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MINIREVIEW

Resistance of *Candida* Species to Fluconazole

JOHN H. REX,[1,2]* M. G. RINALDI,[3] AND M. A. PFALLER[4]

Center for Infectious Diseases, Department of Internal Medicine, University of Texas Medical School,[1] and Department of Medical Specialties, M. D. Anderson Cancer Center,[2] Houston, Texas; Department of Pathology, University of Texas Health Science Center at San Antonio, San Antonio, Texas[3]; and Department of Pathology, University of Iowa College of Medicine, Iowa City, Iowa[4]

INTRODUCTION

Although they are often present as benign commensal organisms in the digestive tract of healthy individuals, *Candida* species produce a broad range of serious illnesses in compromised hosts. Such infections are clearly on the rise. Data from the ongoing National Nosocomial Infections Surveillance System conducted in the United States showed a 487 percent increase in *Candida* bloodstream infections between 1980 and 1989 (11), while oropharyngeal candidiasis is the most common fungal infection in patients with human immunodeficiency virus (HIV) infection (32). Therapy for serious *Candida* infections has been difficult because of the limited number of available antifungal agents. Although long the mainstay of treatment, amphotericin B is associated with many toxicities and requires intravenous administration (16). Flucytosine's use is limited by its bone marrow toxicity and the high rate of spontaneous mutation to resistance (16). With the introduction of azole antifungal agents that are bioavailable after oral administration, the approach to the treatment of serious *Candida* infections began to change (72). Ketoconazole, the first of these agents to become available, was quickly found to be efficacious in the setting of chronic mucocutaneous candidiasis (41). However, not long after the introduction of this agent, reports of clinical failure in association with elevated MICs of ketoconazole that developed during prolonged therapy began to appear (41, 79). This problem did not achieve much prominence until the subsequent introduction of fluconazole. Fluconazole, a water-soluble triazole with greater than 90% bioavailability after oral administration, has been used extensively to treat a wide range of *Candida* infections (20, 72). In particular, it has been widely used as therapy for oropharyngeal candidiasis in patients with advanced HIV infection and AIDS. Although oropharyngeal candidiasis usually responds readily to fluconazole, it is difficult to completely eradicate the infection and relapse often occurs within several months following the completion of therapy (55, 81). For this reason, many AIDS patients receive fluconazole either continuously or intermittently over long periods of time. As with ketoconazole, reports of the development of resistance to fluconazole when used in this setting have begun to appear (55, 56). Furthermore, reports of the failure of or resistance to fluconazole therapy in other settings have also begun to appear (see below). A major difficulty in assessing many of these reports is the lack of an established definition of resistance as it applies to antifungal agents. In some cases the term resistance has been used when a patient fails to respond clinically to antifungal therapy (55). In others it has been used to describe a strain for which the MIC of an antifungal drug is greater than the MIC of the drug for other strains tested in the same laboratory (56). This definition of resistance is quite problematic. Correlation of clinical results with MICs is difficult, as has long been recognized both for antibacterial agents (35, 73, 82) and more recently for antifungal agents (67). While correlations between the fluconazole MIC and outcome have been established in animal models (5), therapeutic failures and successes in humans may be seen with isolates for which MICs are both high and low (66). Rarely has the term resistance been used in the classic sense, describing a therapeutic failure in association with an increase from pretherapy levels in the MIC for the same fungal strain and subtype during therapy. Interpretation of these reports is further complicated by variations in the dose and duration of fluconazole therapy, the presence of drug-drug interactions that may lower serum fluconazole concentrations, the variable nature of the patients' immunologic status and questions of drug compliance.

The purpose of this minireview is to survey the literature and place these reports of resistance in context. This minireview focuses almost solely on fluconazole since, because of their lower bioavailabilities, ketoconazole and the recently licensed triazole itraconazole are not extensively used for the management of serious *Candida* infections and, other than as just noted, resistance to fluconazole during prolonged therapy has not been widely reported. Furthermore, this minireview focuses on resistance among *Candida* isolates. Much less is known about fluconazole resistance in *Cryptococcus neoformans*, the other major yeast commonly treated with fluconazole (9, 23, 91). The three described mechanisms of azole resistance (reduced permeability, alterations in the target fungal enzyme, and overproduction of the target fungal enzyme) are not reviewed; recent discussions of these areas can be found elsewhere (39, 84).

WHAT IS MEANT BY RESISTANCE?

