We developed and compared five scoring systems designed to quantitate therapeutic response in cases of oropharyngeal candidiasis. We utilized prospectively collected data on 114 patients treated with several doses of the azole D0870. Patients were infected with fluconazole-susceptible (n = 49) or -resistant organisms (MIC, ≥16 mg/mL; n = 61). Patients with fluconazole resistance had lower CD4+ cell counts at baseline; more symptoms (P = .0006); a higher frequency of dysgeusia (P = .004), dysphagia (P = .006), and throat pain (P = .0034); and greater oral coverage by plaques of Candida. There was no difference between the two groups in terms of colony-forming units, and any change did not correlate with response to therapy. Resolution of dysphagia (P < .01) and oral pain (P < .01) correlated well with response to therapy, unlike retrosternal pain and throat pain, which were also less frequent. Xerostomia, a “furry” taste, and dysgeusia were frequent nonspecific symptoms. Scoring system C, weighting resolution of a symptom higher than absence of a symptom at baseline, yielded the best correlation with global outcome (r = 0.86) and allows the quantitation of incomplete but clinically beneficial responses to therapy.

Episodes of oropharyngeal candidiasis (OPC) are almost universal occurrences for patients with AIDS [1, 2]. Esophageal candidiasis is the AIDS-defining event in 13% of patients, and 22% develop it during the course of AIDS [3]. OPC and esophageal candidiasis tend to be chronic, relapsing, and increasingly symptomatic, with progressive immune paresis. OPC in HIV-infected patients usually responds to oral imidazole therapy [4]. However, at later stages of disease, episodes become more frequent and often refractory to treatment with these agents [1]. The widespread use of fluconazole, itraconazole, and ketoconazole has led to the emergence of resistant isolates of Candida albicans [5, 6], especially in the context of HIV infection [1, 7–9]. The ongoing development of new agents is necessary to increase the therapeutic options; the main therapy currently available is with intravenous amphotericin B, which has attendant problems of toxic effects, particularly renal impairment.

Previously, the clinical assessment of OPC in therapeutic trials has received little attention. In AIDS patients with the pseudomembranous forms of OPC, disappearance of visible lesions, with some diminishment of symptoms, has been taken as sufficient evidence of a therapeutic response. However, several problems have hampered the interpretation of clinical trials. First, there are often diverse oral symptoms, some of which may not be attributable to OPC. For example, there is overlap with other HIV-associated conditions such as gingivitis and side effects of antiretroviral drugs (such as dry mouth with use of didanosine), so the lack of a symptomatic response may not be a reliable indicator of persistence of OPC.

Similarly, signs may be diverse. Pseudomembranous candidiasis is the classic form, but OPC may also present as an atrophic form with ulcers, as well as angular cheilitis, with localized disease at the corners of the mouth, and as an erythematous form with localized discomfort and erythema [10]. Assessment of response in patients with extensive oral hairy leukoplaikia may be imprecise. Individual clinicians are likely to be inconsistent in their assessment of extent of disease. In addition, the symptoms of esophageal candidiasis may be mimicked by a number of other pathologies, such as cytophagalovirus or herpes simplex virus esophageal infection, in the presence or absence of OPC. This can make accurate diagnosis and assessment of therapeutic response with regard to esophageal symptoms particularly problematic, unless patients undergo endoscopic examination [11].

In patients with early AIDS or AIDS-related complex, response to treatment can usually be simply evaluated by inspection of the oral mucosa for the presence or absence of the plaques of pseudomembranous thrush. However, in those with OPC due to azole-resistant Candida, partial resolution is common, and degrees of improvement vary substantially. In addition, immediate relapse on discontinuation of therapy is common [12], in contrast to the situation with OPC caused by fully
susceptible organisms. Although clearly not a full response or cure with therapy, symptomatic improvement is of benefit to patients. However, in order to compare one therapy with another, some objectivity is required in the assessment of response, especially in the evaluation of novel antifungal agents. From the clinician’s standpoint, it would be helpful to understand more about the utility of certain symptomatic responses in predicting a mycologic resolution and, conversely, whether certain symptoms and clinical findings at the start of therapy could reliably predict the presence of a resistant strain, with a correspondingly high MIC value for the isolate.

