Difficult-to-manage mucosal candidal infection has been a hallmark of individuals with advanced infection due to human immunodeficiency virus type 1. In this AIDS Commentary, Drs. Fichtenbaum and Powderly comprehensively review the literature and their experience with refractory candidiasis in such patients. Of interest is their delineation of resistance, a lack of susceptibility to an antifungal agent in vitro among patients with refractory or clinically unresponsive disease. These authors believe that the establishment of resistance should be based upon standards established by the National Committee on Clinical Laboratory Standards, which they propose to define as a failure to respond to systematic therapy with specific doses of itraconazole, fluconazole, or parenterally or orally administered amphotericin B within 14 days. There have been many definitions of “refractory candidiasis,” and one proposed by these authors will be debated; however, this definition has the advantage of establishing a standard by which to judge the efficacy of their proposed algorithm for the treatment of persistent or refractory oropharyngeal candidal infections. Drs. Fichtenbaum and Powderly have performed a useful service in their attempt to bring coherence to the management of this common and often vexing problem.

—John P. Phair

Mucosal candidiasis is a common problem, and oropharyngeal candidiasis (OPC) was among the initial manifestations recognized in association with HIV infection [1,2]. Since these initial reports of OPC, this relatively easily manageable disease has become increasingly difficult to treat in some patient populations.

Refractory candidiasis has emerged as an important opportunistic illness affecting patients with advanced HIV disease [3–21]. The morbidity associated with refractory mucosal disease can be clinically significant. Progression to esophagitis and interference with adequate nutritional intake, weight loss, and inability to swallow oral medications may occur [22].

Most of the reported therapeutic failures have occurred in patients who were treated with fluconazole. Fluconazole has been the focus of these reports for several reasons. It is a first-line agent for the treatment of OPC as well as esophageal and vaginal candidiasis. Fluconazole is predictably absorbed, well tolerated, and safe. Mucosal disease that is unresponsive to topical therapy or to ketoconazole usually responds to fluconazole. Fluconazole was the first triazole approved for use in the United States and is perhaps the most commonly used agent for the treatment of mucosal candidiasis. Finally, refractory OPC is difficult to treat and often requires the use of intravenous amphotericin B which is inconvenient, expensive, and toxic.

Refractory mucosal candidiasis is a relatively new problem. The incidence of azole failures, in particular fluconazole failures, has not been well defined. There is no standard, accepted definition of a clinical failure. In addition, the mechanisms for refractory disease and resistance are incompletely understood. Furthermore, the optimal treatment for fluconazole-refractory disease is not known. Finally, there is very little information on how to prevent the development of refractory disease and the emergence of resistance. Over the past 2 years, several new drugs have become available for the treatment of fluconazole-refractory disease, new mechanisms of fungal resistance have been described, and several studies have further defined the epidemiology of clinical disease. Thus, it is important to review our current understanding of refractory mucosal candidiasis and define what we still need to learn to prevent and treat this problem.

Definitions of Resistance and Refractory Disease

Resistant mucosal candidiasis has a variety of meanings. Resistance often implies the recovery of an organism with
decreased in vitro susceptibility to a particular antimicrobial agent. Resistance has also been used to indicate clinical failure of therapy. This terminology is confusing. The term resistance should be reserved to indicate a lack of in vitro susceptibility. Clinical failure, refractory disease, or clinically unresponsive disease are the terms that should be used to indicate episodes of mucosal candidiasis that failed to respond to treatment.

Recently, a working group for the National Committee on Clinical Laboratory Standards (NCCLS) proposed definitions of in vitro susceptibilities for selected antifungal agents on the basis of standard methodologies (table 1) [23]. This group studied a large number of isolates and compared the findings with clinical outcomes. Despite encouraging results of this work, there are still patients infected with organisms that are “resistant” in vitro and that respond to standard therapy. Furthermore, some patients fail to respond to therapy despite having a relatively “sensitive” organism isolated. Thus, although there are now standard definitions for what constitutes in vitro resistance there is still further work to be done in this area.

