

Month/Year of Review: March 2013

PDL Classes: Oral Antifungals

Date of Last Review: January 2010

Source Document: Provider Synergies

- Preferred Agents: CLOTRIMAZOLE TROCHE, FLUCONAZOLE TABLET/SUSPENSION, KETOCONAZOLE, NYSTATIN
- Non Preferred Agents: TERBINAFINE (LAMISIL), GRISEOFULVIN, TERBINAFINE, KETOCONAZOLE, FLUCYTOSINE, ITRACONAZOLE, VORICONAZOLE, POSACONAZOLE (NOXAFIL), AMPHOTERICIN B SUSPENSION (FUNGIZONE)

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Recommend inclusion of at least one medication from this group
- Recommend including nystatin for pediatric use

PA Criteria/QL:

- PA for non-preferred antifungals to approve use for only OHP covered diagnoses. Minor fungal infections of the skin are only covered when complicated by an immunocompromised host (Appendix 1).

Methods:

A Medline OVID search was conducted with the following search terms: clotrimazole, fluticasone, flucytosine, itraconazole, ketoconazole, miconazole, posaconazole, nystatin, voriconazole, griseofulvin, terbinafine, tinea unguium, tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea pedis, lichen planus, pityriasis versicolor, systemic sclerosis, Candidiasis, cryptococcal meningitis, candidemia, vulvovaginal candida, Trichophytosis, Blastomycosis, Candida endophthalmitis, Candida pyelonephritis, Cryptococcosis, Leishmaniasis, Cutaneous sporotrichosis, mycosis, Histoplasmosis, Onychomycosis, tinea, Candida endophthalmitis, Aspergillosis, Chromoblastomycosis, Coccidioidomycosis, febrile neutropenia, Paracoccidioidomycosis, Sporotrichosis, seborrheic dermatitis, Allescheriosis, Fusarium infection. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to November week 3 2012.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC), the Center for Disease Control (CDC) and Infectious Diseases Society of America (IDSA).

New Trials:

A total of 305 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo or IV antifungals), or outcome (non-clinical). After review of titles and abstracts for inclusion, ten relevant head-to-head clinical trials were identified and are discussed here. Please see Appendix 2 for the full abstracts.

Two trials compared prophylactic fluconazole and nystatin in very low weight neonates. Infants studied by Violaris et al¹ were randomly assigned to fluconazole or nystatin groups and were followed up to 15 months. Study enrollment was stopped early due to several deaths in both treatment groups from infection. The study finished underpowered. In the study by Aydemir et al², infants were randomized into one of the two treatments groups or a third placebo group and followed for 12 months. Neither study showed a significant difference between fluconazole and nystatin in preventing fungal infections. Both studies were low quality with multiple flaws in design and methods.

Treatment of vaginal yeast infection was the topic of two trials comparing oral fluconazole and a topical antifungal agent. Consolaro et al³ showed fluconazole was more effective at eradicating vaginal candidiasis than topical nystatin (87% to 74%; $p < 0.05$). Fluconazole was also more effective than intra-vaginal clotrimazole (80.5% vs. 70%; $p < 0.001$) in the trial conducted by Sekhvat et al⁴. Both trials were fair to low quality. Blinding was an issue for both trials, neither trial discussed treatment allocation, and randomization methods were not clearly explained.

Three recent studies compared antifungal regimens for invasive fungal infections in fragile or immunocompromised populations. For the fair quality SMILES study, Vazquez et al⁵ compared buccal miconazole with clotrimazole troches for oropharyngeal candidiasis (OPC) in patients with HIV. Miconazole was found to be noninferior to clotrimazole in resolving the signs and symptoms OPC 61% vs. 65% (a treatment difference of -0.059; 95% CI -0.140-0.022). A small open-label study conducted by Nussbaum et al⁶ examined the efficacy of adding flucytosine to fluconazole to treat cryptococcal meningitis in HIV patients. Combination therapy was found to have a more rapid clearance rate of infection than fluconazole alone (treatment difference of 0.17; 95% CI 0.09–0.25) in this low quality trial. The number of deaths at the end of treatment however, was not significantly different between the treatment groups. In a high quality study, Wingard et al⁷ compared fluconazole with voriconazole for prevention of invasive fungal infections (IFI) in hematopoietic cell transplantation patients. No statistical difference was found between treatments for any of the primary endpoints including freedom from IFI and death.

