Correlation of In Vitro Fluconazole Susceptibility with Clinical Outcome for Severely Ill Patients with Oropharyngeal Candidiasis

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We investigated the correlation between in vitro susceptibility to fluconazole and clinical response in severely ill patients with oropharyngeal candidiasis treated with fluconazole. The study included 48 adult patients, of whom 23 were neutropenic (absolute neutrophil count, $<500/mm^3$). Forty-eight isolates (20 *Candida albicans,* 12 *Candida krusei,* 10 *Candida kefyr,* 3 *Torulopsis glabrata,* and 3 *Candida tropicalis*) were tested for susceptibility to fluconazole with use of the macrodilution method of the National Committee for Clinical Laboratory Standards. A strain was considered to be susceptible to fluconazole if the MIC was ≤ 8 μg/mL and resistant if the value was ≥ 64 μg/mL. All but one of the resistant strains were *C. krusei* isolates. Species of causative *Candida,* persistent neutropenia, and susceptibility to fluconazole were significant predictors of clinical response by univariate analysis. Logistic regression analysis indicated that the only significant factor was the species of *Candida* isolates, validating the recently recommended MIC breakpoint and the correlation between clinical outcome and in vitro antifungal susceptibility.

A reference method for in vitro susceptibility testing of yeasts has been proposed and recently approved by the National Committee for Clinical Laboratory Standards (NCCLS) [1]. This progress has been followed by research focusing on three main topics: definition of a less labor-intensive method [2–4], determination of relevant interpretive MIC breakpoints for antifungals, and assessment of the correlation of the clinical outcome with in vitro results [5].

Establishing the clinical relevance of in vitro results has been a complicated issue, since the antifungal susceptibility pattern is not the only factor influencing clinical outcome [6]. In any particular patient, pharmacokinetic properties of the antifungal drug as well as several host factors, such as underlying disease and immune status, also determine the fate of the infection. Thus, an infection caused by a susceptible organism may fail to respond to antifungal therapy; conversely, an infection due to a resistant strain usually—but not always—results in clinical failure. Proposal of a tentative MIC breakpoint value for evaluation of in vitro results, on the other hand, requires determination of distribution of susceptibility levels of the infecting species and pharmacokinetic properties of the antifungal drug [7].

The present study was conducted to investigate the correlation between in vitro fluconazole susceptibility and clinical response in severely ill patients with oropharyngeal candidiasis treated with fluconazole.

Patients and Methods

Patients

The study group consisted of 48 adult patients who were severely ill due to various underlying disorders and were treated with fluconazole for oropharyngeal candidiasis. The patients were categorized according to the underlying disease: hematologic malignancy, nonhematologic malignancy, or nonmalignant disorder. Patients with more than one underlying disease were categorized according to the one for which the prognosis was worst (table 1).

Clinical diagnosis of oropharyngeal candidiasis was established by the presence of removable pearly white elevated patches on the mucosal surface, together with one or more additional signs and symptoms such as erythema, a burning sensation, and pain. The diagnosis was confirmed microbiologically by visualization of yeast cells and/or hyphae or pseudohyphae on gram-stained smears prepared from swabs of the visible lesion(s) and by isolation of *Candida* species. Patients whose oral swab cultures failed to yield a *Candida* species were excluded from the study.

The patients were monitored for neutropenia (absolute neutrophil count in peripheral blood, $<500/mm^3$) at the beginning and three times weekly during the course of therapy. Antifungal therapy was accomplished by administration of fluconazole for 14 days. Fluconazole was given at a dosage of 200 mg/d intravenously during the neutropenic period and 100 mg/d orally after recovery from neutropenia. Oral therapy was administered to nonneutropenic patients at a dosage of 100 mg/d. The outcome of the infection for an individual patient

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Table 1. Characteristics of the study group of 48 adults who were severely ill due to underlying disorders and were treated with fluconazole for oropharyngeal candidiasis.

