In vitro antifungal activities of anidulafungin and micafungin, licensed agents and the investigational triazole posaconazole as determined by NCCLS methods for 12,052 fungal isolates: review of the literature

Ana Espinel-Ingroff

Division of Infectious Diseases, VCU Medical Center, Richmond, Virginia 23298-0049, USA

Summary

The echinocandins anidulafungin and micafungin and the triazole posaconazole are currently undergoing phase III clinical trials. Caspofungin and voriconazole have recently been licensed for the treatment of aspergillosis (both agents), other less common mould (voriconazole) and candidal (caspofungin) infections. This review summarizes the published in vitro data obtained by NCCLS or NCCLS modified methods on the in vitro fungistatic and fungicidal activities of these five agents for yeasts and moulds in comparison to the established agents, amphotericin B, fluconazole, itraconazole, and flucytosine. Among the yeasts, the echinocandins have less activity for *Candida parapsilosis* and *Candida guilliermondii*, no activity for *Cryptococcus neoformans* and *Trichosporon* spp., but good fungistatic and fungicidal activity in vivo and in vitro for most of the other *Candida* spp.; this fungicidal activity has been reported by minimum fungicidal concentrations (MFCs) or time kill curve results. The new triazoles exhibit good fungistatic activity (but not fungicidal) for most *Candida* spp., *C. neoformans*, and *Trichosporon* spp. For the *Aspergillus* spp. evaluated, the echinocandins have similar or better fungistatic activity than those of amphotericin B and the triazoles, but fungicidal activity has been demonstrated only with amphotericin B and the triazoles, with the exception of fluconazole. Most studies showed posaconazole and voriconazole minimum inhibitory concentrations (MICs) ranging from 0.25 to 8 µg/ml for non-*solani Fusarium* spp., while MIC and minimum effective concentration (MEC) endpoints of the echinocandins were >8 µg/ml. The fungistatic activity of the triazoles is also superior to that of the echinocandins for most of the dimorphic fungi and the Zygomycetes. However, micafungin has activity for the mould phase of most dimorphic fungi, but not for the parasitic or yeast phase of *Paracoccidioides brasiliensis*. The echinocandins appear to have variable and species dependent fungistatic activity for the dematiaceous fungi, but all agents have poor or no activity against most isolates of *Scedosporium prolificans*. Only amphotericin B exhibit good fungistatic activity against the Zygomycetes. The combination of caspofungin with some triazoles, amphotericin B or liposomal amphotericin B has been synergistic in vitro, in animal models and in patients. Breakpoints are not available for any mould and antifungal agent combination. In vitro/in vivo correlations should aid in the interpretation of these results, but standard testing conditions are needed for the echinocandins, especially for mould testing, to obtain reliable results.

Key words

Antifungal, New and Established Triazoles, Echinocandins, Amphotericin B, Flucytosine, Yeast, Mould, NCCLS, Fungistatic, Fungicidal

Address for correspondence:
Dr. Ana Espinel-Ingroff
Division of Infectious Diseases
VCU Medical Center
P.O. Box 49, Richmond
Virginia 23298-0049, USA
Phone: (804) 828-9711
Fax: (804) 828-3097
E-mail: avingrof@hsc.vcu.edu

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Actividades in vitro de anidulafungina y micafungina, de los antifúngicos habituales de uso clínico y del triazol en investigación posaconazol, determinadas por métodos del NCCLS, contra 12.052 aislamientos fúngicos: revisión de la literatura

Resumen

Las equinocandinas anidulafungina y micafungina y el triazol posaconazol están en fase de ensayo clínico III. La caspofungina y el voriconazol han sido recientemente comercializados para su uso clínico en el tratamiento de la aspergilosis (ambos), las micosis por hongos filamentosos menos comunes (voriconazol) y las candidiasis (caspofungina). Esta revisión resume los datos obtenidos in vitro mediante los métodos propuestos por el NCCLS o con modificaciones de éstos sobre las actividades fungistáticas y fungicidas de estos cinco fármacos contra levaduras y mohos en comparación con las actividades mostradas por otros antifúngicos de uso clínico ya establecido, como anfotericina B, fluconazol, itraconazol y 5-fluorocitosina. Dentro de las levaduras, las equinocandinas muestran una menor actividad sobre *Candida parapsilosis* y *Candida guilliermondii*, y son inactivas contra *Cryptococcus neoformans* y *Trichosporon* spp., pero su actividad fungistática y fungicida es buena contra el resto de las especies de *Candida*. Esta actividad fungicida se ha demostrado mediante la determinación de la concentración mínima fungicida (MFCs) o mediante curvas de tiempo-destrucción celular *(time-kill curves).* Los nuevos triazoles muestran una buena actividad fungistática (aunque no fungicida) contra la mayoría de las especies de *Candida* y *Trichosporon* y contra *C. neoformans*. En el caso de las especies de *Aspergillus* estudiadas, las equinocandinas tienen una actividad fungistática similar e incluso mejor que las mostradas por la anfotericina B y los triazoles, pero es con la anfotericina B y con los triazoles, con la excepción de fluconazol, con los que se han observado efectos fungicidas. La mayoría de los estudios han mostrado que las concentraciones mínimas inhibitorias (CMIs) del posaconazol y voriconazol están entre 0,25 y 8 µg/ml para las especies de *Fusarium* diferentes a *Fusarium solani*, mientras que las CMIs y las concentraciones mínimas efectivas (CMEs) para las equinocandinas eran >8 µg/ml. La actividad fungistática de los triazoles es también superior a la de las equinocandinas para la mayoría de los hongos dimorfos y los Zygomycetes. Sin embargo, la micafungina tiene actividad contra la fase micelial de la mayoría de los hongos dimorfos, pero no contra la fase parásita o de levadura de *Paracoccidioides brasiliensis*. Las equinocandinas parecen tener una actividad fungistática variable y dependiente de especie contra los hongos dematiáceos, aunque todos los fármacos estudiados tienen poca o ninguna actividad contra la mayoría de las cepas de *Scedosporium prolificans*. Únicamente la anfotericina B muestra una buena actividad fungistática contra los Zygomycetes. La combinación de caspofungina con algunos triazoles, la anfotericina B o la anfotericina B liposómica ha tenido un efecto sinérgico in vitro, en modelos animales y en pacientes. No existen puntos de corte para ninguna de las combinaciones de antifúngico y hongo filamentoso. Las correlaciones in vitro/in vivo deberían ayudar en la interpretación de estos resultados, pero para esto son necesarias condiciones estándares de ensayo para las equinocandinas, especialmente para el estudio de los hongos filamentosos si se desea obtener resultados fiables.

Palabras clave

Antifúngico, Triazoles, Equinocandinas, Anfotericina B, 5-fluorocitosina, Levadura, Moho, NCCLS, Fungistático, Fungicida

The incidences of invasive infections caused by *Candida* spp. [1], *Cryptococcus neoformans* [2], and *Aspergillus* spp. [3] have increased since the 1980s. An increase in the use of antifungal agents led to the development of resistance to these agents, especially among AIDS patients [4,5] and in patients undergoing immunosuppressive therapy [6,7]. In the 1990s, the successful prevention of candidiasis and CMV disease early after hematopoietic stem cell transplantation and corticosteroid treatment for severe graft-versus host disease have also increased the incidence of infections caused by non-*fumigatus Aspergillus* spp., the Zygomycetes and *Fusarium* spp. [8-11]. The increased incidence and prevalence of mould invasive diseases, as well as those caused by non-*albicans Candida* species and other emerging fungi, has become a serious problem, because these organisms can be resistant to both amphotericin B and established azole antifungals [7,9, 12,13]. The associated mortality rate in organ transplant patients could be as high as 80 to 100% for zygomycosis and other non-*Aspergillus* hyalohyphomycosis and 54% for aspergillosis [14,15]; the former infections are usually associated with dissemination and a lower rate of successful outcome to therapy [16]. However, the mortality rate for aspergillosis among patients with acute leukemia and bone marrow transplantation is 60 to 80% [14,15]. Despite the development of amphotericin B lipid formulations and the use of fluconazole, nosocomial candidiasis has continued to be another serious problem [7].

In response to these trends, the echinocandin caspofungin (L-743,872, MK-0991, Cancidas; Merck&Co., USA) has been licensed for the treatment of refractory aspergillosis and the primary treatment of candidal infections [12,17-24] and voriconazole (Vfend, Pfizer, UK) has been recently licensed for the primary treatment of aspergillosis and other less common mould infections [25,26]. Pharmacokinetic data indicate that achievable serum levels for caspofungin range from ≤1 to 10 µg/ml and for voriconazole from 2 to 6 µg/ml, depending upon the dosing used [27,28]. In addition, two other echinocandins, anidulafungin (Vicuron Pharmaceuticals, VER-002, V-echinocandin, LY303366 [Lilly, USA]) and micafungin (FK463, Fujisawa, Japan) and another triazole, posaconazole (SCH56592, Schering, USA), are currently undergoing phase III clinical trials. Anidulafungin has been effective in the treatment of disseminated candidiasis in persistently neutropenic rabbits [29] and aspergillosis caused by amphotericin B-susceptible and -resistant *Aspergillus fumigatus* in a temporarily neutropenic mouse model [30]. Plasma peak concentrations were equal or exceeded the minimum inhibitory concentration (MIC) or minimum fungicidal concentration (MFC) for the infecting *Candida albicans* isolate, e.g., 0.5 to 51 µg/ml for 0.1 to 20 mg/kg in healthy rabbits [31]. Micafungin has shown antifungal activity in the treatment of disseminated *Candida tropicalis* infection in persistently neutropenic mice [32], azole-resistant *C. albicans* infections in mice [33] and for the treatment of temporarily neutropenic mice infected with either an itraconazole-resistant *A. fumigatus* strain or an *Aspergillus terreus* isolate [34]. On the other hand, in persistently neutropenic rabbits micafungin has demonstrated significant concentration-and dose-dependent clearance of *C. albicans* in disseminated candidiasis, but rabbits treated with this agent had no quantitative reduction in *A. fumigatus* growth in the lung tissue [35]; however, prolonged survival was similar to that achieved by liposomal amphotericin B.

Several reviews have been published regarding the efficacy, safety and pharmacokinetics of caspofungin and other echinocandins [36-49], but none of these articles has focused on the in vitro activities of these agents. This paper summarizes and discusses the published data on the in vitro antifungal activities of anidulafungin, micafungin and posaconazole and the licensed agents with which they have been compared, including caspofungin and voriconazole.

Literature review. A careful search of entries in the Medline database of the National Library of Medicine revealed 60 publications containing original data on the fungistatic and fungicidal activities of these new agents alone or in combination with other agents. This review summarizes only those fungistatic data that were obtained in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) guidelines for antifungal susceptibility testing of yeasts [50] and moulds [51] or by modified versions. The reader is referred to references 52-58 for data on the in vitro fungistatic activity obtained by commercial and other procedures; in some instances the NCCLS data were compared to those obtained by the other methods. The reader is also referred to references 59,60 for further information on in vitro results and methods; to reference 61 regarding the evaluation of testing conditions for caspofungin versus *Candida* spp. and *A. fumigatus* and to reference 62 for further voriconazole in vitro data.

Isolates. The results obtained with 12,052 fungal isolates, 10,637 of which were yeasts and yeast-like organisms and 1,415 of which were moulds, are summarized in tables 1 and 2. Most isolates were recovered from clinical specimens; ATCC strains were evaluated in addition to the clinical isolates in some studies [63-66]. The yeast and yeast-like organisms included 19 *Candida* spp., 1 *Trichosporon* sp. (reported as *Trichosporon asahii*, *Trichosporon cutaneum*, *Trichosporon beigelii*), and other species including *Cryptococcus neoformans* and *Cryptococcus humicola*, *Pichia anomala*, *Rhodotorula rubra* and *Saccharomyces cerevisiae*. The moulds included 21 moniliaceous species, six species of dimorphic fungi, five species belonging to the class Zygomycetes, and 11 species of dematiaceous fungi. In addition, some isolates were reported only as the genus, e.g., *Aspergillus* spp. When species names were provided for these groups, they are found under the footnote of each table.

