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PREVALENCE AND FLUCONAZOLE SUSCEPTIBILITY OF *CANDIDA SPP.* RECOVERED FROM THE OROPHARYNX OF HEALTH CARE WORKERS AND NON- HEALTH CARE WORKERS

Piper J, Couch K, Steele-Moore L, Tuttle D, Christiana Care Health System, Newark, United States

Candida species with reduced susceptibility to fluconazole are being noted in increasing numbers. A retrospective review of sequential clinical *Candida* isolates helped clarify demographics, risk factors, and outcomes of patients with non-susceptible *Candida* isolates. Antifungal susceptibility testing is done upon request in our institution. Thirty-six isolates from 31 patients were tested in 2002 with 22 being susceptible (S). Of the fourteen non-susceptible isolates, five were dose dependent (S-DD) and nine were high-level resistant (R) to fluconazole. Dose-dependent and high-level resistant species included *C. glabrata* (2/11), *C. parapsilosis* (13/0), *C. tropicalis* (6/0), *C. guilliermondii* (1/0), *C. lusitaniae* (0/1), and *C. krusei* (0/1).

Risk factors for non-susceptible isolates included younger age, prior azole use, blood stream isolates, prolonged hospitalization, prolonged intensive care unit stay, and non-abdominal surgical procedures. Two patients in the non-susceptible group expired, whereas no patients in the susceptible group expired. Although not significant, this may indicate a trend towards higher mortality in the non-susceptible fluconazole group. Fluconazole resistance is increasing among non-albicans *Candida*. Subtle differences among the patient populations may help to predict and eventually control spread of the resistant isolates.

EPIDEMIOLOGY OF CLINICAL ISOLATES OF FLUCONAZOLE RESISTANT *CANDIDA*

Piper J, Couch K, Steele-Moore L, Tuttle D, Christiana Care Health System, Newark, United States

Candida species with reduced susceptibility to fluconazole are being noted in increasing numbers. A retrospective review of sequential clinical *Candida* isolates helped clarify demographics, risk factors, and outcomes of patients with non-susceptible *Candida* isolates. Antifungal susceptibility testing is done upon request in our institution. Thirty-six isolates from 31 patients were tested in 2002 with 22 being susceptible (S). Of the fourteen non-susceptible isolates, five were dose dependent (S-DD) and nine were high-level resistant (R) to fluconazole. Dose-dependent and high-level resistant species included *C. glabrata* (2/11), *C. parapsilosis* (13/0), *C. tropicalis* (6/0), *C. guilliermondii* (1/0), *C. lusitaniae* (0/1), and *C. krusei* (0/1).

Risk factors for non-susceptible isolates included younger age, prior azole use, blood stream isolates, prolonged hospitalization, prolonged intensive care unit stay, and non-abdominal surgical procedures. Two patients in the non-susceptible group expired, whereas no patients in the susceptible group expired. Although not significant, this may indicate a trend towards higher mortality in the non-susceptible fluconazole group. Fluconazole resistance is increasing among non-albicans *Candida*. Subtle differences among the patient populations may help to predict and eventually control spread of the resistant isolates.

FLUCONAZOLE HETERORESISTANCE IN *CANDIDA PARAPSILOSIS*

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Background: We experience a case of blood stream infection due to *C. parapsilosis* in a patient following cardiac surgery. Here we describe the characteristics of serial isolates of *C. parapsilosis* demonstrated increasing resistance to fluconazole in vitro.

Methods: The five isolates of *C. parapsilosis* were obtained from a patient operated on mitral valve. Antifungal susceptibility was determined by NCCLS microdilution method and E test. Strain identity was determined by pulse field gel electrophoresis. Population analysis was performed to determine whether the phenotype switch is a clonal event or associated with substrain selection. Fluconazole resistant isolates were subcultured in medium without fluconazole to examine stability.

Results: The initial isolate(CP1) was fluconazole susceptible(MIC 2 µg/ml), however, the isolates(CP2 – CP5) developed resistance after a brief usage of fluconazole. DNA typing revealed development of resistance in a persistent strain. On population analysis, CP1 formed colonies on plates containing 64 µg/ml fluconazole at frequencies of 10^{-4} . Clinical isolates CP2, 5 and resistant subclone derived from CP1 demonstrated a homogenous population of resistant cells on plates containing 64 µg/ml fluconazole. The induced resistance was reversible through serial transfers in fluconazole-free media over a period of 30 days.

Conclusions: Fluconazole-heteroresistant phenotype of *C. parapsilosis* was observed in blood stream isolates from a cardiac surgery patient. Fluconazole resistance can be developed by a selection from heteroresistant clones by exposure to fluconazole.

SUSCEPTIBILITY OF GLOBAL ISOLATES OF *CANDIDA* SPECIES TO FLUCONAZOLE AND VORICONAZOLE BY DISK DIFFUSION

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Purpose: To determine the in vitro susceptibility of *Candida* species to fluconazole and voriconazole using a disk diffusion method recently endorsed by the NCCLS. For fluconazole, 79,664 yeast isolates were tested from mid-1997 through 2001 and, for voriconazole, 18,569 yeast isolates were tested in 2001. Study data were contributed by 89 centers in 35 countries.

Methods: All isolates were adjusted to provide inocula equivalent to a 0.5 McFarland turbidity standard, and were cultured onto Mueller-Hinton agar medium supplemented with 2% glucose and 0.5 mcg/mL methylene blue. Antifungal agents were tested employing a commercially prepared 25 mcg fluconazole disk, or a 1 mcg disk for voriconazole. Test plates were incubated for 18-24 hrs, and automatically read and electronically recorded using BIOMIC Image Analysis Systems. Duplicate isolates and uncontrolled test results were not included in the analyses. In accordance with NCCLS-accepted guidelines for fluconazole, zones of inhibition of 19 mm or more indicated Susceptible (S) isolates, 15-18 mm indicated Susceptible-Dose Dependent (S-DD) isolates, and 14 mm or less indicated Resistant (R) isolates.

Results: 98.4% of 52,987 *C. albicans* were susceptible to fluconazole. The highest resistance rate for *C. albicans* was found in Ecuador (8.6% of 512 isolates). Between 1997-1998 and 2001, the proportion of *C. albicans* decreased from 69.7% to 63% of all isolates, and there was a parallel increase in the numbers of *C. tropicalis* and *C. parapsilosis* isolates. Excluding *C. krusei*, the overall susceptibility of all *Candida* species to fluconazole was 93.0% (S only) or 96.1% (S and S-DD). For voriconazole, zone diameters were reported, although interpretive criteria have yet to be determined.

Conclusions: The disk diffusion assay provides a rapid, reproducible, and cost-effective method for determining the susceptibility of *Candida* species to the triazoles, fluconazole and voriconazole. Additionally, this assay may serve as the basis for development of disk diffusion susceptibility testing for other classes of antifungal agents.

SEROTYPES DISTRIBUTION AND DRUG SUSCEPTIBILITIES OF *CRYPTOCOCCUS NEOFORMANS* AND *CANDIDA ALBICANS* FROM CLINICAL SOURCES IN NAIROBI, KENYA

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The HIV epidemic in Africa has led to an increase in the incidence and morbidity due to opportunistic fungi. Cryptococcal meningitis and *Candida albicans* infections are some of the most commonly encountered conditions in clinical practice in Kenya. It is estimated that up to 40% of HIV/AIDS develop cryptococcal meningitis. Due to the high frequency and the severe clinical manifestations of *Cryptococcus* infection, we determined the serotype distributions and drug susceptibility profiles of *Cryptococcus neoformans* and *Candida albicans* from clinical sources.

Twenty-eight *C. neoformans* isolates from cerebrospinal fluids of patient with meningitis and thirty-two *Candida albicans* from sputum, blood culture, broncho alveolar lavage fluid and urine were serotyped and drug susceptibility determined. Preliminary identification was done on ChromAgar *Candida* and confirmed by Api 20 C aux (bioMérieux, France). Serotyping was done by slide agglutination test using *Candida* and Crypto Check antisera (Iatron Co., Japan). *Candida* susceptibility to amphotericin b, fluconazole, 5-fluorocytosin, and miconazole was done using Asty antifungal susceptibility testing for yeasts (Asty, Kyokuto, Japan). Susceptibility of *Cryptococcus* to amphotericin B was determined using broth microdilution technique.

All *C. albicans* isolates were serotype A while 19/32 (59.4%) had MIC $\geq 1\mu\text{g/ml}$ to amphotericin b. Only one strain of *C. albicans* had MIC $\leq 64\mu\text{g/ml}$ to 5-fluorocytosin while 2 and 6 strains were susceptible dose dependent (MIC of 16-32 $\mu\text{g/ml}$) to fluconazole and miconazole respectively.

Most [9/28 (32.1%)] *C. neoformans* isolates were serotype A the rest were either serotype D, AD or AB but there were 9/28 isolates which did not agglutinate with the typing sera. Seventy five percent of the *C. neoformans* isolates had MIC of 0.5 $\mu\text{g/ml}$ to amphotericin b while 4 isolates had MIC of $\geq 1\mu\text{g/ml}$. The rest of the isolates had MIC of $<0.25\mu\text{g/ml}$.

The study highlighted the high prevalence and significance of Cryptococcal infection in Kenya and the existence of different serotypes, there is need to establish a possible environmental source contributing to high cryptococcal infections in Kenya. There are some fungal strains with elevated MIC to antifungal drugs that needs to be further characterized. Due to HIV/AIDS pandemic, opportunistic fungal pathogens have increased significantly, therefore, there is a need to improve technical and infrastructural capabilities for diagnosis of fungal infections. Molecular characterization and drug resistance studies are essential for mounting appropriate clinical management strategies for fungal infections in third world countries.

TRENDS OF CANDIDEMIA AMONG SURGICAL INTENSIVE CARE UNIT (SICU) PATIENTS

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Candida species have become a common cause of bloodstream infections (BSI) among patients in surgical intensive care units. Starting in 1995, early presumptive therapy with fluconazole 400mg IV was recommended for SICU patients at high-risk for systemic *candida* infection. The emergence of non-*albicans* *Candida* species should direct efforts to re-evaluate antifungal use.

Purpose: Evaluate SICU specific antifungal drug use and the trend in incidence of BSI due to different *Candida* species.

Method: A 2-year retrospective analysis of patients admitted to the 27-bed SICU between January 1, 2001 and December 31, 2002 was done. SICU specific antifungal drug usage data was electronically transferred to a program specific for this analysis. Antifungal use was expressed in defined daily doses (DDD) listed in the table. Microbiology data included all *Candida* BSI from 1995-2002. Microbiology data from 1995-2000 was pooled since SICU specific antifungal use was not available. Demographic data included the total number of patients admitted or transferred to the SICU and their mean length of stay.

Results:

Candidemia	2001 n=8	2002 n=13	Antifungal DDD	2001 doses (%)	2002 doses (%)
<i>C. albicans</i>	0	6	Fluconazole 400mg	2713 (67%)	2599 (62%)
<i>C. tropicalis</i>	5	4	ABLC 350mg	330 (8%)	322 (8%)
<i>C. glabrata</i>	2	1	Amphotericin B 50mg	990 (25%)	814 (19%)
<i>C. parapsilosis</i>	0	2	Caspofungin 50mg	0	448 (11%)
<i>C. utilis</i>	1	0			

Microbiology data from 1995-2000 revealed an average of 14 *Candida* BSI/year, 56% were *C. albicans*. Non-*albicans* *Candida* species accounted for 100% of BSI in 2001 and 54% in 2002. The number of patient admits/transfers to the SICU in 2001 and 2002 were 2,706 and 2,641 respectively, with an average length of stay = 4.81 and 4.87 days.

Conclusion: Non-*albicans* *Candida* BSI are prevalent in this SICU. Fluconazole is the primary empiric/presumptive antifungal. Caspofungin or high-dose fluconazole may be more prudent for empiric/presumptive use, until the *Candida* species is identified. The recent availability of SICU specific antifungal data will allow us to perform analyses correlating fluconazole use and rates of BSI due to non-*albicans* species of *Candida*.

SUPERFICIAL AND CUTANEOUS FUNGAL INFECTIONS IN RENAL TRANSPLANT PATIENTS OF GUATEMALA

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old -- Pellecer D, Samayoa B, Logemann H, Clinica Familiar, Hospital General San Juan de Dios, Guatemala City, Guatemala

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Background: Patients undergoing renal transplants are immunocompromised and susceptible to infections. 5-14% of the transplant patients acquire fungal infections, especially during the first 3 to 6 months following the transplantation. The object of this study is to determine the agents and factors that contribute to superficial and cutaneous fungal infections following renal transplantation.

Methodology: 93 renal transplant patients were enrolled in the study. All patients received a renal transplant between the years of 1987 to 2000. Patients were invited to participate in the study during their post-surgery examination. After enrolling in the study, the patients were interviewed and examined for any dermatological lesions during the months of January and May of 2001. Samples were taken of any skin lesion for laboratory investigation, and clinical and epidemiological data were collected. Epidemiological data included demographical description, daily habits, and pre- and post-transplant clinical features and lab findings. The data was collected in EPI INFO 6.0 and statistical analysis was performed using univariate and bivariate analysis, through the Chi square frequency tests.

Results: 43% of the patients (40) had diagnosed skin lesions, 65% of which were of fungal etiology. Of those with diagnosed skin lesions, 70% of the men were found to have fungal lesions where as only 43% of the women had confirmed fungal lesions. In general, we did not observe any variable that predisposed patients to fungal infections.

Conclusions: The fungal agent most frequently isolated in the transplant patients was *Trichophyton rubrum*. The toenail was the major site of infection by this agent. The second most common fungal agent was *Malassezia furfur*. Although there were no statistically significant differences in any of the predictive variables, we found the prevalence of fungal infection in renal transplant patients (26%) is higher than those found in other studies.

COCCIDIOIDOMYCOSIS AND RENAL TRANSPLANTATION: A RETROSPECTIVE STUDY OF 33 CASES OF COCCIDIOIDOMYCOSIS IN RENAL TRANSPLANT RECIPIENTS FROM EL PASO AND THE SOUTHWEST

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Coccidiomycosis is endemic in the southwestern United States and impaired cellular immunity profoundly increases the susceptibility to life threatening coccidial infections. This study examines the clinical presentation of Coccidiomycosis in renal recipients transplanted in El Paso from 1987-2002 and 28 other cases published in the literature from 1966-2002. The five El Paso cases occurred in a population of 297 transplant recipients (Cadaveric 203, living related donor 94) and represented XXXX of that population. (By contrast the background rate in the population over those years is estimated to be roughly 1 per 10,000). The total population of 33 patients included 24 males (73%) and 9 females (27%). The age distribution was 14- 63 yrs with a median age of 38 years. Fifty-four % patients were Caucasian, 33% Hispanic 3%, African- American, 3% Indian, and 3% Asian. There were 23 cadaveric recipients (70%) and 10 live related donor recipients (30%). Underlying renal diseases included CGN 48%, diabetes mellitus 30% SLE 3%, Alport's 3%, and unknown 15%. *Coccidioides immitis* was isolated from the lung in 79% of patients, spleen in 18% of patients, and urine in 21% pts. The initial clinical presentation included fever with clinical and radiographic evidence of pneumonia in a majority of the patients. The average time between transplantation and the diagnosis of infection was XXXX months. The shortest interval was 15 days and the longest interval was 50 months. Disseminated coccidiomycosis occurred in 8 patients who were treated with amphotericin B. Treatments included amphotericin in 29 (88%) of the pts and fluconazole in 6 (18%) patients). Death occurred in 18 (55%) patients with half of these dying from disseminated coccidiomycosis and the other half dying of causes unknown to us. There did not appear to be an increase in the mortality in patients who had diabetes mellitus. In this retrospective study, a majority of case of coccidioidomycosis occurred in white males. Pulmonary coccidiomycosis appeared to be the major presentation but a significant number of patients presented with involvement of the genitourinary tract. The majority of the patients were treated with amphotericin. Successful cure occurred in 15 (45%) of the patients. Prospective studies to determine appropriate antifungal medication, duration of treatment and risk factors would be helpful in preparing guidelines for these patients.