Characteristic of study group	Data
No. of patients (male/female)	48 (22/26)
Age in years, range (mean)	17–72 (44.6)
Underlying disease category, specific condition (no. of patients)	
Hematologic malignancy	30
Acute myeloblastic leukemia	13
Acute lymphoblastic leukemia	5
Chronic myelocytic leukemia	5
Non-Hodgkin's lymphoma	4
Non-Hodgkin's lymphoma and nasopharyngeal carcinoma	1
Multiple myeloma	1
Aplastic anemia	1
Nonhematologic malignancy	10
Tongue carcinoma	2
Gastric carcinoma	1
Nasopharyngeal carcinoma	1
Astrocytoma	1
Ovarian carcinoma	1
Metastatic hepatocellular carcinoma	1
Renal cell carcinoma	1
Maxillary sinus carcinoma	1
Laryngeal carcinoma	1
Nonmalignant disorder	8
End-stage renal failure	4
Myasthenia gravis	1
Diabetes mellitus	1
Cardiac transplantation	1
Head trauma	1
No. of patients with persistent neutropenia (absolute neutrophil count, $<500/mm^3$)	23
No. of patients without neutropenia or who recovered from neutropenia during the course of antifungal therapy	25

was evaluated clinically as a treatment success or failure according to the disappearance or persistence of the visible oral lesion(s) and other signs and symptoms related to candidiasis.

Microbiological Methods

Isolation. Sabouraud dextrose agar (SDA) was used for isolation of the strains from the oral swab samples of the patients. In cases involving a positive germ tube test [8], the strain was identified as *Candida albicans.* The API 20C system (bioMérieux, Marcy l'Etoile, France) was used for species identification if the germ tube test was negative. The isolates were stored at −70°C until testing and were subcultured on SDA at 35°C prior to the antifungal susceptibility assay.

Fluconazole susceptibility testing. Application of the method and interpretation of the results were performed by using the methodology approved by the NCCLS [1, 9]. In brief, twofold serial dilutions of fluconazole (Pfizer, Istanbul, Turkey) were prepared in RPMI-1640 medium, resulting in final drug concentrations ranging from 64 μg/mL to 0.125 μg/mL. Previously diluted yeast inocula were added to tubes containing the antifungal dilutions. Test tubes, including the drug-free and yeast-free control tubes, were incubated at 35°C for 48 hours.

MIC endpoints were determined by the concentration of drug causing >80% inhibition of growth. The strain was considered to be susceptible to fluconazole if the MIC was $\leq$8 μg/mL and to be resistant if the value was $\geq$64 μg/mL. For strains associated with MICs of 16–32 μg/mL, the in vitro result was interpreted as susceptible in a dose-dependent fashion if the administered dose of fluconazole was >100 mg/d [7].

Statistical Methods

The outcome variable of the study was clinical response to fluconazole therapy. The possible explanatory variables for predicting clinical response to antifungal therapy were the species of the infecting *Candida,* in vitro susceptibility to fluconazole, persistence of neutropenia, age, sex, and underlying disease. As it has been previously reported that patients who recovered from neutropenia during antifungal therapy for oropharyngeal candidiasis responded more favorably than those with persistent neutropenia [10], the patients who recovered from neutropenia during the course of antifungal therapy were categorized together with those who were nonneutropenic at the beginning of therapy. Since we previously noted a better clinical cure rate among patients with oropharyngeal candidiasis due to *C. albicans* than among those infected with a non-albicans strain [10], the infecting *Candida* strains were classified as *C. albicans* and *non-albicans* Candida.

All these variables were categorical except age. The association between outcome and explanatory variables was analyzed with the χ^2 test, and odds ratios and corresponding 95% confidence intervals were calculated. Logistic regression analysis was used to adjust the effect of intercorrelation between explanatory variables on clinical response. Variables were selected by means of the forward stepwise method (removal of the variables was based on the likelihood-ratio statistics).

Entry and removal criteria were defined as P values less than .05 and .10, respectively. The model worked as follows. The variable with the smallest P value, if less than .05, was entered first in the model. Then, this variable was tested for removal on the basis of the removal criteria defined above. If it remained in the model, then other variables were tested for entry. Following the entry of a new variable, all previously entered variables were retested for removal. The selection process stopped when no variables could be entered or removed. The statistical analysis was performed with SPSS (Statistical Package for Social Sciences; SPSS, Cary, NC) for Windows, version 5.0. Statistical significance was assigned to P values less than .05.

Table 2. Correlation of clinical outcome with in vitro susceptibility to fluconazole and state of neutropenia in 48 patients with oropharyngeal candidiasis.