D0870 is a bis-triazole agent with good in vitro activity against C. albicans and other Candida species [13–15]. Early clinical trial results are encouraging [16, 17]. We had the opportunity to examine the therapeutic response data from all these trials of D0870 for OPC to find the optimal means of assessing response in those with fluconazole-susceptible and -resistant OPC.

The aims of the present study were (1) to compare symptoms, signs, and results of quantitative Candida cultures for patients with fluconazole-susceptible and fluconazole-resistant OPC; (2) to compare assessments of therapeutic response of OPC caused by azole-susceptible and fluconazole-resistant Candida, in order to define the optimal criteria for assessing therapeutic response; and (3) to validate, if possible, a clinical scoring system that accurately reflects therapeutic response.

To do this, we investigated whether patients infected with azole-susceptible and -resistant strains of Candida differ in their clinical presentation and determined the correlation (if any) of therapeutic outcome of individual symptoms with global outcome. We also examined the effect of treatment on cfu measurements of isolates from these patients. We sought to derive a simple means of assessing the efficacy of antifungal agents in OPC caused by fluconazole-resistant Candida. We propose a standard means of objective assessment of outcome of therapy for OPC caused by azole-resistant Candida in HIV-infected patients.

In this article, the term fluconazole-refractory OPC is synonymous with therapeutic failure of fluconazole, and the term fluconazole-resistant OPC means OPC that failed to respond to fluconazole and is caused by a fluconazole-resistant strain of Candida.

Methods

We analyzed data gathered for three studies (numbered 003 [16], 012 [17], and 018 [unpublished]) of D0870 in HIV-positive individuals with pseudomembranous OPC. All three were prospective multicenter studies conducted before the introduction of protease inhibitors and mostly during the era of monotherapy for HIV infection. Adults with normal electrocardiographic and liver function test findings who had no history of heart or liver disease were enrolled. Comedication with warfarin, cyclosporine, sulfonylureas, nortriptyline, antiarhythmics, terfenadine, astemizole, or systemic antifungals was an exclusion criterion. Female patients who were pregnant, breast-feeding, or using unreliable contraception were also excluded.

Description of Studies

Study 003. Study 003 [16] was a two-phase single-dose study with an open phase (12 subjects) followed by a double-blind, parallel randomized phase with two doses (12 subjects in each group). Treatment was given for 5 days. Patients were excluded from the study if they had previously received fluconazole therapy that failed. Clinical assessments were made at enrollment, on day 3, at the end of therapy, and on days 7 and 14 after the end of therapy.

Study 012. For study 012 [17], patients who had OPC that had failed to respond to fluconazole therapy at dosages of ≥100 mg/d for at least 7 days were recruited. This was an open, nonrandomized trial assessing a single dose of D0870 in 27 subjects. Treatment was given for 7 days. Clinical assessment was made at enrollment, on day 3, at the end of therapy, and on days 7 and 14 after the end of therapy.

Study 018. Enrollment criteria for study 018 were the same as for study 012. The trial was a dose-escalation study in which 48 patients were recruited. Patients in the first cohort were treated with a given dose of D0870 (dose A), and if the response rate was ≥80% and safety had been established, the next cohort was treated with a higher dose. The same criteria were used to elevate the dose further, for a total of five dosing steps. Forty-eight patients were recruited at four doses. Subjects were assessed for clinical response on days 4, 7, and 10 (end of therapy) and following therapy.

Clinical Assessment of Efficacy

Comparable clinical data concerning symptoms and clinical signs of OPC, in addition to the response of each to treatment, were collected in all the studies. Each symptom was graded as mild (causing minimum discomfort and not interfering with everyday activities), moderate (interfering with everyday activities), or severe (e.g., incapacitating). For study 018, data on the symptom “burning of mouth” were not recorded; hence, the highest grading of “burning of mouth” and “oral pain” in studies 003 and 012 was taken as equivalent to that of “oral pain” for study 018.