CRYPTOCOCCUS NEOFORMANS INFECTION IN SOLID ORGAN TRANSPLANT (SOT) RECIPIENTS

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OBJECTIVE: *C. neoformans* is the third most common type of fungal infection complicating SOT. We performed a retrospective study to assess the clinical characteristics and outcomes of cryptococcal infection following SOT.

METHODS: Using the Mayo Clinic clinical microbiology laboratory database, 89 patients with cryptococcal infection, as indicated by culture, microscopy, and/or serology, were identified during a 10-year period from 1990 to 1999. The medical records of SOT patients were reviewed for clinical characteristics, treatment and outcome.

RESULTS: Fifteen (17%) of 89 cases occurred in kidney (n = 7), liver (n = 5), or heart (n = 3) transplant recipients. The mean patient age was 55 years (range, 40-71); 11 were male. The median time to onset of infection was 30 months post-SOT (range, 2-159); 75% of cases occurred > 6 months post-SOT. All patients were receiving prednisone (median daily dose, 12.5 mg); 11, cyclosporine; and 7, azathioprine. The median CD4 count at diagnosis was 85 cells/uL (range, 5-195). Nine (60%) of the 15 patients had meningitis with or without other organ involvement; headache (9/9), fever (8/9), and changes in mental status (2/9) were the presenting symptoms; spinal fluid studies [median (range)] included WBC 20/uL (1-56), protein 98 mg/dL (52-495), glucose 51 mg/dL (10-137), and cryptococcal antigen titer of 1:128 (up to 1:8192). Six (40%) of the 15 patients had non-meningeal [urinary tract (n = 2) and pulmonary (n = 4)] infections, including two with asymptomatic pulmonary cryptococcoma. Skin involvement was documented by biopsy in 3 (20%) and skeletal symptoms were observed in 4 (27%) of 15 patients. Fourteen patients received therapy with fluconazole alone (n = 4) or an amphotericin B preparation (n = 10; median total dose of amphotericin B deoxycholate, 1161 mg) in combination with 5-FC (n = 5) followed by fluconazole for a median duration of 4 months (range, 0.5-48). During the median follow up period of 44 months (range, 0.5-123), two patients died of cryptococcal infection; nine patients were cured and died of causes unrelated to cryptococcal infection; three patients were alive and free of cryptococcal infection; and one patient remained on fluconazole because of relapse following the discontinuation of anti-fungal therapy.

CONCLUSION: Cryptococcal infection is usually a late complication of SOT. While meningitis is the most common presentation, the clinical spectrum varies widely from an asymptomatic lung nodule to fatal multiorgan disease. Amphotericin B and/or fluconazole are effective for treatment. The duration of drug administration should be individualized. Multicenter collaboration is being undertaken to further identify risk factors and to define optimal strategies for prevention and treatment of cryptococcosis in SOT recipients.

CANDIDA GLABRATA FUNGEMIA IN IMMUNOCOMPROMISED CANCER PATIENTS: EPIDEMIOLOGY AND OUTCOME ANALYSIS

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Between January 1993 and may 1998, we identified 96 immunocompromised cancer patient (Pts) with *Candida glabrata* fungemia. With the widespread use of Fluconazole prophylaxis after 1992 at our center, the incidence of *C.glabrata* fungemia increased. Most immunocompromised cancer Pts with *C.glabrata* fungemia were neutropenic (47%). The underlying disease was leukemia (47%), solid tumor (38%) , and lymphoma(15%) . Most (64%) of these Pts with *C.glabrata* fungemia received flucnazole prophylaxix prior to the onset of fungemia.

Disseminated infection occurred in 37 Pts(39%), while 15% of all *c. glabrata* fungemia infections were catheter – related. Breakthrough candidemia on omphotencin Bor liposomal compound regimen occurred in 10 Pts , 5 of whom had disseminated infection. *C. glabrata* fungemia was the primary cause of death in 13 Pts (14%) and was a contributing factor to death in 29 other Pts (39%). In conclusion, *C.glabrata* fungemia in immunocompromised cancer Pts is associated with high frequency of dissemination and mortality. This infection should be considered in any febrile immunocompromised cancer patient.

PATHOGENICITY, HEAVY METAL AND OXIDATIVE STRESS SENSITIVITY OF *CANDIDA ALBICANS* MORPHOLOGICAL MUTANTS AND THEIR HYBRIDE

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The wild-type strain of *Candida albicans* (ATCC 10261) was used to obtain stable auxotrophic colony morphological mutants by repeated induced mutagenesis. Mutant M5 produced wavy colonies containing only true hyphae while mutant M2 exhibited undulated colonies containing 90% blastospores and 10% pseudohyphae. The intraspecific somatic hybride of these two mutants induced by Ca²⁺-PEG produced two types of prototrophic stable clones. The colonies of clone VI.9S were smooth and contained only blastospores which proved the full complementation and recessive character of genes responsible for morphogenesis. Clone VI.1M exhibited regular-wrinkled colonies containing a new, unipolar budding, extended cell type that has never been observed in natural isolates. This phenotype suggested the partial complementation and semi-dominant character of mutated genes.

The increased DNA content of hybride clones was detected by flow cytometry measurement. Eight ctosomes of mutants were visualized by karyotyping while hybride clones VI.9S and VI.1M had ten and twelve bands of different type, respectively. It might suggest their aneuploidity. Increased ploidity did not result in an elevated level of tolerance to heavy metals (CrO₂-7, Cu²⁺) and oxidative stressors (Cd²⁺, menadione), but the sensitivity of mutant M5 to these agents was inherited and expressed in hybride clone VI.1M. All other behaviour types of clone VI.1M namely sensitivity to nystatine, amphotericin B, miconazole; adhesion ability to inert surface; pathogenicity to mice; isoenzyme patterns, and RAPD-PCR patterns, showed genetic similarity to M5 parental mutant, while hybride clone VI.9S reminded us of M2 parental one.

DERMATOPHYTE FUNGI CONTAMINATIONS IN 16 PUBLIC BATHROOMS IN GOLPAYEGAN, IRAN

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It has been established that bathrooms contribute to the spread of dermatophytosis in susceptible hosts. The recent studies indicate that, the infection of dermatophytosis is increasing in different cities of Iran, but the species of fungus agent in each city is different. The fungal contamination of 16 indoor public bathrooms was investigated by the method of carpet sampling. 224 samples from the floor, slippers, dressing rooms and related areas of each bathroom were tested for the presence of dermatophyte fungi in different places of the city. In this investigation, different dermatophytes such as *Trichopyton rubrum* and *Trichophyton mentagrophytes* were observed in very low level, but the most common dermatophyte recovered was *Microsporum gypseum*. *M.gypseum* is a geophilic dermatophyte and it seems that, the reason of high spreading level of this fungus in this city, is because of materials that are used in bathroom buildings (clay and straw) and special climate condition of Golpayegan. The fungal contamination of these bathrooms under specific conditions could be an alarm for induction of dermatophytosis in compromised and susceptible hosts.

ASSESSMENT OF CASES WITH PULMONARY ASPERGILLOMA ADMITTED TO MASIH DANESHVARI HOSPITAL BETWEEN 1990-2000

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Pulmonary aspergilloma generally arises from colonization of aspergillus in pre-existing lung cavities. Among the predisposing factors, pulmonary tuberculosis, bronchiectasies, sarcoidosis and lung tumors are of high prevalence. The majority of the patients were free of symptoms, but if symptomatic haemoptysis was the most common clinical presentation. Fungus ball sign is the hallmark of radiological examination. Pathologic examination is the most accurate diagnostic method. Symptomatic patients especially with haemoptysis need treatment. Emergent surgery is the method of choice, though many successful results have been reported by application of various medical treatments.

13 patients were retrospectively evaluated with definite pathological diagnosis of pulmonary aspergilloma, representing patients admitted to Masih Daneshvari hospital between 1990 and 2000.

7 male (54%) and 6 female (46%) with a mean age of 43 years (ranging from 22 to 60 years) were examined. Eleven patients (85%) were Iranian and 2 (15%) were Afghan. Haemoptysis (92%) was the most common clinical finding and Tuberculosis (70%) was the most common underlying lung disease. Considering radiological examinations only 5 patients (38%) had probable diagnosis of Aspergilloma prior to surgery. All the patients were undergone operation among which the most frequent symptoms indicating surgery was haemoptysis (77%). Left upper lobe (62%) was the most frequent anatomic site of disease. Among the study population, no preoperative or postoperative deaths occurred.

Our results confirm that aspergilloma is of high prevalence in Iran. Clinical presentations, epidemiological etiology, radiological and pathologic findings must be considered to make accurate diagnosis and prompt treatment.

FUNGAL TOENAIL INFECTIONS IN NEUTROPENIC PATIENTS

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Toenail onychomycosis is characteristically caused by *Candida* and dermatophytes in immunocompetent patients. Less than 1% of onychomycosis is related to *Fusarium*. We have observed at our institution that toenail infections in neutropenic patients with hematologic malignancy can lead to disseminated fungal infections, especially the mold *Fusarium*. We reviewed all positive fungal cultures from nails removed for suspected fungal infection during the time period of 1985 to present at the our center. Cancer diagnosis, stem cell transplant status, duration of neutropenia, imaging of sinuses and lungs, treatment, and outcome were noted.

Sixteen cases met study requirements. Ten infections were secondary to *Fusarium*, four secondary to *Aspergillus*, two to *Trichophyton* and one to *Paecilomyces*. One patient was infected with both *Fusarium* and *Aspergillus*. Dissemination occurred more commonly in patients with prolong neutropenia, a *Fusarium* isolate, and resulted in death more often than non-disseminated cases. The key to treatment is to remove and culture the nail as this practice allows for an accurate diagnosis. In addition, it is important to remove the nail as a foreign body and to eradicate the primary focus of infection. In relation to *Fusarium*, proposed portals of entry for disseminated *Fusarium* infection have included the sinuses, gastrointestinal tract, intravascular catheters and toenails. Previously, few treatment options existed for disseminated *Fusarium* infections. *Fusarium* is relatively resistant to Amphotericin B including lipid formulations, fluconazole, itraconazole and caspofungin. In our experience, the newer generation azoles such as voriconazole are effective in treating disseminated *Fusarium* infections with a lower mortality and more rapid clinical response even when the brain is involved. Regardless of treatment, the longer the duration of neutropenia, the higher the mortality rate.

ANTIFUNGAL AGENTS PROBABLY INFLUENCE THE CHANGE OF THE EPIDEMIOLOGY OF FUNGEMIA

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Background: It is reported that the incidence of invasive fungal infections is increasing over the past 2 decades. Several investigators have reported that the incidence of fungemia caused by non-*albicans* species of *Candida* is increasing because of indiscriminate use of fluconazole (FLCZ), but others have reported that such change of the epidemiology of fungemia was not observed. In our country, the new antifungal agent can be used from December 2002, it is important that the analyzing of trends in antifungal use and the epidemiology of fungemia before clinical use of the new agent.

Purpose: To evaluate the trends in incidence of fungemia due to different yeast species during the past 2 decades, we analyzed data from 1982 to 2001 in a university hospital.

Methods: The medical records of patients with fungemia at our university hospital between 1982 and 2001 were retrospectively reviewed. We divided the 20 years into 4 periods according to the change of antifungal agents use (period 1: 1982-1985 (before miconazole use), period 2: 1986-1988 (before FLCZ use), period 3a: 1989-1994 (dose of FLCZ use were below 1000g/year at the hospital), period 3b: 1995-2001 (FLCZ use were over 1000g/year)). Both the trends in the epidemiology of fungemia and antifungal agents use were analyzed.

Results: 188 isolates of fungi were isolated from 181 patients in the 20 years. The incidence of fungemia increased until period 3a, but significantly decreased in period 3b. The isolated fungi were *Candida parapsilosis* (31%), *C. albicans* (31%), *C. tropicalis* (10%), *C. glabrata* (8%), *Trichosporon asahii* (7%), and so on. During the study period, there was no change in incidence of *C. albicans* infection but a significant increase of *C. glabrata* infection ($p < 0.05$) and a significant decrease of *T. asahii* infection ($p < 0.01$). In addition, of 36 cases of breakthrough fungemia, the incidence of *T. asahii* isolates was decreasing but *C. glabrata* isolates was increasing in recent period.

Conclusions: There was a significant increase of *C. glabrata* infection and a significant decrease of *T. asahii* in study period. Antifungal agents probably influence the change of the epidemiology of fungemia.

TOXINOGENICITY OF *ASPERGILLUS FUMIGATUS* AND *A. VERSICOLOR* STRAINS ISOLATED FROM PULMONARY ASPERGILLOMA

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Pulmonary aspergilloma-secondary form of pulmonary aspergillosis, is caused mainly by *Aspergillus* species chronic colonisation of lung tissue. Some strains of *Aspergillus* species have ability to produce mycotoxins, and their role in development of aspergilloma is not well understood. The aim of this study was to determine toxinogenicity of *Aspergillus* species isolated from operated lung tissue (pulmonary lobes) in 12 cases (8 males and 4 females) of pulmonary aspergilloma. Defrost tissue samples were twice examined by aseptic inoculation on Sabouraud agar with streptomycin and penicillin (20:40), and incubation at 25°C+2 for 7 days. Identification of *Aspergillus* species was done on basis of macro and microscopic subculture characteristics on Czapek agar according to keys (Thom and Raper, 1945; de Hoog et al., 2000). Toxinogenicity of isolated *Aspergillus* strains was examined in vitro on liquid yeast medium. One ml of suspension of conidia (10⁸/mL) from each strain was inoculated in sterile liquid yeast medium (25 mL), and incubated at 25°C for 14 days with daily shaking. Qualitative and quantitative analysis of mycotoxins were carried out by previously described multityxin TLC method (Balzer et al., 1978), and by TLC method for detection of gliotoxin (Richard et al., 1996). *Aspergillus* species were found in 5 samples of lung tissue, including 3 strains of *A. fumigatus* and 2 strains of *A. versicolor*. In biosynthesis, *A. fumigatus* strains produced aflatoxin B₁ (AFB₁) in concentration range from 0,0025 to 0,145 µg/ml, and 2 strains produced AFB₁ and AFG₁ simultaneously, in range from 0,033 to 0,042 µg/ml of biomass. Gliotoxin production was not detected. Multityxinogenicity of 2 *A. versicolor* strains was also established. These strains produced AFB₁ (0,0035-0,0094 µg/ml), and sterigmatocystin (0,5-6,67 µg/ml). Mycotoxinogenicity of *Aspergillus* can be one of possible virulence factors responsible for development of pulmonary aspergilloma.

FUNGAL INFECTIONS AS AN IMPORTANT CAUSE OF SEVERE SEPSIS

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Severe sepsis affects over 750,000 Americans annually with a mortality rate of 30-50%. This process is associated with a significantly increased inflammatory response and coagulopathy which leads to multi organ system failure and death. Although previously associated with gram negative bacterial infections recent studies have delineated the equal importance of gram positive organisms. Fungal infections are known to cause severe sepsis but the importance of their role is not clear. Fungal infections are often considered more indolent in nature and mortality (M) is ascribed to the underlying disease and infirmity of the patient. In the recently published PROWESS Study, drotrecogin alfa (activated) (DAA) was shown to be effective in reducing absolute mortality from severe sepsis by 6.1% compared to placebo. Analysis by infecting organisms for DAA group showed placebo mortality from gram positive infections at 30.4% and gram negative mortality at 28.8%.

Fungal infections (N=62) had a placebo mortality of 56.3% but a 6.3% decline in mortality in the treatment arm similar to the other infectious groups. Biomarker analysis showed that D-Dimers were similarly elevated in gram negative and fungal infections compared to gram positives. Protein C levels were similarly reduced at 41% of normal. Protein S levels were lowest in fungal infections and IL-6 levels were highest compared with other infectious causes. This suggests a particularly high inflammatory response and coagulopathy in this group of fungal infections with severe sepsis. APACHE II scores were similar by infection type but the higher mortality suggests that the fungal infection and not the underlying patient condition contributed to the excess mortality. Fungal infection has been underappreciated as a cause of severe sepsis. This data suggests the importance of early diagnosis and treatment of fungal infection as the key to preventing fungal sepsis complications.