Clinical response to treatment	Number of patients (infecting *Candida* species)			
	Persistent neutropenia (n = 23)		Recovery from neutropenia (n = 25)*	
	Isolates resistant	Isolates susceptible	Isolates resistant	Isolates susceptible
Success	3 (*C. krusei*)	10 (*C. albicans,* 7; *C. kefyr,* 3)	3 (*C. krusei*)	18 (*C. albicans,* 12; *C. kefyr,* 5; *C. tropicalis,* 1)
Failure	6 (*C. krusei,* 5; *C. glabrata,* 1)	4 (*C. tropicalis,* 2; *C. glabrata,* 1; *C. kefyr,* 1)	1 (*C. krusei*)	3 (*C. albicans,* 1; *C. kefyr,* 1; *C. glabrata,* 1)

* This category includes both patients who were nonneutropenic and those who were neutropenic initially but recovered from neutropenia during the course of antifungal therapy.

Results

Of the 48 patients included in the study, 30 (62%) had a hematologic malignancy, 10 (21%) had a solid tumor, and 8 (17%) had a nonmalignant illness. Other characteristics of the patients and their underlying diseases are shown in table 1. While 23 patients remained neutropenic, 25 recovered from neutropenia during the course of antifungal therapy or were nonneutropenic at the time of initiation of therapy and remained so thereafter.

Forty-eight Candida strains (one from each patient) were isolated from the patients enrolled in the study. There were 20 strains of *C. albicans,* 12 of *Candida krusei,* 10 of *Candida kefyr,* 3 of *Candida glabrata,* and 3 of *Candida tropicalis.* The MIC_{50} and MIC_{90} values of fluconazole against *C. albicans* isolates were 0.25 μg/mL and 1 μg/mL, respectively, within a range of $\leq$0.125–2 μg/mL. For *C. kefyr* isolates, MIC_{50} and MIC_{90} values were 1 μg/mL and 4 μg/mL, respectively (range, 0.125–8 μg/mL). MICs against all *C. krusei* and one of three *C. glabrata* isolates were $\geq$64 μg/mL. The MIC range for *C. glabrata* was 8–64 μg/mL. For all *C. tropicalis* strains, the MIC of fluconazole was 0.50 μg/mL. None of the MICs against the *Candida* strains were 16 μg/mL or 32 μg/mL.

Clinical response to fluconazole, with respect to in vitro susceptibility of the isolated strains and the course of neutropenia, is documented in table 2. Thirty-four patients (71%) responded to fluconazole therapy, of whom 13 (38%) were consistently neutropenic during the course of antifungal treatment. Of the 12 patients infected with *C. krusei,* 6 (50%), including 3 patients with persistent neutropenia, were successfully treated with fluconazole. The success rates for patients infected with *C. albicans, C. kefyr,* and *C. tropicalis* were 95%, 80%, and 33%, respectively.

Among patients with *C. albicans* infections, only one failed to respond to fluconazole therapy, in spite of the resolution of neutropenia and recovery of a fluconazole-susceptible isolate. In two additional patients infected with *C. kefyr* and *C. glabrata,* respectively, treatment failure occurred even though the above ''favorable'' conditions were present. None of the infections caused by *C. glabrata* were treated successfully with fluconazole.

All patients failing to respond to fluconazole therapy had received oral or parenteral fluconazole within the previous 2 months of the current treatment. The daily dose of fluconazole for these therapies had ranged between 100 mg and 200 mg. All patients (n = 6) but one with *C. krusei* infections that did not respond to fluconazole had persistent neutropenia and received intravenous amphotericin B (0.6 mg/[kg · d]). Four of these patients responded well to the treatment. A patient with gastric carcinoma recovered from neutropenia during the course of amphotericin B treatment, and improvement in oral lesions was noted. However, the patient died on the 20th day of therapy.

The only patient without neutropenia had nasopharyngeal carcinoma and was treated locally with oral nystatin and bicarbonate gargles. The patient responded clinically, but *C. krusei* was persistently isolated. Six weeks later, clinical infection reappeared and was treated with amphotericin B.

The two patients with infections due to fluconazole-susceptible *C. glabrata* (MIC, 8 μg/mL) were given fluconazole (400 mg/d) parenterally. The lesions healed, but the yeast persisted in the oral cavity. The other patient who was infected with a resistant *C. glabrata* strain and had persistent neutropenia was cured with parenteral amphotericin B.