There are three possible avenues by which a patient might acquire a resistant organism: (i) a colonizing or infecting organism is initially susceptible but mutates and becomes resistant, (ii) the patient is colonized or infected with multiple strains or species and an inherently resistant strain or species is selected, or (iii) the patient is initially colonized or infected with an inherently resistant species. Ideally, the appearance of the resistant *Candida* isolate would be associated with clinical failure (failure of drug therapy to resolve signs and symptoms

* Corresponding author. Mailing address: 6431 Fannin, 1728 JFB, Houston, TX 77030. Phone: (713) 792-4929. Fax: (713) 792-4937. Internet: jrex@heart.med.uth.tmc.edu.

TABLE 1. Factors relevant to interpretation of reports of fluconazole resistance

Factor	Description
Patient status	$CD4^+$ cell count, neutrophil count, other immunosuppression
	Compliance with drug regimen (levels of drug in serum)
	Potential drug-drug interactions (levels of drug in serum)
	Management (removal of intravenous catheters, drainage of abscesses)
Antifungal therapy	
Prior therapy	Drug(s), dosage, duration, route
Current therapy	Drug(s), dosage, duration, route
	Episodic or maintenance therapy
	Dosage escalation, if any
Mycological studies of pre- and posttreatment cultures	Same species and strain (DNA-based typing methods)
	Increases in MICs over time
	Culture findings at time of dosage escalation
Test method(s)	Reproducibility and correlation to clinical outcome
	Use of appropriate controls

of infection), and this minireview will focus on reports that use this definition. Mycological failure (failure of therapy to eradicate the yeast) is hard to interpret because many patients improve clinically despite the persistence of yeasts. The least satisfactory definition of resistance is one based solely on MICs, but unfortunately, isolates are sometimes labeled as resistant on the basis of arbitrarily chosen breakpoints without reference to clinical outcome. The presence or development of elevated MICs is of little importance if the patient improves clinically. This is true even if the MICs exceed the achievable concentrations of the given antifungal agent in serum; antifungal agent MICs can be varied as much as 50,000-fold simply by manipulating the assay conditions (67), and the MIC obtained by any given method is a function of a series of arbitrary decisions made during development of the method. There is thus no predictable relationship between MICs and drug levels in serum, and interpretive breakpoints for MICs should not be assigned without supporting clinical data.

FACTORS THAT MUST BE CONSIDERED

The factors that must be considered when interpreting reports of resistance of *Candida* to azoles are listed in Table 1. In the case of clinical resistance encountered in immunosuppressed patients, it is essential to have complete details of the patient's status such as the underlying disease (e.g., malignancy, leukemia, HIV infection), the $CD4^+$ cell count, the neutrophil count, and whether other immunosuppressive agents have been used. All current and prior courses of antifungal therapy should be documented; data on the drugs administered, the indication for therapy, the dosage and route of administration, and whether dosage increases were attempted are all valuable. Dosage variations can be quite important. During early clinical trials, it was common to use as little as 50 mg of fluconazole per day, while current data suggest that 800 mg/day (a 16-fold increase!) is safe and efficacious and may be warranted under certain circumstances (17, 34). It is also important to know how well the patient complied with the prescribed drug regimen and whether or not other medications that might potentially interact with the antifungal agent were being taken concurrently. If compliance problems or potential drug interactions are noted, measurement of serum drug levels becomes quite important. Finally, other events (abscess drainage, recovery from neutropenia, removal of intravascular catheters) can significantly alter the course of the infection. For example, recent data from a trial of fluconazole therapy for candidemia in nonneutropenic patients have shown that complete catheter exchanges are associated with a substantial reduction in the subsequent duration of candidemia. Analysis of the MICs for the isolates from that trial suggested that the effect of these interventions appeared to outweigh any effects owing to differences in MICs (63, 64, 66).

Optimally, pretreatment and posttreatment culture data should be available for comparison. Specimens for culture should also be obtained if there is an increase in dosage. In order to document mutation to resistance, the same species and strain (as determined by DNA-based typing methods) should be isolated throughout, and a significant increase in MICs should be demonstrated and correlated with the clinical outcome (i.e., failure or relapse). It is also important that the in vitro test methods used be reproducible and include appropriate controls. Use of methodologies similar to the M27-P broth methodology developed by the National Committee for Clinical Laboratory Standards (NCCLS) will facilitate comparison of MICs between reports (53).