NCCLS methods. In 1997, the NCCLS published an approved reference broth macrodilution method (Approved Standard M27-A) and its microdilution modifications for the in vitro testing of the activities of five agents against *Candida* spp. and *C. neoformans* [50]. This was followed in 1998 by the publication of the Proposed Standard M38-P document, which described both broth macrodilution and microdilution methods for the susceptibility testing of moulds. Both documents moved to the next level of development in 2002 (M27-A2 and M38-A) [50,51] to include MIC ranges for two quality control yeast isolates by the microdilution method and the new triazoles, voriconazole, posaconazole and ravuconazole. Although optimal conditions were identified for determining the fungicidal activity of antifungal agents against moulds [67,68], no standard guidelines have been established by the NCCLS for either yeasts or moulds. However, the fungicidal activity of investigational and newly licensed agents has been evaluated by non-standardized MFC and kill-curve procedures. The relevance of fungicidal results has only been reported for amphotericin B in candidemia, trichosporonosis and in animal models for aspergillosis [69]. The fungistatic susceptibilities of yeast isolates to the various agents were determined by the macrodilution method in three studies [70-72] and by the microdilution method in the other studies. Of the 15 articles that report MICs for moulds, four report macrodilution data [71,73-75] and the others present microdilution results. Only five studies evaluated both yeasts and moulds [65,71,76-78].

Method modifications. Because the NCCLS documents do not describe testing conditions for the echinocandins, a variety of inoculum sizes, media, temperatures and incubation times as well as different criteria of MIC determination have been used for evaluating the in vitro susceptibilities of fungi to the echinocandins. Results have been contradictory when MICs with the antibiotic medium 3 (M3) were compared to those obtained with the standard RPMI-1640 broth (RPMI) for yeast testing. In two yeast reports, the differences were not substantial (mostly one to two dilutions) for caspofungin [72,79], anidulafungin [72] and micafungin [80] MICs, while in one report, anidulafungin MICs with M3 were substantially lower than those with RPMI (MIC_{s90} or MIC_{s50}: 0.003-0.01 vs. 0.5-2 µg/ml) for most *Candida* spp. and *Saccharomyces cerevisiae* [81]; the exception were results for *Candida parapsilosis* (MIC_{s90}: 2 and 4 µg/ml with both media). In addition to M3, other media were evaluated for testing the echinocandins [65,72,80] for yeasts, including RPMI supplemented with 2% dextrose [79,80,82,83], but no substantial differences (mostly, one to two dilutions) were observed among

MICs obtained with the different media. In one study [83], MICs anidulafungin and caspofungin for *Candida* spp. were higher with 2% dextrose RPMI than with standard RPMI, while in another study [52], caspofungin MICs were lower; however, the latter study followed the testing guidelines of the EUCAST method. The criterion of MIC determination was mostly 100% or "complete" growth inhibition for yeasts, but some investigators also used the 50% or prominent [77,83] to 80% [84] growth inhibition. Although anidulafungin and caspofungin 50% growth inhibition MICs tended to be lower than 100% or "complete" growth inhibition MICs, no substantial differences were reported between the two MIC determination criteria, with the exception of caspofungin MICs for *Candida guilliermondii* (Ranges: 0.5 to 8 µg/ml vs. >8 µg/ml) [77].

Since the NCCLS proposed M38 document was not available until 1998, several studies follow the M27 methodology to test mould isolates [64,65,71] or also replaced the standard RPMI with M3 [85]. In the two studies that compared MICs for *Aspergillus* spp. [58,86] and *Fusarium* spp. [86], M3 only slightly decreased most caspofungin MICs or MECs (minimum effective concentrations). In five of the 16 mould reports, the 10^3 CFU/ml inoculum [65,71,73,75,85] was used instead of the 10^4 CFU/ml density recommended in the NCCLS M38-A mould document [51]. Since trailing is a common phenomenon when testing echinocandins against moulds, some studies reported the MIC as well as the MEC [58,71,85-88], where morphological alterations are the indicators of susceptibility (Figures 1a, 1b, and Figure 2).

Figure 1a. Visual MECs. Shown are the microscopic microcolonies (wells 6-1) that represent trailing growth above the MIC endpoint in contrast to the normal growth seen in the control wells (#12) and lower caspofungin concentrations; caspofungin MICs for these eight isolates of *Aspergillus* spp. are <1.0 µg/ml.

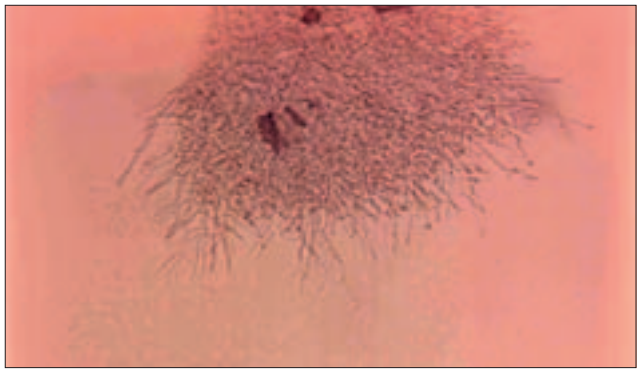

Figure 1b. Microscopic MEC. Shown are the hyphal alterations caused by caspofungin for an isolate of *A. fumigatus* [58].

Figure 2. Caspofungin and voriconazole Etest MICs for *A. fumigatus*. Shown are the trailing growth seen when testing caspofungin against *Aspergillus* spp. and other mould isolates (left etest strip) and the voriconazole clear inhibition ellipse (right etest strip). However, both MICs are < 1.0 mcg/ml [58].

Tables 1 and 2 summarize the in vitro antifungal data for each of the yeast and mould species evaluated and list the references from which the data were obtained. When results were provided by both standard and other testing conditions, results displayed in these two tables are those obtained by standard conditions (NCCLS M27 and M38 documents). Fewer than five isolates were tested for some yeast, yeast-like fungi and moulds. Breakpoints are not available for the echinocandins or the new triazoles versus MICs for any organism. Therefore, caution should be used in the interpretation of these fungistatic and fungicidal results until in vitro/in vivo correlation results become available. However, reliable susceptibility profiles are presented in tables 1 and 2 for species for which large numbers of isolates have been investigated.

Fungistatic activity against yeasts and yeast-like organisms. Caspofungin in vitro fungistatic activity against most *Candida* spp. ($MICs_{90}$ ≤2 µg/ml) was similar or superior to those of amphotericin B, flucytosine and the triazoles (Table 1). However, against *Candida famata* [89], *C. guilliermondii* [56,89], and *C. parapsilosis* [89,90], caspofungin $MICs_{90}$ or $MICs_{50}$ >2 µg/ml were reported. Anidulafungin $MICs_{90}$ >2 µg/ml were also obtained for some of these species [72,81,91-93] as well as for *Candida dubliniensis* [91,94], *Candida glabrata* and *Candida lusitaniae* [72]. The high caspofungin MICs are consistent with the caspofungin data obtained in clinical trials, where five patients with *C. parapsilosis* infection had persistently positive blood cultures as compared with three patients infected with *C. albicans* [7,21]. Micafungin $MICs_{90}$ >2 µg/ml were only obtained for *C. parapsilosis* [95]; however, fewer reports for this agent were found in the literature (Table 1) and in some reports, the antifungal in vitro activity corresponded to 50% or the prominent growth inhibition MICs [83,95]. In general, echinocandin MICs were low for the less common or emerging *Candida* spp. [55,66,70,78,81,83,93,96]. It is noteworthy that the three echinocandins have good antifungal activity in vitro for most isolates of *Candida* spp. that are either fluconazole- or itraconazole-resistant [54,65,78,82,89,95-99] and amphotericin B-resistant [99]; anidulafungin has also shown activity to resistant *Candida* spp. by the EUCAST method [53] (references 53 and 99 are not listed in Table 1).

Although voriconazole and posaconazole MIC ranges included high MICs (>8 µg/ml) for *C. albicans* and some emerging *Candida* spp., $MICs_{90}$ >2 µg/ml were only reported for *C. glabrata* and *C. tropicalis* (Table 1). Resistance to itraconazole (MICs >1.0 µg/ml) was found in most of the yeast or yeast-like species; the exceptions were some of the emerging or less common yeast or yeast-like species and both *Cryptococcus* spp. (Table 1). Similar results were reported with fluconazole. Posaconazole also exhibited good in vitro fungistatic activity against *C. neoformans* and *Trichosporon* spp. [77], while the three echinocandins did not exhibit antifungal activity against these species (Table 1). Anidulafungin MICs of 32 µg/ml were documented for *Rhodotorula rubra* [93].

Caspofungin [100,101] and micafungin [101] also have activity against *Candida* spp. biofilms in vitro (results not shown in Table 1) that was similar to that of liposomal amphotericin B and amphotericin B lipid complex, while *Candida* spp. biofilms were resistant to voriconazole, amphotericin B and fluconazole [101].

Although standard conditions are not available for the echinocandins and the majority of published data for yeasts have been obtained with the 100% growth inhibition criterion, recent studies suggest that the most reliable testing conditions appear to be ~50% growth inhibition MICs obtained after 24 h of incubation with the standard RPMI. Further studies are needed to evaluate the reproducibility of these testing conditions as well as their clinical utility.

Fungistatic activity against moniliaceous fungi. The isolates from the moniliaceous fungi comprised the clinically important pathogens *Aspergillus* spp. and *Fusarium* spp., the dimorphic fungi and few isolates of other mould species. Although caspofungin MICs >8 µg/ml were reported for *Aspergillus fumigatus* and *Aspergillus flavus*, $MECs_{90}$ were lower (0.06 to 0.5 µg/ml) than the $MICs_{90}$ of amphotericin B (1.0 to 4 µg/ml) and itraconazole (0.06 to 4 µg/ml), and similar to those of voriconazole (0.06 to 1.0 µg/ml) and posaconazole (0.5 µg/ml). In general, anidulafungin and micafungin results were lower than caspofungin MICs and MECs; MECs were not determined for micafungin in any of the reported studies. However, as for the yeasts, less anidulafungin and (even less) micafungin data are available. MICs of the echinocandins were usually ≤2 µg/ml for most of the other species of *Aspergillus* evaluated; the exceptions were caspofungin data for *Aspergillus nidulans* (0.25-4 µg/ml) and anidulafungin for *Aspergillus glaucus* (≤0.03->8 µg/ml). Cross-resistance was not observed between the echinocandins and the other agents, probably because the echinocandins have different action mechanisms than those of amphotericin B and the triazoles. In addition, the data suggest that the more stable caspofungin MEC endpoint [58,86-88] provides data that better reflect the efficacy of caspofungin in the treatment of aspergillosis [22-24].

Voriconazole and posaconazole fungistatic activity against *Fusarium* spp. were variable and species dependent; MICs ranging from 0.25 to >8 µg/ ml were reported against non-*solani Fusarium* spp. [77,87] and posaconazole MICs >8 µg/ml for *F. solani* [77]. For *Fusarium* spp. as a group, the echinocandins did not show fungistatic activity, even when MEC values were determined for caspofungin [86,87] (Table 2). Voriconazole has been licensed for salvage treatment of fusariosis [26] and posaconazole could have an important role in the treatment of these infections; however, the mortality rate due to disseminated fusariosis continues to be high. Itraconazole had less in vitro activity against *Fusarium* spp. than that of the other triazoles and amphotericin B.

Only two *Acremonium* isolates were tested [77,102]. The results suggest, however, that the susceptibility of this genus to anidulafungin is species dependent. On the other hand, caspofungin MICs for both *Acremonium* isolates and posaconazole MICs for *Acremonium strictum* were below 1.0 µg/ml. Less than 10 isolates each of *Paecilomyces* spp. and *Trichoderma* spp. were evaluated. Caspofungin had good fungistatic activity against *Paecilomyces variotii* and *Trichoderma* spp., and little activity for *Paecilomyces lilacinus*. In contrast, micafungin had excellent activity against these two species (Table 2). High MICs were also reported for amphotericin B against the latter species [78] and lower posaconazole MICs than those of the other triazoles for the six isolates grouped as *Paecilomyces* spp. [87]. Excellent to good fungistatic activity was also reported for micafungin and itraconazole against *Penicillium* spp. (78, only one isolate per species), while caspofungin activity appears to be species dependent (MEC range: 0.01 to >8 µg/ml) [87].

