Almost any solid-organ transplantation will require a surgical procedure that penetrates the gut wall, predisposing the recipient to fungal peritonitis or fungemia. Fluconazole has historically been the first-line prophylactic treatment for transplant recipients. However, recent studies of newer antifungal drugs suggest that alternatives are available and that not all transplant recipients may require antifungal prophylaxis.

**Fluconazole in Solid-Organ Transplants**

Winston et al showed in a randomized, placebo-controlled study of more than 200 adult liver recipients that fluconazole 400 mg daily for 10 days as prophylaxis significantly reduced proven invasive fungal infections compared with placebo (6% vs 23%, P < .001). There were also significantly fewer deaths due to invasive fungal infection. (Although the fluconazole-treated patients had a lower overall mortality, the difference was not significant.) Also of importance, prophylactic fluconazole decreased fungal colonization and prevented superficial infection. However, fluconazole treatment was also associated with significantly higher cyclosporine levels, so at this point in time, fluconazole as prophylaxis is usually only given to the higher-risk liver transplant patients.

In pancreatic transplantation, it is imperative for surgeons to use some form of antifungal prophylaxis because of the high rate of intra-abdominal yeast infections. A retrospective study of 445 consecutive pancreatic transplants in patients with type 1 diabetes underscores the benefit of fluconazole as prophylaxis. Of these patients, 108 received fluconazole 400 mg for 7 days and 327 did not receive any antifungal prophylaxis. Invasive fungal infections were less frequent in the fluconazole group than the placebo group (6% vs 10%). In the 22% of fluconazole recipients who also had a yeast infection, the yeast infection resolved and graft function persisted; in 58%, the infection resolved after transplant pancreatectomy. Death occurred despite pancreatectomy in 20%. Given the higher morbidity and mortality with intra-abdominal fungal infections involved in post-pancreatic transplant, the authors note that, “In addition to aggressive treatment, including transplant pancreatectomy and reduction of immunosuppression, efforts must be made toward better prevention of intra-abdominal fungal infections.” For surgeons, prophylaxis and infection control are very important to avoid a second operation to explant the pancreas.

Lung transplant recipients can still have yeast or Aspergillus recovered in surveillance bronchoscopy cultures in the weeks following transplant that may be occult. As a result, the risk of perioperative fungemia is usually not high enough in lung transplant recipients to warrant prophylaxis.

Kidney transplantation does not involve any surgical breakdown of the gut wall, just vasculature, so peri-operative antifungal prophylaxis is often not necessary.

**Fluconazole in Hematopoietic Stem Cell Transplantation**

During hematopoietic stem cell transplantation (HSCT), the immune system is ablated during the
conditioning period leading up to the transplantation. During this time and in the days immediately following the procedure (the peritransplant period), mucositis can develop. Because of the lack of a functioning immune system during this time, the patient is at increased risk for Candida, mostly manifesting as fungemia (rather than a fungal peritonitis as in solid-organ transplants). Antifungal prophylaxis should occur in the weeks prior to and after the transplantation, until the patient’s donor neutrophils begin to engraft.

In an early study of fluconazole versus placebo as prophylaxis for H SCT, the incidence of both systemic (2.8% vs 15.8%; \( P < .001 \)) and superficial (8.4% vs 33.3%; \( P < .001 \)) fungal infections was significantly reduced, and deaths due to invasive fungal infections were significantly reduced (1% vs 6%; \( P < .001 \)) with fluconazole treatment.3 Fluconazole 400 mg or placebo was administered from the start of the conditioning regimen until the neutrophil count returned to 1000/µL, toxicity was suspected, or a systemic fungal infection was suspected or proved.

Since then, a study comparing 200 mg with 400 mg fluconazole per day in 253 patients undergoing H SCT found similar results.4 Patients received these doses of fluconazole daily while they were neutropenic. The rate of fever by day 10 or 11 after transplant was the same for both groups (60% in the 400-mg group vs 59% in the 200-mg group). The number of yeast or mold infections by day 50 was essentially the same (4% vs 1%, yeast; 4% vs 2%, molds). Even low-dose fluconazole prophylaxis is appropriate for reducing fungal infections in the H SCT patient during the peritransplant period.