The definition of clinical failure has varied within the published literature; a consensus definition has not emerged. The important components of a definition of clinical failure should include the organism responsible for the infection, the type of medication used, and the dose and the duration of therapy. One alternative is to define clinical failures as the persistence or progression of disease despite the use of maximally tolerated doses of a particular medication for a duration normally expected to provide a cure (e.g., patients who could tolerate 1,000–2,000 mg of fluconazole daily for 2 weeks but have persistent OPC). However, this definition is inherently imprecise. Some patients can tolerate very high doses of certain medications, whereas others are intolerant of standard doses. It is nearly impossible to predict prospectively the dose beyond which higher doses of a medication would be unlikely to produce a clinical response in a particular patient without subjecting that individual to repeated trials of escalating doses of medications. The definition of refractory disease requires empirical data for each medication and organism. These data are lacking. Thus, it has been difficult to determine what constitutes a true clinical therapeutic failure.

The medical literature contains a variety of definitions for clinical failures. Garcia-Hermoso and colleagues [24] reported clinical failures in patients with OPC who were receiving as little as 50 mg of fluconazole daily for 7 days. Maenza and colleagues [8] characterized failures after using fluconazole dose levels of between 100 mg/d and 200 mg/d for 1 week. In a large natural history study of patients with advanced HIV infection, the definition of fluconazole-refractory disease required the use of 200 mg of fluconazole for a minimum of 14 days [25]. This absence of consensus has made it difficult to compare studies and develop a common approach to the treatment of refractory mucosal candidiasis.

We have developed a set of guidelines for defining refractory infections (table 2). These guidelines are based on the premise that the failure to respond to treatment with standard doses of medications should be viewed as refractory disease. Although these definitions may seem somewhat arbitrary, they provide an important starting point for developing a consensus on this issue, which is essential for comparing future studies of refractory disease and for reducing the time that patients are exposed to ineffective treatment regimens. Topical therapy with nystatin or clotrimazole and oral therapy with ketoconazole are omitted from table 2 because clinical failures are more common with these agents, and patients often respond to treatment with either fluconazole or itraconazole. Finally, distinctions should be made between patients who fail to respond to one vs. multiple antifungal regimens (e.g., lack of response to itraconazole vs. all azoles).

Clinical failures must also be distinguished from true drug-resistant disease. Clinical failures can result from a number of causes. A major problem for patients with HIV infection is the improper use of prescribed medications. Clinical failures may also result from inadequate absorption of an antifungal medication. This is particularly important in patients with advanced HIV infection who have hypochlorhydria or achlorhydria, which may affect the absorption of ketoconazole or itraconazole [26–27]. Drug interactions may also result in decreased levels of antifungal medications (e.g., use of the rifamycins lowers levels of itraconazole) [28]. There are some patients

### Table 1. Definition of in vitro resistance for Candida species.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Range of MICs (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>≤0.125</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>≤8.0</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>≤1.0</td>
</tr>
</tbody>
</table>

**NOTE.** Data are from [23].

### Table 2. Proposed definitions for clinical drug failure in patients with mucosal candidiasis.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Probable</th>
<th>Definite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole, 200 mg po b.i.d. (tablets or solution)</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Fluconazole, 200 mg po or iv daily</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Amphotericin B oral solution, 500 mg po q.i.d.*</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>iv Amphotericin B, 1 mg/(kg · d)</td>
<td>7</td>
<td>14</td>
</tr>
</tbody>
</table>

**NOTE.** These data refer to progressive disease or lack of improvement after a defined period of therapy or lack of complete resolution of the signs and symptoms of mucosal candidiasis after completion of therapy; failures with lower doses of any of the above-listed medications should be considered “possible failures.”

* Applicable to patients with oropharyngeal or esophageal candidiasis.

† Duration of treatment in days.
who do not respond to therapy despite the fact that susceptible organisms are recovered. In the absence of noncompliance, absorption, or drug distribution problems, there may be host factors that explain some clinical failures. Thus, it is important to distinguish true in vitro drug resistance from clinical failures due to host factors, medication delivery, absorption, or metabolism problems.

The Incidence and Prevalence of Resistant and Refractory Disease

Mucosal candidiasis is very common in HIV-infected patients. The incidence of this fungal infection increases as the CD4⁺ lymphocyte count decreases [29]. More than 60% of patients with CD4⁺ lymphocyte counts of <100/mm³ will develop OPC each year [29–36]. Recurrent disease occurs in more than one-half of these patients [34–36]. Esophageal candidiasis affects 10%–20% of patients with AIDS [37]. The incidence of vaginal candidiasis is less well studied. In several studies, vaginal candidiasis was noted in 30%–60% of patients, rates similar to those for OPC [38–39]. In a recent study of fluconazole prophylaxis for mucosal candidiasis, the incidence of vaginal candidiasis was 27% in the placebo group, with a median duration of follow-up of 29 months [40].