Fungistatic activity against dimorphic fungi. Most studies that evaluated activity against the dimorphic fungi [63,71,74,77,78] tested the mould rather than the parasitic yeast phase, but one study evaluated both phases with micafungin [63]. Caspofungin and anidulafungin had little or no activity ($MICs_{90}$ or GMICs: 1.3 to >8 µg/ml) [71,77] against the dimorphic fungi evaluated. However, micafungin activity was excellent against most mycelial forms of the dimorphic fungi (MIC range: ≤0.01-2 µg/ml), but MICs ranged from 4 to >8 µg/ml for both forms of *Paracoccidioides brasiliensis* [63]. When evaluated, itraconazole and posaconazole had excellent fungistatic activity against five of the six species of dimorphic fungi tested (MIC range: ≤0.01 to 0.12 µg/ml) [63,77,78], but less activity against *Sporothrix schenckii* (MIC range: 0.12 to 2 µg/ml) [63,77]. Amphotericin B showed in vitro activity that was similar or superior to that of the echinocandins, and fluconazole fungistatic activity was similar or lower than those of the other agents for this group of fungi (Table 2).

Fungistatic activity against Zygomycetes species. Although the in vitro activity of licensed and new agents against species of the Zygomycetes class was also evaluated with a small number of isolates, only amphotericin B had good fungistatic activity against the representatives of this group that were tested. The echinocandin MICs were >8 µg/ml, whereas those of itraconazole, posaconazole and voriconazole (when tested) appear to be more species dependent: 0.03 to >8 µg/ml MIC ranges (Table 2).

Fungistatic activity against the dematiaceous fungi. The fungistatic activity of the echinocandins was variable and species dependent. Caspofungin and anidulafungin had lower activity (MICs 1.0 to ≤8 µg/ml) than micafungin (MICs ≤0.12 to 0.5 µg/ml) for *Cladophialophora bantiana* and *Scedosporium prolificans*, while caspofungin had better activity than micafungin against *Fonsecaea pedrosoi*. Caspofungin and anidulafungin exhibited similar activity (0.25≥8 µg/ml) against *Bipolaris* spp., *Phialophora* spp., and *Scedosporium* spp. Low voriconazole fungistatic effect was demonstrated for the one isolate of *S. prolificans* investigated with this agent (8 µg/ml); voriconazole MICs reported elsewhere have ranged from 0.5 to >8 µg/ml [62]. Amphotericin B had lower activity (MICs 1.0 to 8 µg/ml) against both *Scedosporium* spp. as previously reported [62]. Itraconazole and posaconazole showed excellent in vitro activity (MICs ≤1.0 µg/ml) against nine of the 11 species of dematiaceous fungi for which one or both agents were tested against (Table 2). Again, fewer than five isolates were evaluated for most of these species.

Fungicidal activity against yeasts. The fungicidal activities of the echinocandins and the new triazoles have been investigated by MFC methods (Table 1) and time-kill curves. Wide MFC ranges (≤0.01-≥8 µg/ml) were reported for *C. albicans*, *C. guilliermondii*, *C. parapsilosis* (three echinocandins), *C. tropicalis* (caspofungin and micafungin), *C. glabrata*, *C. kefyr*, and *C. lusitaniae* (caspofungin). However, better fungicidal activities (MFCs ≤2 µg/ml) were observed for *C. krusei* (three echinocandins), *C. lusitaniae*, *C. tropicalis* (anidulafungin) and *C. glabrata* (anidulafungin and micafungin). In general, when fungicidal MFC data were obtained with the triazoles, MFC results were high, as expected, but low itraconazole MFCs ($MFCs_{90}$ ≤0.5 µg/ml) were reported for most of the common *Candida* spp. [65,103] (Table 1).

Standard parameters are not available for performing time-kill assays, but several studies have obtained such results by non-standardized procedures [84,104-110]. The fungicidal activity of anidulafungin has been corroborated by time-kill curves for *C. albicans*, other common *Candida* spp. [108] and *S. cerevisiae* [106]. However, the killing activity of anidulafungin has been drug dose independent [107], but medium and strain dependent [105,109]. M3 medium has a beneficial effect in the fungicidal activity (rate and concentration) of anidulafungin against *Candida* spp., e.g., fungicidal activity was demonstrated for six isolates with M3 and for only three isolates when tested in standard RPMI [109]. It was also demonstrated in two studies that anidulafungin MFC results correlate better with 80% than with 100% growth inhibition MICs [105,108].

Caspofungin fungicidal activity against *C. albicans* biofilms [110] was superior to that of amphotericin B, where the former agent's ≥99% killing (0.12 to 1.0 µg/ml, after 24 and 48 h, respectively) was at physiologic concentrations achievable in humans, but killing with amphotericin B was not at therapeutic concentrations. Micafungin killing activity was 4 to 16 times the 80% growth inhibition MIC for 7 of 10 *Candida* spp. isolates [84] and had superior activity to that of amphotericin B for one isolate of *C. albicans*.

Fungicidal activity against moniliaceous fungi. Several studies compared the fungicidal activities of micafungin and anidulafungin with those of itraconazole and amphotericin B for *A. fumigatus* [65,85], as well as caspofungin and anidulafungin with those of posaconazole against some moulds [77] (MFC results for moulds not shown in Table 2). The fungicidal activities of itraconazole and amphotericin B were superior (0.25 to 4 µg/ml) to that of the three echinocandins (MFCs ≥8 µg/ml) for all moulds tested in these two studies [65,77], but in another study anidulafungin MFCs ranged from <0.01 to >5 µg/ml for 60 *Aspergillus* isolates using M3 medium [85]. Posaconazole MFCs ranged from 0.06 to >8 µg/ml. One study investigated the fungicidal activity of caspofungin by time kill procedures for *A. fumigatus*; although there was no reduction in the number of cells from the killing-curve measurements [76], lysis of the hyphal tips has been reported [111]. Fungicidal activity has not been reported with the echinocandins against other moulds.

Synergistic studies. The outcome of therapy in clinical trials of voriconazole and caspofungin and the refractory nature of most mould infections to established agents indicate that ≥50% of these infections do not respond to antifungal therapy [9,23-26,112-114]. With the development of the echinocandins that have a different mechanism of action (cell-wall based) than those of amphotericin B and the triazoles, the investigation of synergy has been underscored [115]. Because of that, combination therapy has been proposed and used especially for infections caused by *Scedosporium* spp., *Fusarium* spp., and non-*fumigatus Aspergillus* [112]. Although standard guidelines are not available for either combination therapy or to study the in vitro synergistic activities, synergistic data have been documented with the new agents (results not shown in Tables 1 and 2). In vitro, caspofungin and amphotericin B had an additive (or indifferent) effect against *C. albicans* biofilms [116] as well as a positive interaction against azole-resistant isolates of *C. albicans* [117], but fluconazole inhibited the activity of caspofungin [116]. In vivo, the combination of caspofungin and fluconazole did not show any additive or antagonistic effect in murine candidiasis [118]. Caspofungin was synergistic to additive in vitro in combination with amphotericin B [119], itraconazole [120,121], voriconazole [122], and posaconazole [121] against *Aspergillus* spp. [119-122] and *Fusarium* spp. [119]. In a guinea pig model of invasive aspergillosis, the combination of voriconazole and caspofungin reduced fungal burden to a higher extent than when either agent was administered alone [123]; an immunocompetent child with a *S. prolificans* osteomyelitis infection was successfully treated with a combination of caspofungin and voriconazole [75]. However, this patient also had debridement and local irrigation with polyhexamethylene biguanide. In contrast, lack of interaction between caspofungin in combination with either voriconazole or ravuconazole for *A. fumigatus* has also been reported [121]. In patients, caspofungin in combination with either itraconazole [124] or liposomal amphotericin B [22,125] has been successfully (improvement shown) used for the primary or salvage treatment of invasive aspergillosis. In addition, anidulafungin and the chitin inhibitor, nikkomycin Z, have shown synergistic activity for some fungi [126]. In vitro/in vivo studies should clarify the role of combined therapy and the utility of in vitro synergistic results in patient management, but standardization of in vitro testing is needed to obtain reliable results.

Resistance mechanisms. Although the mechanisms of azole resistance among yeasts and *Aspergillus* spp. have been extensively researched [69,112,114], little information is available regarding the resistance mechanisms of the echinocandins. Resistance to the echinocandins may be related to mutations in the *FKS1* and *FKS2* genes that code the synthesis of glucan synthase proteins [127]. By an agar plate resistance assay, it was demonstrated that isolates of *C. albicans* with azole cross-resistance also have elevated caspofungin MICs and high levels of CDR1 and CDR2 expression [128]. It was then concluded that this overexpression might contribute to clinical resistance. An earlier publication had reported contradictory results, where the investigators concluded that caspofungin is not a substrate for multidrug transporters [129]. The mechanism of resistance in *C. neoformans* to the echinocandins has not been elucidated. Since both 1,3 - and 1,6-D-glucan linkages are present in *C. neoformans*, it has been concluded that an additional mechanism of action is responsible for the potent antifungal activities of the echinocandin agents against *Candida* spp. and *Aspergillus* spp. [130]. Further studies should investigate the mechanisms of resistance of the echinocandins.

Summary and conclusions. Echinocandin MICs are high for certain yeast and yeast-like isolates, but cross reaction is uncommon with the triazoles or amphotericin B. However, in vitro cross reactions of posaconazole and

voriconazole with itraconazole and amphotericin B have been reported for some moniliaceous or dematiaceous fungal isolates, but it is not frequent. In normal volunteers, peak plasma concentrations of caspofungin are above MICs/MECs for some isolates of the most common pathogens, *Candida* and *Aspergillus* species. Although the literature reports that the echinocandins have good fungistatic and fungicidal activity against a variety of yeasts, they do not exhibit fungistatic activity against *C. neoformas* and *Trichosporon* spp. and a variety of mould species. However, caution should be used in interpreting these results until in vitro versus in vivo correlations become available. Both voriconazole and caspofungin have been licensed for the systemic treatment of certain fungal infections; posaconazole, anidulafungin and micafungin could also have an important role in the treatment of severe fungal infections. Their alternative use alone or in combination with other agents may reduce the high mortality rate of fungal diseases, despite therapy with amphotericin B, its lipid zformulations or other licensed agents.

Table 1. In vitro activities of anidulafungin, micafungin, caspofungin, new triazoles and established agents against 10,637 yeast and yeast-like species.

