active triazole with less toxicities and drug-drug interactions
- Echinocandins are safe and may be more efficacious than azoles for invasive candidiasis

Slide 23-24: References

Slide 25: Disclosures/Potential Conflicts of Interest

Slide 26: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Antifungal Agents**."