All of these studies were conducted before the introduction of highly active antiretroviral therapy. It is likely that the incidence of mucosal candidiasis will decline as more patients receive this antiretroviral therapy.

There have been several retrospective studies of the incidence of fluconazole-refractory OPC in clinic cohorts. Quereda et al. [20] reported a failure rate of 14% for fluconazole in a cohort of 50 patients followed up prospectively in Spain. Others have reported a fluconazole-failure incidence of 6%–7% among HIV-infected patients with OPC [4–5]. Bailey and colleagues [3] reviewed the records of 155 HIV-infected patients with CD4⁺ lymphocyte counts of <300/mm³ and reported an incidence of fluconazole failures (with a dosage of ≥100 mg/d for 10 days) of 5.8%. Many of these retrospective studies were performed on relatively small numbers of patients at single centers. Because of the regional differences in azole-use patterns, the variations in the level of immunosuppression of the populations under study, and the inherent statistical biases in these small retrospective reports, the incidence of fluconazole-refractory disease was not clear.

The published prospective information on the incidence of refractory OPC is limited. We recently reported preliminary results from ACTG (AIDS Clinical Trials Group) 816, a prospective, multicenter observational study of resistant mucosal candidiasis in patients with advanced HIV infection [25]. In that study of 846 patients with advanced HIV disease, the annual incidence of fluconazole-refractory OPC was 4%. A similar rate of fluconazole-refractory OPC was also recently reported in a large multicenter study of fluconazole prophylaxis for vaginal candidiasis in women. In that study the incidence of clinical fluconazole failures was also 4% [40]. Thus, although initial retrospective reports suggested that the incidence of clinical failures of fluconazole might be substantially higher, the incidence is in fact probably no more than 5%, with the majority of those cases occurring in patients with advanced HIV disease.

There are several important caveats to consider in interpreting data on the incidence of refractory mucosal candidiasis. First, there are limited data on the incidence of non-fluconazole-associated drug failures. Second, the major focus of the published studies has been on refractory OPC, and there are limited data on esophageal or vaginal disease. The rate of fluconazole-refractory vaginal disease appears to be very low, and there have been only scattered reports of fluconazole-refractory vaginal candidiasis [41]. Finally, it is again important to note that all of these studies were completed before the widespread use of highly active antiretroviral therapy. Findings from informal surveys of various clinical centers suggest that the incidence of refractory mucosal candidiasis may well be declining. This decline is supported by recent evidence of slow enrollment in trials of new therapies for refractory OPC.

The rates of in vitro resistance to antifungal medications have been studied more widely [17, 20–21, 42–52]. The incidence and prevalence of resistance varies widely in these studies. Overall, the rates of fluconazole resistance vary from 5% to 56% [17, 20–21, 42–45]. The rates of ketoconazole and itraconazole resistance have been reported less frequently, but they vary from 0 to 25% [6, 46–50]. Amphotericin B resistance has been reported but is extremely uncommon [48].

Much of the variance in the rates of in vitro resistance to antifungal agents can be explained by several factors, including differences in the level of host immunosuppression and exposure to antifungal agents, differences in the type of study (longitudinal vs. cross-sectional), differences in the prevalence of non-albicans species of Candida, and differences in the in vitro methods used to define resistance. For example, Chavanet et al. [51] conducted a cross-sectional study of 154 patients with HIV infection. Fluconazole resistance was present in 13.8% of the C. albicans isolates, five of six C. glabrata isolates, one of five C. tropicalis isolates, and all three C. krusei isolates. No resistance to ketoconazole, miconazole, or econazole was detected. Chavanet et al. used a microtiter broth dilution method and reported the results as an MIC₅₀ of each drug. The mean CD4⁺ lymphocyte counts were well above 100/mm³. In contrast, Korting and colleagues [42] studied 84 patients by using an MIC₅₀ and found much lower rates of resistance to fluconazole, ketoconazole, and itraconazole in <10% of 62 isolates. The CD4⁺ lymphocyte counts were not reported in that study, and nearly two-thirds of the patients had asymptomatic HIV infection or generalized lymphadenopathy.