Fungus	No. Isolates	Antifungal Agent	MIC range (µg/ml)	MIC_{90} (MIC_{50} or G) (µg/ml)	MFC range (µg/ml)	References
Candida albicans	2394	Anidulafungin	<0.01->8	0.01-0.5	0.03-4	66,71,72,77,81-83,91-93,98
	4265	Caspofungin	<0.01->8	0.12-1.0	0.12->8	52,54-56,70,72,77,83,89,90,96,98
	966	Micafungin	≤0.01-0.5	0.01-0.25	≤0.01-4	65,78,80,83,84,95,103
	2453	Amphotericin B	≤0.03-2	0.25-1.0	0.06-2	54,65,66,71,76,80,81,82, 83,92,93,95,96,98,103
	5292	Fluconazole	≤0.12->64	0.25-≥64	≥64	54,65,66,70,71,72,76,78,80,83,89 93,95,96,98,103
	4963	Itraconazole	≤0.01-≥8	≤0.03-4	1.0->8[1]	54,65,78,81-83,89,93,95,96,98,103
	1293	Voriconazole	<0.01->8	0.01-0.5	NR	52,80,82,83,90,92,95
	928	Posaconazole	<0.01->8	0.01-1.0	NR	77,83,90,95
	2129	Flucytosine	≤0.06->64	0.5-4	NR	71,78,80-83,92,93,95,96,98
Candida dubliniensis	92	Anidulafungin	0.12-8	0.06-4	NR	83,91,94
	177	Caspofungin	0.01-1.0	0.5	NR	83,89,97
	40	Micafungin	≤0.06-1.0	0.03-0.5	NR	78,80,83
	147	Amphotericin B	0.12-1.0	0.12-1.0	NR	78,80,83,94,97
	273	Fluconazole	≤0.12->64	0.5->64	NR	78,80,83,89,91,94,97
	252	Itraconazole	0.01->8	0.06->8	NR	78,83,89,91,94,97
	146	Voriconazole	<0.01-0.5	0.03-0.12	NR	80,83,94,97
	125	Posaconazole	0.01-1.0	0.06-0.5	NR	83,94,97
	235	Flucytosine	≤0.03-0.12	≤0.03-0.12	NR	78,80,83,89,97
Candida famata	11	Anidulafungin	0.01->16	8	NR	66,91
	13	Caspofungin	0.06->8	(0.5-4)	1.0->8	70,89
	1	Amphotericin B	1.0	NR	NR	66
	24	Fluconazole	0.12-64	(2) 16	>64	66,70,89,91
	19	Itraconazole	0.03->8	(0.25) 1.0	NR	89,91
Candida glabrata	993	Anidulafungin	<0.01-8	0.03-8	0.12-2	66,71,72,77,81-83,91-93,98
	1289	Caspofungin	<0.01->8	0.25-1.0	0.5->8	52,54-56,70,72,76,77,83,90,96-98
	524	Micafungin	≤0.01->8	0.01-0.5	≤0.01-0.03	65,78,83,84,95,103
	1072	Amphotericin B	≤0.03-2	0.25-2	0.06[1]-2	54,65,66,71,76,78,81-83 92,93,95,96,98,103
	1629	Fluconazole	≤0.12-≥64	(4) 8-≥64	4[1]->64	54,65,66,70-72,78,81-83, 89-93,95,96,98,103
	1584	Itraconazole	≤0.01->8	1.0-≥8	0.5[1]->8	54,65,78,81-83,89-93,95,96,98,103,
	558	Voriconazole	≤0.03-4	0.01-4	NR	52,82,83,90,92,95
	515	Posaconazole	0.03-4	1.0-4	NR	77,83,90,95
	981	Flucytosine	≤0.06-16	0.06-2	NR	66,71,81-83,92.93,95,96,98
Candida guilliermondii	27	Anidulafungin	0.06-4	(1.0-4)	4-8	77,81,83
	158	Caspofungin	0.12->8	(0.5-2) 1.0->8	0.25->8	52,56,70,76,77,83,89,96
	24	Micafungin	0.03-2	(0.5-2) 2	1->8[1]	65,78,83
	58	Amphotericin B	0.03-1.0	(0.06) 0.25-0.5	0.12-2	65,76,78,81,83,96
	117	Fluconazole	0.25->64	(4) 0.5-16	>64[1]	65,70,78,81,83,89,96
	113	Itraconazole	0.03->8	(025-0.5) 1.0	>8[1]	65,78,81,83,89,96
	13	Voriconazole	0.03-0.12	(0.06-0.12)	NR	52,83
	17	Posaconazole	≤0.03-0.25	(0.06-0.25)	NR	77,83
	26	Flucytosine	0.06-8	(≤0.12-4)	NR	78,81,83,96
Candida inconspicua	4	Caspofungin	≤0.01	(≤ 0.19)	1.0	70
	1	Micafungin	0.03	NR	NR	78
	1	Amphotericin B	0.25	NR	NR	78
	5	Fluconazole	8-32	(14.9)	>64	70,78
	1	Itraconazole	0.5	NR	NR	78
	1	Flucytosine	8	NR	NR	78
Candida kefyr	21	Anidulafungin	0.03-0.5	(0.06) 0.5	NR	66,83,93
	27	Caspofungin	0.06-1.0	(≤0.25-0.5)	0.25-4	70,83,96
	4	Micafungin	0.06-0.5	(0.06)	NR	83
	46	Amphotericin B	0.12-2	(0.25-0.5) 1.0	NR	66,76,83,93,96
	30	Fluconazole	0.12-2	(≤0.25-1.0) 1.0	4->64	66,70,83,93,96
	12	Itraconazole	0.03-0.5	(0.12-0.25)	NR	83,93,96
	12	Flucytosine	0.06-0.12	(0.08-0.12)	NR	83,93,96
	4	Voriconazole	NR	(0.03)	NR	83
	4	Posaconazole	0.06-0.25	(0.06)	NR	83

Table 1 (continuation). In vitro activities of anidulafungin, micafungin, caspofungin, new triazoles and established agents against 10,637 yeast and yeast-like species.

Fungus	No. Isolates	Antifungal Agent	MIC range (µg/ml)	MIC_{90} (MIC_{50} or G) (µg/ml)	MFC range (µg/ml)	References
Candida krusei	207	Anidulafungin	<0.01-8	0.03-1.0	0.06-1.0	66,72,77,81-83,91-93,98
	221	Caspofungin	0.12->4	0.5-2	0.5-2	52,55,56,70,72,76,77,83,89,96,98
	82	Micafungin	0.06-4	0.12-0.25	0.12-0.25	65,78,83,84,95,103
	216	Amphotericin B	0.06-2	0.5-2	0.25-2	65,66,76,78,81,83,91,93,95,98,103
	304	Fluconazole	0.25-≥64	16-≥64	≥64	65,70,72,78,81-83,89, 92,93,95,96,98,103
	260	Itraconazole	0.03->8	0.5>8	0.5-8	65,81-83,89,91-93,95,96,98,103
	87	Voriconazole	≤0.03-0.5	0.25-1.0	NR	52,82,83,92,95
	71	Posaconazole	0.03[1]	0.5-1.0	NR	77,83,95
	151	Flucytosine	0.5-64	16-64	NR	52,78,81-83,92,93,96,98
Candida lambica	1	Micafungin	0.03	NR	NR	78
	1	Amphotericin B	0.03	NR	NR	78
	1	Fluconazole	>64	NR	NR	78
	1	Itraconazole	0.25	NR	NR	78
	1	Flucytosine	4	NR	NR	78
Candida lipolytica	2	Anidulafungin	0.12-0.5	(0.5)	NR	83
	7	Caspofungin	0.5-2	(0.46-2)	0.5-2	55,70,83
	2	Micafungin	0.12-0.5	(0.5)	NR	83
	2	Amphotericin B	1.0	NR	NR	83
	6	Fluconazole	1.0-16	(2.6-16)	>64	70,83
	2	Itraconazole	0.06-2	(2)	NR	83
	2	Voriconazole	0.030.06	(0.06)	NR	83
	2	Posaconazole	0.03-0.25	(0.25)	NR	83
	2	Flucytosine	2-4	(4)	NR	83
Candida lusitaniae	81	Anidulafungin	0.03-≥8	0.12->8	1.0-2	72,77,81,83,91,93
	114	Caspofungin	0.12-4	(2.6) 0.5-2	0.06-4	52,55,56,70,72,76,77,83,89,96
	23	Micafungin	0.03-0.06[1]	(0.06)[1] 2[1]	NR	78,83
	70	Amphotericin B	≤0.5-4	≤0.5-2	0.5-4	76,78,81,83,93,96
	107	Fluconazole	0.12-16	<0.25-4	32->64[1]	70,72,78,81,83,89,91,93,96
	91	Itraconazole	<0.01-2	≤0.12-0.25	NR	65,81,83,89,91,93,96
	27	Voriconazole	<0.01-0.03	(0.01) 0.06	NR	52,83
	32	Posaconazole	<0.03-0.25	0.06-0.12	NR	77,83
	50	Flucytosine	≤0.03->64	0.06->64	NR	78,81,83,93,96
Candida parapsilosis	231	Anidulafungin	0.01->8	(1.0)2->8	1.0-4	66,71,72,77,81-83,91,93,98
	1034	Caspofungin	0.03-≥8	(0.25)1-4	0.25->8	52,54-56,70,72,76,77, 83,89,90,93,98
	439	Micafungin	0.03->8	1.0->8	0.5->8	65,78,83,95,103
	641	Amphotericin B	0.12-2	(0.12) 0.5-2	0.12-4	54,65,66,71,76,81-83, 92,93,95,96,98,103
	1103	Fluconazole	≤0.12-64	(0.5-2) 0.12-8	0.12[1]->64	54,65,66,70-72,78,81-83, 89-93,95,96,98,103
	1069	Itraconazole	0.01-2	≤0.12-0.5	0.03->8	54,65,78,81-83,89,93,95,96,98,103
	506	Voriconazole	<0.01-0.5	≤0.03-0.06	NR	52,82,83,90,92,95
	455	Posaconazole	0.01-0.5	0.12-0.5		77,83,90,95
	564	Flucytosine	≤0.03->64	012-1.0	NR	66,71,81-83,92,93,95,96,98
Candida pelliculosa	4	Caspofungin	<0.25-0.5	(0.22)	0.5-8	70
	4	Fluconazole	2-16	(2.62)	>64	70
Candida rugosa	14	Anidulafungin	0.03-4	(1.0-4)	NR	81,83
	7	Caspofungin	1.0-2	(2)	NR	78
	7	Micafungin	0.03->8	(0.06)	NR	78
	14	Amphotericin B	0.03-1.0	(0.12-1.0)	NR	81,83
	14	Fluconazole	1.0->8	(4-1.0)	NR	81,83
	14	Itraconazole	0.03-1.0	(0.03-0.06)	NR	81,83
	14	Flucytosine	0.12-1.0	(0.25-0.5)	NR	81,83
Candida sphaerica	1	Anidulafungin	0.12	NR	NR	83
	1	Caspofungin	2	NR	NR	83
	1	Micafungin	0.25	NR	NR	83
	1	Amphotericin B	0.12	NR	NR	83
	1	Itraconazole	0.12	NR	NR	83
	1	Voriconazole	0.03	NR	NR	83
	1	Posaconazole	0.12	NR	NR	83
	1	Flucytosine	0.12	NR	NR	83
Candida stellatoidea	10	Anidulafungin	0.12-0.5	(0.5)	NR	81
	10	Amphotericin B	0.25-1.0	(0.5)	NR	81
	10	Fluconazole	0.25-0.5	(0.5)	NR	81
	10	Itraconazole	0.01-0.12	(0.03)	NR	81
	10	Flucytosine	0.06-0.5	(0.5)	NR	81
Candida tropicalis	548	Anidulafungin	0.03-32	0.06-2	0.12-1.0	66,71,72,77,81-83,91-93,98
	811	Caspofungin	0.03->8	0.12-1.0	0.25-4	52,54-56,70,72,76,77,83, 89,90,96,98
	364	Micafungin	<0.01->8	(0.12) 0.03-2	0.01->8	65,78,83,84,95,103

Table 1 (continuation). In vitro activities of anidulafungin, micafungin, caspofungin, new triazoles and established agents against 10,637 yeast and yeast-like species.

Fungus	No. Isolates	Antifungal Agent	MIC range (µg/ml)	MIC_{90} (MIC_{50} or G) (µg/ml)	MFC range (µg/ml)	References
Candida tropicalis	601	Amphotericin B	≤0.03-2	0.12-2	0.03[1]-2	54,65,66,76,78,81-83, 92,95,96,98,103
	922	Fluconazole	≤0.12->64	(0.39-2) 1.0-≥64	0.25[1]->64	54,65,66,70-72,78,81-84, 89-93,95,96,98,103
	888	Itraconazole	0.01-≥8	0.12->8	0.06->8	54,65,78,81-83,89,93,95,96,98,103
	394	Voriconazole	≤0.03->8	0.12-4	NR	52,82,83,90,92,95
	350	Posaconazole	0.01-≥8	0.25-≥8	NR	77,83,90,95
	523	Flucytosine	≤0.03->64	0.25-64	NR	71,78,81-83,92,93,95,96,98
Candida utilis	1	Micafungin	<0.01	NR	NR	78
	1	Amphotericin B	0.5	NR	NR	78
	1	Fluconazole	4	NR	NR	78
	1	Itraconazole	0.25	NR	NR	78
	1	Flucytosine	0.12	NR	NR	78
Candida zeylanoides	1	Micafungin	<0.01	NR	NR	78
	1	Amphotericin B	0.5	NR	NR	78
	1	Fluconazole	4	NR	NR	78
	1	Itraconazole	0.25	NR	NR	78
	1	Flucytosine	0.12	NR	NR	78
Candida spp.[A]	11	Anidulafungin	≤0.03->8	(0.12-1.0)	NR	92,98
	44	Caspofungin	0.03->8	(0.12-1.0) 1.0->8	NR	52,89,90,98
	11	Amphotericin B	0.06-2	(0.12-1.0)	NR	92,98
	43	Fluconazole	0.12->64	2-64	NR	89,90,92,98
	43	Itraconazole	0.06->8	1.0-2	NR	89,90,92,98
	24	Voriconazole	0.01-4	(0.06-0.12) 0.5	NR	52,90,98
	13	Posaconazole	0.12->8	1.0	NR	90
	11	Flucytosine	0.06-2	(≤0.12-0.5)	NR	92,98
Cryptococcus neoformans	40	Anidulafungin	>8	>8	NR	71,72,77
	46	Caspofungin	>8	>8	≥8[1]	55,72,76,77
	23	Micafungin	>8	>8	NR	65,71,78
	42	Amphotericin B	<0.12-1.0	0.25-0.5	0.12-0.5	65,71,76,78
	38	Fluconazole	0.25-32	1.0-8	NR	65,66,71,72
	8	Itraconazole	0.01-0.5	0.5	NR	65,78
	10	Posaconazole	0.25-0.5	0.25	0.25-0.5	77
	18	Flucytosine	<0.03-64	8	NR	71,78
Cryptoccocus humicola	3	Micafungin	>8	NR	NR	78
	3	Amphotericin	0.12	NR	NR	78
	3	Fluconazole	32	NR	NR	78
	3	Itraconazole	0.12	NR	NR	78
	3	Flucytosine	16	NR	NR	78
Pichia anomala	3	Micafungin	0.01-0.03	NR	NR	78
	3	Amphotericin	0.5-1.0	NR	NR	78
	3	Fluconazole	8-16	NR	NR	78
	3	Itraconazole	1.0	NR	NR	78
	3	Flucytosine	0.12-64	NR	NR	78
Rhodotorula rubra	4	Anidulafungin	>8	NR	NR	93
	4	Amphotericin B	0.5-1.0	NR	NR	93
	4	Fluconazole	0.12->64	NR	NR	93
	4	Itraconazole	0.25-05	NR	NR	93
	4	Flucytosine	<0.12-0.25	NR	NR	93
Saccharomyces cerevisiae	46	Anidulafungin	0.25-2	1.0-2	NR	81,93
	10	Caspofungin	1.0	(1.0 -2)	NR	52,55
	2	Micafungin	0.12	NR	NR	78
	48	Amphotericin B	0.12-1.0	1.0	NR	78,81,93
	48	Fluconazole	≤0.12-16	2-16	NR	78,81,93
	48	Itraconazole	≤0.03-4	0.5-2	NR	78,81,93
	9	Voriconazole	0.03-0.25	(0.12)	NR	52
	48	Flucytosine	≤0.06-0.5	0.12-0.25	NR	78,81,93
Trichosporon spp.[B]	8	Anidulafungin	>8	>8	NR	66,77
	5	Caspofungin	>8	>8	NR	77
	8	Micafungin	>8	>8	NR	65,78
	11	Amphotericin B	0.5->8	(1.0)>8	NR	65,66,78
	11	Fluconazole	2-16	(2)16	NR	65,66,78
	8	Itraconazole	0.5-1.0	0.5	NR	65,78
	5	Posaconazole	0.12-1.0	1.0[g]	NR	77
	3	Flucytosine	≥64	NR	NR	78