Several trials looked at skin and nail fungal infections. A low quality, open-label, cross-sectional study by Grover et al⁸ evaluated oral griseofulvin, fluconazole or terbinafine to treat tinea capitis in children under the age of 12. Although griseofulvin was found to be the most effective at resolving infections (90% cure rate vs. 88% for terbinafine and 84% for fluconazole), the differences between the three were not statistically significant. Elewski et al⁹ examined several different posaconazole regimens with terbinafine and placebo in a fair quality, phase two trial of adult patients with toenail infections. Compared with placebo, all patients in the posaconazole treatment arms had a significantly ($p < 0.01$) greater proportion of patients with complete cure. Several posaconazole arms also had a higher rate of complete cure than terbinafine, although none were statistically significant.

A low quality study by Dehghan et al¹⁰ compared topical clotrimazole with oral fluconazole for treating adults with tinea versicolor. Patients were treated for twelve weeks; at the end of treatment both groups had high rates of response (92% clotrimazole vs. 81.8% fluconazole, $p = 0.77$) but the difference between the two treatments was not significant.

New drugs:

No new oral antifungal medications were approved.

New Formulations/Indications:

A new buccal formulation of miconazole was approved in April 2010. Oravig™ is indicated for the treatment of oropharyngeal candidiasis for patients over 16 years old.¹¹

New FDA safety alerts:

In August 2011, the FDA released a safety alert regarding systemic fluconazole use. The FDA found treatment with chronic, high doses (400-800mg/day) of fluconazole during the first trimester of pregnancy was associated with birth defects in infants. Single low dose fluconazole (i.e. 150 mg) to treat vaginal yeast infection (candidiasis) was not implicated. Based on this information, the pregnancy category for fluconazole indications (other than for vaginal candidiasis) was changed from category C to category D.¹²

Several safety label changes were updated for oral antifungals in the last few years. In September 2010, the FDA added a label warning for increased risk of QT prolongation with posaconazole use.¹³ In October 2010, the FDA revised the griseofulvin safety labeling to include a warning for increased risk of severe skin and hepatic adverse events.¹⁴ The FDA also added a label warning for increased risk of hearing impairment with terbinafine use in April 2012.¹⁵

New Systematic Reviews:

Three new or updated, relevant systematic reviews were identified. None of the reviews' conclusions require altering current practice for oral antifungal use. Please see Appendix 3 for the full abstracts.

Tey et al¹⁶ compared the effectiveness of griseofulvin and terbinafine in treating tinea capitis. Seven studies with 2163 patients were included in the meta analysis. Although patients treated with terbinafine had a higher rate of symptom resolution, it was not statistically significant (OR 1.22; 95% CI 0.975-2.277). Information for individual trial quality was not described.

Wang et al¹⁷ compared the efficacy and safety of using fluconazole or itraconazole to prevent fungal infections in severely neutropenic patients with hematologic malignancies. Nine randomized control trials of mostly fair quality (four had no explanation of allocation concealment; only one trial attempted blinding) were included in the meta analysis for a total of 2254 patients. Itraconazole was more likely to prevent an invasive fungal infection (RR 1.33; 95% CI 1.02-1.73), although there were no statistically significant differences between the two regarding overall mortality (RR 0.95; 95% CI 0.77-1.17) or fungal-related mortality (RR1.28; 95%CI 0.80-2.07).