Two patients with acute myeloblastic leukemia were infected with susceptible *C. tropicalis* strains (MIC of fluconazole, 0.50 μg/mL). One of these patients was also unresponsive to parenteral amphotericin B but improved upon recovery from neutropenia. The other patient received fluconazole (400 mg/d) intravenously, resulting in clinical improvement, but cultures of oral swab specimens were persistently positive.

Of the two patients infected with susceptible *C. kefyr* (MICs of fluconazole, 1 μg/mL and 2 μg/mL), the one with persistent neutropenia was treated with parenteral amphotericin B and responded. The second patient received fluconazole (400 mg/d) parenterally, resulting in clinical improvement. The cultures of oral swab specimens continued to persistently yield the same yeast during and after the treatment.

Table 3. Univariate analysis of the correlation between clinical response to fluconazole therapy and tested variables.

Variable	Clinical response: no. (%) of patients		OR	95% CI	*P* value
	Failure	Success			
Infecting *Candida* species					.002
Non-*albicans Candida*	13 (46)	15 (54)			
C. albicans	1 (5)	19 (95)	16.5	1.9–140.4	
Neutropenia					.04
Persistent	10 (44)	13 (57)			
Resolved	4 (16)	21 (84)	4.1	1.1–15.6	
Fluconazole susceptibility					.02
Resistant	7 (54)	6 (46)			
Susceptible	7 (20)	28 (80)	4.7	1.2–18.3	
Gender					.79
Male	6 (27)	16 (73)			
Female	8 (31)	18 (69)	0.8	0.2–3.0	
Underlying disease					.13
Hematologic malignancy	10 (33)	20 (67)			
Nonhematologic malignancy	4 (40)	6 (60)			
Nonmalignant disorder	—	8 (100)	0.8	0.2–3.3	
Age, mean ± SD	45 ± 14	44 ± 15			.60*

* Per Mann-Whitney *U*-test.

A patient with aplastic anemia and oropharyngeal candidiasis caused by a susceptible strain of *C. albicans* (MIC of fluconazole, 1 μg/mL) was given parenteral amphotericin B. No improvement was noted, and the patient died after 8 days of therapy.

The results of the statistical analysis by univariate model indicated that a better clinical response could be achieved in patients infected with *C. albicans* than in those infected with a non-*albicans Candida* strain (OR, 16.5; 95% CI, 1.9–140.4; $P = .002$). Recovery from neutropenia (OR, 4.1; 95% CI, 1.1–15.6; $P = .04$) and susceptibility to fluconazole (OR, 4.7; 95% CI, 1.2–18.3; $P = .02$) were significant predictors of a favorable clinical outcome (table 3). The gender and age of the patients and the type of underlying disease did not seem to have an effect on the outcome. When the effects of relationships between these variables on clinical response were adjusted by means of the above-described logistic regression model, the only significant factor was the species of *Candida* isolates recovered (OR, 16.4; 95% CI, 1.9–140.1; $P = .01$).

The cause of discrepancy between univariate and multivariate approaches regarding the significance of recovery from neutropenia and susceptibility to fluconazole could be appreciated when the relationship between these variables and the recovered *Candida* species (*albicans* vs. non-*albicans*) and clinical response was examined (data not shown in table 3). Although recovery from neutropenia seemed to be associated with a favorable clinical response ($P = .04$), when subgroup analysis was performed this was valid only for patients infected with a non-*albicans* strain ($P = .049$); it was insignificant for those infected with *C. albicans* ($P = .65$). Therefore, multivariate analysis eliminated ''recovery from neutropenia'' as a significant variable for treatment success.

The associations between susceptibility to fluconazole, species of infecting *Candida,* and clinical response presented a different picture. All 20 *C. albicans* strains were susceptible to fluconazole, of which 19 (95%) were associated with clinical success. However, for patients infected with non-*albicans Candida,* susceptibility to fluconazole did not affect the outcome of therapy ($P = .46$). Consequently, logistic regression analysis found the species of infecting *Candida* to be the only factor significant for clinical outcome.

Discussion

Candidal infections have become a life-threatening problem in immunocompromised patients, mainly because of prolonged use of antibiotics, wide application of indwelling central venous catheters, and administration of intensive chemotherapeutic regimens [11]. The antifungals used in management of candidal infections are limited [12]. Fluconazole is a bistriazole compound that offers some advantages in the treatment of candidiasis: it has both oral and parenteral formulations, excellent bioavailability, and a low level of toxicity [10, 11].