Geometric mean (G) or MIC_{50}= Values within parenthesis.

A= Species listed (reference)= *Candida dubliniensis* (52); *C. famata* (52,90,92,98); *C. guilliermondii* (92,98); *C. humicola* (89); *C. inconspicua* (52,90); *C. kefyr* (52,89); *C. lambica* (89); *C. lipolytica* (89); *C. norvegensis* (52); *C pelliculosa* (89); *C. rugosa* (89,98); *C. zeylanoides* (89)

B=Repported as *T. asahii, T. cutaneum* and *T. beigelii*.

[1] Data from only one study

NR= Not reported

Table 2. In vitro activities of anidulafungin, micafungin, caspofungin, itraconazole, voriconazole posaconazole and amphotericin B against 1,415 mould isolates.

Fungus	No. Isolates	Antifungal Agent	MIC range (µg/ml)	MEC range (µg/ml)	MIC_{90}/ MEC_{90} (µg/ml) (MIC_{50}/ MEC_{50})	References
Moniliaceous moulds						
Acremonium sp.	1	Anidulafungin	0.5	NR	NA	102
	1	Caspofungin	0.03	NR	NA	102
	1	Amphotericin B	2	NR	NA	102
	1	Itraconazole	1.0	NR	NA	102
Acremonium strictum	1	Anidulafungin	>8	NR	NA	77
	1	Caspofungin	0.5	NR	NA	77
	1	Posaconazole	0.06	NR	NA	77
Aspergillus clavatus	1	Micafungin	≤0.01	NR	NA	78
	1	Amphotericin B	0.5	NR	NA	78
	1	Itraconazole	0.06	NR	NA	78
Aspergillus flavus	53	Anidulafungin	≤0.03-0.12	≤0.01->0.5	≤0.03 (0.08)/1.0	71,77,85,88,102
	127	Caspofungin	0.03->8	0.01-2	(4) 0.12-0.5/(0.3)0.06-0.5	58,73,77,86-88,102
	18	Micafungin	≤0.01	NR	0.01/NR	64,65,78
	112	Amphotericin B	0.06->8	0.5-1.0	1.0-4/NR	58,64,65,71,78,85,87,88,102
	107	Itraconazole	≤0.03-8	0.06-0.25[1]	0.06-4/NR	58,64,65,78,85,87,88,102
	59	Voriconazole	≤0.03-1.0	NR	0.06-1.0/ NR	87,88
	41	Posaconazole	0.03-1.0	NR	(0.1) 0.5/ NR	77,87
Aspergillus fumigatus	94	Anidulafungin	<0.01-0.12[>8][1]	≤0.01[1]	(≤0.03)0.06/<0.01	71,77,85,88,102
	480	Caspofungin	0.03->8	<0.01->8	(>8) [1]0.12-0.5/0.06-0.5	58,73,77,86-88,102
	35	Micafungin	≤0.01-.03	NR	≤0.01/NR	64,65,78
	509	Amphotericin B	0.06->8	0.06-0.25[1]	1.0-2/NR	58,64,65,71,78,85,86,88,102
	503	Itraconazole	≤0.03->8	0.12-0.25[1]	0.12-2/ NR	58,64,65,78,85,86,88,102
	284	Voriconazole	≤0.03-4	NR	0.12-0.5/NR	87,88
	269	Posaconazole	<0.03-2	NR	(0.13)0.5/NR	77,87
Aspergillus glaucus group	11	Anidulafungin	≤0.03->8[1]	≤0.01	(≤0.03)/NR	71,88
	8	Caspofungin	NR	≤0.03-0.12	NR/0.12	88
	11	Amphotericin B	0.06-2	NR	1.0/NR	71,88
	8	Itraconazole	≤0.03-0.25	NR	0.25/NR	88
	8	Voriconazole	0.06-0.12	NR	0.06/NR	88
Aspergillus japonicus	1	Micafungin	≤0.01	NR	NA	78
	1	Amphotericin B	0.5	NR	NA	78
	1	Itraconazole	0.12	NR	NA	78
Aspergillus nidulans	1	Anidulafungin	NR	<0.01	NA	85
	16	Caspofungin	0.25-4	0.25-2	(0.63)0.5/0.5	58,86
	3	Micafungin	≤0.01	NR	NR	64,65,78
	17	Amphotericin B	0.25-4	NR	2/NR	58,64,65,78,85
	17	Itraconazole	0.06-0.25	NR	0.25[1]/NR	58,64,65,78,85
Aspergillus niger	21	Anidulafungin	≤0.03-0.06	≤0.01[1]	≤0.03/<0.01	71,85,88
	68	Caspofungin	0.12-2	0.01-1.0	0.5/(0.42)0.06-0.25	58,86-88
	20	Micafungin	≤0.01	NR	<0.01/NR	64,65,78
	83	Amphotericin B	0.06-1.0	0.03-0.12	0.5-1.0/NR	58,64,65,78,85,87,88
	79	Itraconazole	≤0.03->8	0.12-0.5	0.25-8/NR	58,64,65,78,85,87,88
	38	Voriconazole	≤0.03-4	NR	0.12-2/NR	87,88
	29	Posaconazole	0.25-1.0	NR	1.0/NR	87
Aspergillus oryzae	1	Micafungin	<0.01	NR	NA	78
	1	Amphotericin B	0.5	NR	NA	78
	1	Itraconazole	0.5	NR	NA	78
Aspergillus terreus	10	Anidulafungin	<0.03	<0.01[1]	NR/<0.01	77,85
	42	Caspofungin	0.25-0.5	<0.01-0.5	0.5/0.06-0.5	58,77,86,87
	12	Micafungin	≤0.01	NR	<0.01/NR	64,65,78
	51	Amphotericin B	0.06-8	0.06-1.0[1]	0.5-8/NR	58,64,65,78,85,87
	51	Itraconazole	≤0.01-1.0	0.03-0.5[1]	0.12-0.5/NR	58,64,65,78,85,87
	16	Voriconazole	0.06-1.0	NR	1.0/NR	87
	18	Posaconazole	<0.03-0.5	NR	1.0/NR	77,87
Aspergillus versicolor	2	Anidulafungin	NR	<0.01	NR	71
	20	Caspofungin	NR	0.01-4	NR/0.12	87
	3	Micafungin	≤0.01	NR	NR	64,65,78
	25	Amphotericin B	0.25-2	NR	2/NR	64,65,71,78,87
	23	Itraconazole	0.06-2	NR	2/NR	64,65,78,87
	20	Voriconazole	0.06-2	NR	1.0/NR	87
	20	Posaconazole	0.06-2	NR	1.0/NR	87

Table 2 (continuation). In vitro activities of anidulafungin, micafungin, caspofungin, itraconazole, voriconazole posaconazole and amphotericin B against 1,415 mould isolates.

Fungus	No. Isolates	Antifungal Agent	MIC range (µg/ml)	MEC range (µg/ml)	MIC_{90}/ MEC_{90} (µg/ml) (MIC_{50}/ MEC_{50})	References
Aspergillus spp.[A]	6	Anidulafungin	≤0.03-0.06	NR	NR	88,102
	6	Caspofungin	0.03-0.06	0.06-0.12[1]	NR	88,102
	6	Amphotericin B	0.12-2	NR	NR	88,102
	6	Itraconazole	≤0.03-1.0	NR	NR	88,102
	4	Voriconazole	≤0.03-0.12	NR	NR	88
Fusarium moniliforme	3	Micafungin	>8	NR	NR	78
	3	Amphotericin B	1.0-2	NR	NR	78
	3	Itraconazole	2->8	NR	NR	78
Fusarium oxysporum	6	Anidulafungin	>8	NR	(>8)/NR	77
	15	Caspofungin	>8	>8	(>8)/(>8)	73,77,86
	3	Micafungin	>8	NR	NR	78
	3	Amphotericin B	0.5-2	1.0[1]	NR	78
	3	Itraconazole	≤8	NR	NR	78
	6	Posaconazole	1->8	NR	(4.16)/NR	77
Fusarium solani	6	Anidulafungin	>8	NR	(>8)/NR	77
	29	Caspofungin	≥8	>8	(>8)/(>8)	73,77,86
	5	Micafungin	>8	NR	NR	64,65,78
	5	Amphotericin B	0.25-8	0.25-1.0	NR	64,65,78
	5	Itraconazole	≥8	NR	NR	64,65,78
	6	Posaconazole	>8	NR	(>8)/NR	77
Fusarium spp.[B]	13	Anidulafungin	>8	NR	(>2)/NR	102
	24	Caspofungin	≥8	>8	(>8)/>8	87,102
	24	Amphotericin B	1.0-2	NR	2/NR	87,102
	24	Itraconazole	2->8	NR	>8/NR	87,102
	11	Voriconazole	0.25->8	NR	>8/NR	87
	11	Posaconazole	0.5->8	NR	>8/NR	87
Paecilomyces lilacinus	5	Caspofungin	4->8	NR	>8/ NR	73
	2	Micafungin	≤0.01	NR	NR	78
	2	Amphotericin B	≥8	NR	NR	78
	2	Itraconazole	≤0.01-0.5	NR	NR	78
Paecilomyces variotii	2	Caspofungin	≤0.12	NR	(≤0.12) /NR	73
	2	Micafungin	≤0.01	NR	NR	78
	2	Amphotericin B	1.0	NR	NR	78
	2	Itraconazole	0.5-8	NR	NR	78
Paecilomyces sp.[C]	1	Anidulafungin	2	NR	NA	102
	7	Caspofungin	0.3-8	NR	(0.06)/NR	87,102
	7	Amphotericin B	0.06->8	NR	(0.5)/NR	87,102
	7	Itraconazole	0.06-4	NR	(0.25)/NR	87,102
	6	Voriconazole	0.03-2	NR	(0.25)/NR	87
	6	Posaconazole	0.03-0.5	NR	(0.12)/NR	87
Penicillium citeoviride	1	Micafungin	<0.01	NR	NA	78
	1	Amphotericin B	2	NR	NA	78
	1	Itraconazole	0.06	NR	NA	78
Penicillium decumbens	1	Micafungin	≤0.01	NR	NA	78
	1	Amphotericin B	1.0	NR	NA	78
	1	Itraconazole	≤0.01	NR	NA	78
Penicillium expansum	1	Micafungin	≤0.01	NR	NA	78
	1	Amphotericin B	1.0	NR	NA	78
	1	Itraconazole	0.5	NR	NA	78
Penicillium notatum	1	Micafungin	≤0.01	NR	NA	78
	1	Amphotericin B	1.0	NR	NA	78
	1	Itraconazole	0.06	NR	NA	78
Penicillium spp.[D]	35	Caspofungin	NR	0.01->8	0.12/NR	87
	35	Amphotericin B	0.12-2	NR	2/NR	87
	35	Itraconazole	0.25-2	NR	2/NR	87
	35	Voriconazole	0.03->8	NR	2/NR	87
	35	Posaconazole	0.06-2	NR	1/NR	87
Trichoderma sp.	1	Anidulafungin	0.06	NR	NA	102
	1	Caspofungin	0.25	NR	NA	102
	1	Amphotericin B	1.0	NR	NA	102
	1	Itraconazole	2	NR	NA	102

Table 2 (continuation). In vitro activities of anidulafungin, micafungin, caspofungin, itraconazole, voriconazole posaconazole and amphotericin B against 1,415 mould isolates.