Finally, the infecting *Candida* species needs to be considered. It is clear that different species have different intrinsic in vitro susceptibilities to fluconazole. For example, by using the NCCLS M27-P methodology, the MICs inhibiting 50% of a group of pathogenic bloodstream *Candida* isolates were found to be as follows: *C. albicans*, 0.25 μg/ml; *C. tropicalis*, 1 μg/ml; *C. parapsilosis*, 1 μg/ml; *C. glabrata*, 16 μg/ml; and *C. krusei*, 32 μg/ml (66). Numerically similar data have been obtained by using microtiter variants of the NCCLS methodology (28, 61, 66), and qualitatively similar data have been obtained by other methods (48). As will be discussed below, these MIC differences appear to correspond to differences in response to a given dosage of fluconazole.

REPORTS OF FLUCONAZOLE RESISTANCE

The clearest examples of fluconazole resistance have been reported in AIDS patients being treated for oropharyngeal candidiasis with or without esophageal involvement. The appearance of this problem seems closely linked to advanced AIDS and the cumulative dose of azole (47, 83, 85). In the majority of patients, *C. albicans* is the pathogenic organism and mutation of a previously susceptible strain to resistance appears to have occurred. On the other hand, reports of resistance in clinical settings other than AIDS patients with oropharyngeal candidiasis usually involve *C. krusei* or *C. glabrata* and are often associated with the prophylactic use of doses of fluconazole that are now considered relatively low (see below). Resistance to fluconazole does not appear to develop during the shorter courses of therapy used for invasive *Candida* infections (24, 66).

AIDS Patients with oropharyngeal candidiasis. Of 33 recent publications reporting resistance to fluconazole during treatment of AIDS patients for oropharyngeal candidiasis, 5 contain insufficient information regarding the actual cases (2, 14, 21, 30, 45) and a sixth defines resistance entirely in terms of MIC changes without providing any clinical details (51). The remaining 27 publications contain enough information to allow at least some interpretation. All but three (6, 57, 58) provide information on in vitro susceptibility determined by either the

proposed NCCLS method (19, 37, 52, 60, 62, 70, 74, 75) or other methods (10, 13, 15, 26, 27, 31, 43, 47, 54, 68, 71, 76, 78, 83, 85, 88).

In the typical scenario, a patient with advanced AIDS ($CD4^+$ cell counts were reported in 13 publications and were $<50/mm^3$ in the majority of patients [6, 10, 37, 54, 57, 58, 62, 68, 71, 75, 76, 83, 85]) has relapsing oropharyngeal candidiasis that has been treated variously with topical agents or ketoconazole and then finally with either repeated courses of therapy or prolonged therapy with low doses of fluconazole. These therapies are often effective for an extended period of time (estimated at an average of 13 prior relapses in one report [83]), but finally a relapse fails to respond clinically to a course of 100 to 200 mg of fluconazole per day. At this juncture, the patient is found to be carrying a strain of *C. albicans* for which the MIC is ~16 μg/ml by the NCCLS methodology. Therapy with 200 to 400 mg of fluconazole per day produces relief, but after one or more rounds of therapy at this dose the patient's relapses again cease to respond and the patient is found to be carrying a *C. albicans* strain for which the MIC is >64 μg/ml by the NCCLS methodology. In a particularly well documented example of this scenario, Redding and coworkers (62) described a patient included in a larger study (60) who was successfully treated with 100 mg of fluconazole per day during each of nine recurrences of oropharyngeal candidiasis. At the time of the fifth episode, this patient's $CD4^+$ cell count was $9/mm^3$. During these first nine courses of therapy, the MIC for the infecting strain of *C. albicans* gradually rose from 0.25 to 8 μg/ml by the NCCLS methodology. The MIC for the isolate continued to rise during episodes 10 through 14, but these episodes still responded to increasing fluconazole dosages of 200, 400, and finally 800 mg/day. However, after a period of 2 years of successful use of fluconazole for the treatment of recurrent infections, the next episode (episode 15) failed to respond to 800 mg of fluconazole per day and the patient required parenteral amphotericin B therapy. The fluconazole MIC for the isolate was >64 mg/ml at recurrences 12 and 14 (the isolate from episode 15 was not available). Results of DNA subtyping demonstrated the persistence of the same *C. albicans* subtype throughout the 2 years of fluconazole therapy.

