New Antifungals Just in Time to Counter a Surge

A garden variety of T. rubrum *is showing resistance. Autoimmunity and mobility probably play a role.*

BY ERIK L. GOLDMAN
Contributing Writer

SAN DIEGO — The incidence of cutaneous fungal infections is on the rise in the United States, and the old standby antifungal drugs aren't working as well as they used to, Dr. Ted Rosen said at the American Academy of Dermatology's Academy 2006 conference.

Fortunately, new antifungals are emerging that could stem the mycologic mayhem, at least for a while.

The rise in fungal infections can be partly attributed to an increase in the number of immunosuppressed people living ever-longer lives. HIV-positive people on highly active antiretroviral therapy (HAART), survivors of cancer chemotherapy, and organ transplant recipients on immunosuppressive drugs are all highly susceptible to systemic mycoses, said Dr. Rosen of the department of dermatology at Baylor College of Medicine, Houston.

Another key factor is the unprecedented mobility of the population. More people travel more often and farther than at any other time in history. Immigrants come to the United States from regions that are endemic for fungi seldom seen here in the past.

Tertiary care centers like Baylor are reporting increases in fungi such as *Cryptococcus, Histoplasma capsulatum, Sporothrix, Fusarium, Rhizopus,* and *Fonsecaea,* which often go unrecognized or misdiagnosed for a long time. Given the high numbers of military and oil-industry personnel in Texas, Baylor clinicians are seeing a rise in strange fungal infections in troops and oil workers returning from Iraq, the Persian Gulf, and South America.

Moreover, mainstay drugs like fluconazole, itraconazole, ketoconazole, terbinafine, and griseofulvin are more widely used than ever, applying plenty of selective pressure on the fungi to develop resistance.

Which is just what is happening.

Dr. Rosen cited a recent report of terbinafine-resistant *Trichophyton rubrum* in a patient with onychomycosis who had never before been treated with an antifungal. "We're seeing innate resistance in a garden-variety form of *T. rubrum*. This old 'friend' is suddenly nonresponsive to a very powerful antifungal drug. This is problematic," he said.

Fortunately, he noted, a passel of new antifungals is making its way into clinical practice, including a whole new class of cell wall–smashing echinocandins.

All of the azoles, including new ones like voriconazole (Vfend) and posaconazole (Noxafil)—as well as ravuconazole, which is not yet approved—attack fungal cell membranes.

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Voriconazole has a broad spectrum and is highly effective against all species of *Candida*. It also works against *Aspergillus* and *Fusarium,* which generally won't yield to fluconazole. In vitro, voriconazole bests griseofulvin and ketoconazole, and it equals terbinafine in killing dermatophytes. It is also extremely bioavailable in oral dosing forms, Dr. Rosen said.

This new drug does have its downside, mainly its strong potential for adverse effects. It is metabolized via two cytochrome P450 enzymes, so it is capable of interacting with other drugs, at least in theory. It induces liver enzyme elevations, which are reversible, and it can also trigger morbilliform eruptions.

The most common adverse effect of voriconazole, though, is visual disturbances. Dr. Rosen said that a number of patients experience photophobia or a very specific visual disturbance characterized by bluish purple halos around objects.

Purple haze aside, Dr. Rosen said he's used this drug a lot, and in his experience, it is reasonably problem free. "I've used it off-label to treat patients who've failed everything else."

Posaconazole was approved in September under the brand name Noxafil for the treatment of aspergillosis. Metabolism of posaconazole involves only one CYP 450 enzyme, so this drug is less likely to cause interactions. Side effects are "pretty reasonable," said Dr. Rosen, the most common being headache and nausea.

"What really makes this drug stand out, aside from its ability to deal with weird fungi, is that it really works for zygomycetes—those deep fungi that really penetrate the nasopharynx in diabetes patients and transplant recipients. It's also great for everything refractory, and it does this orally," Dr. Rosen said.

Ravuconazole initially looked quite promising, with excellent in vitro efficacy against dermatophytes, but further development seems to have stalled for reasons that are not clear, he said.

Albaconazole, the newest triazole, is still in a very early developmental stage, but "it is better than itraconazole, fluconazole, or voriconazole for almost all of the common dermatophytes and saprophytes, and at least as good as or better than all the existing triazoles," Dr. Rosen said.

The good news for physicians is that albaconazole will be initially formulated as a nail lacquer along with oral and intravenous forms.