In another study, St. Germain and colleagues [49] studied 250 isolates from 93 patients with HIV infection treated in a randomized trial of ketoconazole vs. itraconazole. These investigators used a modified microtiter method for measuring sus-
The MIC₉₀ of itraconazole was >0.25 mg/L for three of 43 patients treated with itraconazole and >0.25 mg/L for one of 59 patients treated with ketoconazole. All of these cross-sectional studies showed very different rates of resistance.

There have been some longitudinal studies conducted, most of which included patients who were exposed to fluconazole. For example, Sangeorozan et al. [52] observed 92 patients randomized to clotrimazole vs. fluconazole for the treatment of OPC. Sixty percent of these patients had CD4⁺ lymphocyte counts of ≥200/mm³. Over the course of 1 year, 35 of these patients were evaluated for fluconazole MICs, and there was a change for those who received fluconazole prophylaxis (i.e., the MIC₉₀ increased from 0.5 µg/mL to 8 µg/mL).

In summary, resistance is associated with greater immunosuppression and more frequent exposure to antifungal agents. However, because of the methodological differences in survey studies, it is impossible to draw meaningful conclusions about the true prevalence or incidence of in vitro resistance.

**Risk Factors for Refractory and Resistant Candidiasis**

Refractory candidiasis is almost always seen in patients with very advanced AIDS. Factors associated with refractory disease can be divided into those related to the host, the organism, or the environment. It is likely that a combination of these factors is required for the development of refractory disease.

Host-related factors are important in the pathogenesis of OPC. The level of immunosuppression is paramount. In general, the incidence of OPC among HIV-infected individuals without advanced immunodeficiency varies between 7% and 48% [53–55]. Up to 92% of patients with progressive immunodeficiency will develop OPC [56]. The vast majority of fluconazole treatment failures have occurred in persons with very advanced HIV disease [3–12]. Few cases of fluconazole treatment failures have been reported among persons with CD4⁺ lymphocyte counts of >50/mm³. In addition, a history of prior opportunistic illnesses such as Mycobacterium avium complex (MAC) disease and toxoplasmosis have been associated with the occurrence of fluconazole treatment failures [44]. Although this association may simply represent a nonspecific measure of generalized, severe immunodeficiency, it is possible that some individuals may have specific defects that make them more susceptible to a variety of pathogens.

The relationship between the level of immunosuppression and vaginal candidiasis may not be as strong. In one cross-sectional study of 833 HIV-infected women and 427 non-HIV-infected women, the incidence of vaginal candidiasis was similar (9%) in both groups [57].

In addition to deficient cell-mediated immunity, there are other host-related factors that may contribute to the occurrence of OPC, including diminished salivary flow rates, cigarette smoking, blood-group secretor status, and the antimycotic constituents of saliva [31–33, 56, 58]. There is conflicting evidence as to whether neutrophil or macrophage killing of yeasts are impaired in persons with HIV infection [59, 60]. Local cytokines may also play a role in host defense and susceptibility.

Whether any of these factors predispose to refractory candidiasis has not been investigated.

The relationship between organism-specific factors and the development of resistance and refractory disease is not entirely clear. Refractory disease is almost always associated with in vitro resistance; however, in vitro resistance is not associated invariably with refractory disease. Two patterns have been observed. First, resistance may emerge within the same strain of a colonizing organism over time [61]. Alternatively, a different species or strain of Candida may colonize some patients with AIDS [62]. The latter trend has also been described for neutropenic patients [63]. C. albicans is the most common species associated with mucosal disease and is also the leading organism associated with fluconazole treatment failures. Candida parapsilosis, C. tropicalis, C. krusei, and C. glabrata have been implicated in mucosal infections and refractory disease, although at much lower rates than C. albicans.

Colonization with Candida species is an important predisposing event for the occurrence of mucosal disease. Colonization with Candida species occurs in up to one-third of healthy hosts [64]. Colonization occurs in two-thirds of patients with advanced HIV infection [44]. Colonization with a resistant organism may occur weeks to months before the development of refractory disease [44]. However, it is not always clear that organisms cultured from an asymptomatic individual are responsible for disease that occurs at a later date.

The individual Candida strains that affect patients with HIV infection do not appear to be different from those that affect other immunosuppressed hosts, and each patient appears to be infected with a unique, individual strain [65]. Furthermore, there are no detectable differences in the virulence of strains isolated from HIV-infected and non-HIV-infected persons. There is little information available on the virulence properties among strains that cause refractory disease and those that do not. It is curious that some animal models of mucosal candidiasis have demonstrated that organisms associated with refractory disease appear to be less virulent (P. Fidel, personal communication).