Wang and Chang et al¹⁸ also looked at immunocompromised patients with hematologic malignancies to determine the comparative safety of various antifungals used to treat or prevent invasive fungal infections. 8745 patients were included from 39 trials of low-to-fair quality (very few trials described allocation concealment; the majority were not blinded); of the oral antifungals examined, itraconazole had the highest percentage of patients to discontinue due to adverse effects (18.8%; 95% CI 14.3-23.2) and discontinued patients due to elevated liver enzymes (1.5%; 95% CI 0-4.0). Fluconazole (adverse event discontinuation rate: 2.2%, 95% CI 0-4.6; discontinuation due to liver enzymes: 0.7%, 95% CI 0-1.4) and voriconazole (adverse event discontinuation rate: 9.5%, 95% CI 2.3-16.8; discontinuation due to liver enzymes: not calculated) were also included.

Guidelines:

The updated guideline¹⁹ for pulmonary infections from the American Thoracic Society was reviewed; as was the updated sexually transmitted disease guideline²⁰ from the Centers for Disease Control. Updated treatment guidelines for cryptococcal diseases²¹, febrile neutropenia²², and intra-abdominal infections²³ from the Infectious Disease Society of America were also evaluated. No changes regarding the use of antifungals were found.

Recommendations:

- No further research or review needed at this time.
- Evaluate comparative costs in executive session.

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10. Dehghan M, Akbari N, Alborzi N, Sadani S, Keshtkar AA. Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: A double-blind randomized controlled trial. *The Journal of Dermatology*. 2010;37(8):699–702.
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Appendix 1

Randomized Control Trials

Grover C, Arora P, Manchanda V. Comparative evaluation of griseofulvin, terbinafine and fluconazole in the treatment of tinea capitis. *International Journal of Dermatology*. 2012; 51(4):455–458.

Tinea capitis (TC) is a common childhood fungal infection which, if untreated, can cause long-term scarring. A number of antifungal drugs with proven efficacy are available for the treatment of TC. However, varying dosage schedules, changes in epidemiology, and rising drug resistance are factors that hamper treatment in some cases. A prospective, non-blinded, cross-sectional study of three commonly used drugs (terbinafine, griseofulvin, and fluconazole) was undertaken in children aged ≤ 12 years, presenting to a pediatric superspecialty hospital. The comparative efficacies of these three drugs were evaluated. A total of 75 patients (25 in each treatment group) who completed the designated treatment protocol were included in the final analysis. Of these, 60% had non-inflammatory TC and 56% had an ectothrix pattern on hair microscopy. *Trichophyton violaceum* was the most commonly isolated fungus. Cure rates of 96%, 88%, and 84% were achieved with griseofulvin, terbinafine, and fluconazole, respectively. Overall, seven patients required prolonged therapy. No side effects to therapy were seen. Griseofulvin remains the drug of choice in the treatment of TC. Terbinafine was the second best agent and offered the advantage of a shorter course of therapy. Fluconazole had comparatively low cure rates but was easier to administer than the other two medications.

Consolaro M, Martins H, Da Silva M, Paiva L, Svidzinski T. Efficacy of Fluconazole and Nystatin in the Treatment of Vaginal Candida Species. *Acta Dermatologica Venereologica*. 2012; 92(1):78–82.

The aim of this study was to determine and compare the efficacy of treatment with fluconazole and nystatin in Brazilian women with vaginal *Candida*. In a population of 932 women, vaginal cultures were performed for yeasts, whether or not the women showed signs and symptoms of vulvovaginal candidiasis. Yeasts were isolated from 12.2% of the women (114/932): 53.2% of the yeasts were *Candida albicans*, 27.0% *C. glabrata*, 13.5% *C. tropicalis* and 6.3% *C. parapsilosis*. Treatment was carried out with both drugs. The overall mean cure rates with fluconazole (87.0%) and nystatin (74.0%) were similar; among women with non-*albicans*, the cure rate with fluconazole was 100%, whereas that with nystatin was 44.4%. The cure rate for women with *C. albicans* was high with both fluconazole and nystatin; however, for those with non-*albicans* species the cure rate was excellent with fluconazole and very low with nystatin, differing from the majority of in vitro studies.