Fungus	No. Isolates	Antifungal Agent	MIC range (µg/ml)	MEC range (µg/ml)	MIC_{90}/ MEC_{90} (µg/ml) (MIC_{50}/ MEC_{50})	References
Dimorphic fungi						
Blastomyces dermatitidis	34	Anidulafungin	2-8>8	NR	(4)/NR	71,77
	5	Caspofungin	0.5-8	NR	(2)/NR	77
	6	Micafungin	>8/<0.01-0.03*	NR	NR	63
	35	Amphotericin B	≤0.03-0.25*	NR	0.25/NR	63,71
	35	Fluconazole	1.0-32*	NR	16/NR	63,71
	6	Itraconazole	≤0.01-0.03*	NR	NR	63
	5	Posaconazole	<0.03-0.06	NR	(0.05)/NR	77
Coccidioides immitis	4	Micafungin	0.01	NR	NR	63
	25	Caspofungin	≥8	NR	>8/NR	74
	29	Amphotericin B	0.06-0.5	NR	0.5/NR	63,74
	29	Fluconazole	4-64	NR	64/NR	63,74
	4	Itraconazole	0.06-0.12	NR	NR	63
Histoplasma capsulatum	5	Anidulafungin	2-4	NR	(3.6)/NR	77
	5	Caspofungin	0.5-4	NR	(1.3)/NR	77
	4	Micafungin	>8/0.03-0.06*	NR	NR	63
	4	Amphotericin B	0.06-0.5*	NR	NR	63
	4	Fluconazole	1.0-16*	NR	NR	63
	4	Itraconazole	≤0.01-0.03*	NR	NR	63
	5	Posaconazole	<0.03-0.06	NR	(0.04)/NR	77
Paracoccidioides brasiliensis	7	Micafungin	>8/4->8*	NR	NR	63
	7	Amphotericin B	<0.01-0.25	NR	NR	63
	7	Fluconazole	0.12-1.0	NR	NR	63
	7	Itraconazole	<0.01	NR	NR	63
Penicillium marneffei	8	Micafungin	4->8/0≤0.01-2*	NR	NR	63,78
	8	Amphotericin B	0.12-1.0*	NR	NR	63,78
	8	Fluconazole	1.0-8*	NR	NR	63,78
	8	Itraconazole	≤0.01-0.06*	NR	NR	63,78
Sporothrix schenckii	5	Anidulafungin	0.25->8	NR	(3.9)/NR	77
	5	Caspofungin	1.0->8	NR	5.4/NR	77
	7	Micafungin	>8/0.5-1.0*	NR	NR	63
	7	Amphotericin B	0.5-2*	NR	NR	63
	7	Fluconazole	64*	NR	NR	63
	7	Itraconazole	0.5-2*	NR	NR	63
	5	Posaconazole	0.12-1.0	NR	(0.7)/NR	77
Zygomycetes						
Absidia corymbifera	4	Micafungin	>8	NR	NR	64,78
	4	Amphotericin B	0.25-0.5	NR	NR	64,78
	4	Itraconazole	0.03-0.25	NR	NR	64,78
Cunninghamella elegans	1	Micafungin	>8	NR	NA	64
	1	Amphotericin B	0.5	NR	NA	64
	1	Itraconazole	0.5	NR	NA	64
Mucor circinelloides	3	Micafungin	>8	NR	NR	78
	3	Amphotericin B	0.12-0.5	NR	NR	78
	3	Itraconazole	≤8	NR	NR	78
Mucor spp.[E]	3	Caspofungin	NR	>8	NR/(>8)	87
	3	Amphotericin B	0.5-1.0	NR	(0.5)/NR	87
	3	Itraconazole	2->8	NR	(2)/NR	87
	3	Voriconazole	1.0->8	NR	(2)/NR	87
	3	Posaconazole	0.5->8	NR	(1.0)/NR	87
Rhizopus arrhizus (*R. oryzae*)	10	Caspofungin	>8	NR	(>8)/NR	73,77
	5	Anidulafungin	>8	NR	(>8)/NR	77
	4	Micafungin	>8	NR	NR	64,78
	4	Amphotericin B	0.12-0.25	NR	NR	64,78
	4	Itraconazole	0.25-0.5	NR	NR	64,78
	5	Posaconazole	2	NR	(2)/NR	77
Rhizopus microsporus var. *rhizopodiformis*	1	Micafungin	>8	NR	NA	64
	1	Amphotericin B	0.12	NR	NA	64
	1	Itraconazole	0.5	NR	NA	64

Table 2 (continuation). In vitro activities of anidulafungin, micafungin, caspofungin, itraconazole, voriconazole posaconazole and amphotericin B against 1,415 mould isolates.

Fungus	No. Isolates	Antifungal Agent	MIC range (µg/ml)	MEC range (µg/ml)	MIC_{90}/ MEC_{90} (µg/ml) (MIC_{50}/ MEC_{50})	References
Rhizopus spp.[F]	6	Anidulafungin	>2	NR	(>2)/NR	102
	11	Caspofungin	>8	>8	(>8)/(>8)	87,102
	11	Amphotericin B	0.5-2	NR	(1.0)/NR	87,102
	11	Itraconazole	0.5->8	NR	(1.0-4)/NR	87,102
	5	Voriconazole	1.0->8	NR	(2)/NR	87
	5	Posaconazole	1.0-4	NR	(2)/NR	87
Dematiaceous fungi						
Alternaria spp.	1	Caspofungin	≤0.12	NR	≤0.12/NR	73
Alternaria alternata	3	Micafungin	>8	NR	NR	78
	3	Amphotericin B	0.5	NR	NR	78
	3	Itraconazole	≤0.01	NR	NR	78
Bipolaris hawaiiensis	3	Anidulafungin	1.0-4	NR	2.7	77
	3	Caspofungin	1.0-2	NR	1.7	77
	3	Posaconazole	0.06-0.25	NR	(0.14)/NR	77
Bipolaris spicifera	3	Anidulafungin	1.0-4	NR	(2.7)/NR	77
	3	Caspofungin	1.0-2	NR	(1.7)/NR	77
	3	Posaconazole	0.06-0.25	NR	(0.14)/NR	77
Cladophialophora bantiana	5	Anidulafungin	1.0-4	NR	(2)/NR	77
	5	Caspofungin	2-8	NR	3.6/NR	77
	6	Micafungin	0.12-0.5	NR	NR	64
	6	Amphotericin B	0.12-0.5	NR	NR	64
	6	Itraconazole	<0.01-0.06	NR	NR	64
	5	Posaconazole	<0.03-0.06	NR	(0.05)/NR	77
Curvularia lunata	4	Caspofungin	<0.12-1.0	NR	(0.5)/NR	73
Exophiala jeanselmei	2	Caspofungin	0.5-4	NR	(1.1)/NR	73
Exophiala spinifera	7	Micafungin	0.12-2	NR	NR	64
	7	Amphotericin B	0.12-0.5	NR	NR	64
	7	Itraconazole	0.03-0.12	NR	NR	64
Fonsecaea pedrosoi	4	Caspofungin	≤0.12-0.25	NR	(0.13)/NR	73
	7	Micafungin	0.5-8	NR	NR	64
	7	Amphotericin B	0.12-0.5	NR	NR	64
	7	Itraconazole	0.01-0.12	NR	NR	64
Phialophora spp.	5	Caspofungin	1.0->8	NR	(2.8)/NR	77
	5	Anidulafungin	1.0->8	NR	(9)/NR	77
	5	Posaconazole	0.06-1.0	NR	(0.4)/NR	77
Pseudallescheria boydii	11	Anidulafungin	1.0-4	NR	(1.0-2.5)/NR	77,102
(Scedosporium apiospermum)	15	Caspofungin	0.25-4	NR	(0.5-1.3)/NR	73,77,102
	4	Micafungin	>8	NR	NR	64,78
	9	Amphotericin B	1.0-4	NR	(4[1])/NR	64,78,102
	9	Itraconazole	≤0.01-1.0	NR	(1.0[1])/NR	64,78,102
	6	Posaconazole	0.5-2	NR	(1.0)/NR	77
Scedosporium prolificans	2	Anidulafungin	4	NR	NR	77
	5	Caspofungin	4-≥8	NR	(>8)/NR	73,75,77
	1	Micafungin	0.5	NR	NA	78
	1	Amphotericin B	8	NR	NA	78
	1	Itraconazole	0.25	NR	NA	78
	1	Voriconazole	8	NR	NA	75
	2	Posaconazole	>8	NR	NR	77
Wangiella dermatitidis	7	Micafungin	1.0->8	NR	NR	64
	7	Amphotericin B	0.12-0.5	NR	NR	64
	7	Itraconazole	0.03-0.12	NR	NR	64

Geometric mean (G mean) or MIC_{50} (Values within parenthesis).

[1] MIC_{90}, MIC_{50} or G MIC values from only one study.

A= Species listed: *A. niger* (102), *A. terrreus* (88,102) and *A. flavipedes* (88); B=*F. oxysporum*, *F. solani* (102); G=*Phialophora parasitica, P. repens, P. verrucosa* (77); C,D,E,F=No species were provided.

[1] Data from only one study

NR=Not reported

*Data for yeast and mycelial forms were provided (ref.63)