The echinocandins bring a new therapeutic mechanism into the antifungal picture: They break down the fungal cell walls by attacking the glucan building blocks and inhibiting the enzyme complexes involved in synthesizing glucans.

According to Dr. Rosen, the candins are strong medicine for "seriously sick patients with really bad bugs." Basically, the candins make it impossible for the fungi to build their cell walls, and the current trend among fungal infection specialists is to combine an echinocandin with one of the new triazoles.

He noted that he has worked with caspofungin (Cancidas) quite a bit and has found that it greatly extends *Candida* coverage. In HIV-positive patients, it can clear refractory esophageal candidiasis very quickly.

Micafungin (Mycamine) is the other hot candin these days. It is excellent for *Candida* and *Aspergillus,* though it does not work as well against Zygomycetes or *Fusarium*.

The main drawback to the candins as a class is that they are available only in intravenous forms. "All these drugs are cyclic hexapeptides, and all are destroyed by acids. Therefore, oral formulations are not possible," Dr. Rosen said.

There are a few other antifungals in the offing. PLD-118, also known as icofungipen, is neither an azole nor a candin. It is a tiny molecule that binds to fungal isoleucyl transfer RNA, thus affecting a wide range of *Candida* species. PLD-118 is being developed as topical as well as systemic therapy.

Milbemycin, derived from *Streptomyces,* trips up the fungal gene that enables resistant fungi to "spit out" other antifungals, he said. When it eventually comes to market, it will probably find its place as an adjunct for many of the more conventional antifungals, potentiating their effects against resistant pathogens.

Finally, there's the yet-to-be properly named P-113, the world's first "swish and spit" antifungal. This drug, which is being developed as a therapeutic mouthwash, is a 12–amino acid fragment of histatin 5, a compound produced by the body that has fungistatic effects, especially against *Candida*. Histatin 5 is "basically what prevents most of us from getting thrush. So this drug is essentially a duplication of the natural mechanism for controlling yeasts," Dr. Rosen said. ■

Community-Acquired Pneumonia Advice May Hamper Care

BY DIANA MAHONEY
New England Bureau

TORONTO — Adherence to guidelines that recommend early use of antibiotics may lead to inaccurate diagnosis of community-acquired pneumonia and inappropriate use of antibiotics, according to a study presented at the annual meeting of the Infectious Diseases Society of America.

The IDSA guidelines for community-acquired pneumonia (CAP), published in November 2003, recommend the initiation of antibiotics within 4 hours of hospitalization—an indicator that has been linked to incentive compensation of third-party payers to hospitals, said Dr. Manreet K. Kanwar of St. John Hospital and Medical Center in Detroit.

Given the potential for providing less than optimal care by promoting compliance with the current CAP quality indicator, a more feasible target should be established, Dr. Kanwar suggested. "It's possible that prolonging the antibiotic window to 6 hours may be enough time to better evaluate a patient."

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To determine the effect of this recommendation on the diagnosis of CAP and associated antibiotic utilization, Dr. Kanwar and colleagues reviewed the charts for 518 patients older than age 21 years who were admitted to their institution through the emergency department both prior to (January through June 2003) and following (January through June 2005) the publication of the guidelines. They collected data on clinical signs and symptoms at presentation, as well as chest x-ray findings, preantibiotic blood cultures, time to antibiotic administration data, Pneumonia Severity Index (PSI) scores, intensive care unit (ICU) transfer rates, and mortality data.

There were no significant differences between the 199 patients in the preguideline group and the 319 in the postguideline group in age, gender, PSI score, ICU transfer rates, or mortality. In the postguideline group, 66% of patients received antibiotics within 4 hours of triage, compared with 54% of the preguideline patients. The percentage of blood cultures prior to antibiotic administration was higher (70%) in the 2005 group compared with 47% in the 2003 group. But the final diagnosis of CAP dropped significantly, from about 76% in 2003 to 59% in 2005, and the mean antibiotic utilization per patient increased significantly, Dr. Kanwar reported in a poster presentation.

The increases in both the misdiagnosis in CAP and inappropriate antibiotic use as a result of compliance with the 4-hour antibiotic rule suggest that many patients received antibiotics for noninfectious processes. The increase in blood cultures obtained without indication suggests potential antibiotic use for contaminant-related positive cultures.

Dr. Kanwar reported having no financial disclosures related to this presentation. ■