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## Update on Antifungal Susceptibility Testing

### Background

- Advances in medicine over the past two decades, particularly in the fields of bone marrow and solid organ transplantation, cancer chemotherapy, and intensive care, coupled with the widespread use of antibacterial agents in empiric therapeutic regimens has contributed to an increased incidence of invasive and potentially life-threatening opportunistic fungal infections caused by various yeasts (especially *Candida* species) and filamentous fungi.
- *Candida* species are the fourth most common cause of hospital-acquired bloodstream infection and account for a significant proportion of nosocomial infection-related increased health care costs, length of hospital stay, morbidity, and mortality.
- While amphotericin B has remained the first-line antifungal agent for empiric therapy of most severe human mycoses, several newer classes of antifungals have recently been approved for specific clinical indications and appear to offer some advantages over amphotericin B, particularly with respect to side effect profile and availability of oral formulations.
- Concurrently, there has been an increase in the frequency of resistance of *Candida* spp. and other fungi to some of these newer agents and, on a lesser scale, to amphotericin B. Hence, antifungal susceptibility testing may be indicated in specific clinical situations.

### Currently Available Systemic Antifungal Agents

- **Amphotericin B** (formulations include amphotericin B deoxycholate, amphotericin B colloidal dispersion, amphotericin B lipid complex, and liposomal amphotericin B) is a naturally occurring broad-spectrum polyene antifungal drug that specifically binds to ergosterol in fungal cell membranes resulting in increased membrane permeability and eventual cell death. This fungicidal agent has potent activity against most clinically important fungi except for *Candida lusitanae*, *Aspergillus terreus*, *Pseudallescheria boydii*, *Scedosporium prolificans*, *Trichosporon asahii*, *Fusarium* spp., and *Paecilomyces lilacinus*. Nephrotoxicity and infusion-related toxicities commonly occur, particularly with the deoxycholate formulation. Drug resistance, while not common, is usually related to content or structural changes in fungal ergosterol.
- **Triazoles (Fluconazole, Itraconazole, Voriconazole)** are synthetic antifungal compounds with mainly fungistatic properties. They act by inhibiting enzymatic biosynthesis of ergosterol. Fluconazole is active against most *Candida* spp. (except *C. krusei* and 10-50% of *C. glabrata*). It is also active against systemic dimorphic fungi (*Histoplasma*, *Blastomyces*, *Coccidioides*) but is inactive against filamentous fungi, while the spectrum of activity of itraconazole and voriconazole also includes *C. krusei*, *Aspergillus* spp., dematiaceous (pigmented) fungi, and *Fusarium* spp. (voriconazole only). Resistance mechanisms are not completely understood, but usually involve drug efflux or ergosterol biosynthetic enzyme modification/overexpression.

## Currently Available Systemic Antifungal Agents(cont'd)

- **5-Fluorocytosine (5-FC)** is a synthetic, fluorinated analogue of cytosine that, after conversion to 5-fluorouracil by fungus-specific enzymes, causes inhibition of DNA synthesis. It has activity against various *Candida* spp., *Cryptococcus neoformans*, and several pigmented (dematiaceous) filamentous fungi. This agent is usually administered in combination with amphotericin B or triazoles since resistance may emerge during therapy if used as a single agent.
- **Caspofungin** is a member of the echinocandin class of antifungal agents recently approved for clinical use in the US and Canada. It inhibits synthesis of 1,3-beta-D-glucan, a polysaccharide in the cell wall of many pathogenic fungi. This agent has fungicidal activity against *Candida* spp. and fungistatic activity against *Aspergillus* spp. Casopfungin is not active against *Cryptococcus* spp. Although drug resistance has been described it is currently uncommon.

## Antifungal Susceptibility Testing Strategy

- Currently, our laboratory routinely performs susceptibility testing on all blood and cerebrospinal fluid isolates of *Candida* spp. and *Cryptococcus neoformans*. Isolates from other sterile body sites are tested upon request. These isolates are currently being tested against the following antifungal agents: fluconazole, itraconazole, 5-FC, and amphotericin B. Test turnaround time is approximately 1 to 2 days.
- By autumn of 2004, routine testing will expand to include blood and most other sterile body site isolates of these yeasts, with the addition of voriconazole and caspofungin to the antifungal test menu.
- Requests to test isolates from other sources or to other antifungal agents require approval by the CLS Microbiologist on call at 770-3757.
- Given the complexity of antifungal susceptibility testing of filamentous fungi, this service is not yet available in Calgary, but is planned for implementation in the near future.

## Interpretation of Antifungal Susceptibility Test Results

- Antifungal susceptibility test results should be interpreted with caution. Only a few of the antifungal agents being tested in our laboratory have official interpretive criteria (fluconazole, itraconazole, and 5-FC). The interpretations [S (sensitive), I (intermediate), or R (resistant)] are based on official interpretive guidelines (if available) or studies published in the medical literature.
- Based on this literature, there appears to be a relationship between in-vitro resistance and clinical failure, but not necessarily between in-vitro susceptibility and clinical success. Clinical outcome of serious yeast infections are dictated by other factors such as the relative pathogenicity of the infecting fungus, the pharmacology of the antifungal agent chosen for therapy, and various host-specific factors. Hence, the complete clinical picture must always be factored in before deciding on the appropriate agent for therapy.

**IF YOU HAVE ANY QUESTIONS OR COMMENTS ABOUT HOW THE LABORATORY WORKS,  
PLEASE CALL US AT 770-3396 (Brenda Kirkham, Manager, Microbiology) or  
770-3281 (Dr. Church, Division Head, Microbiology)**

The Microbiology Newsletter is also available on the Internet and may be accessed at:

<http://www.crha-health.ab.ca/clin/cme/microbio.htm>

or

<http://www.calgarylabservices.com/LabTests/Microbiology/MicrobiologyNewsletters.htm>