However, fluconazole therapy may fail under certain circumstances. Colonization and infection with intrinsically resistant *Candida* species such as *C. krusei* may develop after fluconazole treatment [12, 13]. Moreover, prophylactic use of the drug by patients with AIDS may even cause emergence of resistance among *C. albicans* isolates [14].

Predicting the clinical outcome of fluconazole treatment by determination of MICs against the infecting yeasts has been troublesome so far. This is mainly attributable to the fact that

host factors such as effective treatment of the underlying disease, recovery from neutropenia, and removal of intravenous catheters may also influence the therapeutic outcome [5, 10, 15]. Assessment of relevant MIC breakpoints is another problem complicating the issue.

Studies have been carried out to define the correlation of clinical response with in vitro susceptibility in cases involving AIDS patients with oropharyngeal candidiasis [6]. The results have pointed out that there is a constant relationship between MIC and outcome when the MICs are interpreted in a dose-dependent fashion, a finding suggesting that the tentative breakpoint should be chosen according to the achievable levels of fluconazole in blood.

The peak level of the drug is ~6 μg/mL and 0–30 μg/mL for dosages of 100 mg/d and 400 mg/d, respectively, suggesting that isolates for which MICs are <64 μg/mL can be inhibited when a 400-mg/d dosage of fluconazole is used [6, 7]. However, data obtained in another study could not correlate clinical outcome with in vitro MICs in cases involving AIDS patients with oropharyngeal candidiasis [16]. These data were similar to those of Rex et al. [5], who studied candidemic nonneutropenic patients without AIDS.

Following these preliminary reports, the NCCLS antifungal susceptibility testing subcommittee proposed interpretive MIC breakpoints for fluconazole that seemed to correlate the in vitro results with the clinical outcome. According to these guidelines, strains for which the MIC values are ≤8 μg/mL and ≥64 μg/mL are interpreted as susceptible and resistant, respectively. MICs of 16 μg/mL and 32 μg/mL were considered to denote susceptibility, depending upon dose, on the basis of the data indicating clinical success with fluconazole at a dosage of >100 mg/d. These results were more definite for *C. albicans* and oropharyngeal infections but not for non-*albicans Candida* species and invasive infections. For *C. krusei,* the intrinsically resistant *Candida* species, this scale was not suggested and not required to be used [7].

We attempted to predict the outcome of fluconazole treatment with respect to in vitro MIC values as well as other variables like species of infecting *Candida* isolates, underlying disorder, presence of neutropenia, gender, and age in a group of severely ill patients with candidiasis. The strains for which MICs were ≥64 μg/mL included all of the *C. krusei* isolates tested and one of three *C. glabrata* isolates. These two species, intrinsically less susceptible to fluconazole, were associated with well-documented high MICs in previous reports [7, 12].

Statistical analysis of the data showed that species of causative *Candida,* persistence of neutropenia, and susceptibility to fluconazole were significant predictors of clinical response by univariate model. However, the logistic regression model proved the only significant factor to be the infecting *Candida* species. Most of the *Candida* strains for which the fluconazole MIC was ≥64 μg/mL were *C. krusei* isolates, and these data were confirmatory of the recently recommended MIC breakpoints.

Although our findings may suggest that species identification can assist in predicting the in vitro susceptibility pattern and clinical outcome, such a prediction may not always be relevant since emergence of resistance to fluconazole among susceptible species (like *C. albicans*) may emerge in AIDS patients and others who receive long-term antifungal prophylaxis [14]. Furthermore, species like *C. glabrata* that are less susceptible to fluconazole may be associated with MIC values of ≥64 μg/mL [9]. This was the situation for one of the *C. glabrata* strains included in our study, which was isolated from a neutropenic patient who did not respond to fluconazole therapy. None of our isolates was associated with an MIC of 16–32 μg/mL, so dose-dependent evaluation of the in vitro results was not applicable.

As indicated in table 2, infection with some of the susceptible strains resulted in clinical failure, and with some resistant strains clinical success could be achieved; this emphasizes the significance of multifactorial evaluation of the outcome of the infection. Not only the in vitro susceptibility pattern but also the host factors such as neutrophil count and management of underlying disease should be taken into consideration to predict the clinical outcome. These data show that in vitro susceptibility results should still be viewed cautiously.