Elewski B, Pollak R, Ashton S, Rich P, Schlessinger J, Tavakkol A. A randomized, placebo- and active-controlled, parallel-group, multicentre, investigator-blinded study of four treatment regimens of posaconazole in adults with toenail onychomycosis. *British Journal of Dermatology*. 2012; 166(2):389–398.

Onychomycosis accounts for up to 50% of all onychopathies. OBJECTIVES: To evaluate the efficacy of four posaconazole regimens compared with placebo in the treatment of toenail onychomycosis, to assess the safety and tolerability of posaconazole, and to estimate the relative efficacy of posaconazole against terbinafine. METHODS: A phase 2B, randomized, placebo- and active-controlled, parallel-group, multicentre, investigator-blinded (double blind for placebo) study (ClinicalTrials.gov identifier: NCT00491764). Onychomycosis patients aged 18–75 years ($n=218$) were randomized equally to one of six treatment regimens: posaconazole (oral suspension) 100, 200 or 400mg once daily (24weeks); posaconazole 400 mg once daily (12weeks); terbinafine (tablets) 250mg once daily (12weeks); or placebo (24weeks). The primary efficacy variable was complete cure (negative mycology and 0% nail involvement) at week 48. RESULTS: All posaconazole treatment arms had a significantly ($P<0.012$) greater proportion of patients with complete cure at week 48 compared with placebo. The proportions of patients with complete cure were numerically higher for posaconazole 200mg/24weeks (54.1%) and 400mg/24weeks (45.5%), but lower for 400mg/12weeks (20%) compared with terbinafine (37%; differences were not statistically significant). Posaconazole was well tolerated. Seven patients receiving posaconazole withdrew because of asymptomatic liver enzyme increases, as mandated by protocol discontinuation criteria. CONCLUSIONS: The efficacy and favourable safety profile of posaconazole suggest a potential new treatment for onychomycosis. The availability of low-cost generic terbinafine may limit posaconazole use to second-line treatment of infections refractory to, or patients intolerant of, terbinafine, or nondermatophyte mould infections.

Sekhvat L, Tabatabaai A, Tezerjani FZ. Oral fluconazole 150mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. *Journal of Infection and Public Health*. 2011; 4(4):195–199.

To compare the safety and efficacy of fluconazole 150 mg single dose and intra-vaginal clotrimazole 200mg per day for six days in the treatment of the acute episode of vulvovaginal candidiasis (VVC). METHODS: In a prospective study, 142 patients with acute clinical and mycological confirmed VVC were enrolled and divided randomly in two groups. 70 patients received intra-vaginal tablet (200mg) daily for seven days, whereas 72 patients received single dose oral fluconazole (150 mg). Second and third visits were done for all patients seven days and one month after treatment and the clinical and mycological outcomes evaluated. The analysis performed using SPSS statistical software (version 15). RESULTS: At the second visit, 61 patients (84.7%) were cured clinically (inflammation and discharge) and 58 patients (80.5%) mycologically in fluconazole group and 60 patients (83.3%) were cured clinically and 49 patients (70%) mycologically in clotrimazole group ($P=0.01$). At the third visit, only one patient in fluconazole group and 17 patients in clotrimazole group had clinical sign of VVC ($P=0.001$). CONCLUSION: Oral fluconazole single dose seems to be a valid and promising therapy to cure acute signs and symptoms of VVC.

Aydemir C, Oguz SS, Dizdar EA, et al. Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonisation and invasive fungal infection in very low birth weight infants. *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 2010; 96(3):F164–F168.