A COMPARISON OF CLINICAL SYMPTOMS OF *PNEUMOCYSTIS CARINII* PNEUMONIA BETWEEN HIV AND NON-HIV PATIENTS

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[Background] *Pneumocystis carinii* pneumonia (PCP) is known as an opportunistic infection which occurs in patients with human immunodeficiency virus (HIV) infection, with malignancies or receiving steroid therapy. It is reported that PCP in patients with HIV may develop in a course of several weeks without any clinical symptoms, but in contrast to this, PCP in non-HIV patients can rapidly develop with severe clinical symptoms in three to six days. We therefore divided patients with PCP into HIV positive and negative groups and evaluated their clinical symptoms.

[Materials and Method] We retrospectively evaluated 17 patients with PCP which was diagnosed by Grocott's stain or polymerase chain reaction from specimens of bronchoalveolar lavage. 11 patients were HIV positive and 6 patients were HIV negative.

[Results] In non-HIV group, their underlying diseases included three patients with solid malignancies, three hematologic malignancies, one dermatomyositis and one who had received renal transplantation. All patients had started receiving steroid therapy and had been under tapering the doses of steroid. The mean interval of steroid administration was about 7.3 weeks. Between the two groups, serological parameters such as white blood cell count, C-reactive proteins and lactate dehydrogenase were not statistically different, but CD4/CD8 was statistically different (0.13 in HIV group and 1.07 in non-HIV group). The interval from onset of symptoms to diagnosis of PCP was 42.6 days in HIV group and 9.4 days in non-HIV group. The area of pulmonary infiltration in chest X-ray was 61.8% in HIV group and 88.3% in non-HIV group.

[Conclusion] A comparison between HIV group and non-HIV group revealed a slowly progressing clinical course in HIV group and a relatively larger area of pulmonary infiltration in non-HIV group.

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH A HISTORY OF PRIOR INVASIVE ASPERGILLOSIS: OUTCOMES AND RISKS FOR POST-TRANSPLANT INVASIVE ASPERGILLOSIS

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Background: Patients with a history of invasive aspergillosis (IA) prior to transplantation may be at high risk for IA recurrence and transplant-related mortality (TRM) after allogeneic hematopoietic stem cell transplantation (HCT). This study was performed to compare the incidence of post-transplant IA, TRM, and overall survival among patients undergoing allogeneic HCT with or without a history of IA, and to identify the risk factors for post-transplant IA and TRM in patients with a history of prior IA.

Methods: Data from 2319 patients who underwent first allogeneic HCT at the FHCRC between December 1992 and May 2001 were reviewed. Prospective monitoring by pre-transplant evaluation of the recipients identified 45 patients (1.9%) with a history of IA prior to HCT. In general, patients with a history of IA were treated with antifungals for at least one month prior to HCT.

Results: Post-transplant IA occurred earlier (median onset; day 26 vs. day 54, $p=0.03$) and more often (at day 100; 22% vs. 7%, $p=0.0001$) in patients with a prior history of IA compared to those without prior IA. Patients with a history of IA had a higher risk for transplant-related death by day 100 (38% vs. 21%, $p=0.0001$), associated mainly with IA recurrence and other pulmonary complications. Overall survival at day 100 was significantly lower (56% vs. 77%, $p=0.0001$) in patients with a history of IA compared to those without prior IA. Factors that predicted a low risk for post-transplant IA recurrence included receipt of antifungals for greater than one month prior to HCT (6/39 vs. 4/6, $p=0.001$) and resolution of abnormal chest X-ray (1/15 vs. 6/19, $p=0.06$). Cord blood transplantation appeared to be associated with a high risk of IA recurrence (2/2 vs 8/43, $p=0.001$) and TRM (2/2 vs 16/43, $p=0.008$). TBI-containing myeloablative conditioning was associated with an increased risk of day 100 TRM when compared to nonmyeloablative and non-TBI myeloablative conditioning regimens (16/31 vs. 2/14, $p=0.03$).

Conclusions: Duration of antifungal therapy, conditioning regimens, and stem cell source are important variables to consider to minimize the risk for IA recurrence after allogeneic HCT.

INVASIVE FUNGAL INFECTIONS IN RECIPIENTS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION AFTER NONMYELOABLATIVE CONDITIONING: RISKS AND OUTCOMES

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The incidence of invasive mould infections has increased during the 1990s among allogeneic hematopoietic stem cell transplantation (HCT) recipients after myeloablative conditioning. In this study, we determined risk factors for invasive fungal infections and infection-related death among 163 patients after allogeneic HCT with nonmyeloablative conditioning at a single transplant center between December 1997 and October 2001. The cumulative incidence rates of proven or probable invasive fungal infections, invasive mould infections, invasive aspergillosis, and invasive candidiasis during the first year after allogeneic HCT with nonmyeloablative conditioning were 19%, 15%, 14%, and 5%, respectively, which were similar to those after conventional myeloablative HCT. Invasive mould infections occurred late after nonmyeloablative conditioning (median, day 107), with primary risk factors including severe acute graft-versus-host disease (GVHD), chronic extensive GVHD, and cytomegalovirus (CMV) disease. Half of the invasive mould infections occurred within 46 days and 84% occurred within 6 months after beginning corticosteroid therapy for GVHD. The one-year survival after diagnosis of mould infections was 32%. High dose of corticosteroid therapy at diagnosis of mould infection was associated with an increased risk for mould infection-related death. Overall, non-relapse mortality was estimated at 22% (36 patients) after nonmyeloablative conditioning, of which 39% (14 patients) were mould infection-related (9% of the overall mortality). More effective strategies are needed to prevent invasive mould infections, which currently account for a notable proportion of non-relapse mortality after nonmyeloablative allogeneic HCT.

CLINICAL PREDICTIVE MODELING IN CHILDREN

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Background: Neonatal candidemia is difficult to diagnose and often fatal. Empirical antifungal therapy is associated with improved survival in neonates and patients with fever and neutropenia. Although guidelines for empirical therapy exist for patients with fever and neutropenia, these do not exist for neonates.

Design: Multi-center retrospective cohort study of neonatal intensive care unit patients (N=6,172). We evaluated all blood cultures (N=21,233) from neonates older than day of life 3 with birthweight \leq 1250 grams, and performed multivariable conditional logistic regression of risk factors for candidemia. From the regression modeling coefficients, we developed a candidemia score.

Results: In multivariable modeling, thrombocytopenia [Odds Ratio (OR)=3.56; 95% Confidence Interval (CI) 2.68, 4.74] and cephalosporin or carbapenem use in the seven days prior to obtaining the blood culture (OR=1.77; 95%CI=1.33,2.29) were risk factors for subsequent candidemia. Children 25-27 weeks estimated gestational age [OR=2.02; 95%CI=1.52,3.05] and children born $<$ 25 weeks (OR=4.15, 95%CI 3.12,6.29) were at higher risk of developing candidemia than children born \geq 28 weeks. Children with a candidemia score \geq 2 points were classified as having a "positive" candidemia score. The candidemia score had a sensitivity of 85% and specificity of 47%.

Conclusions: We developed a clinical predictive model for neonatal candidemia with high sensitivity and reasonable specificity for candidemia. Based on our model, when a physician obtains a blood culture, all neonates $<$ 25 weeks estimated gestational age and all neonates who have thrombocytopenia at the time of blood culture should receive empirical antifungal therapy. Additionally, if a physician obtains a blood culture from a child 25-27 weeks estimated gestational age that is not thrombocytopenic but has a history of third generation cephalosporin or carbapenem exposure in the seven days prior to the blood culture, the neonate should receive empirical antifungal therapy.

RISK FACTORS OF BREAKTHROUGH INVASIVE FUNGAL INFECTION (IFI) UNDER SECONDARY PROPHYLAXIS (SP) → MULTINATIONAL EUROPEAN STUDY OF THE ID WORKING GROUP OF THE GERMAN SOCIETY FOR HEMATOLOGY AND ONCOLOGY

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Background: With the advent of novel less toxic compounds, fungal infections are treated with more success. Chemotherapy can now even be resumed despite prior proven IFI. The need for SP evolved without prior systematic analysis of risk factors for breakthrough IFI or without defining the population at risk.

Methods: We conducted an ongoing survey in 41 tertiary care centers in on SP regimens currently applied. Multilingual case report forms were accessible via www.neutropen.de. Inclusion criteria are: leukemia or lymphoma, proven/probable IFI according to EORTC/BAMSG during the most recent neutropenic episode (E1), and planned to undergo a next neutropenia (E2).

Results: As of Jan 31, 2003, 169 evaluable pts were included: age 11-88, median 46y, 41% female, 82% AML. Proven IFI (35.5%) in E1 were 39 (23%) aspergillosis, 12 (7.1%) candidiasis, 4 (2.4%) mucormycosis, and geotrichosis, hyalohyphomycosis, trichosporosis, fusariosis and other mycosis in 1 (0.6%) each; probable IFI (64.5%) in E1 involved the lungs in 102 (60.4%) pts, lungs/liver in 4 (2.4%), liver alone, liver/spleen, and lungs/sinus in 1 (0.6%) each.

SP in E2 contained of amphotericin B iv in 60 (35.5%), itraconazole in 91 (53.8%), voriconazole in 10 (5.9%), fluconazole in 13 (7.7%), caspofungin in 9 (5.3%), posaconazole in 1 (0.6%), flucytosine in 1 (0.6%), and none in 22 (13%) patients. Incidences of proven/probable/possible breakthrough IFI under SP among 60 amphotericin B pts were (3/9/5, i.e. 28%), among 91 itraconazole pts (3/11/10, i.e. 26%), and among all (8/24/16, i.e. 28%). Proven IFI in E2 were aspergillosis in 5, and candidiasis, fusariosis and aspergillosis with candidiasis in 1 patients each; probable IFI in E2 involved the lungs in 18, liver in 2, lungs/liver in 2, lungs/spleen in 1 and lungs/CNS in 1 pts; possible IFI accounted for 16 pts. Death occurred in 20 (12%) pts and was attributable to IFI in 6 (4%) pts.

Applying logistic regression for the analysis of possible risk factors revealed that the use of steroids of >2mg/kg for >7d is the only highly significant risk factor for breakthrough IFI ($p < 0.001$). In our model risk factors without statistical significance are the following: laminar air flow, HEPA filter, construction work, remission status of the underlying malignancy, duration of neutropenia, mucositis grade, diabetes mellitus, central venous catheter, parenteral nutrition, cytostatics chosen, anti-lymphocyte antibodies, number of antibiotics, and number of days on antibiotics.

Conclusions: SP after proven or probable IFI is instituted frequently and with various regimens. The incidence of breakthrough second IFI and crude mortality is high in this population. Use of high dose steroids increases the risk for breakthrough IFI. Prospective studies on secondary prophylaxis and risk factors for breakthrough IFI are urgently warranted.

COMPARATIVE SAFETY OF AEROSOLIZED AMPHOTERICIN B LIPID COMPLEX (ABELCET®) AND AMPHOTERICIN B DEOXYCHOLATE (FUNGIZONE®) AS ANTIFUNGAL PROPHYLAXIS IN LUNG TRANSPLANT RECIPIENTS: A RANDOMIZED, DOUBLE-BLIND STUDY

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Purpose: We compared the safety and tolerability of aerosolized administrations of amphotericin B deoxycholate (AmBd) and amphotericin B lipid complex (ABLC) in lung transplant recipients. A secondary objective was to observe the incidence of invasive fungal infections in patients receiving aerosolized amphotericin B formulations as sole prophylaxis.

Methods: We conducted a prospective, randomized (1:1), double-blinded trial in 100 subjects. ABLC (Abelcet®:Elan Pharmaceuticals) and AmBd (Fungizone®:Bristol-Myers Squibb) were administered by nebulizer at doses of 50mg and 25mg (respectively), which were doubled in patients requiring mechanical ventilation. The planned postoperative treatment was once every day for 4 days, then once per week for 7 weeks (total 11 doses). Observations for treatment-related adverse events and invasive fungal infections were continued for 2 months after initiation of study drug.

Results: Intent-to-treat analysis revealed that study drug was discontinued for intolerance in 6/49 (12.2%) and 3/51 (5.9%) in the AmBd and ABLC treated groups, respectively ($p=0.313$). Subjects who received AmBd were more likely to have experienced an adverse event (odds ratio 2.16 95% confidence interval 1.10, 4.24; $p=0.02$). Primary prophylaxis failure within 2 months of study drug initiation was observed in 7/49 (14.3%) of AmBd-treated patients and 6/51 (11.8%) of ABLC-treated patients. No fungal pneumonias were observed. Only 2 patients (2%) experienced documented primary prophylaxis failure with *Aspergillus* infections within the follow-up period.

Conclusions: We conclude that both AmBd and ABLC administered by aerosol following transplant appear to be associated with an acceptable rate of invasive pulmonary fungal infection in the early period after transplant. Furthermore, patients receiving ABLC were less likely to experience a treatment-related adverse event when compared to those who received AmBd.

LOW DOSE LIPOSOMAL AMPHOTERICIN IS EFFECTIVE IN FUNGAL PREVENTION IN ALLOGENEIC STEM CELL TRANSPLANT

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Invasive fungal infections are a significant problem and still a major cause of mortality in the setting of severe neutropenia as seen in allogeneic stem cell transplant (SCT). Empiric use of amphotericin B deoxycholate is associated with as much as 80% nephrotoxicity in the allogeneic SCT setting. These high risk patients may develop fungal infections early in the course of neutropenia or in the setting of severe mucositis and waiting to start empiric broad spectrum may increase the risk of severe breakthrough fungal infections. We report data from 2 institutions using low dose Liposomal amphotericin (LA) (AmBisome™) to prevent fungal infections in these high-risk patients. At one institution, 90 SCT patients were treated with fluconazole as prophylaxis and then switched to LA at 1 mg/kg/day as pre-emptive therapy with the onset of severe mucositis or within the first 1-3 days of neutropenic fever, whichever comes first. In the second institution, LA is started at the beginning of the chemotherapy as a prophylactic agent at 2 mg/kg three times a week and 58 patients have been treated with this approach. These approaches have resulted in less than a 2% incidence of invasive fungal infection. An update of this information and a comparison of the outcomes from these two approaches, including nephrotoxicity and cost will be reported.

Conclusions: Two different approaches using low dose liposomal amphotericin have resulted in a very low incidence of fungal infection in high risk allogeneic stem cell transplant patients. Further analysis comparing a prophylactic and pre-emptive strategy in the prevention of fungal infections will be reported.

PHARMACOECONOMICS OF PROPHYLAXIS OF FUNGAL INFECTIONS IN PATIENTS UNDERGOING A HEMATOPOIETIC STEM CELL TRANSPLANT

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Background. A recent multi-center, blinded, randomized head-to-head comparative study evaluated the safety and efficacy of prophylaxis in 882 hematopoietic stem cell transplant (HSCT) patients using either micafungin or fluconazole. The primary efficacy endpoint was treatment success, defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy, AND the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period. The overall success rate for micafungin was significantly higher than the rate for fluconazole patients (80.0% versus 73.5%). The treatment difference was +6.5% (95% CI: 0.9%, 12.0%). The overall incidence of proven or probable systemic fungal infections was 1.6% in the micafungin treatment arm and 2.4% in the fluconazole treatment arm. The objective of this economic evaluation is to determine outcomes and costs associated with micafungin prophylaxis in HSCT compared to a no prophylaxis protocol. **Methods.** A cost minimization study was performed to compare the cost of two alternative treatment strategies: (1) no prophylaxis versus (2) prophylaxis with micafungin. The analysis was conducted from the hospital perspective and focused on hospital costs incurred from hospital admission through hospital discharge. A decision analysis model was developed to incorporate costs and outcomes associated with prophylaxis treatment success or failure, which resulted in the need for empirical therapy and developing fungal infection. Clinical outcomes for no prophylaxis were derived from a review of published literature. Clinical outcomes for prophylaxis with micafungin were based on the results of the clinical study. Published literature was used to assess hospital costs associated with HSCT patients treated with prophylaxis treatment, treated with empirical anti-fungal treatment, and with a probable or proven infection. The cost per course of micafungin was varied as part of a sensitivity analysis. In addition, sensitivity analyses were performed to evaluate the impact of all assumptions on hospital results. **Results.** Hospital costs were highest for HSCT patients who developed a fungal infection and were \$136,000 per episode. Hospital costs for patients who required empirical therapy were \$91,000 per episode. Hospital costs for patients who did not require empirical therapy were \$64,000 per episode. At baseline, the model indicated that mean total hospital costs were \$79,000 for patients with no prophylaxis compared to \$69,000 for patients treated with micafungin prophylaxis without including the cost of micafungin. The results of the model were sensitive to assumptions about the need for empirical therapy and likelihood of developing a fungal infection. **Conclusions.** Micafungin prophylaxis in HSCT reduces hospital costs compared to no prophylaxis. Micafungin treatment reduces hospital costs due to: (1) decreased use of empirical anti-fungal therapy and (2) lower rates of probable and proven fungal infection.