References

1. Edwards JE Jr. International conference for the development of a consensus on the management and prevention of severe candidal infections. Clin Infect Dis 1997; 25: 43-59.
2. Haijeh RA, Brandt ME, Pinner RW. Emergence of cryptococcal disease: Epidemiologic perspectives 100 years after its discovery. Epidemiol Rev 1995; 17: 303-320.
3. Denning DW, Venkateswarlu K, Oakley KL, et al. Itraconazole resistance in *Aspergillus fumigatus*. Antimicrob Agents Chemother 1997; 41: 1364-1368.
4. Law D, Moore CB, Wardle HM, Ganguli LA, Kenney MGL, Denning DW. High prevalence of antifungal resistance in *Candida* spp. from patients with AIDS. J Antimicrob Chemother 1994; 34: 659-668.
5. Powderly WG. Resistant candidiasis. AIDS Res Hum Retroviruses 1994; 10: 925-929.
6. Anaissie E, Kantarjian H, Ro H, et al. The emerging role of *Fusarium* infections in patients with cancer. Medicine 1988; 67: 77-83.
7. Walsh TJ. Echinocandins-An advance in the primary treatment of invasive candidiasis. N Engl Med 2002; 347: 2070-2072.
8. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood 2003; 102: 827-833.
9. Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002; 34: 909-917.
10. Marr KA, Carter RA, Boeckh M, et al. Invasive aspergillosis in allogeneic stem cell transplant recipients: Changes in epidemiology and risk factors. Blood 2002; 100: 4358-4366.
11. Walsh T, Petraitis V, Petraitiene R, et al. Experimental pulmonary aspergillosis due to *Aspergillus terreus*: Pathogenesis and treatment of an emerging fungal pathogen resistant to amphotericin B. J Infect Dis 2003; 188: 305-319.
12. Colombo AL, Perfect J, DiNubile M, et al. Global distribution and outcomes for *Candida* species causing invasive candidiasis: Results from an international randomized double-blind study of caspofungin versus amphotericin B for the treatment of invasive candidiasis. Eur J Clin Microbiol Infect Dis 2003; 22: 470-474.
13. Pfaller M, Messer SA, Hollis RJ, et al. In vitro activities of ravuconazole and voriconazole compared with those of four approved systemic antifungal agents against 6,970 clinical isolates of *Candida* spp. Antimicrob Agents Chemother 2002; 46: 1723-1727.
14. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: Systematic review of the literature. Clin Infect Dis 2001; 32: 358-366.
15. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis: Disease spectrum, treatment practices, and outcomes. Medicine 2000; 79: 250-260.
16. Husain S, Alexander BD, Munoz P, et al. Opportunistic mycelial fungal infections in organ transplant recipients: Emerging importance of non-*Aspergillus* mycelial fungi. Clin Infect Dis 2003; 37: 221-229.
17. Kartsonis N, DiNubile MJ, Bartizal K, et al. Efficacy of caspofungin in the treatment of esophageal candidiasis resistant to fluconazole. JAIDS 2002; 31: 183-187.
18. Villanueva A, Arathoon EG, Gotuzzo E, et al. A randomized double-blind study of caspofungin versus amphotericin B for the treatment of candidal esophagitis. Clin Infec Dis 2001; 33: 1529-1535.
19. Arathoon EG, Gotuzzo E, Noriega LM, et al. Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiasis. Antimicrob Agents Chemother 2002; 46: 451-457.
20. Villanueva A, Gotuzzo E, Arathoon EG, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. Am J Med 2002; 113: 294-299.
21. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002; 347: 2020-2029.
22. Kontoyiannis DP, Hachem R, Lewis RE, et al. Efficacy and toxicity of caspofungin in combination with liposomal amphotericin B as primary or salvage treatment of invasive aspergillosis in patients with hematologic malignancies. Cancer 2003; 98: 292-299.
23. Maertens J, Raad I, Petrikkos G, et al. Update of the multicenter noncomparative study of caspofungin in adults with invasive aspergillosis refractory or intolerant to other antifungal agents: Analysis of 90 patients. 42nd ICAAC Abstracts 2002; No. M-868.
24. Maertens J, Boogaerts M. Caspofungin in the treatment of candidosis and aspergillosis. Int J Infect Dis 2003; 7: 94-101.
25. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347: 408-415.
26. Perfect J, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis 2003; 36: 1122-1131.
27. Stone JA, Holland SD, Wickersham PJ, et al. Single-and multiple-dose pharmacokinetics of caspofungin in healthy volunteers. Antimicrob Agents Chemother 2002; 46: 739-745.
28. Sabo JA, Abdel-Rahman SM. Voriconazole: A new triazole antifungal. Annals Pharmacother 2000; 34: 1032-1043.
29. Petraitiene R, Petraitis V, Groll AH, et al. Antifungal activity of LY303366, a novel echinocandin B, in experimental disseminated candidiasis in rabbits. Antimicrob Agents Chemother 1999; 43: 2148-2155.
30. Verweij PE, Oakley KL, Morrissey J, et al. Efficacy of LY303366 against amphotericin B-susceptible and –resistant *Aspergillus fumigatus* in a murine model of invasive aspergillosis. Antimicrob Agents Chemother 1998; 42: 873-878.
31. Groll AH, Mickiene D, Petraitiene R, et al. Pharmacokinetic and pharmacodynamic modeling of anidulafungin (LY303366): Reappraisal of its efficacy in neutropenic animal models of opportunistic mycoses using optimal plasma sampling. Antimicrob Agents Chemother 2001; 45: 2845-2855.
32. Warn PA, Sharp A, Morrissey G, Denning DW. In vivo activity of micafungin in a persistently neutropenic murine model of disseminated infection caused by *Candida tropicalis*. J Antimicrob Chemother 2002; 51: 1071-1074.
33. Maesaki S, Hossain MA, Miyazaki Y, et al. Efficacy of FK463, a (1,3)-ß-D-glucan synthase inhibitor, in disseminated azole-resistant *Candida albicans* infection in mice. Antimicrob Agents Chemother 2000; 44: 1728-1730.
34. Warn PA, Morrissey G, Morrissey J, Denning DW. Activity of micafungin (FK463) against an itraconazole-resistant strain of *Aspergillus fumigatus* and a strain of *Aspergillus terreus* demonstrating in vivo resistance to amphotericin B. J Antimicrob Chemother 2003; 51: 913-919.
35. Petraitis V, Petraitiene R, Groll AH, et al. Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits. Antimicrob Agents Chemother 2002; 46: 1857-1869.
36. Denning DW. Echinocandin antifungal drugs. Lancet 2003; 362: 1142-1151.
37. Wiederhold NP, Lewis RE. The echinocandin antifungals: An overview of the phamacokinetics, spectrum and clinical efficacy. Expert Opin Investig Drugs 2003; 12: 1313-1333.
38. Morrison VA. The role of caspofungin and echinocandins in the antifungal armamentarium. Curr Opin Invest Drugs 2002; 3: 1432-1436.
39. Keating GM, Figgitt DP. Caspofungin: A review of its use in esophageal candidiasis, invasive candidiasis and invasive aspergillosis. Drugs 2003; 63: 2235-2263.
40. Pacetti SA, Gelone SP. Caspofungin acetate for the treatment of invasive fungal infections. Ann Pharmacother 2003; 37: 90-98.
41. Letscher–Bru V, Herbrecht R. Caspofungin: The first representative of a new class. J Antimicrob Chemother 2003; 51: 513-521.
42. Johnson MD, Perfect JR. Caspofungin: The first approved agent in a new class of antifungals. Expert Opin Pharmacother 2003; 4: 807-823.
43. Stone EA, Fung HB, Kirschenbaum, H.L. Caspofungin: An echinocandin antifungal agent. Clin Ther 2002; 24: 351-377.
44. Keating GM, Jarvis B. Caspofungin. Drugs 2001;61: 1121-1129.
45. Cornely OA, Schmitz K, Aisenbrey S. The first echinocandin: Caspofungin. Mycoses 2002; 45: 356-360.
46. Deresinski SC, Stevens DA. Caspofungin. Clin Infect Dis 2003; 36: 1445-1457.
47. Hoang A. Caspofungin acetate: An antifungal agent. Am J Health Syst Pharm 2001; 58: 1206-1214.
48. Chandrasekar PH, Manavathu EK. Caspofungin. Drugs Today 2002; 38: 829-846.
49. Fromtling RA. Micafungin sodium (FK-463). Drugs Today 2002; 38: 245-257.
50. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved standard M27-A2. National Committee for Clinical Laboratory Standards 2002; Wayne, Pa.
51. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi. Approved standard M38-A. National Committee for Clinical Laboratory Standards 2002; Wayne, Pa.

52. Chryssanthou E, Cuenca-Estrella M. Comparison of the antifungal susceptibility testing Subcommittee of the European Committee on Antibiotic Susceptibility Testing proposed standard and the E-test with the NCCLS broth microdilution method for voriconazole and caspofungin susceptibility testing of yeast species. Antimicrob Agents Chemother 2002; 46: 3841-3844.
53. Cuenca-Estrella M, Mellado E, Diaz-Guerra T, et al. Susceptibility of fluconazole-resistant clinical isolates of *Candida* spp. to echinocandin LY303366, itraconazole and amphotericin B. J Antimicrob Chemother 2000; 46: 475-477.
54. Laverdiere M, Restieri C, Habel F. Evaluation of the in vitro activity of caspofungin against bloodstream isolates of *Candida* species from cancer patients: Comparison of Etest and NCCLS reference methods. Int J Antimicrob Agents 2002; 20: 468-471.
55. Lozano-Chiu M, Nelson PW, Paetznick VL, Rex JH. Disk diffusion method for determining susceptibilities of *Candida* spp. to MK-0991. J Clin Microbiol 1999; 37: 1625-1627.
56. Pfaller MA, Messer SA, Mills K, et al. Evaluation of Etest method for determining caspofungin (MK-0991) susceptibilities of 726 clinical isolates of *Candida* species. J Clin Microbiol 2001; 39: 4387-4389.
57. Arikan S, Paetznick V, Rex JH. Comparative evaluation of disk diffusion with microdilution assay in susceptibility testing of caspofungin against *Aspergillus* and *Fusarium* isolates. Antimicrob Agents Chemother 2002; 46: 3084-3087.
58. Espinel-Ingroff, A. Evaluation of broth microdilution testing parameters and agar diffusion Etest procedure for testing susceptibilities of *Aspergillus* spp. to caspofungin acetate (MK-0991). J Clin Microbiol 2003; 41: 403-409.
59. Sutton DA. Laboratory evaluation of new antifungal agents against rare and refractory mycoses. Curr Opin Infect Dis 2002; 15: 575-582.
60. Espinel-Ingroff A, Pfaller MA. Susceptibility test methods: Yeasts and filamentous fungi. In: Manual of Clinical Microbiology, 8th ed., 2003. Washington, DC: ASM Press.
61. Bartizal C, Odds FC. Influences of methodological variables on susceptibility testing of caspofungin against *Candida* species and *Aspergillus fumigatus*. Antimicrob Agents Chemother 2003; 47: 2100-2107.
62. Espinel-Ingroff A, Boyle K, Sheehan DJ. In vitro antifungal activities of voriconazole and reference agents as determined by NCCLS methods: Review of the literature. Mycopathologia 2001; 150: 101-115.
63. Nakai T, Uno J, Ikeda F, et al. In vitro activity of micafungin (FK463) against dimorphic fungi: Comparison of yeast-like and mycelial forms. Antimicrob Agents Chemother 2003; 47: 1376-1381.
64. Nakai T, Uno J, Otomo K, et al. In vitro activity of FK463, a novel lipopeptide antifungal agent, against a variety of clinically important molds. Chemotherapy 2002; 48: 78-81.
65. Tawara S, Ikeda F, Maki K, et al. In vitro activities of new lipopeptide antifungal agent, FK463, against a variety of clinically important fungi. Antimicrob Agents Chemother 2000; 44: 57-62.
66. Uzun O, Kocagoz S, Cetinkaya Y, et al. In vitro activity of a new echinocandin, LY303366, compared with those of amphotericin B and fluconazole against yeast isolates. Antimicrob Agents Chemother 1997; 41: 1156-1157.
67. Espinel-Ingroff A, Fothergill A, Peter J, et al. Testing conditions for determination of minimum fungicidal concentrations of new and established antifungal agents for *Aspergillus* spp.: NCCLS collaborative study. J Clin Microbiol 2002; 40: 3204-3208.
68. Espinel-Ingroff A, Chaturvedi V, Fothergill A, Rinaldi, MG. Optimal testing conditions for determining MICs and minimum fungicidal concentrations of new and established antifungal agents for uncommon molds: NCCLS collaborative study. J Clin Microbiol 2002; 40: 3776-3781.
69. Espinel-Ingroff A. Utility of mould susceptibility. Curr Opin Infect Dis 2003; 16: 527-532.
70. Barchiesi F, Schimizzi AM, Fothergill AW, et al. In vitro activity of the new echinocandin antifungal, MK-0991, against common and uncommon clinical isolates of *Candida* species. Eur J Clin Microbiol Infect Dis 1999; 18: 302-304.
71. Zhanel GG, Karlowsky JA, Harding GA, et al. In vitro activity of the new semisynthetic echinocandin, LY303366, against systemic isolates of *Candida* species, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and *Aspergillus* species. Antimicrob Agents Chemother 1997; 41: 863-805.
72. Krishnarao TV, Galgiani JN. Comparison of the in vitro activities of the echinocandin LY303366, the pneumocandin MK-0991, and fluconazole against *Candida* species and *Cryptococcus neoformans*. Antimicrob Agents Chemother 1997; 41: 1957-1960.
73. Del Poeta M, Schell WA, Perfect JR. In vitro activity of pneumocandin L-743-872 against a variety of clinically important molds. Antimicrob Agents Chemother 1997; 41: 1835-1836.
74. Gonzalez GM, Tijerina R, Najvar LK, et al. Correlation between antifungal susceptibilities of *Coccidioides immitis* in vitro and antifungal treatment with caspofungin in a mouse model. Antimicrob Agents Chemother 2001; 45: 1854-1859.
75. Steinbach WJ, Schell WA, Miller JL, Perfect JR. *Scedosporium prolificans* osteomyelitis in an immunocompetent child treated with voriconazole and caspofungin, as well as locally applied polyhexamethylene biguanide. J Clin Microbiol 2003; 41: 3981-3985.
76. Bartizal K, Gill CJ, Abruzzo GK, et al. In vitro preclinical evaluation studies with the echinocandin antifungal MK-0991 (L-743,872). Antimicrob Agents Chemother 1997; 41: 2326-2332.
77. Espinel-Ingroff A. Comparison of in vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol 1998; 36: 2950-2956.
78. Uchida K, Nishiyama Y, Yokota N, Yamaguchi H. In vitro antifungal activity of a novel lipopeptide antifungal agent, FK463, against various fungal pathogens. J Antibiot 2000; 53: 1175-1181.
79. Laverdiere M, Restieri C, Habel F. Adding 2% dextrose to culture media does not influence the activity of caspofungin against *Candida* species. J Antimicrob Chemother 2003; 51: 183-184.
80. Muller FM, Kurzai O, Hacker J, Frosch M, Muhlschlegel F. Effect of the growth medium on the in vitro antifungal activity of micafungin (FK-463) against isolates of *Candida dubliniensis*. J Antimicrob Chemother 2001; 48: 713-715.
81. Pfaller MA, Messer SA, Coffman S. In vitro susceptibilities of clinical yeast isolates to a new echinocandin derivative, LY303366, and other antifungal agents. Antimicrob Agents Chemother 1997; 41: 763-766.
82. Chavez M, Bernal S, Valverde A, et al. In vitro activity of voriconazole (UK-109,496), LY303366 and other antifungal agents against oral *Candida* spp. isolates from HIV-infected patients. J Antimicrob Chemother 1999; 44: 697-700.
83. Ostrosky-Zeichner L, Rex JH, Pappas PG, et al. Antifungal susceptibility survey of 2,000 bloodstream *Candida* isolates in the United States. Antimicrob Agents Chemother 2003; 47: 3149-3154.
84. Ernst EJ, Roling EE, Petzold CR, et al. In vitro activity of micafungin (FK-463) against *Candida* spp.: Microdilution, time kill, and postantifungal-effect studies. Antimicrob Agents Chemother 2002; 46: 3846-3853.
85. Oakley KL, Moore CB, Denning DW. In vitro activity of the echinocandin antifungal agent LY303,366 in comparison with itraconazole and amphotericin B against *Aspergillus* spp. Antimicrob Agents Chemother 1998; 42: 2726-2730.
86. Arikan S, Lozano-Chiu M, Paetznick V, Rex JH. In vitro susceptibility testing methods for caspofungin against *Aspergillus* and *Fusarium* isolates. Antimicrob Agents Chemother 2001; 45: 327-330.
87. Diekema DJ, Messer SA, Hollis RJ, Jones RN, Pfaller MA. Activities of caspofungin, itraconazole, posaconazole, ravuconazole, voriconazole, and amphotericin B against 448 recent clinical isolates of filamentous fungi. J Clin Microbiol 2003; 41: 3623-3626.
88. Serrano MC, Valverde-Conde A, Chavez M, et al. In vitro activity of voriconazole, itraconazole, caspofungin, anidulafungin (VER002, LY303366) and amphotericin B against *Aspergillus* spp. Diag Microbiol Infect Dis 2003; 45: 131-135.
89. Pfaller MA, Diekema DJ, Messer SA, et al. In vitro activities of caspofungin compared with those of fluconazole and itraconazole against 3,959 clinical isolates of *Candida* spp., including 157 fluconazole-resistant isolates. Antimicrob Agents Chemother 2003; 47: 1068-1071.
90. Pfaller MA, Jones RN, Doern GV, et al. Internartional surveillance of blood stream infections due to *Candida* species in the European SENTRY program; Species distribution and antifungal susceptibility including the investigational triazole and echinocandin agents. Diag Microbiol Infect Dis 1999; 35: 19-25.
91. Arevalo MP, Carrillo-Munoz AJ, Salgado J, et al. Antifungal activity of the echinocandin anidulafungin (VER002, LY-303366) against yeast pathogens: A comparative study with M27-A microdilution method. J Antimicrob Chemother 2003; 51: 163-166.
92. Marco F, Danes C, Almela M. Trends in frequency and in vitro susceptibilities to antifungal agents, including voriconazole and anidulafungin, of *Candida* bloodstream isolates. Results from a six-year study (1996-2001). Diagn Microbiol Infect Dis 2003; 46: 259-264.
93. Zhanel GG, Karlowsky JA, Zelenitsky SA, et al. Susceptibilities of *Candida* species isolated from the lower gastrointestinal tracts of high-risk patients to the new semisynthetic echinocandin LY303366 and other antifungal agents. Antimicrob Agents Chemother 1998; 42: 2446-2448.
94. Quindós G, Carrillo-Muñoz AJ, Arévalo MP, et al. In vitro susceptibility of *Candida dubliniensis* to current and new antifungal agents. Chemotherapy 2000; 46: 395-401.