Similarly, Ruhnke et al. (71) reported the development of fluconazole-resistant candidiasis in 2 of 23 HIV-infected patients. All patients had $CD4^+$ cell counts of $<180/mm^3$ and were given repeated 5-day courses of fluconazole at 100 mg/day. After five and six courses of therapy, respectively, the two patients no longer responded to therapy, even when doses of 300 to 400 mg/day were administered. By using a method similar to the NCCLS method, the MICs for the *C. albicans* isolates from these two patients were found to have risen from <1 to ≥25 μg/ml. As with the patient described by Redding et al. (62), a gradual rise in the fluconazole MIC was shown for the isolate from one patient, and there was a period during which the MIC for the infecting isolate was intermediate (6 to 12.5 μg/ml) and during which the isolate responded to 300 mg of fluconazole per day.

This pattern of development of resistance is well described by several other groups of investigators (13, 15, 47, 52, 68, 74, 75, 83, 85). When it is examined, the resistant isolate often appears to have the same genotype as the initial isolate (15, 51, 52, 75, 85), although acquisition of a new infecting strain may also occur (15, 75).

In the other reports of fluconazole-resistant *C. albicans* in AIDS patients with oropharyngeal and/or esophageal candidiasis, either a relatively high MIC was detected at the time of clinical failure or recurrence (19, 26, 27, 31, 37, 43, 54, 68, 70, 76, 78, 88), the MIC was stated to be high but actual data were not reported (10), or no MICs were determined (6, 57, 58). Many of the patients from whom *C. albicans* strains for which MICs were high were isolated had infections that had failed to respond to prior courses of therapy with other topical (i.e., clotrimazole and nystatin) or systemic (i.e., ketoconazole) agents (19, 31, 37, 76, 78, 88). Some patients had received prior therapy with fluconazole given at low dosages (≤150 mg/day) as prophylaxis or maintenance therapy (31, 37, 43, 70, 88). Moreover, the last dosage of fluconazole administered to most of the patients to treat a recurrence was ≤200 mg/day (19, 31, 37, 43, 78, 88); only a few patients who failed to respond to fluconazole received dosages in excess of 200 mg/day (19, 37, 54, 76, 88).

In addition to correlating with advanced AIDS, the development of resistance has also been reported to correlate with the cumulative dose of fluconazole. Vuffray et al. (85) reported 161 episodes (in 46 patients) of resistance to single-dose (150-mg) fluconazole therapy. When these refractory episodes of oropharyngeal candidiasis were treated with higher doses of fluconazole, there were 91 treatment failures and 119 treatment successes. The median pretreatment cumulative dose of fluconazole was 10,600 mg/day in the treatment failures compared with 4,400 mg/day in the 119 treatment successes ($P = 0.001$). A subsequent analysis of data from 25 consecutive patients who received fluconazole at 200 to 400 mg/day for 7 to 14 days as therapy for oropharyngeal candidiasis demonstrated that, compared with responders, nonresponders had a longer median interval since the diagnosis of AIDS (27 versus 2 months; $P = 0.001$), a lower median $CD4^+$ cell count (6 versus $21/mm^3$; $P = 0.005$), a higher median number of previous episodes of oropharyngeal candidiasis treated with fluconazole (13 versus 2 episodes; $P = 0.01$), and a smaller mean inhibition zone diameter (13 versus 36 mm; $P < 0.001$) when the susceptibilities of the *C. albicans* isolates were tested by a disk diffusion method (83). Finally, use of any azole antifungal therapy during the preceding month has been associated with the presence of *C. albicans* isolates for which fluconazole MICs are higher (21).

The role of non-*C. albicans* isolates in reports of resistance varies. As noted above, MICs for these organisms tend to be higher. They are not usually isolated initially (71, 75), but more often appear to be acquired after previous courses of therapy (21, 68, 71). The species reported in the publications reviewed herein have included *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. kefyr*, and *C. krusei* (2, 10, 13, 14, 19, 21, 30, 31, 45, 47, 54, 58, 68, 71, 78). The presence of a non-*C. albicans* isolate is sometimes (2, 13, 19, 31, 45, 54), but not always (10, 13, 68, 75), associated with the failure of fluconazole therapy. As is the case with *C. albicans*, clinical failure appears to correlate with the acquisition of strains for which MICs are elevated (13).