AN INVESTIGATION OF NON-SPECIFIC REACTIONS IN MEASUREMENT OF PLASMA (1,3) β D-GLUCAN

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We investigated the detection of non-specific reaction in measurement of plasma (1,3) β -glucan (β -glucan) by alkaline treatment, chromogenic automated kinetic assay (alkaline-kinetic assay) and dilution and heating method, chromogenic endpoint assay (dilution heating endpoint assay). In this study, we reexamined the values of β -glucan by both methods with and without 4-amidinophenyl benzoate hydrochloride (APB) as protease inhibitor that blocks Limulus reaction in the 142 serum samples from 142 patients who had been treated and measured β -glucan in Kawasaki medical school hospital between January 1999 and May 1999. Non-specific reactions were judged by the calculated value under APB additive condition. The non-specific reactions were found in 135 of total 142 samples (95.1%) in the alkaline-kinetic assay while no non-specific reactions were recognized in dilution heating endpoint assay. The alkaline-kinetic assay has been used widely and been evaluated its usefulness because of good sensitivity. However, we found very high frequency of non-specific reaction in this method. Further studies are needed to define the reasons of non-specific reaction. On the other hand, although non-specific reactions were not detected in dilution heating endpoint assay, its clinical utilities should be evaluated in future clinical studies.

DETECTION OF *ASPERGILLUS* GALACTOMANNAN ANTIGEN IN PEDIATRIC SERUM SAMPLES: A PERFORMANCE EVALUATION OF THE BIO-RAD PLATELIA™ *ASPERGILLUS* EIA

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Background: Invasive Aspergillosis (IA) is a life-threatening invasive fungal infection in severely immunocompromised pediatric patients. Establishing a definitive, early diagnosis can be difficult, as it requires invasive procedures; and the sensitivity of both microbiologic and histopathologic tests are often low. The Bio-Rad Laboratories Platelia™ *Aspergillus* EIA is a one-stage immunoenzymatic sandwich microplate assay that uses rat monoclonal antibody EBA-2 to detect circulating galactomannan (GM). We retrospectively evaluated the utility of the Platelia™ *Aspergillus* EIA for the detection of GM, using sera collected prospectively from immunocompromised pediatric patients with cancer, and pediatric recipients of hematopoietic stem cell transplants (HSCT) at high risk for IA. **Methods:** A total of 661 serum specimens, collected from 47 patients were analyzed. An investigator blinded to assay results used EORTC/IFICG and NIAID/MSG standardized criteria to define patients as having Proven (9 patients, 136 samples), Probable (5 patients, 31 samples), or no IA (33 control patients, 494 samples.) Serum samples were tested for GM with the Platelia™ EIA, utilizing the manufacturer's directions. Negative, positive, and 2 cut-off controls were run on each plate to validate the test results. A GM Index was calculated as the ratio of sample optical density relative to mean optical density of the 2 cut-off controls. **Results:** Utilizing a positive GM Index cut-off of ≥ 0.5 , 7 of 14 (50%) patients with either proven or probable IA were detected. Three of the seven patients in whom no GM antigen was detected had only specimens prior to IA diagnosis available for testing, and three had only 2 specimens available for testing. GM antigen was detected by Platelia™ *Aspergillus* EIA an average of 10.7 days prior to IA diagnosis using clinical criteria. Specificity was 98.4% (485/493 specimens) in the control population. **Conclusions:** Bio-Rad Platelia™ *Aspergillus* EIA demonstrated excellent specificity and the ability to significantly increase the speed with which some cases of IA are diagnosed. Sensitivity of 50% was lower than in previous studies possibly due to the inherent difficulty of specimen availability in a retrospective study, and to the concomitant use of multiple mold-active antifungal therapeutic agents.

ACCURACY OF THE YEAST IDENTIFICATION USING COMMERCIAL PRODUCTS SUCH AS API 20C AUX AND RAPID YEAST PLUS SYSTEM IS ENHANCED SIGNIFICANTLY BY THE CORNMEAL MORPHOLOGY

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We isolated 330 yeasts from clinical specimens and identified them to species level using two commercial kits, API 20C AUX and RapID Yeast Plus System. Identification was confirmed by the cornmeal morphology of the yeasts having species specific structures. Both kits identified yeast and *Candida* species (91.2%) very well, but when yeast isolates recovered from patients on antifungal treatment were tested they were difficult to identify by each system and overall ID rate decreased (83% for API 20C & 33.7% for RapID Yeast). In 301 cases, identifications produced by one or both kits (86 *C. parasilosis*, 71 *C. tropicalis*, 59 *T. glabrata*, 33 *C. albicans*, 23 *C. krusei*, 11 *Cryptococcus neoformans*, 6 *C. lusitaniae* and 12 others) agreed with those of the cornmeal morphology. Commercial products achieved no identification for 12 yeasts identified only by cornmeal morphology (confirmed by the reference laboratory), and identification of a further six disagreed with that of cornmeal. Eight isolates were unidentified by all methods, while six isolates were identified without cornmeal information and 19 isolates were sent to the reference laboratory for conventional identification methods. When a discrepant reaction was observed, the cornmeal morphology was extremely useful, particularly in producing species identification with confidence values greater than 90%. We concluded that regardless of which system we adopt to identify yeast isolated from clinical specimens, cornmeal morphology information is always desirable, and in some cases necessary, for producing useful information with high confidence value to the clinician.

Data for 89 Yeast Isolates Tested and Identified by API20C & RapID Yeast Plus System in Combination Agreed by Cornmeal Morphology

	BC	PD	WD	BX	URINE	CSF	FLD	EYE	CATH	BAL	ORAL/VAG	
API 20C	40	8	3	3	3	4	4	3	1	4	1	(83%)
RapID Yeast	15	3	2	3	0	1	3	2	0	0	1	(33.7%)

BC (blood culture), PD (peritoneal dialysate), WD (wound), BX (biopsy), CSF (cerebrospinal fluid), FLD (fluid), CATH (catheter), BAL (bronchial alveolar lavage), VAG (vaginal)

MOLECULAR IDENTIFICATION OF RHIZOMUCOR PUSILLUS AS A CAUSE OF SINUS-ORBITAL ZYGOMYCOSIS IN A PATIENT WITH ACUTE MYELOGENOUS LEUKEMIA

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Introduction. *Rhizomucor pusillus* is recognized as an uncommon cause of human disease. Accurate identification of this pathogen through the development of zygospores requires time-consuming culture methods not readily available to most clinical diagnostic laboratories. We describe a case of sinus-orbital zygomycosis caused by *R. pusillus* using a PCR-based method to identify the pathogen from culture. **Case Report.** A 62-year old male rancher from the Midwest with acute myelogenous leukemia received standard induction and consolidation chemotherapy followed by a low-intensity related allogeneic peripheral stem cell transplant. He received fluconazole prophylaxis. At day 8-post transplant (PT), the patient complained of nasal congestion with peri-orbital edema noted on day 13-PT, at which time the neutropenia resolved. A CT scan showed pan-sinusitis, leading to surgical debridement of the sinus with culture of the tissue which was negative for viral, bacterial and fungal pathogens. Amphotericin B (AMB) lipid complex (5 mg/kg/day) was begun for presumed fungal sinusitis, in addition to ongoing antibacterials. At day 16-PT, the patient developed pain, proptosis, and blurred vision in the right eye. Extensive sinus debridement and a right orbitotomy were performed. An exam of tissue showed fibrovascular changes with acute inflammation and necrosis containing non-septate hyphae. A presumed *Rhizopus* species was identified from culture after 4 days of growth. Increased dosing of AMB lipid complex to 7.5 mg/kg/day, AMB nasal irrigation, and GM-CSF were initiated. Additional orbital and sinus debridement were performed on day 24-PT with no evidence of fungus. The patient was discharged at day 33-PT in stable condition. Shortly after discharge, the patient developed mental status changes with a progressive respiratory deterioration, ultimately leading to death on day 55-PT. No postmortem exam was performed. **Molecular testing.** DNA was extracted from the culture and evaluated by PCR using consensus fungal primers to amplify a 607 bp product which included the complete internal transcribed spacer 1 and 2 regions and the 5.8S rDNA gene of the fungal genome. The amplicon was sequenced and evaluated by comparison sequence analysis using the BLAST search engine available within the GenBank database (NCBI, Washington, DC). The sequence showed >99% homology when aligned to a *Rhizomucor pusillus* sequence within the database. The isolate was subsequently submitted to a reference laboratory where morphological and mating studies confirmed the identity as *R. pusillus*. **Conclusion.** This report highlights the value of molecular testing for the accurate identification of fungal species and expands the conditions of infections caused by *R. pusillus* in immunocompromised patients.

DISK DIFFUSION METHOD IN FOUR DIFFERENT AGAR MEDIA FOR DETERMINING SUSCEPTIBILITY OF *CANDIDA SPP.* TO VORICONAZOLE

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Objective: The purpose was to evaluate the disk diffusion test for determining susceptibility of *Candida spp.* to voriconazole (V) in comparison with the reference method (NCCLS M27-A2 document).

Material and Methods: We studied 203 *Candida spp.* (168 *C. albicans*, 26 *C. glabrata*, 9 *C. tropicalis*) isolated from clinical specimens. Susceptibility test was carried out by the agar diffusion method using disk with 1 mcg of V (Beckton Dickinson) on four different agar media: Yeast Nitrogen Base (YNB, Difco) plus 1.5% agar, Casitona (CAS), RPMI 1640 agar + 2% glucose (RPG) and Mueller-Hinton agar with 2% of methilen blue 2 % glucose (MH). The MICs obtained by the reference broth microdilution method (NCCLS M27-A2 document) (MDB) were defined as the lowest concentration of V that inhibited the 50 % of growth. Both methods were read after 24 and 48h of incubation at 35°C.

Results: At 24h, 201 strains (99%) had MIC values minor or equal to 2mcg/ml, showing 188 (93,5%) of these by YNB and 195 (97%) by CAS, RPG and MH zone diammeter major or equal to 18mm. Only 2 *C. albicans* strains (1%) showed MICs values major to 2 mcg/ml to V by MDB but none of these strains had inhibition zone diammeter minor to 18mm by disk diffusion method in the four media. At 48h, 144 strains (71%) had MIC values minor or equal to 2 mcg/ml, showing 106 (73,6%) of these by YNB, 123 (85.4%) by CAS, 135 (93.7%) by RPG and 132 (91.6%) by MH and inhibition zone diammeter major to 18mm. Fifty nine strains (57 *C. albicans*, 2 *C. glabrata*) (29%) had high MIC values (major to 2 mcg/ml) to V by MDB, 8 (13.5%) of these by YNB, 5 (8.5%) by CAS, 9 (15.5%) by RPG and 7 (12%) by MH had inhibition zone diammeter minor to 18mm.

Conclusions: Similar results were obtained using the four different agar media.

Better correlation between disk diffusion and the reference broth microdilution method at 24h/24h than at 48h/48h for strains with low MICs values to voriconazole.

By disk diffusion, reading was easier in Casitona and Mueller-Hinton agar.

Double inhibition zone diammeter was observed in all media excepted in Casitona.

The disk diffusion is a method easier to perform and easier to read than the reference broth microdilution method and is more available to clinical laboratories.

More studies are necessary with strains with high MIC values to voriconazole.

AMPHOTERICIN B FOR THE TREATMENT OF SYSTEMIC FUNGAL INFECTIONS: A META-ANALYSIS OF CONVENTIONAL VERSUS LIPID FORMULATIONS

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BACKGROUND: While it has been postulated that lipid formulations of amphotericin B (AmB) may offer improved tolerability and efficacy over conventional amphotericin B, this remains to be established.

OBJECTIVES: To determine if lipid AmB formulations are superior to conventional AmB for the treatment of suspected or documented systemic fungal infections. To sub-analyse whether individual lipid formulations are superior to conventional AmB.

METHODS: Medline, Cochrane Library, Embase, and IPA were searched for randomized comparative trials of any language. Unpublished data were obtained from authors, manufacturers, and the United States Food and Drug Administration CDER database. The primary outcome of interest was all-cause mortality. Secondary outcomes included treatment failure, nephrotoxicity, hypokalemia, and infusion reactions. Each outcome was analysed for lipid formulations, in aggregate, versus conventional amphotericin B, and for individual lipid formulations versus conventional amphotericin B. Jadad scores were used to assess trial quality. Data were extracted and odds ratios with 95% confidence intervals were calculated using the random or fixed effects model according to presence or absence of heterogeneity, respectively.

RESULTS: Eighteen studies met the inclusion criteria. Four different lipid formulations of AmB were identified: liposomal AmB, AmB lipid complex (ABLc), AmB colloidal dispersion (ABCD), and AmB in Intralipid suspension. Patients enrolled in these trials had documented or suspected systemic fungal infections and included those with febrile neutropenia, AIDS, or those in an intensive care unit. Compared to conventional AmB deoxycholate, the lipid group was associated with an OR of 0.76 [95% CI, 0.59-0.98] for mortality, 0.84 [95% CI 0.70-1.00] for treatment failure, 0.38 [95% CI, 0.32-0.46] for nephrotoxicity, 0.61 [95% CI, 0.48-0.79] for hypokalemia, and 0.39 [95% CI, 0.32-0.47] for infusion reactions. Sub-analyses comparing individual lipid formulations with conventional AmB demonstrated that only liposomal AmB significantly reduced mortality (OR 0.63 [95% CI, 0.44-0.90]). Liposomal AmB also significantly reduced nephrotoxicity (OR 0.39 [95% CI, 0.30-0.51]), hypokalemia (OR 0.59 [95% CI, 0.44-0.78]), and infusion reactions (OR 0.22 [95% CI, 0.17-0.28]). Sub-analyses also indicated that the ABLc formulation was associated with significantly less nephrotoxicity compared to the conventional formulation (OR 0.49 [95% CI, 0.29-0.82]).

Sub-analyses of ABCD versus conventional AmB showed that there was a significant reduction in nephrotoxicity (OR 0.28 [95% CI, 0.17-0.44]), but a significant increase in infusion reactions (OR 2.35 [95% CI, 1.52-3.64]). Sub-analyses of Intralipid preparations showed a significant reduction in nephrotoxicity (OR 0.42 [95% CI, 0.23-0.76]) and infusion reactions (OR 0.27 [95%CI, 0.17-0.43]) compared with conventional AmB.