Invasive fungal infections are a major cause of morbidity and mortality in preterm infants. The authors conducted the first prospective, randomised controlled trial of nystatin compared with fluconazole for the prevention of fungal colonisation and invasive fungal infection in very low birth weight (VLBW) neonates. METHODS: During a 12-month period, all VLBW neonates were assigned randomly to receive nystatin (1 ml suspension, 100 000 U/ml, every 8 h), fluconazole (3 mg/kg body weight, every third day) or placebo from birth until day 30 of life (day 45 for neonates weighing <1000 g at birth). The authors performed weekly surveillance cultures and systemic fungal susceptibility testing. RESULTS: During the study period, 278 infants (fluconazole group, $n=93$; nystatin group, $n=94$; control group, $n=91$) weighing <1500 g at birth were admitted. There were no differences in birth weight, gestation, gender or risk factors for fungal infection among the groups. Fungal colonisation occurred in 11.7% of the nystatin group and 10.8% of the fluconazole group, as compared with 42.9% of the control group. The incidence of invasive fungal infection was 4.3% in the nystatin group and 3.2% in the fluconazole group, as compared with 16.5% in the control group. There were no differences in fungal colonisation and invasive fungal infection between the nystatin and fluconazole groups. CONCLUSIONS: Prophylactic nystatin and fluconazole reduce the incidence of colonisation and invasive fungal infection in VLBW neonates. The authors believe that nystatin is an alternative to fluconazole, because nystatin is safe, inexpensive, well tolerated and effective.

Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010; 116(24):5111–5118.

Invasive fungal infection (IFI) is a serious threat after allogeneic hematopoietic cell transplant (HCT). This multicenter, randomized, double-blind trial compared fluconazole (N = 295) versus voriconazole (N = 305) for the prevention of IFI in the context of a structured fungal screening program. Patients undergoing myeloablative allogeneic HCT were randomized before HCT to receive study drugs for 100 days, or for 180 days in higher-risk patients. Serum galactomannan was assayed twice weekly for 60 days, then at least weekly until day 100. Positive galactomannan or suggestive signs triggered mandatory evaluation for IFI. The primary endpoint was freedom from IFI or death (fungal-free survival; FFS) at 180 days. Despite trends to fewer IFIs (7.3% vs 11.2%; P = .12), Aspergillus infections (9 vs 17; P = .09), and less frequent empiric antifungal therapy (24.1% vs 30.2%, P = .11) with voriconazole, FFS rates (75% vs 78%; P = .49) at 180 days were similar with fluconazole and voriconazole, respectively. Relapse-free and overall survival and the incidence of severe adverse events were also similar. This study demonstrates that in the context of intensive monitoring and structured empiric antifungal therapy, 6-month FFS and overall survival did not differ in allogeneic HCT recipients given prophylactic fluconazole or voriconazole. This trial was registered at www.clinicaltrials.gov as NCT00075803.

Vazquez JA, Patton LL, Epstein JB, et al. Randomized, Comparative, Double-Blind, Double-Dummy, Multicenter Trial of Miconazole Buccal Tablet and Clotrimazole Troches for the Treatment of Oropharyngeal Candidiasis: Study of Miconazole Lauriad[®] Efficacy and Safety (SMILES). *HIV Clinical Trials*. 2010; 11(4):186–196

Oropharyngeal candidiasis (OPC) is the most common opportunistic infection among persons infected with human immunodeficiency virus (HIV). Once-daily miconazole 50 mg buccal tablet (MBT) is a novel delivery system using an extended-spectrum azole with potent in vitro activity against many *Candida* species, including some that may be resistant to other azoles. METHODS: This phase 3, double-blind, double-dummy, multicenter trial evaluated 578 randomized patients with HIV infection and OPC. The study compared the efficacy and safety of MBT once daily with clotrimazole 10 mg troches (CT) 5 times daily for 14 days. The primary efficacy endpoints were clinical cure at test of cure (TOC) visit (days 17–22) in the intent-to-treat (ITT) and per protocol (PP) populations. RESULTS: Clinical cure rate at TOC visit for MBT-treated patients was statistically noninferior to CT-treated patients in both the ITT (61% vs 65%) and PP (68% vs 74%) populations. Secondary endpoints, safety, and tolerability were similar between treatment groups. CONCLUSIONS: In this large trial, once-daily MBT was shown to be noninferior to CT 5 times daily in the treatment of OPC in HIV-positive patients. MBT offers an effective, safe, and well-tolerated topical treatment option for OPC administered as a convenient once-daily dose.