An oral-cavity examination was performed and estimated coverage over the soft palate, left and right buccal areas, and tongue areas was scored as nil, scant, moderate, or confluent. For study 018, coverage was graded slightly differently, as absent, <25%, 25%–50%, 51%–75%, 76%–99%, or 100%. For the purposes of comparison between studies, 25%–75% coverage was deemed equivalent to “patchy” in the previous studies, and 76%–100% was considered equivalent to “severe” or “confluent.” In addition, for study 018, the overall coverage of the mucosa was estimated.
At the end of therapy, the individual outcome for each sign and symptom was defined as cleared (complete resolution of signs and symptoms), improvement (partial clearance of signs and symptoms), failure (no diminishment of signs or symptoms), relapse, or unevaluable/misdiagnosis. Global outcome was defined as resolved (determined by clinical resolution of lesions and symptoms), improvement (determined by reduction in the severity and/or number of symptoms and lesions but without complete resolution), or failure (by persistent signs and symptoms of equal or greater severity than at baseline). Patients were deemed unevaluable if their conditions were judged to be misdiagnosed, if there were major violations of entry criteria, if any concomitant antifungal agent had been used, or if pretherapy cultures were negative.

Quantitative Culture Procedure

Specimens were collected by oral swabs from each of the four areas of the oral cavity. Oral “swish” samples were also collected. Patients were instructed in the method before being asked to rinse and gargle 10 mL of sterile distilled water for at least 20 seconds, before spitting the liquid into a sterile container. These specimens were stored at 4°C until dispatch to the microbiology laboratory within 48 hours (usually immediately).

Each oral swab was immersed in 5 mL of sterile PBS in a sterile tube that was agitated for 15 seconds, and then serial decimal dilutions in sterile PBS were made; 100-µL aliquots of the dilutions were subcultured onto Sabouraud dextrose agar. PBS was added to each “swish” sample to make dilutions of 1:10, 1:50, 1:100, 1:200, and 1:400. Each dilution was agitated for 15 seconds, and a 0.1-mL sample from each dilution was subcultured onto Sabouraud dextrose agar. In both cases the culture plate was then incubated at 37°C for 48 hours, and the following day the plate was inspected for colonies typical of Candida species. The number of cfu per milliliter was quantified as no growth; <10 colonies; 10–100 colonies; >100 colonies but not countable; or confluent growth.

In Vitro Susceptibility Testing

MIC testing of isolates against fluconazole and D0870 was performed as follows [13, 18]. RPMI-1640 broth buffered with MOPS (3-[N-morpholino]propanesulfonic acid) at a pH of 7.0 was the test medium. Five colonies of 1 mm each were picked off the culture plate, resuspended together in 5 mL of sterile physiological saline, and centrifuged, and the turbidity was adjusted to a 0.5 McFarland standard with sterile physiological saline. The resulting 1 × 10⁶-cfu/mL suspension was then diluted 1:50 in RPMI broth to give the final inoculum of 2 × 10⁴ cfu/mL. D0870 was dissolved in dimethyl sulfoxide and fluconazole in water, and each was diluted to give a final dilution series of 32–0.03 µg/mL in 100-mL microtiter wells after addition of 100 mL of yeast inoculum. Plates were incubated at 35°C for 24 hours. Endpoints were determined spectrophotometrically, with the first well showing ≥50% inhibition being defined as the MIC. C. albicans ATCC 10231 (MICs: D0870, 0.03 µg/mL; fluconazole, 0.5–2 µg/mL) served as a control strain. Resistance was defined as an MIC of ≥16 µg/mL for fluconazole.

Comparison of Patients with Fluconazole-Susceptible and -Resistant Isolates at Baseline

Patients with fluconazole-susceptible isolates were compared with those with resistant isolates at study enrollment with respect to CD4+ cell count, total number of symptoms and frequency of individual symptoms, degree of coverage, and cfu measurement at start of treatment. In the comparison of coverage, patients in studies 003 and 012 had coverage expressed as absent, patchy, or confluent in four areas (tongue, soft palate, and left and right buccal mucosae). To enable a comparison with study 018 patients (with global coverage estimated as a percentage: 0%, 1%–25%, 26%–50%, 51%–75%, 76%–99%, and 100%), absent was scored as 0, patchy, or confluent as 1; then the scores for each area were added, for a total score of 0–8. Zero corresponded with 0%, 1 and 2 with 1%–25%, 3 and 4 with 25%–50%, 5 and 6 with 51%–75%, and 7 and 8 with 76%–100%. The comparisons were performed with a Mann-Whitney U test and Wilcoxon rank sum W test.