MICAFUNGIN (MCFG), AN ECHINOCANDIN ANTIFUNGAL AGENT FOR THE TREATMENT OF NEW AND REFRACTORY CANDIDEMIA

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Background: *Candida spp.* are the fourth leading cause of bloodstream infections and non-albicans spp. (NAC) are increasing in importance. MCFG is an echinocandin antifungal agent with activity against *Candida spp.*, including NAC, and the clinical success of MCFG across *Candida spp.* is of interest. **Methods:** Pediatric, neonatal, and adult patients (pts) with new or refractory candidemia were enrolled into this open-label, non-comparative, multi-national study. The initial dose of MCFG was 50 mg/d (1 mg/kg for pts < 40 kg) for infections due to *C. albicans* and 100 mg/d MCFG (2 mg/kg for pts < 40 kg) for NAC infections. Dose escalation was allowed in cases of incomplete response. Maximum length of therapy was 42 days. **Results:** Between Feb-99 and Jan-02, 119 candidemic pts received at least 5 doses of MCFG. Mean duration of therapy was 20 days; 49/119 (41%) pts underwent dose escalation. Success (complete or partial response) was seen in 60/68 (88%) pts with a new infection and 39/51 (76%) pts with a refractory infection. Success was 86/101 (85%) for adults and 13/18 (72%) for pediatric pts, including 6/7 (86%) for neonates. Success was documented across a variety of organisms; *albicans* (39/46, 85%), *glabrata* (28/30, 93%), *parapsilosis* (18/21, 86%), *tropicalis* (9/11, 82%), *krusei* (6/9, 67%), *pelliculosa* (2/2, 100%), *inconspicua* (1/1, 100%), *lusitaniae* (1/1, 100%). Success was 30/40 (75%) for pts undergoing chemotherapy and 14/17 (82%) for stem cell transplant pts. Success was 19/26 (73%) for pts neutropenic at baseline and 79/92 (86%) for non-neutropenic pts. Mycological persistence was documented in 4/68 (6%) with a new infection and 9/51 (18%) with a refractory infection. These results were confirmed by an independent reviewer. Adverse events considered related to MCFG were infrequent with no change in transaminase values from baseline to EOT. Treatment-related hepatic events, phlebitis and allergic-type reactions were minimal.

Conclusions: MCFG was safe and effective in treating adult, pediatric, and neonatal pts with new or refractory candidemia. Good activity was demonstrated for both *albicans* and NAC, with particularly strong results for *C. glabrata*.

AZOLE TREATMENT OF TWO UNUSUAL PATHOGENS

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We report on voriconazole therapy in two immunosuppressed patients, one with a phaeohyphomycosis soft tissue infection and the other with a *Fusarium cutaneous* infection.

The first patient, a long surviving renal transplant recipient, presented to general medicine clinic with a soft tissue swelling in the carpal-metacarpal area of the thumb. The presumptive clinical diagnosis was a ganglion cyst and the patient had surgery to remove the swelling. Pathologic examination of the surgical specimen reported hyphael elements, and the patient was referred to infectious diseases clinic where cultures were obtained. An extensive literature search suggested a role for empiric voriconazole therapy and it was started. After a minimally favorable local response the area was further surgically debrided. Both clinic and surgery specimens on several growth medias grew a phaeohyphomycosis thought to be a *Phoma* species. Samples were sent to a reference laboratory for assistance with identification. The patient remains well on voriconazole treatment and all signs of local infection have resolved.

The second patient had a history of reactive airways disease requiring long standing systemic steroid therapy and was hospitalized with extensive left upper extremity disease consisting of numerous erythematous, violaceous 0.5 to 2 cm² nodular lesions. Multiple cultures grew *Fusarium* species. Careful clinical evaluation did not show evidence of distant metastasis. A literature search and review suggested voriconazole might be effective and it was begun. Clinical follow up through 6 weeks of therapy shows resolution of most lesions and continued improvement of remaining lesions.

These two immunosuppressed patients demonstrated good clinical response with voriconazole, which was well tolerated. Both had soft tissue infections that improved with this novel orally available therapy.

CASPOFUNGIN (CSP): WHAT MEASURES RESISTANCE?

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BACKGROUND: There are no clear in vitro standards which predict clinical response to CSP. Resistant isolates are few and tend to be laboratory mutants which are avirulent in mice. We present a patient with rising MIC to CSP and clinical failure. We evaluated 3 sequential isolates of *C. albicans* in mice to determine whether this model could predict in vivo failure.

METHODS: A patient with HIV associated *C. albicans* esophagitis sequentially failed multiple antifungals, including fluconazole (FLU) and other triazoles. He then responded to 4 weeks with CSP at 50 mg/day. Later he relapsed, and then failed second course of CSP. Isolate 1 was pre-CSP; isolate 2 followed a successful 4 week CSP treatment; isolate 3 was post CSP failure. MIC values were done by NCCLS M27-A methods. Groups of 8-10 mice were infected intravenously with *C. albicans* and treated with water (controls) PO, FLU at 5 mg/kg PO BID or increasing doses of CSP intraperitoneally. Mann Whitney test was used to compare kidney counts. *= $p < 0.05$ treatment versus control (0 drug). Values are $\mu\text{g/ml}$ for MIC at 48hrs and median \log_{10} CFU/kidney/mouse.

RESULTS:	MIC	INCREASING DOSE OF CSP in mg/kg						
		FLU	5	0	0.0625	0.125	0.250	0.50
Isolate 1	0.25	5.9	5.8	5.1*	4.0*	3.8*	2.6*	3.0*
Isolate 2	0.25	6.0						
		5.6	4.8	2.5*	2.2*	1.9*	1.8*	
Isolate 3 (pulled studies)		<64	5.5	5.4	5.2	5.3	5.3	
	5.0	4.5*						

Mice infected with isolate 3, (clinical failure and CSP MIC of $<64 \mu\text{g/ml}$) required a much higher dose of CSP to reduce kidney counts.

CONCLUSIONS: In this patient, a high MIC to CSP was associated with clinical failure. The resistant isolate 3 was virulent in mice (unlike prior lab mutants) and required 1 mg/kg CSP to reduce kidney counts. Thus, the in vitro and animal studies are consistent with the clinical course. The fact that 1 mg/kg CSP did reduce kidney counts suggested that higher doses of CSP may be effective in treatment of more resistant isolates.

MEDICAL VERSUS SURGICAL THERAPY FOR CANDIDA ENDOCARDITIS: REVIEW OF 879 CASES AND A METAANALYSIS OF THE LITERATURE

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Background: The current standard of care for *Candida* endocarditis includes surgery. The mortality of *Candida* endocarditis with medical therapy alone is thought to be higher than that achievable with adjunctive surgery. There are well-defined clinically-tested algorithms for medical and surgical therapy in bacterial endocarditis, but clinicians lack prospective clinical trial data for *Candida* endocarditis. We sought to review published treatment regimens of *Candida* endocarditis, including animal models, clinical reports, and observational series.

Methods: We conducted a MEDLINE search (1966 – December 2002) for all English language peer-reviewed articles related to *Candida* endocarditis. Inclusion criteria for the clinical case review required definite *Candida* endocarditis cases diagnosed by modified Duke criteria. We excluded cases where no antifungal therapy was employed, or there was not sufficient detail to determine antifungal therapy used or patient outcome.

Results: We reviewed a total of 879 *Candida* endocarditis cases from 418 reports. We analyzed a total of 163 cases of *Candida* endocarditis from 105 reports that met inclusion criteria. We also reviewed 13 animal model reports with 42 experimental antifungal treatment regimens. From these clinical reports, we were also able to evaluate 22 observational case-series for the treatment of *Candida* endocarditis using meta-analytic techniques. Amongst the 22 observational series, 97 patients were included. Reported mortality ranged from 0-100%, and there was evidence of heterogeneity (Egger p -value < 0.10). The most common medical therapy used was amphotericin B deoxycholate, and the most common combination regimen was amphotericin B deoxycholate + 5-fluorocytosine. We employed meta-regression using mortality as the outcome, and found that in studies where patients underwent adjunctive surgery for *Candida* endocarditis, there was a lower reported proportion of deaths [prevalence odds ratio (POR) = 0.56; 95% confidence interval (CI) = 0.16, 1.99]. Studies published prior to 1980 were associated with a higher reported mortality (POR = 2.03; 95% CI = 0.55, 7.61). Furthermore, in those studies where all of the patients received antifungal monotherapy there was a higher reported proportion of deaths (POR = 1.49; 95% CI = 0.39, 5.81). Similarly, studies where all of the patients were infected with *Candida parapsilosis* (POR = 1.51; 95% CI = 0.41, 5.52) or had left-sided *Candida* endocarditis (POR = 2.36; 95% CI = 0.55, 10.07) were also associated with a higher proportion of deaths.

Conclusions: Optimal antifungal therapy for *Candida* endocarditis is unknown. In our review of the medical literature there was substantial heterogeneity. There was a higher reported mortality in case series published prior to 1980 and in case series that reported exclusive use of antifungal monotherapy (generally amphotericin B deoxycholate). There was also a higher mortality rate in case series that reported a lower proportion of patients who underwent adjunctive surgery, infected with *C. parapsilosis*, or had left-sided endocarditis. With the recent availability of several new antifungals, including the echinocandins and other fungicidal therapies, management for *Candida* endocarditis should be revisited. We now have an appreciation for *Candida* endocarditis patients with poor outcomes and specific criteria for surgery should be integrated into future clinical study designs.

CLINICAL EXPERIENCE OF CASPOFUNGIN AND CYCLOSPORIN A (CsA) IN PATIENTS TREATED IN CASPOFUNGIN CLINICAL TRIALS

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Objective: In a Phase I study in healthy subjects, mild transient elevations in ALT had been seen in 5 of 12 subjects after a single day of concomitant dosing with caspofungin and CsA. As a result of this finding, use of CsA with caspofungin is not recommended unless the benefit to the patient outweighs the potential risk. The caspofungin salvage invasive aspergillosis (IA) protocol and compassionate use protocol (CUP) were amended in 2001 to obtain additional data on use of caspofungin and CsA in patients treated in a setting with appropriate risk-benefit.

Methods: The caspofungin salvage IA study and CUP enrolled patients with documented invasive fungal infections (IFI) who were refractory to or intolerant of standard antifungal therapies. Patients who were receiving CsA could be enrolled in the study provided their AST and ALT were < 3 times normal at study entry. Liver enzymes (ALT, AST, alkaline phosphatase) were to be monitored every other day for the first 14 days of caspofungin plus CsA therapy and twice weekly thereafter. The dosing regimen for patients on CsA was caspofungin 35 mg daily, after a loading dose of 70 mg on day 1.

Results: Data on 6 patients who received concomitant CsA and caspofungin are available. The patients were all adults with mean age of 48 years. Five had undergone allogeneic hematopoietic stem cell transplants and one had received a kidney transplant. All had IA (5 with pulmonary and 1 with sinus involvement); 5 were refractory to at least 1 other antifungal agent. Patients received concomitant therapy with caspofungin and CsA for 2 to 56 days. Five patients were receiving CsA in the prestudy period prior to the onset of caspofungin therapy; one patient was started on CsA while receiving caspofungin. During careful monitoring, none of the patients had elevations in serum transaminases on caspofungin plus CsA therapy, and no patient had concomitant therapy discontinued or interrupted due to a drug-related adverse event.

SUCCESSFUL TREATMENT OF CANDIDEMIA WITH CASPOFUNGIN AND LIPOSOMAL AMPHOTERICIN B AFTER FAILURE OF MONOTHERAPY

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Introduction:Recent data show caspofungin is equivalent to amphotericin B (AmB) in the treatment of invasive candidiasis. In vitro data indicate that echinocandins may have an advantage over AmB in the treatment of fungal infections involving biofilm. This has not been shown clinically. We present two cases, one pediatric and one adult, of invasive candidiasis, which failed treatment with AmB and that responded to the addition of caspofungin.

Case 1: A previously healthy three-year-old female was admitted for intussusception and underwent bowel resection with anastomosis, complicated by perforation. Her ICU course included ventilator-associated pneumonia, and poor weight gain. She received numerous antibiotics and total parenteral nutrition (TPN). She subsequently developed *C. albicans* line infection, fungemia, and endocarditis. She was initially treated with fluconazole for 7 days and switched to AmB due to a lack of response. On day 14 of therapy, 5-flucytosine (5-FC) was added due to persistent fungemia. On day 36, AmB was changed to liposomal AmB. Despite this combination, fungemia persisted. On day 41 of therapy, caspofungin was added. Within 48 hours, fungemia was cleared. Fevers and leukocytosis resolved within two weeks.

Case 2: A 44-year-old woman with a history of multiple medical problems was admitted for a diverticular perforation. The hospital course was complicated by necrotizing fasciitis, enterocutaneous fistula, gastrojejunostomy leak, and a right subclavian venous thrombosis associated with IV catheters. She subsequently developed *C. glabrata* fungemia. AmB was initiated and catheters were removed. She was diagnosed with septic thrombophlebitis. On day 15 of therapy, liposomal AmB was substituted due to persistent fungemia. On day 24 she remained fungemic, and caspofungin was added. Repeat blood cultures 4 days later were sterile.

Conclusion: These cases demonstrated the rapid improvement in the clinical outcome after the addition of caspofungin for the treatment of candidemia. While both cases failed therapy with liposomal AmB +/- 5FC, success was achieved rapidly with the addition of caspofungin. Susceptibility data suggested that treatment could have been effective without adding caspofungin. The cases raise three questions. First, does caspofungin have an additive or synergistic effect in combination with AmB in the treatment of candidemia? Does *Candida* biofilm play a role in treatment failure? If so, is the addition of caspofungin necessary for the eradication of candidemia in the presence of biofilm? Further studies are needed to answer these questions.

FAILURE OF TREATMENT OF CRYPTOCOCCOSIS IN A NON-HIV INFECTED PATIENT

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Background: Most of the studies investigating the treatment of cryptococcosis in non-human immunodeficiency virus (HIV) infected patients have been with Amphotericin B (AmB) and 5-flucytosine (5FC). Retrospective studies indicate that treatment of this patient population with fluconazole (FCZ) is successful for most cryptococcal infections (88%). We report a case of cryptococcal cellulitis in a non-HIV patient who failed FCZ therapy.

Case: A 72 year-old man with a history of cirrhosis developed erythema around his left ankle. Medical history was significant for compensated cirrhosis with splenomegaly and pancytopenia. He was treated with different antibiotics for bacterial cellulitis without improvement for approximately one month. The lesion progressed over the entire left leg, leading to blisters and deep ulcers. He was admitted to the hospital with fever and hypotension, and cultures of the blood and wound grew *Cryptococcus neoformans*. His serum cryptococcal antigen (CrAg) was 1:512. He was started on FCZ 400mg/day with improvement. However, his leg infection required further surgical debridement and after 6 weeks of FCZ therapy he was transferred to our hospital for further care.

Cultures from his left lower extremity continued to show *C. neoformans*. Repeat serum CrAg was 1:256. HIV ELISA was negative. Susceptibility testing using standard microdilution methodology revealed a susceptible isolate (MIC to AmB and FCZ was 0.125 and 2, respectively). Additional nodular lesions were found on his right leg. Therapy was changed to liposomal-AmB and 5-FC. After 1 week, his repeat CrAg was 1:32. Despite aggressive care, his infection progressed and an amputation was performed. His status worsened and after discussions with the family, care was withdrawn.

Conclusion: We report a case of cryptococcosis in a non-HIV patient that failed FCZ therapy. Despite 6 weeks of FCZ, his serum CrAg was essentially unchanged, the patient's skin lesions did not improve, and new lesions developed on the other leg. We hypothesize FCZ failure despite susceptibility data for a number of reasons. First, he had multiple poor prognostic factors including age >60 and organ dysfunction. In addition, mortality is increased with delays in diagnosis due to atypical presentations, like cellulitis. Second, susceptibility testing is routinely performed at 35°C, however heteroresistance to azoles has been described at lower temperatures. The patient's core body temperature was lower due to his cirrhosis, and the location of the ulcerations around his ankles provided an even lower temperature. *Cryptococcus* may have been resistant to FCZ in this area despite *in vitro* data. Third, devitalized tissue in his wound provided a reservoir of infection due to poor penetration of FCZ. FCZ therapy for *C. neoformans* in HIV negative patients may be adequate for most infections. We caution its use in severe cellulitis with a high CrAg. Serum CrAg can be used to monitor response to therapy. In addition, adequate surgical debridement is necessary.