Dehghan M, Akbari N, Alborzi N, Sadani S, Keshtkar AA. Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: A double-blind randomized controlled trial. *The Journal of Dermatology*. 2010; 37(8):699–702.

This study was designed to compare the therapeutic effects of topical clotrimazole and systemic fluconazole in pityriasis versicolor. A double-blind randomized controlled trial was carried out in the dermatological clinic of Gorgan, northern Iran, between April 2006 and May 2007. All consecutive patients with pityriasis versicolor were included and randomly divided into two groups. In the first group (G1), patients underwent treatment with a single dose of fluconazole capsule (400 mg) and placebo cream. In the second group (G2), patients underwent treatment with clotrimazole cream (twice daily) and placebo capsule. The course of treatment was 2 weeks. All subjects were re-evaluated 2, 4 and 12 weeks after the end of the therapeutic course. After 2 weeks, the rate of complete resolution of disease was significantly higher in G2 than G1 (49.1% vs 30%). After 4 weeks, 41 patients (81.2%) of G1 and 52 patients (94.9%) of G2 showed complete resolution. After 12 weeks, 46 patients (92%) in G1 and 45 patients (81.8%) in G2 showed complete resolution. Recurrence rate in G1 and G2 were 6% and 18.2%, respectively. No complications were seen in either group. In this study, clinical response at week 4 was greater in the clotrimazole group than the fluconazole group. Recurrence at week 12 after treatment was less with oral fluconazole than clotrimazole cream. So, for better evaluation, more studies need to be done.

Nussbaum JC, Jackson A, Namarika D, et al. Combination Flucytosine and High-Dose Fluconazole Compared with Fluconazole Monotherapy for the Treatment of Cryptococcal Meningitis: A Randomized Trial in Malawi. *Clinical Infectious Diseases*. 2010; 50(3):338–344.

Cryptococcal meningitis is a major cause of human immunodeficiency virus (HIV)-associated morbidity and mortality in Africa. Improved oral treatment regimens are needed because amphotericin B is neither available nor feasible in many centers. Fluconazole at a dosage of 1200 mg per day is more fungicidal than at a dosage of 800 mg per day, but mortality rates remain unacceptably high. Therefore, we examined the effect of adding oral flucytosine to fluconazole. METHODS: From 13 February through 2 December 2008, HIV-seropositive, antiretroviral-naïve patients experiencing their first episode of cryptococcal meningitis were randomized to receive (1) 14 days of fluconazole (1200 mg per day) alone or (2) in combination with flucytosine (100 mg/kg per day) followed by fluconazole (800 mg per day), with both groups undergoing 10 weeks of follow-up. The primary end point was early fungicidal activity, derived from quantitative cerebrospinal fluid cultures on days 1, 3, 7, and 14. Secondary end points were safety and 2- and 10-week mortality. RESULTS: Forty-one patients were analyzed. Baseline mental status, cryptococcal burden, opening pressure, CD4 (+) cell count, and HIV load were similar between groups. Combination therapy was more fungicidal than fluconazole alone (mean early fungicidal activity +/- standard deviation -0.28 +/- 0.17 log colony-forming units [CFU]/mL per day vs -0.11 +/- 0.09 log CFU/mL per day; P < .001). The combination arm had fewer deaths by 2 weeks (10% vs 37%) and 10 weeks (43% vs 58%). More patients had grade III or IV neutropenia with combination therapy (5 vs 1, within the first 2 weeks; P = .20), but there was no increase in infection-related adverse events. CONCLUSIONS: The results suggest that optimal oral treatment for cryptococcal meningitis is high-dose fluconazole with flucytosine. Efforts are needed to increase availability of flucytosine in Africa. Clinical trials registration. isrctn.org Identifier: ISRCTN02725351.