Comparison of Individual Symptom Response with Global Outcome

Our aims were to measure the predictive power of particular clinical findings in relation to overall clinical outcome; to examine the relationship, if any, between change in cfu measurements (pretherapy vs. post-therapy) and clinical response; and to determine the strength of association (assessed with use of Kendall’s tau-B correlation coefficient) in each case. For the first goal, tables of individual symptom outcome against global outcome were produced, and the data were compared with use of Kendall’s tau-B test in each case. For the assessment of cfu measurements, the median cfu values for before and after therapy were calculated, and the Wilcoxon signed-rank test and Spearman’s rank correlation test were performed.

Testing of Scoring Systems

Scoring system A was used initially. This weighted each clinical symptom on a scale of 0–3, with absent scored as 0; mild, 1; moderate, 2; and severe, 3. Dysphagia was scored double, 0–6, to weight esophageal involvement adequately, as no endoscopy was performed. Each clinical sign was also scored from 0 to 3 (no lesions, score of 0; few spots, 1; multiple patches, 2; and confluent disease, 3). The total score was derived by subtracting the post-therapy score from the pretherapy score. Scoring systems B, C, D, and E were later developed.
Table 1. Scoring systems A–E, showing weighting of individual outcomes of signs and symptoms.

<table>
<thead>
<tr>
<th>Outcome of signs/symptoms</th>
<th>Score for outcome in indicated scoring system</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Worse</td>
<td>0</td>
</tr>
<tr>
<td>Unchanged</td>
<td>0</td>
</tr>
<tr>
<td>Improved</td>
<td>1</td>
</tr>
<tr>
<td>Resolved</td>
<td>2</td>
</tr>
<tr>
<td>Absent</td>
<td>3</td>
</tr>
</tbody>
</table>

* See text for explanation of scoring system A.

and applied to the data, as shown in table 1. In scoring systems B–E, a score was given for the degree of change in each sign or symptom. These individual scores were then added together to give an overall score.

Figure 1 illustrates the numbers of patients enrolled in the three studies and their subdivision by history of response to fluconazole (fluconazole-responsive, fluconazole-refractory) and by results of susceptibility testing of Candida isolates (fluconazole-susceptible, fluconazole-resistant). Clearly, a history of clinical response did not always correlate with in vitro susceptibility to fluconazole. Patients were excluded from the final subgroup analyses as indicated. Table 2 summarizes response to therapy in the three studies.

**Comparison of Patients with Fluconazole-Susceptible and -Resistant Isolates at Baseline**

**CD4+ cell count.** There was a significant difference in CD4+ cell counts between the fluconazole-resistant and -sus-

**Results**

**Analysis**

**Figure 1**: Enrollment of patients in the three studies analyzed and their classification by clinical response and in vitro susceptibility to fluconazole (Flu = fluconazole; QTc interval = Q-T interval, corrected for heart rate).
Summary of data concerning enrollment, previous response and susceptibility to fluconazole, and response to D0870 in the three studies. The data shown are numbers of patients.

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Patients enrolled</th>
<th>Fluconazole therapy failed</th>
<th>Elevated MIC of fluconazole (&gt;16 μg/mL)</th>
<th>Eligible for this analysis</th>
<th>Clinical response to D0870</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Resolution Improvement Failure</td>
</tr>
<tr>
<td>003</td>
<td>39</td>
<td>0</td>
<td>4</td>
<td>33</td>
<td>27 4 2</td>
</tr>
<tr>
<td>012</td>
<td>27</td>
<td>26</td>
<td>16</td>
<td>26</td>
<td>1 16 9</td>
</tr>
<tr>
<td>018</td>
<td>48</td>
<td>48</td>
<td>36</td>
<td>40</td>
<td>9 22 9</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>74</td>
<td>56</td>
<td>99</td>
<td>37 44 20</td>
</tr>
</tbody>
</table>

ceptible groups (Mann-Whitney, $P < .0001$). The median CD4$^+$ cell count at baseline for patients with resistant isolates ($n = 61$) was 6 (quartiles: 2, 22.5) × $10^3$/L, and for those with susceptible isolates ($n = 49$), 19 (quartiles: 10, 74) × $10^3$/L.