There are several mechanisms that explain in vitro resistance to antifungals, including target alteration, reduced cell permeability, and active efflux of the drug from the cell. Some yeasts are resistant to a single drug, whereas others are multidrug resistant. Azole resistance has been demonstrated in yeasts that contain enzymes that were the target of the drug’s action or that were involved in ergosterol biosynthesis. The cytochrome P-450-dependent 14c-sterol demethylase (P-450(baz)) and the Δ₅,₆-sterol desaturase are two enzymes that, when altered, result in azole resistance [66, 67]. Reduced cell permeability is another mechanism of azole resistance. For example, two strains of C. albicans that are impermeable to the triazole ICI 153066 have been isolated in cases of treatment failure [68]. These two strains are also resistant to ketoconazole. They differ from the susceptible
permeable strains in having reduced cellular phospholipid/sterol ratios. Finally, active efflux of drug is another mechanism that explains resistance. Crombie and colleagues [69] reported an energy-dependent mechanism for fluconazole resistance in a strain of C. glabrata.

The prevalence of these resistance mechanisms is unknown. Further, it is not clear whether certain mechanisms of resistance may be overcome by higher dosing of the drug. This is likely, since some patients exhibit only partial clinical responses to lower doses but respond to treatment with higher doses of a given agent. In summary, resistance is a complex event with multiple mechanisms. It may well be that several alterations are required to confer azole resistance [70]. Evaluation of isolates before and after the development of resistance will be useful in determining critical events that lead to refractory disease.

The single most important environmental factor in the development of resistance is the exposure to antifungal medications over time. Maenza et al. [8] reported a longer median duration of exposure to antifungal therapy (419 days vs. 118 days; \( P < .001 \)) and of systemic azole therapy (272 days vs. 14 days; \( P < .001 \)) among patients with fluconazole-refractory OPC than among matched controls. In addition, these investigators documented that lower median CD4⁺ lymphocyte counts and a history of more-frequent treated episodes of OPC were also associated with the development of fluconazole-refractory OPC. It is not clear whether the total dose, duration, or the pattern of antifungal use is the most important determinant of the development of resistance.

One important hypothesis worth testing is whether continuous or episodic exposure to azoles is more likely to lead to the emergence of resistant strains. This hypothesis is being studied in an ongoing prospective trial conducted by the ACTG and the Mycoses Study Group (MSG; ACTG 323/MSG 40). There are some data suggesting that resistance is more common with episodic treatment. Heald and colleagues [71] reported that the intermittent use of fluconazole was more frequently associated with the emergence of more-resistant C. albicans and non-albicans species among persons with HIV infection. Finally, the use of trimethoprim-sulfamethoxazole, antiretroviral agents, or macrolide antibiotics does not appear to be associated with the development of fluconazole-refractory disease [25].

There have been intriguing reports of person-to-person transmission of resistant organisms leading to the development of refractory disease. Barchiesi et al. [72] reported transmission of a genetically related fluconazole-resistant strain in a married couple. Proof of this transmission hypothesis is hampered by the fact that it is difficult to exclude the possibility that the organism was acquired from an unidentified other common source. The frequency of this phenomenon is unknown; if it is confirmed and shown to be a common event, it may have important implications for preventing the development of refractory disease.

Clinical Manifestations and Diagnosis

The clinical manifestations of refractory candidiasis are similar to those of responsive disease. The distinction between responsive or refractory disease cannot be made on the basis of clinical findings alone. Symptoms of OPC include burning pain, altered taste, and difficulty swallowing liquids and solids. Many patients are relatively asymptomatic, even in cases of extensive refractory disease. Refractory OPC typically presents as pseudomembranous disease characterized by the occurrence of painless white or tan plaques on the tongue, gums, buccal membranes, or throat. The plaques are composed of necrotic material, desquamated parakeratotic epithelia, hyphae, and yeast cells that do not penetrate beyond the stratum spinosum.

Esophageal candidiasis is usually accompanied by OPC. Dysphagia and odynophagia are typically described. In as many as 40% of patients with OPC, esophageal involvement may be asymptomatic [73]. Occasionally, esophageal disease may present in the absence of clinically detectable oropharyngeal disease. The onset of dysphagia in a patient with OPC is suggestive of esophageal involvement.