NON-AZOLE ANTIFUNGALS AND CALCINEURIN INHIBITORS EXHIBIT SYNERGISTIC ACTIVITY AGAINST *C. ALBICANS*

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Purpose: Azole drugs target the ergosterol biosynthetic enzyme lanosterol 14 α -demethylase and are a widely applied class of antifungal agents due to their broad therapeutic window, wide spectrum of activity, and low toxicity. Unfortunately, azoles are generally fungistatic, and resistance to fluconazole is emerging in several fungal pathogens. It was recently established that the protein phosphatase calcineurin allows survival of *Candida albicans* during the membrane stress exerted by azoles. The calcineurin inhibitors cyclosporin A (CsA) and tacrolimus (FK506) are dramatically synergistic with azoles, resulting in potent fungicidal activity. The purpose of this research was to determine whether terbinafine and fenpropimorph—two non-azole antifungal drugs that target other enzymes in the ergosterol biosynthesis pathway—also exhibit dramatic synergistic antifungal activity against *C. albicans* when combined with CsA or FK506.

Summary: The *in vitro* antifungal susceptibilities of various *C. albicans* strains were tested using disk diffusion halo assays. Strains were grown in YPD media overnight, resuspended in top agar, and poured onto YPD solid media. Sterile drug disks containing combinations of terbinafine, fenpropimorph, FK506, CsA, and L-685,818 or solvent controls were placed over the solidified top agar. Cells were incubated for 24 to 48 hours at 37°C. The minimum inhibitory concentration (MIC) of the different drug combinations was determined according to standard NCCLS criteria for wild-type and mutant *C. albicans* strains. To determine the presence of drug synergy, fractional inhibitory concentration (FIC) and FIC index values were calculated for each drug combination.

Results: Both terbinafine and fenpropimorph exhibited potent fungicidal synergism with FK506 and CsA in *C. albicans*. Similarly, *C. albicans* mutant strains lacking the calcineurin B subunit were markedly hypersensitive to terbinafine and fenpropimorph. The FK506 binding protein FKBP12 was required for FK506 synergism with ergosterol biosynthesis inhibitors and mutations that conferred FK506-resistance abolished this synergism. In wild-type *C. albicans*, there was evidence of drug synergy between the non-immunosuppressive FK506 analog L-685,818 and both ergosterol biosynthesis inhibitors. Additionally, an *erg24/erg24* mutant which lacks the enzyme target of fenpropimorph was hypersensitive to both FK506 and CsA.

Conclusions: In order to combat the growing problem of drug-resistant microorganisms, we must be innovative in our approaches to drug design and vigilant in monitoring current therapies whose properties can be exploited for novel therapeutic purposes. These studies demonstrate that the activity of non-azole antifungal agents that target ergosterol biosynthesis can be enhanced by inhibition of the calcineurin signaling pathway, extending their spectrum of activity and providing an alternative approach to overcoming antifungal drug resistance.

NOVEL ANTIFUNGAL USE IN AN INNER CITY HOSPITAL, A COMPARISON BETWEEN CASPOFUNGIN AND VORICONAZOLE

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Background: Over the past 5 decades, therapeutic options for invasive fungal infections have remained limited and sub-optimal. Recently, novel antifungal agents like caspofungin and voriconazole have been approved for use. These antifungals offer an advancement in antifungal therapy; however, clinical experience with these agents is limited. We therefore sought to examine how these agents are being used and their impact on patient outcomes at an urban medical center. **Methods:** The charts of the first 15 patients receiving voriconazole and 15 consecutive patients receiving caspofungin were retrospectively identified and reviewed. Data extraction included patient demographics, past medical history, current admission diagnosis, laboratory values, radiology results, microbiology, and antifungal use. Follow up care in outpatient clinics were reviewed for patient outcome and radiological improvements, when available.

Results: 11 patients received antifungal treatment with caspofungin, 3 with combination amphotericin-lipid complex/caspofungin and 1 with combination caspofungin/voriconazole. Fourteen of 15 patients were treated with voriconazole alone. Of these, 3 were treated with caspofungin inpatient and switched to oral voriconazole for outpatient use. Ten patients in each treatment began antifungal therapy with a different agent that was discontinued due to intolerance or lack of efficacy. Fifteen of 26 patients had underlying leukemia/lymphoma; 18 patients were neutropenic during admission. Seven and 8 patients with probable fungal pulmonary, 3 and 2 patients with fluconazole-resistant *Candida* infections were treated with caspofungin and voriconazole, respectively. Five (33%) caspofungin-treated and 6 (40%) voriconazole-treated patients improved. Three caspofungin-treated and 2 voriconazole-treated patients with probable fungal pneumoniae progressed and 1 voriconazole-treated *Candida* infection persisted. Caspofungin and voriconazole therapy were discontinued in 5 and 3 patients due to lack of oral regimen/insurance coverage, in 3 and 4 patient who were no longer neutropenic, and 0 and 4 for side-effects, respectively. Three patients receiving caspofungin and 1 patient receiving voriconazole expired during therapy. **Conclusion:** Caspofungin and voriconazole are being used as second-line agents to treat a variety of fungal infections. Caspofungin is used more frequently in combination regimens and may be better tolerated than voriconazole.

IS THE STANDARD DOSE OF SULFAMETHOXAZOLE/TRIMETHOPRIM ADEQUATE IN PATIENTS WITH AIDS-RELATED PNEUMOCYSTIS CARINII PNEUMONIA?

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Background: *Pneumocystis carinii* is recently recognized as a fungus. Sulfamethoxazole(SMX)/trimethoprim(TMP) is most often used as initial therapy for AIDS-related *P. carinii* pneumonia(PCP). The standard dose used in patients with PCP is 75-100mg/kg/day of SMX plus 15-20mg/kg/day of TMP. However, we administrate SMX/TMP at a lower dose in patients with AIDS-related PCP. We study the clinical course of patients received the low dose treatment with SMX/TMP and measure the serum level of SMX/TMP in 4 patients.

Patients and methods: We analyzed the clinical efficacy of low dose treatment with SMX/TMP in 16 patients with AIDS-related PCP(15 males and 1 female, mean age;39.17year). The average count of CD4 lymphocyte was 34.7/mm³ at the onset of PCP. The severity of PCP was mild 6 cases, moderate 9 cases, severe 1 case, respectively.

Results: The average dose of SMX/TMP was SMX 46.4mg and TMP 9.3mg/kg/day. The average period was 4.3 days for disappearance of fever, 12.4 days for disappearance of symptoms, 15.2 days for normalization of serum LDH level, respectively. Ten patients had any adverse reactions and 7 of 10 patients stopped to receive SMX/TMP. The serum level of SMX was 51.6 µg/ml at trough concentration, 84.9 µg/ml at peak concentration and the serum level of TMP was 3.0 µg/ml at trough concentration, 3.6 µg/ml at peak concentration, respectively.

Conclusion: These results suggest that the low dose treatment with SMX/TMP is effective in patients with AIDS-related PCP.

WHEN AN INEXPENSIVE TREATMENT BECAME EXPENSIVE

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We report one case of oropharyngeal and oesophageal candidiasis non responsive to conventional treatment in a 43 year old male patient with AIDS.

C. albicans and *C. glabrata* were isolated from this patient and found to be resistant to fluconazole and itraconazole in vitro. Voriconazole therapy was initiated, but discontinued after nine months of treatment because the patient developed a severe papular erythema. A skin biopsy showed a lichenoid dermatitis-epidermitis.

Due to a new recurrence of severe oropharyngeal and oesophageal candidiasis the patient was admitted at the hospital for treatment with amphotericin B deoxycholate 50 mg/d iv in 24 hours continuous infusion. The treatment was stopped three days later because of renal impairment.

The patient was switched to caspofungin administered once daily, intravenously, with an initial loading dose of 70 mg followed by 50 mg/day. A one week treatment with caspofungin was completed, until resolution of all signs and symptoms. The creatinine levels returned to normal values four days after the end of treatment.

Whilst the cost of one-week treatment with amphotericin B is equivalent to 628 points, treatment with caspofungin of the same duration is equivalent to 5360 points. However, the cost of three hospitalization days for amphotericin B administration increased the costs by 3450 points, and the patient continued hospitalized due to renal impairment during four more days (4600 points). Hence, the total cost of antifungal treatment for this patient was equivalent to 8678 points. This is almost 60% higher than complete treatment with caspofungin. In addition to this, the patient had a significantly lower quality of life due to hospitalization.

This case study highlights the need for effective, less toxic and, in some cases a more cost-effective antifungal treatment as caspofungin.

THROMBOCYTOPENIA ASSOCIATED WITH ITRACONAZOLE IN A PATIENT WITH PULMONARY BLASTOMYCOSIS: CASE REPORT AND LITERATURE REVIEW

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23 year-old male presented with complaints of cough, low-grade fevers, weight loss, exertional dyspnea and pleuritic chest pain of one month duration. Imaging studies revealed right upper lobe consolidation and collapse. Bronchoscopy along with endobronchial biopsy was performed. Histopathological and microbiological results were consistent with infection due to *Blastomyces dermatidis*. There was no evidence of disseminated disease. Human immunodeficiency virus (HIV) serology was negative.

The patient was started on intravenous itraconazole 200 mg per day. Three days later, patient complained of mild epistaxis and was found to have profound thrombocytopenia with platelet count of 2000/uL. Itraconazole was discontinued. No heparin-induced platelet antibody was detected in the serum. A bone marrow biopsy revealed only an increase in megakaryocytes. The platelet count recovered within one week without requiring any supportive measures. The patient is currently on oral fluconazole, with marked improvement in both pulmonary symptoms and chest X-ray appearance. Monthly monitoring of complete blood counts and liver function tests, have revealed no abnormalities. He completes six months of therapy in April 2003.

A review of the literature revealed one case report of reversible thrombocytopenia and leukopenia associated with itraconazole.

Thrombocytopenia is a rare but serious potential side effect of itraconazole. A high index of suspicion should be maintained and platelet counts should be checked in patients who develop bleeding manifestations while receiving itraconazole.

COMPARATIVE NEPHROTOXICITY, ADVERSE EVENTS, AND CLINICAL OUTCOMES OF LIPID-ASSOCIATED AMPHOTERICIN B PRODUCTS

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Other investigations have implied that there are significant differences in the incidence of nephrotoxicity and adverse effects between amphotericin B lipid complex (ABLC) and liposomal amphotericin B (LAMB). Our investigation was begun to determine if there are significant differences in the incidence of nephrotoxicity of ABLC and LAMB, to determine the comparative economic implications of both products, to determine the risk factors associated with nephrotoxicity, to determine the clinical outcomes for patients receiving either agent, and to determine any adverse events for these agents. A combined retrospective and prospective trial was conducted at two tertiary care centers. Patients were identified through a pharmacy database. Data for the two centers was collated, sorted and analyzed. Patients included were at least 18 years of age and had received a minimum of three doses of a lipid associated amphotericin B product. Patients who had baseline end stage renal disease or received dialysis or plasmapheresis were excluded. Three hundred fifty-nine patients were identified for the study. One hundred sixty-five ABLC patients and one hundred thirty-five LAMB patients were included in the data evaluation. Baseline renal function, number of days of therapy, patient age, and gender were similar among the two groups. There was no significant difference in the incidence of nephrotoxicity between ABLC and LAMB. Costs were significantly higher with LAMB therapy as compared with ABLC. Risk factors for nephrotoxicity included elevated baseline serum creatinine and coadministration with other nephrotoxic agents. Clinical outcomes and adverse events were not significantly different between the two groups. Contrary to other published data, there was a lack of significant difference in nephrotoxicity paired with significantly higher costs of LAMB therapy.

A MULTI-CENTER, RETROSPECTIVE COMPARISON OF THE NEPHROTOXIC EFFECTS OF AMPHOTERICIN B LIPID COMPLEX AND LIPOSOMAL AMPHOTERICIN B

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Background: There are currently two lipid formulations of amphotericin B available in Canada, amphotericin B lipid complex (ABLC) and liposomal AmB (L-AmB). Both of these products have been shown to have favorable nephrotoxicity profiles in comparison to amphotericin B deoxycholate (d-amB), however, it is unclear as to whether there are differences in the renal sparing effects of the two lipid formulations. **Methods:** A retrospective and prospective observational study at 11 tertiary care and one community hospital was undertaken in Canada. Patients 2 years of age or older, who received a minimum of 4 doses of ABLC or L-AmB and were not receiving dialysis were enrolled with subsequent data collected. **Measurements and Results:** 150 patients were prescribed ABLC and 104 patients received L-AmB. The mean daily dose and duration of treatment with ABLC was 285 mg/day for 15.9 days (4.0 mg/kg/day) and L-AmB was 221 mg/day for 19 days (3.3 mg/kg/day). Approximately two thirds of patients had underlying hematological malignancies (ABLC 68.7%, L-AmB 59.6%) and 28% and 22% in the ABLC and L-AmB arms respectively ($p>0.05$) had undergone bone marrow transplantation. The groups were comparable with respect to baseline serum creatinine, prior d-amB use, saline loading, and number of concurrent nephrotoxins. The average net change from baseline to peak serum creatinine was 46.7 $\mu\text{mol/L}$ for patients treated with ABLC (143.4 to 190.1 $\mu\text{mol/L}$) and 42.8 $\mu\text{mol/L}$ for patients treated with L-AmB (138.3 to 181.2 $\mu\text{mol/L}$) ($p>0.05$). The mean change from baseline to end of therapy was 9 $\mu\text{mol/L}$ with ABLC compared to 9 $\mu\text{mol/L}$ with L-AmB ($p>0.05$). An increase of at least 50% in serum creatinine was experienced by 43 (30.7%) of ABLC treated patients and 29 (28.4%) of patients in the L-AmB arm; 19 (13.6%) of ABLC and 13 (12.7%) of L-AmB patients had a doubling in creatinine and 3 (2.1%) of ABLC and 4 (3.9%) of L-AmB patients had a tripling of baseline serum creatinine ($p>0.05$). Only 4 (2.8%) ABLC patients and 7 (6.9%) L-AmB patients required dialysis during or within seven days of stopping lipid AmB and 17 (12.1%) and 9 (8.8%) respectively had doses held due to renal effects ($p>0.05$).

Conclusion: We were unable to demonstrate any significant differences in any of the renal parameters we measured between ABLC and L-AmB when used according to current clinical practices. Given potential differences in costs between the two agents, further evaluations of the potential differences in infusion related toxicities and efficacy between the two drugs would be prudent.

INCIDENCE AND CONSEQUENCES OF NEPHROTOXICITY IN HSCT TREATED WITH EMPIRIC AMPHOTERICIN, MICAFUNGIN OR NO ANTI-FUNGAL AGENT

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When choosing prophylactic anti-fungal regimens in the setting of hematopoietic stem cell transplantation (HSCT) it is imperative that the risk of nephrotoxicity be a major consideration in which agents to use. It has been shown retrospectively that nephrotoxicity in this setting results in increased length of stay and higher costs. We report a prospective study in 21 HSCT patients (11 allogeneic and 10 autologous) in which actual creatinine clearance was measured by a 24 hour urine creatinine clearance (CrCl). A baseline was measured at the start of transplantation and then again at 2 weeks, 4 weeks, 3 months and 6 months after transplant. The incidence of nephrotoxicity (defined as a decline in CrCl by 50% or more from baseline) within the first month of transplantation was 55% in the allogeneic transplants with the incidence being 100% in those who received empiric therapy with conventional amphotericin, 20% with micafungin (FK463), and 50% in patients who did not require any anti-fungal agent. In the allogeneic patients with nephrotoxicity there was an average increased cost of \$54,280 and an average increased length of stay of 13.5 days longer than those without nephrotoxicity. In the autologous HSCT there was a 40% incidence of nephrotoxicity despite only two patients requiring empiric anti-fungal treatment. One of these patients received conventional amphotericin and had a rapid 75% decrease in CrCl and one received micafungin and had a slight increase in CrCl. In the autologous patients with nephrotoxicity there was an average increased cost of \$20,722 and an average increased length of stay of 6 days longer than those patients without nephrotoxicity. The majority of patients who developed nephrotoxicity within the first 30 days of transplant continued to have nephrotoxicity when measured at 3 months and 6 months suggesting that early toxicity also leads to long term toxicity sequelae in these patients.