While issues of compliance (2, 19, 31) or drug-drug interactions (19, 76) cast doubt on a few of these cases, the majority are reasonably well documented and, taken together, convincingly demonstrate the potential for the development of resistance to fluconazole in previously susceptible strains and/or the acquisition of inherently relatively resistant strains. While the precise MIC breakpoint is as yet unclear, it appears that MICs of fluconazole of about 16 μg/ml by the NCCLS methodology predict a poor response to ~100 mg of fluconazole per day and that MICs of >64 μg/ml predict a poor response to 400 to 800 mg of fluconazole per day. The off-scale result of >64 μg/ml prevents further delineation of the MIC at which failure becomes likely. Adequate data on the frequency of the development of clinical resistance have not been presented. On the basis of personal experiences and inferences drawn from pub-

TABLE 2. Fluconazole-resistant fungemia[a]

Patient group	Reference	Systemic therapy		Infecting organism		
		Prior to fungemia	Therapy of fungemia	Species (no. of patients)	MIC (μg/ml)[b]	Method
Patients developing fungemia while on fluconazole	18	Flu at 50 mg/day for three courses	AmB	*C. krusei* (1)	25	Broth
	22	Flu at 200 mg/day for 30 days	AmB	*C. krusei* (1)	32	NR
	29	Flu at 50 mg/day three times per day (renal failure)	AmB	*C. albicans* and *C. glabrata* (1)	NR	
	33	Flu at 200 mg/day for 6 to 12 days (all patients) plus AmB at 0.6 mg/kg every other day in two patients	AmB	*C. krusei* (4)	NR	
	38	Flu at 100 mg/day for 8 wk	AmB	*C. albicans* and *C. parapsilosis* (1)	NR	
	49	Flu at 200 mg/day for 8 days	AmB	*C. krusei* (1)	≥25	NR
	59	Flu at 100 to 200 mg/day for 3 to 12 days	AmB	*C. krusei* (4)	>25	Broth
	89	Flu at 400 mg/day	AmB, 5-FC	*C. krusei* (7) *C. glabrata* (2) *C. parapsilosis* (1)	>80	Broth
	90	Flu, dose not stated	AmB, 5-FC	*C. krusei* (1) *C. glabrata* (6) *C. parapsilosis* (1)	5–>80	Broth
Fungemia unsuccessfully treated with fluconazole	1	None	Flu at 3 mg/kg of body wt/day	*C. krusei* (1)	>12	NR
	24	None	Flu at 200 to 400 mg/day	*C. albicans* (1)	1.56–3.25	Broth
	63, 66	None	Flu at 400 mg/day	*C. albicans* (9)[c] *C. glabrata* (3) *C. tropicalis* (2) *C. parapsilosis* (2)	≤0.5 8 ≤1 1	NCCLS
	69	None	Flu at 100 to 400 mg/day	*C. krusei* (1)	NR	
	77	None	Flu at 100 mg/day	*C. glabrata* (1)	NR	

[a] Abbreviations: AmB, amphotericin B; Flu, fluconazole, 5-FC, flucytosine; broth, a broth dilution method; NCCLS, NCCLS M27-P methodology; NR, not reported.
[b] MIC of fluconazole.
[c] This group comprises only 15 patients; some patients were infected with more than one species.

lished data, it appears likely that it occurs in roughly 5 percent of patients with advanced AIDS.

Other clinical settings. There have been fewer reports of fluconazole resistance in clinical settings other than AIDS patients with oropharyngeal candidiasis. In patients with a malignancy and oropharyngeal candidiasis, fluconazole is generally effective. Reported failures have involved the use of relatively low doses of fluconazole (100 to 200 mg/day), failure of recovery from neutropenia, and/or infection with such intrinsically resistant species as *C. krusei* (3, 4, 50). The progressive development of resistance has not been described in this setting, presumably because these patients receive fewer courses of therapy.