Coverage. Percentage of oral coverage was significantly greater at baseline in the fluconazole-resistant group than in the fluconazole-susceptible group (Mann-Whitney, $P = .0003$).

 Colony-forming units. There was no difference in cfu measurements at baseline between patients with OPC due to fluconazole-resistant Candida isolates and those with OPC due to fluconazole-susceptible strains ($P = .64$).

Symptoms

Number and frequency of symptoms. There was a significant difference in both the number of symptoms and the frequency of individual symptoms between the fluconazole-resistant and -susceptible groups. The median numbers of symptoms at baseline for patients completing the study who had fluconazole-resistant disease ($n = 54$) and fluconazole-susceptible disease ($n = 45$) were 3 and 1, respectively ($P = .0006$). Among initial symptoms, the frequency of dysgeusia ($P = .0038$), dysphagia ($P = .006$), and throat pain ($P = .0034$) but not of retrosternal pain or oral pain was significantly greater in patients with resistant disease (table 3).

Symptom frequencies are shown in table 3. The data are consistent with certain symptoms of OPC being more common than others, and some symptoms are more common in fluconazole-resistant OPC than in fluconazole-susceptible OPC. Dysphagia is an infrequent symptom in disease due to fluconazole-susceptible Candida but is frequent in disease due to fluconazole-resistant strains. Burning of the mouth is a less frequent symptom in disease due to fluconazole-susceptible strains than in that due to fluconazole-resistant strains. Oral pain was the second most frequent symptom in disease due to fluconazole-susceptible or fluconazole-resistant isolates. A Kendall correlation coefficient was generated to compare any change in symptom with global outcome to determine the correlation between symptom outcome (worse, unchanged, improved, resolved) and global outcome. This was done for all patients and then for the two subgroups with OPC due to fluconazole-susceptible and -resistant organisms. The results are shown in table 4. Improvement (diminishment) in certain symptoms (dysphagia and oral pain) correlates most closely with overall clinical improvement.

The presence or absence of the “burning of mouth” symptom correlates well with that of oral pain. There was poor agreement between change in “furry” taste and change in tongue lesions (agreement, 38%; kappa = 0.14), and “furry” taste did not correlate with the clinical sign of tongue coating.

Dysgeusia was the most frequent symptom in the study, irrespective of the presence of OPC, and had a relatively poor correlation with outcome. Xerostomia (dry mouth) was also a frequent symptom but again correlated poorly with outcome. White plaques (as reported by the patient) showed a close correlation with objective (i.e., physician-described) measures of outcome.

Measurements of Colony-Forming Units

The change in median number of cfus of all fungal isolates between the start and end of therapy was compared by means

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Dysphagia</th>
<th>Burning of mouth</th>
<th>Dysgeusia</th>
<th>Oral pain</th>
<th>Xerostomia</th>
<th>Retrosternal pain</th>
<th>Throat pain</th>
<th>“Furry” taste</th>
</tr>
</thead>
<tbody>
<tr>
<td>003</td>
<td>11 (28)</td>
<td>7 (18)</td>
<td>17 (44)</td>
<td>10 (26)</td>
<td>21 (54)</td>
<td>4 (10)</td>
<td>11 (28)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>012</td>
<td>20 (74)</td>
<td>13 (48)</td>
<td>21 (78)</td>
<td>15 (56)</td>
<td>19 (70)</td>
<td>10 (37)</td>
<td>18 (67)</td>
<td>22 (81)</td>
</tr>
<tr>
<td>018</td>
<td>20 (42)</td>
<td>NC</td>
<td>30 (63)</td>
<td>30 (63)</td>
<td>NC</td>
<td>13 (27)</td>
<td>19 (40)</td>
<td>NC</td>
</tr>
</tbody>
</table>

NOTE. NC = data not collected.
of the Wilcoxon matched-pairs signed-ranks test. The values for fluconazole-susceptible vs. -resistant disease were compared with Spearman’s rank correlation test.

Among cases of fluconazole-susceptible OPC (n = 40), the median starting cfu score was 4 (quartiles, 3 and 4), equivalent to a value of >100 cfu/mL. There was a nonsignificant reduction in cfu score at end of treatment, to 3 (10–100 cfu/mL; quartiles, 3 and 4). There was no correlation with clinical outcome (rₚ = 0.26; P = .11).