Conclusions: Based on this prospective study in HSCT patients there is a high risk of nephrotoxicity in both allogeneic and autologous patients. Use of conventional amphotericin resulted in 100% nephrotoxicity whereas patients receiving micafungin only had 16.6% nephrotoxicity. Early nephrotoxicity resulted in increased length of stay and significantly increased costs and long term nephrotoxicity. Based on this data it is imperative that the risk of nephrotoxicity be evaluated when choosing an anti-fungal agent in this high risk setting.

IN VITRO AND IN VIVO HUMAN METABOLISM OF ALBACONAZOLE

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Albaconazole (ALBA, UR-9825) is a new triazole antifungal agent that is under clinical development at J.Uriach & Cia. ALBA has shown good in vitro and in vivo antifungal activity in pre-clinical studies and an excellent tolerability in humans.

In vitro studies were carried out to identify the P450 isoenzymes involved in the metabolism of ALBA. [¹⁴C]-ALBA was incubated for 4 h in pooled human liver microsomes, at concentrations ranging 1-20 μM, and yielded a single metabolite fraction in a concentration-dependent manner. The formation of this metabolite (that was later identified as hydroxy-ALBA (ALBA-OH)) was most efficiently catalysed by CYP3A4/5. The values for K_m and V_{max} were 3.1 μM and 125 pmol/h/mg protein, respectively. Calculated intrinsic clearance (C_{int}) and hepatic extraction coefficient (E_h) were 0.65 ml/min/Kg and 0.13%, respectively. These results suggest low first pass effect after oral intake.

In vivo metabolism was investigated following a single oral dose of 80 mg of [¹⁴C]-ALBA in healthy volunteers (n=6). Radioactivity was excreted predominantly in feces and in urine, with means of 55.8±11.2% and 29.9±10.9% of the administered dose, respectively, after 336 hours post dose (total recovery 85.6±12.4%). In feces ALBA-OH, and its corresponding sulfate and glucuronconjugate were found. In urine, only the conjugates were present. A small percentage (5%) of unchanged ALBA was found in feces. In plasma, the major component was ALBA, whereas ALBA-OH and its conjugates were present into a much lesser extent. Pharmacokinetic analysis of plasma ALBA concentrations showed a rapid absorption, good tissue distribution and a bi-exponential decay with a half-life of 55.3±8.9 h (mean±ES).

In summary, in vitro and in vivo studies show that albaconazole undergoes extensive and slow metabolism into a single hydroxy derivative, which in turn is transformed into two conjugate derivatives. Spectroscopic studies aimed at the determination of the position of the hydroxy group in the structure of ALBA-OH are in progress. Further studies will determine the exact contribution of these phase I and phase II metabolites to the overall antifungal activity.

SAFETY AND PRELIMINARY PHARMACOKINETICS OF AN ORAL SOLUTION CONTAINING ALBA- CONAZOLE AFTER SINGLE AND MULTIPLE DOSE ADMINISTRATION TO HEALTHY VOLUNTEERS

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Albaconazole (ALBA, UR-9825) is a triazole antifungal agent that has showed good in vitro and in vivo activity. The aim of this study was to define safety, tolerability and plasma pharmacokinetics (PKs) of an oral solution containing ALBA after single and multiple dose administration to healthy volunteers. Two randomized, double-blind, placebo-controlled studies were performed. In the single dose (SD) study subjects received 80, 160, 240 or 320 mg. In the multiple dose (MD) study, subjects received 80 or 160 mg/q24h during 14 days. Each group of dose had 8 subjects (6 active, 2 placebo). Blood and urine samples were collected for up to 11 days (SD) or 28 days (MD) for PK analysis. Safety was assessed by physical examination and clinical laboratory testing.

A total of 48 subjects (32 SD; 16 MD) were analyzed. ALBA was well tolerated. The reported adverse events (AE) were mild or moderate and resolved prior to discharge. Headache was the most frequent AE (12 %) and it was reported by both active and placebo subjects. No clinically relevant changes were observed in biochemical, hematological, vital signs and ECG parameters. PK analysis of the SD and MD administrations showed high levels of exposure. In SD, C_{max} increased proportionally with the dose. Thus, mean C_{max} values of 0.94, 1.84, 3.24 and 3.60 µg/ml were obtained at the doses of 80, 160, 240 and 320 mg, respectively. AUC_{0-∞} values increased greater than proportionally at these doses, with values 15.1, 35.5, 60.8 and 95.3 µg.h/ml, respectively. Albaconazole was rapidly absorbed, with a mean T_{max} of 1h. Elimination half-life increased with dose (range 55 to 93h). Inter-subject variability following SD was low, with CVs ranging from 15% to 34% for C_{max} and AUC values. In MD, higher levels of exposure and half-life values were obtained after 14 days of administration. Preliminary results indicate that plasma accumulation occurs after MD treatment at high doses.

Conclusion: the single and multiple administrations of ALBA resulted in high levels of exposure that were safe and very well tolerated by all subjects. This study warrants that a wide range of dose regimes is compatible with the treatment of fungal infections with ALBA.

IN VITRO AND IN VIVO ACTIVITY OF ALBACONAZOLE

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Albaconazole (ALBA, UR-9825) is a new, broad-spectrum triazole antifungal agent presently under clinical investigation. We have studied the *in vitro* and *in vivo* activity of ALBA compared to that of other azole compounds.

In vitro activity: MICs of ALBA, fluconazole (FLU), itraconazole (ITR), voriconazole (VOR) and ravuconazole (RAV) were determined in several studies by the NCCLS microbroth dilution method against clinical yeasts (255 isolates for ALBA and VOR, 158 isolates for RAV and 97 isolates for FLU and ITR). ALBA was the most active compound with a MIC₅₀ of 0.03 µg/ml, which was slightly lower than the MIC₅₀ obtained for VOR and RAV (0.06 µg/ml for both drugs) and clearly lower than ITR (MIC₅₀ 0.5 µg/ml) and FLU (MIC₅₀ 2 µg/ml). The *in vitro* activity of ALBA against 30 isolates of filamentous fungi including *Aspergillus ssp* and dermatophytes was comparable to that of VOR and ITR and higher than FLU. Geometric means of MICs were 0.31 µg/ml for ALBA, 0.29 µg/ml for VOR, 0.41 µg/ml for ITR and 22.6 µg/ml for FLU.

In vivo activity: ALBA administered orally showed potent anti-*Candida* and anti-*Aspergillus* activity *in vivo*. It reduced dose-dependently (0.5-20 mg/kg/day) *Candida albicans* burdens in the kidneys and lungs of infected rabbits with a potency about 25-fold that of FLU. ALBA showed similar efficacy compared to FLU in a model of systemic candidosis in rats. ALBA also demonstrated good *in vivo* activity in a systemic aspergillosis (*A. fumigatus*) model in immunosuppressed rats, reducing significantly the fungal burden in the livers of the animals in a clear dose-dependent manner (1-50 mg/kg, bid). At the highest dose tested ALBA eradicated the fungus from the liver. Other investigators have reported ALBA to be also very active in animal models of Cryptococcosis, Scedosporiosis and Chagas' disease.

Conclusion: ALBA shows a very high *in vitro* and *in vivo* activity against a wide variety of pathogenic fungi. These results suggest that albaconazole may be clinically effective in the treatment of human fungal infections. Clinical trials are in progress.

LACK OF QTc EFFECTS OF ALBACONAZOLE , A NEW TRIAZOLE ANTIFUNGAL

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Albaconazole (ALBA, UR-9825) is a new, broad-spectrum triazole antifungal agent that has shown good in vitro and in vivo activity as well as an excellent tolerability in humans. Pre-clinical and clinical studies have been carried out to assess the potential of ALBA in inducing cardiac arrhythmias.

The hemodynamic effects of ALBA were investigated in anesthetized Beagle dogs. No effects on arterial pressure, heart rate, intraventricular and end-diastolic pressures, cardiac output, peripheral blood flow and ECG intervals (including QTc) were observed at doses up to 10 mg/kg iv. ALBA (60 mg/kg po) did not modify either the heart rate or QTc interval in conscious guinea pigs, whereas ketoconazole (KETO) at the same dose produced significant reductions in heart rate and increases in the QTc interval ($p < 0.01$). ALBA did not produce significant changes in action potential parameters in dog Purkinje fibers, whereas KETO increased APD90 and itraconazole reduced APD50. ALBA (10 μ M) did not block HERG potassium channel in HEK-293 transfected cells. At the same concentration ravuconazole and KETO blocked currents by 57 and 71%, respectively.

Although observations from pre-clinical data yielded no evidence of cardiac effects, the possibility that ALBA might have an action on the human heart was rigorously explored. Data from over 126 volunteers involved in four clinical phase I studies were evaluated according to the CPMP/986/96 recommendations. A total of 2872 ECGs were recorded in these studies which involved doses ranging from 5 mg up to 400 mg in single and repeated doses. Four volunteers (3.2%) reported increases in QTcB -greater than 60 msec- from baseline values. These were in the following groups: 5 mg (day 1), 20 mg (day 16), 40 mg (day 1) and placebo (day 16 and 18). No increases over 60 msec were observed in QTcF. All QT, QTcB and QTcF values were lower than 500 msec. No plasma concentration and individual QTcB values relationship was found.

In summary, the QT interval monitoring during pre-clinical and clinical studies with the new antifungal agent ALBA showed no significant effect on cardiac repolarization.

PRELIMINARY RESULTS OF THE EFFECTS OF PENTOXIFYLLINE THERAPY IN THE MURINE MODEL OF PARACOCCIDIOIDOMYCOSIS

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Pentoxifylline (PTX) was found to be an inhibitor of the proinflammatory cytokine tumor necrosis factor (TNF)- α . In murine paracoccidiodomycosis (PCM), TNF- α is considered a determinant factor in resistance to *Paracoccidoides brasiliensis* (Pb). Few hours after i.p. Pb inoculation, TNF- α levels are higher in susceptible than in resistant mice. Released by macrophages, TNF- α is required for this cell accumulation and differentiation into epithelioid cells and for the persistence of well-formed PCM granulomas. Interferon (IFN)- γ can activate infected macrophages to secrete TNF- α , inhibiting the replication of Pb. The effects of PTX therapy were tested in B10.A mice, susceptible to PCM, using as parameters the dissemination of viable fungi to various organs, demonstrated by colony-forming units (CFU) assays, and the development of specific cellular immune responses against Pb antigen, demonstrated by delayed-type hypersensitivity (DTH) reactions. PTX therapy, in dosages of 30 or 50mgPTX/kg/day, was given in drinking water and began 24 hours after Pb i.p. inoculation. Two days after infection, the number of CFU/gram of tissue (CFU/g) in the lungs of mice treated with 30mgPTX/kg/day was diminished when compared with both untreated or 50mgPTX/kg/day treated mice. In the 7th day, both 30 or 50mgPTX/kg/day treated mice showed lower CFU/g in the epiplooo. On the 15th and the 30th day after infection, no difference was found in CFU/g between untreated or 50mgPTX/kg/day treated mice. However, on the 15th day, the number of CFU/100 μ L of organ suspension was lower in the liver of 50mgPTX/kg/day treated mice, while in the 30th day, CFU/100 μ L of liver was higher in mice submitted to this therapy. In DTH reactions, both untreated and 50mgPTX/kg/day treated mice showed a profile in keeping with that described for the susceptibility pattern, characterized by early and ephemeral responses. The animals presented, at the 7th day post-infection, low DTH responses, that increased slightly in the 15th day. It has been reported that the inhibition of TNF- α in murine PCM, either by the use of anti-TNF- α antibodies or by the knock-out of the p55 TNF- α receptor gene, lead to an increase in disease severity and in the mortality rates specially after the 2nd week of infection, confirming the protective role of TNF- α . In our assays, this increase only appears at the 1st month. However, the events occurring at the 2nd day of infection suggest that in a very early phase of PCM TNF- α might have a non-protective role, once its inhibition reduced the fungal load isolated from the lungs of mice. This phenomenon probably is accompanied by alterations in the cytokine profile, that must be investigated in a more deep way.

A NOVEL SMALL MOLECULE ANTIFUNGAL COMPOUND WITH IN VIVO ACTIVITY AGAINST *ASPERGILLUS FUMIGATUS*

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As part of our effort to discover novel drugs for the treatment of invasive fungal infections, a new family of heterocyclic compounds has been synthesized. The lead compound from these studies, GL48656, has in vitro activity against a variety of fungi, including *Aspergillus* spp., *Coccidioides immitis*, *Cryptococcus* serotypes A-D, and the emerging pathogens *Fusarium* and *Scedosporium*. The anti-*Aspergillus* activity of GL48656 is comparable to amphotericin B (AmB), with MIC values of 1-8 and 1-4 µg/ml, respectively. GL48656 is cidal against *A. fumigatus*, *A. flavus* and *A. niger* with MFC values of 2-8 µg/ml, similar to AmB (MFC of 2-4 µg/ml). GL48656 has fungicidal activity comparable to AmB against *Fusarium* and dermatophytes, and was highly active against *S. prolificans* with an MIC of 0.5 µg/ml.

To evaluate acute toxicity, CD-1 mice were injected IV with increasing concentrations of GL48656 and monitored for 48 h for survival. The minimum lethal dose (MLD), i.e., the lowest dose at which death occurred in at least one animal, was determined for GL48656 and compared to caspofungin and AmB. The MLD values were 20 mg/kg for GL48656, 40 mg/kg for caspofungin and 3 mg/kg for AmB. The pharmacokinetics (PK) of GL48656 was studied in mice and rats after IV or IP administration. Plasma concentrations of GL48656 were determined using an LC/MS/MS method. After IV dosing, the t_{1/2} of GL48656 for mouse and rat was 3.7 and 6.0 hours, respectively. The PK after IP dosing were similar to IV dosing - t_{1/2} for mouse and rat of 3.6 and 5.3 hours, respectively, and characterized by low clearance rates and high volumes of distribution. The in vivo activity of GL48656 was studied in a model of systemic aspergillosis by infecting CD-1 mice IV with 8.4 x 10⁶ conidia of *A. fumigatus*. Ten days of therapy began 1 day later, with GL48656 given IP BID and AmB given IP QD, or IV QOD. Residual CFU was quantitated at day 14 postinfection. All untreated controls died, whereas treatment with 1 or 3.3 mg/kg of GL48656 prolonged survival (p ≤ .0008). These doses of GL48656 were equivalent to 0.8 mg/kg AmB IV or 3.3 mg/kg AmB IP in prolonging survival. Fungal burden in the brain and kidney were reduced by all regimens (p ≤ .0054, in both organs) which were equivalent, except that 3.3 mg/kg GL48656 was superior to AmB (p = .0453) in brain. In summary, GL48656 is active in vitro and in vivo vs. *Aspergillus* with efficacy equivalent to the gold standard AmB. GL48656 has favorable pharmacokinetic properties and less acute toxicity than AmB, comparable to caspofungin. Additional studies to characterize the antifungal efficacy of GL48656 are underway.

GLYCOSYL AMINO ACID DERIVATIVES AS INHIBITOR OF DNA TOPOISOMERASE I OF CANDIDA ALBICANS

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DNA topoisomerases are complex unique enzymes which alter the topological state of DNA and play important role in DNA replication, transcription, recombination and chromosomal segregation. Topoisomerases have been reported as a target of many therapeutic agents including antibacterial (quinolones) and antineoplastic agents (camptothecin, etoposide etc.). We have evaluated the inhibitory effect of a series of novel glycosyl amino acid derivatives (synthesized in CDRI on a target-based synthesis against Topo-I) in a number of pathogenic fungi following NCCLS guidelines. Most of the derivatives showed a significant activity (MICs 3.12-25 ug/ml) against *Candida albicans*, a common nosocomial infection in immunocompromised patients. Further, the potential derivatives were tested in target-based assay for Topo-I using cell-free extracts of *C. albicans* which showed 60-70% inhibition (relaxation of supercoiled plasmid pBR322). Camptothecin, used as standard Topo-I inhibitor, exhibited 64% inhibition. A good correlation ($r^2 = 0.902$) was obtained between in vitro MICs of glycosyl amino acid derivatives and their subsequent inhibitory effect on Topo-I catalysis. Further validation is warranted to confirm the antifungal activity of these derivatives.