The diagnosis of refractory disease is made when persistent or progressive disease is observed after adequate treatment with an antifungal agent. In patients with candidiasis, cultures may be helpful in detecting pathogens with intrinsically higher resistance to specific antifungal agents. However, the diagnosis of refractory disease should not be made on the basis of recovery of a resistant organism. For patients with refractory disease, clinicians should always consider alternative diagnoses such as herpes simplex, aphthous ulcers, oral hairy leukoplakia, and histoplasmosis.

Treatment

Treatment of mucosal candidiasis is relatively simple, since most types of disease respond to topical or systemic therapy. Conversely, refractory candidiasis is often difficult to treat and may become increasingly less responsive to therapy over time. The most important step is to determine what medications have been tried, what dosages have been used, and whether the patient was taking the prescribed therapy appropriately. On rare occasions, patients taking medications that affect the metabolism of some antifungal agents, such as rifampin, may present with clinically unresponsive disease [74]. Removal of the interacting medication or an increase in the dose of the antifungal agent may clear the infection.

In general, if a patient with oral candidiasis has failed to respond to therapy with clotrimazole, nystatin, ketoconazole, or itraconazole tablets, most clinicians will use fluconazole (100–200 mg daily for 7–14 days). Patients who are unresponsive to fluconazole at a dose of 200 mg daily, given for 2 weeks, are unlikely to respond to higher doses; however, there have been some reports of successful treatment using higher doses of fluconazole (400–800 mg) in patients who have not responded to standard doses [75].

There are a number of options for the treatment of fluconazole-refractory disease (table 3). There have been few controlled studies of these approaches and no comparative studies.
Table 3. Therapeutic options for fluconazole-refractory mucosal candidiasis.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Clotrimazole troches</td>
<td>100–500 mg 4–5 times daily</td>
</tr>
<tr>
<td>Gentian violet</td>
<td>Apply to oropharynx once</td>
</tr>
<tr>
<td></td>
<td>(may repeat weekly as needed)</td>
</tr>
<tr>
<td>Amphotericin B oral solution*</td>
<td>100 mg/mL, 5 mL po q.i.d.</td>
</tr>
<tr>
<td><strong>Systemic therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Fluconazole tablets</td>
<td>400–800 mg po q.d. or b.i.d.</td>
</tr>
<tr>
<td>(with or without flucytosine)</td>
<td>100–150 mg/(kg·d) po q.i.d.</td>
</tr>
<tr>
<td>Itraconazole solution*</td>
<td>40 mg/mL, 2.5–5 mL po b.i.d.</td>
</tr>
<tr>
<td>Parenteral amphotericin B</td>
<td>0.5–1.0 mg/(kg·d) iv q.d.</td>
</tr>
<tr>
<td><strong>Adjunctive therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Highly active antiretroviral therapy*</td>
<td>Two nucleoside RT inhibitors + one nonnucleoside RT inhibitor</td>
</tr>
<tr>
<td>GM-CSF†</td>
<td>300 µg sc 3–5 times weekly</td>
</tr>
</tbody>
</table>

NOTE. GM-CSF = granulocyte-macrophage colony-stimulating factor; RT = reverse transcriptase.
* Controlled study supports use of this treatment for fluconazole-refractory candidiasis [81, 84].
† May also use two nucleoside RT inhibitors plus one nonnucleoside RT inhibitor.
‡ Investigational.

Parenteral amphotericin B remains the drug of choice for patients with severe disease or esophageal involvement. Typically, patients respond to doses of 0.3–0.5 mg/(kg·d). The duration of treatment is based on the response, but 7–10 days for OPC or vaginal disease and ≤21 days for esophageal disease are typically required. Some patients may require as much as 1 mg/(kg·d) of parenteral amphotericin B for a response. There are few data on the use of liposomal preparations of amphotericin B for refractory mucosal candidiasis.