Among cases of fluconazole-resistant OPC (n = 52), the median cfu value was 4 (quartiles, 3 and 4) at both baseline and end of therapy. Again, there was no correlation with clinical outcome (rₚ = 0.28; P = .04).

Scoring Systems

To assess the five clinical scoring systems against global outcome, Spearman’s rank correlation test was performed for each scoring system. The patients were divided into two groups (fluconazole-susceptible vs. fluconazole-resistant disease) on the basis of MIC data (values of ≥16 µg/mL defined resistance and values <16 µg/mL defined susceptibility). Global outcome of OPC was defined as follows. OPC was considered resolved if all oral lesions and symptoms of disease resolved, improved if there was some diminishment of oral lesions or symptoms or both, unchanged if oral lesions were unchanged, and worse if there was greater coverage with lesions at the end of therapy.

Figures 2 and 3 show outcomes according to scoring systems A and C for fluconazole-resistant and -susceptible disease. Resolution was primarily determined by clearing of patches in the mouth. Equally good differentiation between outcomes can be seen for fluconazole-resistant and -susceptible disease.

Scoring system A, a simple-sum method, was initially tried but differentiated poorly between different outcomes, yielding a correlation of −0.37 (figure 2). Scoring system B weighted the absence of a symptom throughout more positively (+3) than resolution of the symptom (+2), and showed a correlation of 0.81 between score and global outcome. Scoring system C weighted resolution (+3) as a better outcome than absence of a symptom throughout (+2) (figure 3); this gave the best correlation (0.86). Scoring system D (correlation, 0.78) weighted worsening of a symptom (−1) as a worse outcome than no change in the symptom but was otherwise the same as scoring system C. Scoring system E (correlation, 0.82) was the same as scoring system D, except resolution of a symptom was weighted (+3) higher than absence of a symptom (+2).

Figures 4–8 show the degree of correlation between changes in scores for symptoms and changes in scores for degree of coverage by oral patches (signs) following treatment. For each scoring system, in a considerable proportion of patients, a tendency emerged for comparatively greater improvement in symptoms than reduction in oral coverage following treatment. This was most marked for system B and C scores. Our analysis suggests dysphagia, oral pain, and oral burning are the most useful symptoms to include in the scoring system. Xerostomia and dysgeusia are frequent symptoms, irrespective of the presence of OPC, and are best excluded from assessments of efficacy. Scoring system C gives the best degree of differentiation between the groups where symptoms resolved, improved, or remained unchanged/worsened, with no overlap between those whose therapy failed and those whose symptoms cleared. The data also demonstrate that scoring system C works equally

### Table 4. Kendall correlation coefficients of agreement between individual symptom outcome and global outcome.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All patients</th>
<th>P value</th>
<th>Patients with flu-resistant OPC</th>
<th>P value</th>
<th>Patients with flu-susceptible OPC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>.42</td>
<td>&lt;.01</td>
<td>.31</td>
<td>.06</td>
<td>.61</td>
<td>.01</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>.23</td>
<td>.04</td>
<td>.16</td>
<td>.23</td>
<td>.34</td>
<td>.09</td>
</tr>
<tr>
<td>Oral pain</td>
<td>.44</td>
<td>&lt;.01</td>
<td>.36</td>
<td>.02</td>
<td>.52</td>
<td>.01</td>
</tr>
<tr>
<td>Retrosternal pain</td>
<td>.49</td>
<td>.01</td>
<td>.61</td>
<td>.01</td>
<td>.36</td>
<td>.29</td>
</tr>
<tr>
<td>Throat pain</td>
<td>.35</td>
<td>.01</td>
<td>.45</td>
<td>.01</td>
<td>.24</td>
<td>.31</td>
</tr>
</tbody>
</table>

NOTE. Flu = fluconazole; OPC = oropharyngeal candidiasis.
well for fluconazole-resistant and -susceptible disease (figures 3 and 6).