In conclusion, our results indicate that clinical outcome seems to be correlated with the in vitro fluconazole-susceptibility results for oropharyngeal candidiasis in severely ill patients when the proposed MIC breakpoint value of ≥64 μg/mL is validated. In vitro–in vivo correlation for non-*krusei Candida* isolates associated with high MIC values should be evaluated to increase the predictive power of the currently available interpretive breakpoints. However, correlating the MIC of fluconazole with clinical outcome is not a totally clarified issue and requires complex evaluation of several factors.

References

1. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved standard M27-A. Villanova, Pennsylvania: National Committee for Clinical Laboratory Standards, **1997**.
2. Eldere JV, Joosten L, Verhaeghe A, Surmont I. Fluconazole and amphotericin B antifungal susceptibility testing by National Committee for Clinical Laboratory Standards broth macrodilution method compared with E-test and semiautomated broth microdilution test. J Clin Microbiol **1996**;34:842–7.
3. Espinel-Ingroff A, Kish CW Jr, Kerkering TM. Collaborative comparison of broth macrodilution and microdilution antifungal susceptibility tests. J Clin Microbiol **1992**;30:3138–45.
4. Tiballi RN, He X, Zarins LT, Revankar SG, Kauffman CA. Use of a colorimetric system for yeast susceptibility testing. J Clin Microbiol **1995**;33:915–7.
5. Rex JH, Pfaller MA, Barry AL, Nelson PW, Webb CD. Antifungal susceptibility testing of isolates from a randomized, multicenter trial of fluconazole versus amphotericin B as treatment of nonneutropenic patients with candidemia. Antimicrob Agents Chemother **1995**;39:40–4.
6. Ghannoum M, Rex JH, Galgiani JN. Susceptibility testing of fungi: current status of correlation of in vitro data with clinical outcome. J Clin Microbiol **1996**;34:489–95.

7. Rex JH, Pfaller MA, Galgiani JN, et al. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro–in vivo correlation data for fluconazole, itraconazole, and candida infections. Clin Infect Dis **1997**;24:235–47.
8. Roberts GD. Laboratory methods in basic mycology. In: Baron EJ, Finegold SM, eds. Bailey and Scott's diagnostic microbiology. 8th ed. St. Louis: CV Mosby, **1990**;681–775.
9. Arıkan S, Gür D, Akova M. Comparison of Etest, microdilution and colorimetric microdilution with reference broth macrodilution method for susceptibility testing of clinically significant *Candida* species isolated from immunocompromised patients. Mycoses **1997**;7/8 (in press).
10. Akova M, Akalın HE, Uzun Ö, et al. Efficacy of fluconazole in the treatment of upper gastrointestinal candidiasis in neutropenic patients with cancer: factors influencing outcome. Clin Infect Dis **1994**;18:298–304.
11. Wingard JR. Infections due to resistant *Candida* species in patients with cancer who are receiving chemotherapy. Clin Infect Dis **1994**;19 (suppl 1):S49–53.
12. Rex JH, Rinaldi MG, Pfaller MA. Resistance of *Candida* species of fluconazole. Antimicrob Agents Chemother **1995**;39:1–8.
13. Akova M, Akalın HE, Uzun Ö, Gür D. Emergence of *Candida krusei* infections after therapy of oropharyngeal candidiasis with fluconazole. Eur J Clin Microbiol Infect Dis **1991**;10:598–9.
14. Boken DJ, Swindells S, Rinaldi MG. Fluconazole-resistant *Candida albicans.* Clin Infect Dis **1993**;17:1018–21.
15. Akova M, Hayran M, Arıkan S, Gür D, Ünal S, Akalın HE. Correlation of clinical outcome of candida infections with in vitro antifungal susceptibility testing in patients with severe underlying diseases [abstract no 795]. In: Program and abstracts of the 7th European Congress on Clinical Microbiology and Infectious Diseases. Vienna: European Society of Clinical Microbiology and Infectious Diseases, **1995**:155.
16. Steele-Moore L, Schneider B, Berg D, Holloway W. Clinical and in vitro evaluation of 20 AIDS patients with oropharyngeal candidiasis during prolonged antifungal therapy [abstract no 187]. In: Program and abstracts of the 9th International Symposium on Infections in the Immunocompromised Host. Assisi, Italy: The Immunocompromised Host Society, **1996**.