Recently, oral itraconazole solution and oral amphotericin B solution have become available for the treatment of patients with refractory OPC. Amphotericin B oral suspension is an attractive candidate for treatment of fluconazole-resistant candidiasis because resistance to amphotericin B is uncommon [76–78]. Amphotericin B oral suspension was approved by the U.S. Food and Drug Administration in the 1960s for the treatment of OPC; however, there is little published experience with oral amphotericin B for the treatment of fluconazole-resistant thrush. Two small studies have demonstrated some success with relatively low doses of oral amphotericin B [79–80]. In the first study, Dewsnup and Stevens [79] reported the successful treatment of four patients with an extemporaneous preparation of amphotericin B (1 mg in 5 mL of diluent four times daily). In the second study, five patients received 5 mL of a 0.2–1.0 mg/mL solution of amphotericin B five times daily [80]. All patients had an initial, although incomplete, response and relapsed within 1–3 months. The ACTG recently completed an open-label trial of oral amphotericin B solution for patients with OPC that is refractory to fluconazole therapy. In that study, amphotericin B solution was given in doses of 500 mg, four times daily (5 mL, swish and swallow). The response rate was 44%, and the solution was reasonably well tolerated [81].

Itraconazole capsules are generally ineffective. However, there has been greater success with the cyclodextrin solution formulation of itraconazole. This formulation achieves approximately twice the blood levels of equivalent doses of itraconazole capsules and may also have topical activity. Itraconazole solution has been reported to be effective in several trials in patients with fluconazole-refractory OPC [82–85]. Cartledge et al. [82] reported their experience using itraconazole cyclodextrin solution in 27 patients who failed to respond to azole therapy, including 16 patients who did not respond to fluconazole, ketoconazole, or itraconazole tablets. The median CD4 lymphocyte count was 12/µL³, and 13 patients had esophageal disease. Seventy-two percent (18 of 25 evaluable patients) had clinical responses. The median relapse-free time was 93 days for those who continued to receive 400 mg/d, compared with 52.5 days for those who took 200 mg/d. The criteria for azole failure and the response criteria were not specified in that study.

Phillips et al. [83] evaluated the efficacy of itraconazole cyclodextrin solution in 36 patients with fluconazole-refractory candidiasis. Patients in whom treatment failed were defined as those unresponsive to 10 days of therapy with ≥100 mg of fluconazole daily. Response was considered partial or complete by using a scoring system that included visible lesions, subjective symptoms, and the absence of adverse events. The total clinical response rate was 65% (22 of 34 evaluable cases), with 24% of patients demonstrating a complete response. Two patients were unevaluable because they were receiving concomitant antifungal therapy, and two patients discontinued therapy because of nausea and vomiting.

Fessel and colleagues [84] reported the efficacy of itraconazole solution in 78 patients with fluconazole-refractory OPC. Patients were treated with 100 mg twice daily for ≤28 days. A complete clinical response was observed in 59% (40 of 68 evaluable cases). Improvement was noted in an additional 10 cases. Mycological response was achieved in 27% (17 of 62 evaluable cases). All 22 patients who were followed up relapsed a median of 13 days after the cessation of therapy. In the follow-up study of the complete responders (25 of 40 potential subjects enrolled), Moskovitz et al. [85] reported a 52% relapse rate among patients receiving itraconazole solution three times weekly. Ten patients eventually stopped receiving therapy because of adverse events, although only one patient’s adverse event was attributable to itraconazole.

Overall, the response rate for fluconazole-refractory OPC to itraconazole solution is somewhere between 50% and 60%, and may be slightly lower for oral amphotericin B solution. Although the response rate with amphotericin B is generally lower than that reported with itraconazole solution, this finding may well be explained by differences in study design including the response criteria, which was stricter in one trial of amphotericin B oral solution.
Other anecdotal approaches to fluconazole treatment failures have included the use of very-high-dose fluconazole, with or without 5-fluorocytosine. Gentian violet has occasionally been used successfully in difficult-to-treat patients. Some clinicians have opted to use a variety of topical agents along with systemic therapy. Improving the immunologic function of a patient may help in the treatment of clinically unresponsive disease. Indeed, treatment with protease inhibitors has been noted to result in clinical improvement in hard-to-treat cases [86]. We have used protease inhibitors to treat several patients with refractory candidiasis, with mixed results. Typically, patients may respond initially; however, in our experience, relapse is common. Granulocyte-macrophage colony-stimulating factor may also be of some value and is being assessed in an ongoing phase II trial. Finally, newer antifungal agents, including other triazoles and the Echinocandins, may be active against refractory candidiasis; however, there is little clinical experience with these agents.