The largest group of failures reported outside of patients with AIDS and oropharyngeal candidiasis consists of patients with fungemia (Table 2). To date, 31 reported patients have developed fungemia while receiving fluconazole (18, 22, 29, 33, 38, 49, 59, 89, 90), and 19 patients with preexisting fungemia have failed to respond to fluconazole therapy (1, 24, 63, 69, 77). The 31 patients who received fluconazole prior to the occurrence of fungemia had multiple risk factors (leukemia, lymphoma, solid tumor, bone marrow transplant, diabetes mellitus, neutropenia, intravenous catheters, or high-dose steroid therapy). Fluconazole was given as prophylaxis either alone or in combination with amphotericin B or to treat oropharyngeal and/or esophageal candidiasis. Thirteen of the 31 patients received low dosages of fluconazole (50 to 200 mg/day) (18, 22, 29, 33, 38, 49, 59), which were given for prolonged periods of up to 2 months. *C. krusei* was the most frequently isolated species (19 patients) (18, 22, 33, 49, 59, 89, 90); this was followed by *C. glabrata* (8 patients) (89, 90) and *C. parapsilosis* (2 patients) (89, 90). *C. albicans* in combination with either *C. glabrata* or *C. parapsilosis* was isolated from two patients (29, 38). In keeping with other data, the reported MICs of fluconazole for the *C. krusei* isolates were high (25 to >80 μg/ml) (18, 22, 49, 59, 89), and those for *C. glabrata* were variable (5 to >80 μg/ml) (90). While certainly subject to reporting bias, it is interesting to note that the species-specific frequency of these reports parallels the relative MIC rank order noted above. Following the detection of fungemia, the patients were treated with amphotericin B alone or in combination with flucytosine.

Of the 19 patients who failed to respond to fluconazole when it was given to treat fungemia, 4 were from isolated case reports (1, 24, 69, 77), while 15 were from a recently completed trial of fluconazole versus amphotericin B as therapy for candidemia in nonneutropenic patients (63). The patients in the case reports received doses of from 100 to 400 mg/day, while all the patients in the therapy trial received 400 mg/day. When they were reported, the MICs for the infecting organisms were typical of those for the given species. Of special interest are the patients with *C. albicans* fungemia caused by isolates for which MICs were low (24, 63, 66). While it is difficult to determine precisely the cause(s) of failure, a post hoc analysis of the relationship between catheter exchanges and the duration of candidemia in the therapy trial suggested that failure to perform a complete catheter exchange was strongly associated

with the persistence of candidemia (64). When they were tested, fluconazole MICs for organisms isolated serially from patients with persistent candidemia did not show rises (66).

Other settings in which patients have failed to respond to fluconazole therapy include *C. albicans* colonization with persistent fever (two patients) (80), *C. albicans* sternal osteomyelitis (one patient) (25), vaginal candidiasis caused by *C. glabrata* (two patients) (7, 87), hepatosplenic infection caused by *Candida* species (one patient) (29), urinary tract infection in a mechanically ventilated patient colonized with *C. glabrata* (40), and *C. glabrata* funguria in a patient with hepatorenal failure (86). Because of the limited numbers of cases, it is difficult to make generalizations about the reasons for failure in these cases.

APPROACH TO *CANDIDA* INFECTIONS

It is clear from the above review that, as far as fluconazole resistance is concerned, patients with *Candida* infection fall into two groups: patients with AIDS and oropharyngeal candidiasis and all other patients. Barring the presence of an intrinsically resistant species of *Candida* such as *C. krusei*, failure to correct anatomic factors, lack of compliance, or drug-drug interactions, patients without AIDS and oropharyngeal candidiasis are likely to respond to fluconazole and resistance is unlikely to develop. A broader concern, however, is the possibility that the broad usage of fluconazole may shift the spectrum of nosocomial pathogens at an institution from a pattern of *C. albicans* predominance toward the predominance of less susceptible non-*C. albicans* species. Several reports suggest that this may occur (61, 89, 90), although the true incidence of this phenomenon is unknown.

When an AIDS patient with oropharyngeal or esophageal candidiasis fails to respond to fluconazole, several factors should be considered. First, is the diagnosis correct? As illustrated by Parente and coworkers (57, 58), other causes of esophageal symptoms that should be considered include viral infections (cytomegalovirus or herpes simplex virus) and noninfectious conditions such as peptide esophagitis, Kaposi's sarcoma of the esophagus, peritracheal non-Hodgkin's lymphoma, esophageal stenosis, and idiopathic esophageal ulcers. Compliance with the prescribed regimen should be reviewed, as should possible drug-drug interactions. Of particular note is the interaction of the azoles with rifampin (8, 46); one study in AIDS patients with esophageal candidiasis found that there seemed to be a higher rate of relapse among patients receiving polyantibiotic chemotherapy for tuberculosis of *Mycobacterium avium-Mycobacterium intracellulare* infection (57). To further analyze the cause of failure, serum fluconazole concentrations can be determined by several different methods (36, 65).