Recent data suggest, however, that the risk, particularly for inhaled mold infections, can extend beyond the immediate peritransplant period. In a review of autopsies of H SCT transplant recipients, an important trend in fungal infections emerges. In this study, a total of 355 H SCT autopsies from 1990 through 1994 were reviewed.5 Recipients either received fluconazole for the first 75 days posttransplant or did not receive fluconazole. In both groups, the rate of fungal infection at death was about 40% (37% fluconazole, 43% no fluconazole). Although those who received fluconazole had significantly fewer yeast infections (8% vs 27%; \( P < .001 \)), they had significantly more mold infections (29% vs 18%; \( P = .009 \)). The median number of days to death for patients with mold infections at autopsy was 62 days after transplant, compared with 26 days after transplant for those with yeast infections. There is a need for mold prophylaxis for the H SCT recipient that extends beyond the peritransplant neutropenic period. There also appears to be a bimodal distribution of fungal infections— a small number of yeast infections that occur early after the transplant, followed by mold infections that occur later and are often related to graft-versus-host disease (GVHD).

Over the past several years, nonmyeloablative conditioning regimens have been used to avoid long periods of neutropenia. Although patients conditioned with these regimens might have a shorter duration of neutropenia in the peritransplant period, by 1 year after transplant they are at the same risk for the total number of infections as those patients who received myeloablative regimens. There are now populations of H SCT recipients who require mold prophylaxis for longer periods of time. The remaining questions regarding prophylaxis are:

- What is the most appropriate antifungal prophylaxis regimen following neutrophil recovery from H SCT?
- Should prophylaxis be given to all patients who are at risk for GVHD or to only those patients who have GVHD immunosuppressive therapy in place?
- Should prophylaxis be given to only those GVHD patients who are receiving specific high-risk treatment (eg, infliximab)?
- How long should prophylaxis continue—for the first 6 months of immunosuppressive therapy or for the duration of immunosuppressive therapy?

Some fluconazole-resistant Candida albicans as well as other species of Candida have also emerged as a source of clinically significant infection. Is it important to broaden our prophylaxis for yeast prophylaxis during the peritransplant period?

For long-term prophylaxis, safe and tolerable oral formulations are needed because the recipients are often outpatients. Newer azoles may fill this need.

Itraconazole

Itraconazole is used to treat infections due to most yeasts and molds. It has a broader spectrum of activity than fluconazole, with activity against most
Aspergillus isolates and a subset of fluconazole-resistant Candida strains. It is available in both an oral solution and intravenous formulation. Its metabolites also have antifungal activity, so the blood levels of all triazole metabolite compounds should be measured, not just the itraconazole level. Itraconazole is only recently being tested for prophylaxis in transplant recipients.

A randomized, controlled, open-label, multicenter study compared itraconazole 200 mg with fluconazole 400 mg, administered from day 1 to day 100 post-transplant in 138 H SCT patients. Although the rates of invasive fungal infection by day 100 were lower with itraconazole (9% vs 25%; \( P = .01 \)), the percentage of patients with invasive fungal infection at death was not significantly different (9% vs 18%; \( P = .13 \)). In addition, there were more gastrointestinal side effects with itraconazole, suggesting that itraconazole may be useful only in patients who can tolerate it. In a subset of patients with acute GVHD, the percentage of patients who developed an invasive fungal infection was much lower for the itraconazole-treated patients.

A second study of 299 patients comparing itraconazole (200 mg) to fluconazole (400 mg) as prophylaxis again showed significantly fewer patients with mold infections but significantly higher toxicity rates with itraconazole. The number of invasive fungal infections was comparable in the 2 groups. The study drug was given until day 180 or until 4 weeks following the completion of GVHD immunosuppressive therapy. There was no difference in overall survival and fungal-free survival between the 2 groups. So, itraconazole may be used to prevent the mold infections that occur during the later stages of H SCT. However, it has important tolerability issues.

For liver transplant patients, the data are not as convincing for the routine addition of itraconazole as antifungal prophylaxis. A study of 188 patients undergoing liver transplantation compared itraconazole 200 mg twice daily with fluconazole 400 mg once daily administered for 10 weeks. Both groups had significant reductions in colonization by week 8 (from 67% to 25% in the itraconazole group and from 77% to 30% in the fluconazole group), but there was no difference in the number of proven invasive fungal infections (9% vs 4%, \( P = .25 \)). In addition, itraconazole-treated patients experienced more gastrointestinal side effects than the fluconazole-treated patients.