95. Laverdiere M, Hoban D, Restieri C, Habel F. In vitro activity of three new triazoles and one echinocandin against *Candida* bloodstream isolates from cancer patients. J Antimicrob Chemother 2002; 50: 119-123.
96. Vazquez JA, Lynch M, Boikov D, Sobel JD. In vitro activity of a new pneumocandin antifungal, L-743,872, against azole-susceptible and –resistant *Candida* species. Antimicrob Agents Chemother 1997; 41: 1612-1614.
97. Pfaller MA, Messer SA, Gee S, et al. In vitro susceptibilities of *Candida dubliniensis* isolates tested against the new triazole and echinocandin antifungal agents. J Clin Microbiol 1999; 37: 870-872.
98. Marco F, Pfaller MA, Messer SA, Jones RN. Activity of MK-0991 (L-743,872), a new echinocandin, compared with those of LY303366 and four other antifungal agents tested against blood stream isolates of *Candida* spp. Diagn Microbiol Infect Dis 1998; 31: 33-37.
99. Nelson PW, Lozano-Chiu M, Rex JH. In vitro growth-inhibitory activity of pneumocandins L-733,569 and L-743,872 against putatively amphotericin B- and fluconazole-resistant *Candida* isolates: Influence of assay conditions. J Med Vet Mycol 1997; 35: 285-287.
100. Bachmann SP, Vande Walle K, Ramage G, et al. In vitro activity of caspofungin against *Candida albicans* biofilms. Antimicrob Agents Chemother 2002; 46: 3591-3596.
101. Kuhn DM, George T, Chandra J, Mukherjee PK, Ghannoum MA. Antifungal susceptibilities of *Candida* biofilms: Unique efficacy of amphotericin B lipid formulations and echinocandins. Antimicrob Agents Chemother 2002; 46: 1773-1780.
102. Pfaller MA, Messer SA, Jones RN. In vitro activity of two echinocandin derivatives, LY303366 and MK-0991 (L-743,872), against clinical isolates of *Aspergillus*, *Fusarium*, *Rhizopus*, and other filamentous fungi. Diagn Microbiol Infect Dis 1998; 30: 251-255.
103. Mikamo H, Sato Y, Tamaya T. In vitro antifungal activity of FK463, a new water-soluble echinocandin-like lipopeptide. J Antimicrob Chemother 2000; 46: 485-487.
104. Ernst EJ, Klepser ME, Ernst ME, et al. In vitro pharmacodynamic properties of MK-0991 determined by time-kill methods. Diagn Microbiol Infect Dis 1999; 33: 75-80.
105. Ernst ME, Klepser ME, Wolfe EJ, Pfaller MA. Antifungal dynamics of LY303366, an investigational echinocandin B analog, against *Candida* spp. Diagn Microbiol Infect Dis 1996; 26;125-131.
106. Green LJ, Marder P, Mann LL, et al. LY303366 exhibits rapid and potent fungicidal activity in flow cytometric assays of yeast viability. Antimicrob Agents Chemother 1999; 43: 830-835.
107. Karlowsky JA, Harding GA, Zelenitsky SA, et al. In vitro kill curves of a new semisynthetic echinocandin, LY-303366, against fluconazole-sensitive and-resistant *Candida* species. Antimicrob Agents Chemother 1997; 41: 2576-2578.
108. Klepser ME, Ernst EJ, Ernst ME, et al. Evaluation endpoints for antifungal susceptibility determinations with LY303366. Antimicrob Agents Chemother 1998; 42: 1387-1391.
109. Klepser ME, Ernst EJ, Ernst ME, Pfaller MA. Growth medium effect on the antifungal activity of LY303366. Diagn Microbiol Infect Dis 1997; 29: 227-231.
110. Ramage G, Vande Walle K, Bachmann SP, et al. In vitro pharmacodynamic properties of three antifungal agents against preformed *Candida albicans* biofilms determined by time-kill studies. Antimicrob Agents Chemother 2002; 46: 3634-3636.
111. Bowman JC, Hicks PS, Kurts MB, et al. The antifungal echinocandin caspofungin acetate kills growing cells of *Aspergillus fumigatus* in vitro. Antimicrob Agents Chemother 2002; 46: 3001-3012.
112. Kontoyiannis DP, Lewis RE. Antifungal drug resistance of pathogenic fungi. Lancet 2002; 359: 1135-1144.
113. Kontoyiannis DP, Bodey GP. Invasive aspergillosis in 2002: An update. Eur J Clin Microbiol Infect Dis 2002; 21: 161-172.
114. Perea S, Patterson TF. Antifungal resistance in pathogenic fungi. Clin Infec Dis 2002; 35: 7073-7080.
115. Vazquez JA. Combination antifungal therapy against *Candida* species: The new frontier-are we there yet? Med Mycol 2003; 41: 355-368.
116. Bachmann SP, Ramage G, Vande Walle K, Patterson TF, Wickes BL, Lopez-Ribot JL. Antifungal combinations against *Candida albicans* biofilms in vitro. Antimicrob Agents Chemother 2003; 47: 3657-3659.
117. Hossain MA, Reyes GH, Long LA, et al. Efficacy of caspofungin combined with amphotericin B against azole-resistant *Candida albicans*. J Antimicrob Chemother 2003; 51: 1427-1429.
118. Graybill JR, Bocanegra R, Najvar LK, et al. Addition of caspofungin to fluconazole does not improve outcome in murine candidiasis. Antimicrob Agents Chemother 2003; 47: 2373-2375.
119. Arikan S, Lozano-Chiu M, Paetznick V, Rex JH. In vitro synergy of caspofungin and amphotericin B against *Aspergillus* and *Fusarium* spp. Antimicrob Agents Chemother 2002; 46: 245-247.
120. Shalit I, Shadkchan Y, Samra Z, Osherov N. In vitro synergy of caspofungin and itraconazole against *Aspergillus* spp.: MIC versus minimum effective concentration end points. Antimicrob Agents Chemother 2003; 47: 1416-1418.
121. Manavathu EK, Alangaden GJ, Chandrasekar PH. Differential activity of triazoles in two-drug combinations with the echinocandin caspofungin against *Aspergillus fumigatus*. J Antimicrob Chemother 2003; 51: 1423-1425.
122. Perea S, Gonzalez G, Fothergill A, et al. In vitro interaction of caspofungin acetate with voriconazole against clinical isolates of *Aspergillus* spp. Antimicrob Agents Chemother 2002; 46: 3039-3041.
123. Kirkpatrick WR, Perea S, Coco BJ, Patterson TF. Efficacy of caspofungin alone and in combination with voriconazole in a guinea pig model of invasive aspergillosis. Antimicrob Agents Chemother 2002; 46: 2564-2568.
124. Rubin MA, Carroll KC, Cahill BC. Caspofungin in combination with itraconazole for the treatment of invasive aspergillosis. Clin Infec Dis 2002; 34: 1160-1161.
125. Aliff TB, Maslak PG, Jurcic JG, et al. Refractory aspergillosis pneumonia in patients with acute leukemia: Successful therapy with combination of caspofungin and liposomal amphotericin B. Cancer 2003; 97: 1025-1032.
126. Stevens DA. Drug interaction studies of a glucan synthase inhibitor (LY303366) and a chitin synthase inhibitor (nikkomycin Z) for inhibition and killing of fungal pathogens. Antimicrob Agents Chemother 2000; 44: 2547-2548.
127. Kurtz, M.B., Rex, J.H. Glucan synthase inhibitors as antifungal agents. Adv Protein Chem 2001: 56: 423-475.
128. Schuetzer-Muehlbauer M, Willinger B, Krapf G, et al. The *Candida albicans* Cdr2p ATP-binding cassette (ABC) transporter confers resistance to caspofungin. Mol Microbiol 2003; 48: 225-235.
129. Bachmann SP, Patterson TF, Lopez-Ribot JL. In vitro activity of caspofungin (MK-0991) against *Candida albicans* clinical isolates displaying different mechanisms of azole resistance. J Clin Microbiol 2002; 40: 2228-2230.
130. Feldmesser M, Kress Y, Mednick A, Casadevall A. The effect of the echinocandin analogue caspofungin on cell wall glucan synthesis *by Cryptococcus neoformans*. J Infect Dis 2000; 182: 1791-1795.