If none of the aforementioned factors can be implicated, then the results of repeat cultures should be reviewed to determine whether the patient has acquired a new, resistant species or whether a previously susceptible species has mutated to resistance. In either event, a new course of antifungal therapy is required. What are the therapeutic alternatives? A trial of up to 800 mg of fluconazole per day is certainly warranted. Given the imperfect correlation between MIC results and outcome, this is true even if the patient is found to be carrying an isolate for which the MIC is relatively high. If this therapy fails, ketoconazole or itraconazole could be tried. There have, however, been reports of cross-resistance between the various azoles. In several patients with chronic mucocutaneous candidiasis refractory to ketoconazole, *C. albicans* isolates cross-resistant in vitro to itraconazole, miconazole, fluconazole, econazole, terconazole, and tioconazole were demonstrated (42, 79), and in one case, infection with an isolate clinically resistant to ketoconazole failed to respond to itraconazole (79). Cross-resistance has also been reported in *C. albicans* from HIV-infected patients. One study found that the MICs of itraconazole for fluconazole-resistant isolates were significantly higher than those for fluconazole-susceptible isolates, suggesting that HIV-infected patients with oropharyngeal or esophageal candidiasis who fail to respond to fluconazole may require treatment with higher doses of itraconazole than would otherwise be used (12). In another study of *C. albicans* isolates from the oral cavities of patients at different stages of HIV infection, those isolates from patients with late-stage infection were less susceptible to ketoconazole and were significantly ($P = 0.025$) less susceptible to itraconazole, although none of the patients had ever been treated with the latter drug (44). Despite these observations, these drugs are still worth trying since many cases of candidiasis caused by *C. albicans* that fail to respond to ketoconazole will respond to fluconazole, and those that subsequently fail on fluconazole may respond to itraconazole, as noted in the study by Ruhnke and coworkers (71). If these regimens fail, use of flucytosine could be considered, as could use of a variety of topical agents (nystatin, clotrimazole, amphotericin B). As a last resort, many of the reports reviewed herein have documented responses to intravenous amphotericin B.

It would be preferable to prevent or delay the occurrence of resistance. The two patterns of its development (progressive rise in MIC versus acquisition of a strain or species for which the MIC is high) have epidemiological significance and may be best approached with slightly different strategies. The literature reviewed here clearly shows that most patients who develop clinical resistance to fluconazole have received either prolonged therapy or long-term fluconazole prophylaxis with less than 200 mg/day. Although not always observed during long-term prophylaxis (81), it would appear to be prudent to minimize such use. Optimally, oropharyngeal infections in AIDS patients should be treated with a short course of fluconazole. For patients infected with typical *C. albicans* strains for which MICs are low, it may perhaps be preferable to use larger doses for shorter periods of time in an effort to quickly eradicate the organism and minimize the risk of mutation to resistance. On the other hand, patients already known to be colonized with more resistant strains should always be treated with larger doses of fluconazole, and attention should be paid to the possible need to convert to alternative therapies.

CONCLUSIONS

Concomitant with its widespread use (>15 million patients since 1988 [39]), there have been increasing reports of fluconazole resistance. Interpretation of published reports is sometimes hampered by the omission of such key data as immunologic status, complete information on current and prior antifungal therapy, compliance, and use of other drugs. Despite this, it is clear that resistance is a problem in at least a small number of AIDS patients with oropharyngeal and/or esophageal candidiasis. Resistance may be due to either the acquisition of an inherently resistant species of *Candida* or to the acquisition of resistance in a previously susceptible strain. While there is a perception that this problem is growing in frequency, its true incidence is not known, nor is an optimum strategy for its prevention apparent. Because such a pattern of development of resistance has also been seen with ketoconazole, it would appear likely that resistance to any azole used extensively in a similar setting could develop. In other forms of candidiasis, failure of fluconazole more often appears because

of the use of low drug doses or host factors. The development of resistance during short-term use of fluconazole does not appear to be a problem, although on an institutional level the widespread use of fluconazole may shift the range of infecting species toward more resistant species.

These reports should, however, be taken in context. The majority of patients with *Candida* infections, including AIDS patients with oropharyngeal candidiasis, do now and will likely continue in the future to respond at least initially to fluconazole treatment. Future work should be directed toward determining the prevalence of this problem and developing strategies for its prevention.

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