Violaris K, Carbone T, Bateman D, Olawepo O, Doraiswamy B, LaCorte M. Comparison of Fluconazole and Nystatin Oral Suspensions for Prophylaxis of Systemic Fungal Infection in Very Low Birthweight Infants. *American Journal of Perinatology*. 2009; 27(01):073–078.

We compared the efficacy and safety of fluconazole and nystatin oral suspensions for the prevention of systemic fungal infection (SFI) in very low birthweight infants. A prospective, randomized clinical trial was conducted over a 15-month period, from May 1997 through September 1998, in 80 preterm infants with birthweights <1500 g. The infants were randomly assigned to receive oral fluconazole or nystatin, beginning within the first week of life. Prophylaxis was continued until full oral feedings were attained. Blood and urine cultures were obtained at enrollment and then weekly thereafter. Thirty-eight infants were randomly assigned to receive oral fluconazole (group I), and 42 infants were assigned to receive nystatin (group II). Birthweight, gestational age, and risk factors for fungal colonization and SFI at the time of randomization and during the hospital course were similar in both groups. SFI developed in two infants (5.3%) in group I and six infants (14.3%) in group II. The difference between these two rates was not statistically significant (relative risk, 0.37; 95% confidence interval, 0.08 to 1.72). There were no deaths in group I and six deaths in group II (P = 0.03). Two infants died of neonatal sepsis, and four deaths were related to necrotizing enterocolitis and/or spontaneous intestinal perforation. No deaths were due to SFI. Enrollment was halted before completion and the study did not attain adequate power to detect a hypothesized drop in SFI rate from 15 to 5%. Although the results cannot justify any conclusion about the relative efficacy of fluconazole versus nystatin in prevention of SFI, the significantly higher mortality rate in the nystatin group raises questions about the relative safety of this medication.

Appendix 2

New Systematic Reviews

Tey HL, Tan ASL, Chan YC. Meta-analysis of randomized, controlled trials comparing griseofulvin and terbinafine in the treatment of tinea capitis. *Journal of the American Academy of Dermatology*. 2011; 64(4):663–670.

BACKGROUND: Griseofulvin has been the standard treatment for tinea capitis but newer antifungal agents, particularly terbinafine, are increasingly being used because of their shorter duration of treatment and more consistent absorption rates. **OBJECTIVE:** We sought to compare the efficacy of oral griseofulvin and oral terbinafine in the treatment of tinea capitis. **METHODS:** A search of MEDLINE, EMBASE, Cochrane Central Register of Clinical Trials, and the Cochrane Skin Group Ongoing Skin Trials Register was performed up to January 2010 for randomized controlled trials comparing griseofulvin and terbinafine in the treatment of tinea capitis in immunocompetent patients. The primary outcome measure was the complete cure rate. The mycological and clinical cure rates and adverse effects were secondary outcome measures. Pooling of treatment effect was accomplished using a random effects model and the I (2) test was used to check for heterogeneity among the studies. **RESULTS:** Seven studies involving 2163 subjects were included. There was no significant difference in efficacy between griseofulvin (mean duration of treatment 8 weeks, range 6-12 weeks) and terbinafine (mean duration of treatment 4 weeks, range 2-6 weeks); odds ratio = 1.22 favoring terbinafine (95% confidence interval [CI] = 0.785-1.919; P = .37). In the pooled analysis of 5 studies in which Trichophyton species were the predominant (>=65%) pathogenic dermatophyte, terbinafine showed a trend toward greater efficacy (odds ratio 1.49; 95% CI = 0.975-2.277; P = .065). Subgroup analysis revealed that terbinafine was more efficacious than griseofulvin in treating Trichophyton species (1.616; 95% CI = 1.274-2.051; P < .001) and griseofulvin was more efficacious than terbinafine in treating Microsporum species (0.408; 95% CI = 0.254-0.656; P < .001). Both griseofulvin and terbinafine demonstrated good safety profiles in the studies. **LIMITATIONS:** Data on efficacy of griseofulvin and terbinafine for separate groups of Trichophyton and Microsporum species were not available from every study. In the subgroup analysis of Microsporum species, data from only 3 studies were available. **CONCLUSION:** This meta-analysis suggests that terbinafine is more efficacious than griseofulvin in treating tinea capitis caused by Trichophyton species, whereas griseofulvin is more efficacious than terbinafine in treating tinea capitis caused by Microsporum species.