**Discussion**

Treatment options for fluconazole-refractory OPC are limited. High doses of itraconazole capsules or ketoconazole may produce a response, but this is often short-lived [19]. Itraconazole solution has good efficacy in a majority of those with fluconazole-refractory disease [20, 21]. Large doses of oral amphotericin B solution (e.g., 200 mg four times daily) are partially effective [22]. Intravenous amphotericin B in conventional or lipid-associated preparations can be used as a last resort [19]. Few data exist regarding the efficacy of and optimal dosage for this latter option.
involvement. It has been suggested that xerostomia correlates with clinical failure of fluconazole, because reduced saliva production would reduce the amount of fluconazole reaching the oral cavity. This was not confirmed by this study with D0870, another azole secreted in saliva, as the presence of xerostomia at baseline did not correlate with a poor outcome.

The value of susceptibility testing is also emphasized by these data, as it is apparent that patients’ fluconazole therapy may fail for many reasons, one of which is resistance of the infecting organism(s) (76% in this series). Access to susceptibility testing may well prove to be a valuable clinical tool with the continued emergence of azole-resistant isolates of *C. albicans* and other *Candida* species.

The data from the three studies provided a good range of outcomes; there was a good distribution of complete, partial, and no responses, necessary to develop and test a scoring system (table 1). An intuitive approach to formulating a scoring system would rate severity of signs and symptoms at the beginning and end of therapy and would score response on the difference between the two (scoring system A). However, the disadvantage of this is that “absent throughout” equates with “severe throughout.” Unless the baseline total score is integrated into the score, a poor correlation with other outcome measures will be attained, as in scoring system A. In comparison, scoring system C is better because it reflects the severity of disease, in terms of number of symptoms, as well as any change following therapy.

In terms of using scores for degree of coverage of the oral mucosa by plaques of *Candida*, if the score includes “confluent” coverage for an area, then this must be attainable. From the data it became clear that “confluent” coverage was attainable in buccal
Table 5. Proposed scoring system for assessment of OPC in patients with AIDS.

<table>
<thead>
<tr>
<th>Signs</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage of mucosa on</td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td></td>
</tr>
<tr>
<td>Tonsils and posterior pharyngeal wall</td>
<td></td>
</tr>
<tr>
<td>Soft and hard palate (together)</td>
<td></td>
</tr>
<tr>
<td>Left or right buccal area (or both together)</td>
<td></td>
</tr>
<tr>
<td><strong>Score</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Unchanged or worse</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Improved</strong></td>
<td>3</td>
</tr>
<tr>
<td><strong>Resolved</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Absent</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Dysphagia has a double score.

areas. Data from the three studies showed a close correlation between disease in right and left buccal areas; in only one patient in study 12 and five patients in study 18 were the left and right areas judged to have dissimilar degrees of coverage at the end of therapy.

On the basis of these findings, the sum scoring system (A) performed poorly in comparison with the other systems. We propose a modification of scoring system C as the most useful (although the differences between systems B, D, and E in comparison with A were small). The modification of scoring system C assesses outcome (unchanged/worse = 0; improved = 1; resolved = 3; absent = 2) of three symptoms (dysphagia, oral pain, burning of mouth) and signs in four areas (tongue; tonsils and posterior pharyngeal wall; soft and hard palate; and left and/or right buccal mucosa). It is summarized in table 5. The high incidence of marked improvement in symptoms without improvement in signs supports the use of a scoring system for the assessment of therapeutic response in AIDS patients with OPC. A simple scoring system that weights improvement of a symptom more than the absence of a symptom is useful in generating a graded response to therapy. This scoring system may be particularly useful for the assessment of novel agents for the treatment of OPC in HIV-infected individuals.

Few prior attempts have investigated the relationship of cfu measurement to a quantitative assessment of clinical outcome. Eichel et al. [21] reported on yeast count alterations in response of fluconazole-resistant OPC to treatment with itraconazole suspension and noted reductions of yeast count in six of 39 patients successfully treated. Plettenburg et al. showed a lack of correlation between clinical and mycologic assessment of response in >50% of patients [23]. We found cfu changes before and after therapy did not correlate with therapeutic outcome, and thus it could reasonably be concluded that quantitation of cfu is not helpful in assessing the response to therapy for OPC.

In summary, there are substantial differences in symptomatology and coverage of oral mucosa (but not in cfu) between patients with OPC due to fluconazole-susceptible *Candida* and those with OPC due to fluconazole-resistant *Candida*. Beneficial symptomatic responses follow therapy, but often without clearance of lesions, particularly in those infected with fluconazole-resistant strains.

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**References**

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