CANDIDA TRANSLOCATION MODEL MOUSE

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Background: Deep mycoses is the most serious infection which happened to immunocompromised hosts, like leukemia or malignant lymphoma. *Candida albicans* (*C. albicans*) is the most frequent causative agent of the deep mycosis, although it exists in the oral, gastrointestinal, dermal and vaginal flora in humans. Then *C. albicans* is not a component of the indigenous microflora in the rodent gut. To mimic the deep mycosis which the yeast translocated from the intestinal tract and disseminated systemic organs, We made an appropriate mouse model and introduced you.

Method: DBA 2-J mice was given malnutrition or normal feedings for 20 days. We checked whether their stools could consist of *C. albicans* or not and *C. albicans* was colonized in the gastrointestinal tracts. We inoculated them intragastrically with *C. albicans*. The mice were administered intraperitoneally Methotrexate(MTX) on the 4th day and Cyclophosphamide(CPA) on the 4,5,6,7,8th day.

Result: *C. albicans* was isolated from stools of malnutrition mice for 40 days, but not from normal nutrition mice.

On the 9th day the dissemination of *C. albicans* to the livers histologically conformed. The dissemination to the spleen, kidney and lung was also frequently.

The blood cultures were positive after the 8th day.

The liver cultures were positive after the 6,7th day.

5. *C. albicans* invaded the Esophagus-Cardia junction(E-C junction) in all cases. Small intestine or colon were invaded in some cases.

Assessment: To make mice models of deep mycoses leukopenia and injury of the mucous membrane of the gastrointestinal tract is necessary. Originally mice do not have *C. albicans* as their normal flora, but we could settle *C. albicans* in the GI tract by malnutrition and translocate them by using antibiotics and anti-cancer drugs. We use model and endeavored the mechanism of the deep mycosis. We presented the use of the mouse in another poster.

ANALYSES OF USEFULNESS OF THE SERUM FUNGAL DIAGNOSIS BY USING THE PRECEDING DEEP MYCOSES MICE (*C. ALBICANS*) MODEL.

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Background: It is hard to diagnose deep mycoses like disseminated candidiasis. We need early diagnosis and treatment. So it is important to use the serum diagnosis. We recognized what liver culture preceded blood culture in this mice model. In this experiment, we examined the relationship between serum diagnosis and liver culture.

Method: DBA 2-J mice was given malnutrition or normal feedings for 20 days. We checked whether their stools could consist of *C.albicans* or not and *C.albicans* was colonized in the gastrointestinal tracts. We inoculated them intragastrically with *C.albicans*. The mice were administered intraperitoneally Methotrexate(MTX) on the 4th day and Cyclophosphamide(CPA) on the 4,5,6,7,8th day. And we measured beta-D-glucan, mannan antigen and CAND-TEC on the 5,5.5,6,6.5,7,7.5th day.

Result

The blood culture were positive after the 8th day.

The liver culture were positive after the 6,7th day.

CAND-TEC were all negative.

Mannan antigen were all positive in the 7th day.

But a part of the beta-D-glucan were positive and the other remained negative.

In the 7.5th day, Both mannan antigen and beta-D-glucan were positive.

Conclusion: The positive of mannan antigen and beta-D-glucan preceded what *Candida* were isolated from blood culture. The serum fungal diagnosis (mannan antigen and beta-D-glucan) is going to connect with early diagnosis and treatment.

THE COMBINATION OF LOW DOSE AMPHOTERICIN B AND MICA FUNGIN IS COMPARABLE IN ACTIVITY TO HIGH DOSE AMPHOTERICIN B ALONE IN TREATMENT OF EXPERIMENTAL INVASIVE PULMONARY ASPERGILLOSIS

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Background: Micafungin is a new echinocandin with broad-spectrum fungicidal activity against *Candida spp.* and fungistatic activity against *Aspergillus spp.* In order to increase the efficacy of micafungin against invasive aspergillosis, we investigated the in vitro and in vivo interaction and antifungal activity of micafungin in combination with deoxycholate amphotericin B (AMB). **Methods:** The combination of micafungin and AMB was studied over a range of concentrations (micafungin (0 to 0.25 µg/ml) and AMB (0 to 0.25 µg/ml)), using checkerboard MTT assays. We then proceeded to investigate the in vivo antifungal activity of micafungin and AMB in experimental invasive pulmonary aspergillosis in persistently neutropenic rabbits. Antifungal therapy was started 24h after endotracheal inoculation of 1.25x10⁸ *Aspergillus fumigatus* conidia and continued for 12 days in surviving animals. Treatment groups consisted of untreated controls (UC), micafungin at 1 (MICA1), low-dose AMB at 0.25-0.5 (AMB0.5), MICA1+AMB0.5 (MICA+AMB), or high-dose AMB at 1 mg/kg (AMB1). **Results:** MTT checkerboard assays demonstrated an additive interaction between micafungin and AMB. A total of 77 rabbits were studied. Rabbits treated with the combination of micafungin plus AMB demonstrated significant decrease of pulmonary CFU/g in comparison to that of MICA1 (p<0.001), AMB0.5 (p<0.05), and UC (p<0.001). In addition, rabbits treated with MICA+AMB showed a significant reduction in organism-mediated pulmonary injury as measured by infarct scores and lung weights in comparison to MICA1 (p<0.01), AMB0.5 (p<0.05) or UC (p<0.01) rabbits. Survival through the entire study was achieved in 15 (87.5%) of 17 micafungin plus AMB-treated rabbits versus 10 (62.5%) of 16 AMB0.5 (p=0.08), 5 (0.01%) of 16 MICA1 (p<0.001), and 0 of 16 UC (p<0.001) rabbits. **Conclusions:** In summary, the combination of micafungin and AMB was more effective than single agent treatment and comparable to treatment of AMB at 1 mg/kg in treatment of experimental pulmonary aspergillosis.

SYSTEMIC *CANDIDA PARAPSILOSIS* INFECTION AND ANTIBODY RESPONSE IN AN EXPERIMENTAL MODEL

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Abstract: Systemic *C. parapsilosis* infection and the antibody response during infection was evaluated in a rat model of infection. Sprague-Dawley rats were injected intravenously with two different doses (1×10^6 or 1×10^8) of *C. parapsilosis* blastoconidia. Animals were sacrificed beginning 7 days after inoculation until 5 weeks post-inoculation and their organs were cultured to identify systemic fungal infection. Blood was taken at intervals of 3 to 7 days throughout the study period and the IgM response was determined through immunoblotting sera against *C. parapsilosis* cytoplasmic protein antigens. No deaths occurred in the animals given either inoculum doses. Organ culture showed that the liver was the main target organ for this infection. Recovery of yeasts from liver, kidney, spleen and heart showed a decrease by the end of the experimental period with a more rapid decrease observed in the animals given the lower inoculum dose. Immunoblotting showed a generally low level of IgM against *C. parapsilosis* cytoplasmic antigen, with a slight increase in antibody production noted around 9 to 14 days post-inoculation. A 55 kiloDalton antigenic component appeared to be immunogenic in the infected animals. Overall, it could be seen that *C. parapsilosis* has low virulence and its cytoplasmic proteins do not elicit a major antibody response in infected animals.

AMPHOTERICIN B EFFICACY IN THE ACUTE PHASE OF PARACOCCIDIOIDOMYCOSIS: LESSONS FROM A MURINE MODEL

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The golden standard drug for the treatment of paracoccidioidomycosis (PCM) still is amphotericin B (AmB), despite the development of newer, effective antifungal compounds. The efficacy of AmB therapy was tested in B10.A mice, susceptible to *Paracoccidioides brasiliensis* infection, using as parameters the dissemination of fungi to various organs and the development of specific cellular immune responses against homologous antigen in the acute phase of PCM. Dosages of 1 or 2mg AmB/kg/day were administered by the i.p. route, every other day, three times a week; therapy began 24 hours before the fungal inoculation. No side effects were observed. At the 7th day after infection, the number of viable fungi, expressed as the log of colony-forming units (log CFU), was not reduced in mice treated with 1mg AmB/kg/day in any of the organs studied, but was significantly diminished in the lungs of animals treated with 2mg AmB/kg/day, when compared with untreated mice. At the 15th day after infection, therapy with 1mg AmB/kg/day led to lower log CFU counts in the spleen and epiplooo, while the administration of 2mg AmB/kg/day was able to reduce the fungal load in all organs studied, i.e., spleen, epiplooo, liver and lungs. Regarding the development of specific cellular immune responses against homologous *P. brasiliensis* antigen, demonstrated by delayed-type hypersensitivity (DTH) reactions, both untreated and 1mg AmB/kg/day treated mice showed a profile in keeping with that described for the susceptibility pattern, characterized by early and ephemeral DTH responses. These animals presented, at the 7th day after infection, low DTH responses, that increased significantly in the 15th day. On the other hand, therapy with 2mg AmB/kg/day elicited low DTH responses in both time points, in a profile similar to the one developed by mice resistant to PCM infection, whose responses appear later and are sustained. These results suggest that, in our murine model, AmB is efficient in reducing the fungal load during the acute phase of PCM; 2mg AmB/kg/day was the best dosage tested. An interesting parallelism between the severity of infection and the development of antigen-specific cellular immunity could also be noted, once the susceptible pattern of DTH response was accompanied by higher CFU counts, whereas the resistant pattern of DTH response was accompanied by an effective control of the infectious process. Our present data allowed to confirm the efficacy of AmB therapy by real counts of the infectious agent in the animal's tissue. This in vivo observation may help physicians to sustain the indication of AmB for use in humans that for a reason or another cannot be submitted to other therapeutic schedules.

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ANTIFUNGAL THERAPY OF MURINE INFECTION WITH ASPERGILLUS TERREUS

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Background: In recent years, *Aspergillus terreus* has been an increasingly frequent pathogen in both the United States and Europe. Herein, we evaluated posaconazole (POS), amphotericin B (AMB), and caspofungin (CASPO) against *A. terreus* isolate #R-3371 in a neutropenic mouse model. **Methods:** The day before infection ICR mice were rendered neutropenic with 5-fluorouracil at 150 mg/kg intravenously (IV) and cyclophosphamide at 200 mg/kg intraperitoneally (IP). Mice were infected IV with 2×10^5 - 1.5×10^7 conidia/mouse. MICs using the NCCLS M38-P method for POS, AMB, and CASPO respectively, at 48 hrs, were 0.06, 2, and <0.125 $\mu\text{g/ml}$. Therapy began the day after infection and continued through day 7 with POS at 10, 20, or 40 mg/kg orally daily, AMB at 6 mg/kg daily or 10 mg/kg every other day IP, or CASPO at 0.5, 5, 10, or 15 mg/kg IP daily. Control mice received water orally daily. Mice were observed through day 8 for survival. For tissue burden studies mice were treated day 1-7 and were terminated on day 8. Mice succumbing before day 8 had tissues removed for tissue burden. Spleens and lungs were removed, weighed, homogenized, and fungal burden was measured by serial semi-quantitative counts. Statistical analysis was performed using Log rank tests for survival and Mann-Whitney tests for tissue burden studies with $p < 0.05$ for significance. **Results:** In 3 studies AMB was not effective in prolonging survival. Only at 10 mg/kg every other day was AMB effective in reducing the spleen counts lower than those of controls. CASPO at 15 mg/kg prolonged survival and reduced spleen counts, though inconsistently. The lower doses of CASPO were ineffective. POS at 40 mg/kg prolonged survival and reduced both spleen and lung burdens. POS at 20 mg/kg, but not at 10 mg/kg, prolonged survival, while both 20 and 10 mg/kg doses reduced lung, but not spleen, burdens. **Conclusion:** The new broad spectrum triazole POS may have an increasing role in treatment of AMB resistant mycelial pathogens such as *A. terreus*.

SEVERE SEPSIS AND FUNGEMIA WITH *SACCHAROMYCES CEREVISIAE*

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Background: *Saccharomyces cerevisiae* is known as an apathogenic yeast used in human food production. A subspecies, *Saccharomyces boulardii*, even has a role in the treatment of enterocolitis with persistent diarrhea, probably by contributing to the reconstitution of enteral flora. We present a case sepsis with *Saccharomyces cerevisiae* fungemia during treatment with *Saccharomyces boulardii*.

Case: A 61 years old male was admitted to the hospital. He had undergone hemicolectomy with end-to-end anastomosis three weeks earlier because of stenosing carcinoma and had suffered from persistent diarrhea ever since. The patient presented in shock, with somnolence, exsiccosis, fever, dyspnea, non-tender abdomen, vivid bowel sounds. Laboratory values (CrP 299mg/1, leukocytes 17,9 GPt/1) indicated a severe infection. Ultrasound, X-ray, CT scan and intestinal endoscopy revealed no abdominal focus of infection. The patient was intubated, mechanically ventilated and treated with antibiotics and *Saccharomyces boulardii*. A relapsing ventilator-associated pneumonia complicated the further course of disease. The septic shock had successfully been treated, though. On day 24, the patient's condition worsened, he had a fever up to 40.1 °C, developed acute renal failure and again septic shock requiring catecholamine infusion. On this same day, *Saccharomyces cerevisiae* was isolated from three arterial blood cultures. This finding was confirmed on days 26 and 27. Routine mycological diagnostics (nasal, pharyngeal and anal swabs, tracheal secretion, urine) had revealed no more than insignificant anal colonization with *Candida albicans*. The mycotic bloodstream infection was treated with 800 mg fluconazole i.v. for 13 days. Follow-up cultures showed no further sign of fungal bloodstream infection. Within the following five weeks, the patient recovered, yet the diarrhea persisted. Finally, a jejuno-colic fistula turned out to be the cause and the patient underwent surgical revision.

Conclusion: A bloodstream infection with *Saccharomyces cerevisiae* was proven by several cultures. A casual relation to the therapy with *Saccharomyces boulardii* seems possible.

A COMPARISON OF ANTIFUNGAL SUSCEPTIBILITIES OF *CANDIDA GLABRATA* ISOLATED FROM HEAD AND NECK RADIATION PATIENTS TO FLUCONAZOLE AND VORICONAZOLE

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Objectives: The aim of this study was to compare the antifungal susceptibility patterns of *Candida glabrata* specimens isolated from patients receiving radiation treatment for head and neck cancers against both fluconazole and voriconazole. We wanted to evaluate the hypothesis that voriconazole may be a suitable alternative in treating oropharyngeal candidiasis in head and neck radiation patients whose infections are due to *C. glabrata* and have developed resistance to fluconazole. **Methods:** The identities of 163 *C. glabrata* isolates from 14 head and neck radiation patients were established by plating on Chrom-Agar, germ tube evaluation, and API 20C testing. The isolates were subcultured to ensure purity and then subjected to antifungal susceptibility testing against increasing concentrations of both fluconazole and voriconazole at the Fungus Testing Laboratory at the University of Texas Health Science Center. **Results:** 29% of isolates tested had voriconazole MICs of 1 g/ml or higher, and 9.2% of isolates had voriconazole MICs of 2 µg/mL or higher. The average voriconazole MIC of isolates susceptible to fluconazole (MIC < 8 µg/ml) was 0.304 µg/ml, the average voriconazole MIC of isolates that showed dose dependent susceptibility to fluconazole (MIC from 16-32 µg/ml) was 0.871 µg/ml, and the average voriconazole MIC for isolates resistant to fluconazole (MIC > 32 µg/ml) was 2.909 µg/ml. MIC90 for voriconazole was 2 µg/ml. Two of four patients with clinical signs of oropharyngeal candidiasis showed dramatic increases in voriconazole MICs after prolonged exposure to and development of resistance to fluconazole. **Conclusions:** *C. glabrata* isolates with elevated fluconazole MICs often have elevated voriconazole MICs as well. This data would imply that voriconazole would not be a good clinical choice to treat *C. glabrata* oropharyngeal candidiasis that is resistant to fluconazole. However, since clinical MIC breakpoints for treating *C. glabrata* with voriconazole have not been developed, it is premature to say that infections that are clinically resistant to fluconazole will also be resistant to voriconazole even with elevated MICs. This must be confirmed in clinical trials. Supported by NIDCR, Pfizer, and The Dental Oncology Education Program.