Wang J, Zhan P, Zhou R, et al. Prophylaxis with itraconazole is more effective than prophylaxis with fluconazole in neutropenic patients with hematological malignancies: a meta-analysis of randomized-controlled trials. *Medical Oncology*. 2009; 27(4):1082–1088.

Antifungal prophylaxis using fluconazole or itraconazole has been studied for many years but still no consensus has been reached regarding their safety and effectiveness. We performed a systematic meta-analysis to assess the efficacy of fluconazole compared to itraconazole in neutropenic patients with hematological malignancies. We gathered the data for our analysis from MEDLINE, EMBASE, Cochrane-controlled trials register, Cochrane Library, and Science Citation Index (1/1990 to 1/2009) searches. Risk ratio (RR) and 95% confidence intervals (CIs) were calculated using the random effect model. Nine RCTs were identified that were published in full text. Significantly, fewer patients were withdrawn from the studies due to the development of adverse effects with fluconazole prophylaxis when compared with itraconazole (RR 0.45, 95% CI 0.27-0.75, P=0.002). There were statistically significant differences regarding fungal infections (RR 1.34, 95% CI 1.08-1.67, P=0.009) and invasive fungal infections (RR 1.33, 95% CI 1.02-1.73, P=0.03) between the two medications. There were no statistically significant differences regarding overall mortality (RR 0.95, 95% CI 0.77-1.17, P=0.64), fungal-related mortality (RR 1.28, 95% CI 0.80-2.07, P=0.31), and proven fungal infections (RR 1.38, 95% CI 0.75-2.53, P=0.30). The analysis of published evidence reveals that itraconazole administration resulted in significantly fewer episodes of fungal infections and invasive fungal infections compared with fluconazole.

Wang JL, Chang CH, Young-Xu Y, Chan KA. Systematic Review and Meta-Analysis of the Tolerability and Hepatotoxicity of Antifungals in Empirical and Definitive Therapy for Invasive Fungal Infection. *Antimicrobial Agents and Chemotherapy*. 2010; 54(6):2409–2419.

To evaluate the tolerability and liver safety profiles of the systemic antifungal agents commonly used for the treatment of invasive fungal infection, we conducted a systematic review and meta-analysis of randomized controlled trials published before 31 August 2009. Two reviewers independently applied selection criteria, performed quality assessment, and extracted data. We used the beta-binomial model to account for variation across studies and the maximum likelihood method to estimate the pooled risks. We identified 39 studies with more than 8,000 enrolled patients for planned comparisons. The incidence rates of treatment discontinuation due to adverse reactions and liver injury associated with antifungal therapy ranged widely. The pooled risks of treatment discontinuation due to adverse reactions were above 10% for amphotericin B formulations and itraconazole, whereas they were 2.5% to 3.8% for fluconazole, caspofungin, and micafungin. We found that 1.5% of the patients stopped itraconazole treatment due to hepatotoxicity. Furthermore, 19.7% of voriconazole users and 17.4% of itraconazole users had elevated serum liver enzyme levels, although they did not require treatment discontinuation, whereas 2.0% or 9.3% of fluconazole and echinocandin users had elevated serum liver enzyme levels but did not require treatment discontinuation. The results were similar when we stratified the data by empirical or definitive antifungal therapy. Possible explanations for antifungal agent-related hepatotoxicity were confounded by antifungal prescription to patients with a high risk of liver injury, the increased chance of detection of hepatotoxicity due to prolonged treatment, or the pharmacological entity.