Posaconazole also has a broader spectrum than fluconazole. It is available as an oral solution, with 4 times daily dosing for induction phases of treatment followed by 3 times daily dosing for maintenance therapy. The chemical structure has been modified to prevent hepatic metabolism, so there are fewer side effects associated with it.

Posaconazole was recently compared with fluconazole in 603 H SCT recipients with acute GVHD of at least Grade II or chronic GVHD. It was a prospective, randomized, double-blinded, double-dummy study comparing posaconazole 200 mg oral solution 3 times daily with meals to fluconazole 400 mg once daily. Although the database has not yet been unlocked, the incidence of invasive fungal infections appears to be lower than expected (around 6% to 8%). Additional preliminary results will be available in spring of 2004. Importantly, all of the study patients had blood taken for serial Aspergillus antigen testing (the galactomannan assay) as well.

Voriconazole has a broader spectrum of activity than fluconazole. Voriconazole (200 mg twice daily) will soon be compared with fluconazole (400 mg each morning and placebo each evening) in 600 H SCT recipients in a prospective, randomized, double-blind study sponsored by the Bone Marrow Transplant Clinical Trials Network. The study will also examine the galactomannan assay (serial Aspergillus antigen testing twice weekly). The study patients will have had myeloablative transplant and will continue the drug until day 100 or until day 180 in high-risk patients.

Echinocandins inhibit the catalytic and regulatory subunits of the glucan synthase enzyme complex to prevent formation of the beta-D-glucan linkages in the fungal cell wall, thus preventing fungal infection. Echinocandins appear to be fungicidal to yeast organisms; however, they are fungistatic to Aspergillus and the molds, because they work only at the growing tips and at the hyphal branch points. Currently, only 1 echinocandin is available in the United States (caspofungin); micafungin and anidulafungin are currently
under review by the US Food and Drug Administration. The advantages of echinocandins include long half-lives, the possibility of single daily dosing, and linear pharmacokinetics. Echinocandins have an excellent safety profile that is very similar to fluconazole. There is no hepatic or renal metabolism, so no dose adjustments are necessary for those with renal failure, while only minor adjustments are necessary for patients with hepatic failure (primarily with caspofungin). The disadvantages include intravenous formulation only and the fact that this class of drugs is inactive for Cryptococcus, Fusarium, Zygomycetes, and some other organisms. Among drugs within the echinocandin class, there are some differences in drug interactions but no cross-resistance to existing drugs.

Currently, there is only 1 publicly available study of an echinocandin for prophylaxis in H SCT. In a randomized, double-blind, 72-center study of 882 patients, micafungin (50 mg) was compared with fluconazole (400 mg). Study drugs were administered within 48 hours of conditioning and continued until up to 5 days following engraftment to at least 500 cells/mm3 development of a fungal infection, unacceptable toxicity, death, or day 42 following transplant. The results showed reduced need to switch to empiric therapy (15.1% vs 21.4%), reduced invasive fungal infections (1.6% vs 2.4%), and reduced rates of aspergillosis (0.2% vs 1.5%) with micafungin, but only differences in the need for empiric treatment were statistically significant. The proportion of patients with treatment success (as defined by this composite definition) was significantly higher for the micafungin-treated patients, both at the end of the prophylaxis period and into the 4-week follow-up period (P = .025).9

CONCLUSION

Fluconazole remains a safe, first-line drug for prophylaxis in recipients of solid-organ transplants. Itraconazole can be used for the H SCT patient, both for short-term and long-term prophylaxis, but tolerability should be monitored closely. The results of the recently completed posaconazole versus fluconazole study should be out within the next year, and the voriconazole versus fluconazole study with galactomannan testing is ready to start. Echinocandins have a novel mechanism of action and an excellent safety profile but are available only in intravenous formulation. They are fungicidal for yeast and are fungistatic for mold but appear to be cidal for incubating mold spores. The micafungin versus fluconazole study showed that micafungin appears to be safe, including during the conditioning period of H SCT, and all of the results from this study using a composite “treatment success” endpoint favored micafungin. Studies of other echinocandins in transplant prophylaxis would be important for providing treatment alternatives if the number of fluconazole-resistant yeast strains increases.

REFERENCES