Despite the efficacy of initial treatment, relapse rates are high among patients with refractory disease [84]. Patients universally require maintenance therapy to prevent recurrences. Itraconazole solution or amphotericin B oral solution may be quite useful in the prevention of recurrences. It is not clear what dose should be given, although some dose reduction may be possible. However, we suggest caution in reducing the dose and dosing interval. Suboptimal dosing of antifungal agents may preselect the more resistant strains to emerge more rapidly, thus leading to clinical failures of the drug despite escalating doses. If parenteral amphotericin B is required for maintenance suppression, clinicians will often treat episodes of refractory disease intermittently because of the inconvenience, risk, and expense of continuous parenteral therapy. Once or twice weekly suppressive doses of the drug may be effective.

Clinical failures with parenteral amphotericin B have been reported [87]. The therapeutic options in such cases are limited. The addition of another agent or the administration of adjunctive immunotherapy are the most common approaches.

In conclusion, the optimal approach to fluconazole-refractory disease is not known. It is unlikely that comparative studies of different strategies will be performed because there are not enough patients with this disease for conclusive statistical analysis. We have developed a standardized approach for the treatment of patients who present with refractory disease (figure 1). However, it is likely that such patients will require treatment with multiple medications to control their refractory disease.

**Prevention of Fluconazole-Refractory Disease**

Refractory and resistant candidiasis tends to occur in patients with advanced HIV disease who have been exposed to antifungal therapy on a chronic basis. Thus, the two most important principles in avoiding refractory disease are to delay or reverse the onset of immunosuppression and to eliminate unnecessary exposure to antifungal therapy.

Control of HIV replication and reversal of AIDS-associated immunodeficiency may decrease the occurrence of refractory disease. Indeed, several studies of highly active antiretroviral therapy have demonstrated a reduction in the number of opportunistic illnesses; however, there are few available data on the incidence of refractory candidiasis. Anecdotally, it has been difficult to enroll patients in trials of therapeutic agents for the treatment of refractory candidiasis, suggesting that the use of highly active antiretroviral therapy has altered the incidence of this disease. The institution of highly active antiretroviral therapy, with suppression of HIV replication, is probably the single most important method for prevention of refractory candidiasis.

Although mucosal candidiasis is common, antifungal prophylaxis is typically not indicated in most patients with HIV infection. Indeed, one study of the use of fluconazole to prevent fungal infections did not demonstrate prolongation of survival among patients with advanced HIV disease [88]. Continuous use of antifungal agents should be reserved for patients with frequent or severe recurrences of mucosal candidiasis or for those who have systemic mycoses requiring maintenance suppressive therapy. For patients with occasional disease or infrequent recurrences of OPC or vaginal candidiasis (fewer than three episodes per year), we tend to treat each episode separately.
It is not known whether the intermittent or continuous use of fluconazole predisposes patients to refractory disease. This hypothesis is currently being tested in ACTG 323/MSG 40. It is premature to make recommendations on avoiding person-to-person contact to prevent the transmission of resistant isolates, because very little is known about how often this occurs or whether it is a real phenomenon. In conclusion, the judicious use of antifungal therapy and the optimization of antiretroviral therapy are the most important measures for preventing the development of refractory candidiasis.

Summary

Refractory oropharyngeal and esophageal candidiasis have emerged as important infections in patients with very advanced HIV infection. The incidence of fluconazole-refractory oral candidiasis is probably no more than 5% per year among patients with very advanced disease. The incidence has probably decreased further with the use of more-effective antiretroviral strategies. Refractory vulvovaginal candidiasis is very uncommon. The clinical factors associated with the occurrence of fluconazole-refractory candidiasis include prolonged exposure to fluconazole and severe immunosuppression.

Treatment of fluconazole-refractory cases is problematic; response rates are <70% for most medications. Maintenance therapy is usually required for refractory cases. The use of highly active antiretroviral therapy may decrease the incidence of this problem; however, the durability of these strategies is not known, and the tolerability of combination antiretrovirals in patients with advanced HIV disease is by no means universal. Thus, patients and clinicians are likely to be faced with the problem of refractory candidiasis in the foreseeable future.

Completed and ongoing studies to be published in the future should be conducted on the natural history of resistant candidiasis, treatment trials with oral amphotericin B solution and itraconazole solution, and a prevention trial involving two different strategies for fluconazole use (continuous versus episodic treatment) should provide additional data on the optimal approach to the treatment and prevention of refractory candidiasis.

References


