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# The Natural History of Esophageal Candidiasis After Successful Treatment in Patients With AIDS

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***Background/Aims:*** **Antifungal therapy cures esophageal candidiasis in most patients with acquired immunodeficiency syndrome, but the subsequent course of these patients is not established. This study examines the natural history of esophageal candidiasis after successful treatment.** ***Methods:*** **Patients with endoscopic and clinical resolution of esophageal candidiasis after therapy were followed up prospectively with monthly clinical assessment and repeat endoscopy every 3 months or earlier if esophageal symptoms recurred or if the patient was to begin antifungal therapy for another reason.** ***Results:*** **Thirty-five patients met entry criteria; 21 agreed to enroll. The patients were followed up for a mean of 23 ± 4 weeks after their initial posttreatment endoscopy. Nineteen patients (90%) had recurrent esophageal candidiasis at a mean of 11 ± 2 weeks (range, 3–36 weeks). The 19 patients had 31 recurrences; 25 (81%) occurred ≤10 weeks after documented cure of the prior episode of esophageal candidiasis. Twenty-two (71%) of the 31 recurrent episodes were symptomatic, and only 9 (29%) were associated with oral thrush. All symptomatic recurrences responded to treatment with fluconazole; 1 of 22 (5%) failed to show endoscopic resolution.** ***Conclusions:*** **Almost all patients with acquired immunodeficiency syndrome and successfully treated esophageal candidiasis develop a recurrence, usually within 2–3 months. Two thirds are symptomatic and one third are associated with oral thrush. Subsequent episodes of esophageal candidiasis respond well to oral therapy.**

Esophageal disease is common in patients with acquired immunodeficiency syndrome (AIDS); it occurs in 40% of patients during the course of their disease.[1] Most patients with human immunodeficiency virus infection and esophageal symptoms are found to have esophageal candidiasis,[2–4] and antifungal therapy usually eradicates the disease in these patients.[5–7] Surprisingly, however, no study has prospectively evaluated the clinical and endoscopic course of patients after treatment for esophageal candidiasis. Therefore, we followed up a group of patients with AIDS and esophageal candidiasis after successful treatment with oral antifungal therapy in an attempt to determine the natural history of esophageal candidiasis after resolution.

## Materials and Methods

Patients with AIDS were eligible if they had symptomatic esophageal candidiasis (symptoms of odynophagia, dysphagia, or retrosternal pain) documented by endoscopy (typical white exudates) and microscopic examination of esophageal biopsy or brushing specimens, received treatment with an oral antifungal agent (all patients enrolled received a 3–4-week course of 100 mg/day of fluconazole with a 200-mg loading dose), and had resolution of symptoms plus endoscopic documentation of normal-appearing esophageal mucosa after treatment. Patients who needed to remain on continuous antifungal therapy were excluded.

Patients meeting entry criteria and agreeing to enroll were followed up monthly by phone contact or clinic visit to determine if esophageal symptoms had recurred; patients were also instructed to contact us immediately if symptoms recurred. If symptoms recurred, the patient underwent a repeat endoscopy. In addition, patients who were about to be placed on a systemic or topical antifungal medication for another reason (e.g., oral thrush) also received a repeat endoscopy before treatment. Finally, patients who did not develop recurrent symptoms or require antifungal therapy had repeat endoscopies performed at 3-month intervals. The oral cavity was also examined for evidence of thrush at the time of repeat endoscopy. Patients with recurrent esophageal candidiasis received treatment with fluconazole (200-mg loading dose followed by 100 mg/day for 3 weeks) and had repeat endoscopy and clinical assessment to document resolution. Therapy was given to both symptomatic and asymptomatic patients with recurrent esophageal candidiasis.

This protocol was approved by the Research Committee of Los Angeles County + University of Southern California Medical Center, and patients gave written informed consent. Quantitative data (expressed as mean ± SEM) were compared using the Mann–Whitney $U$ test. Kaplan–Meier estimation of the

*Abbreviations used in this paper:* AIDS, acquired immunodeficiency syndrome.


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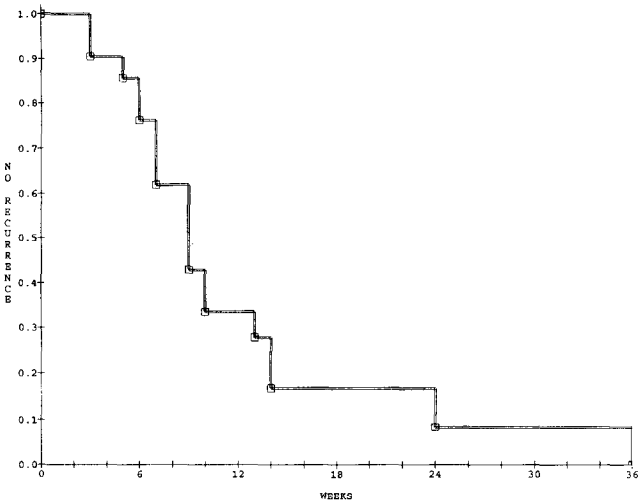


**Figure 1.** Kaplan–Meier estimation of time to first recurrence of esophageal candidiasis.

time to recurrence of esophageal candidiasis was also determined. A two-tailed $P < 0.05$ was considered significant.

## Results

Thirty-five patients met the entry criteria during a 17-month period and were invited to enroll in the study. Twenty-one patients accepted and 14 declined. The two groups were comparable in terms of their mean ages (enrolled, 33.1 ± 2.0 years; declined, 38.1 ± 2.6 years) and their mean T4 cell counts (enrolled, 57 ± 14/mm$^3$; declined, 67 ± 23/mm$^3$). The 21 patients were followed up for a mean of 23 ± 4 weeks (range, 4–70 weeks). At the time of this report, six patients were still being followed up, three patients had moved out of Los Angeles, eight patients had died, and four patients had discontinued participation after 7–24 weeks.

The Kaplan–Meier estimate of time to recurrent disease is shown in Figure 1. Nineteen of the 21 patients (90%) had a recurrent episode of esophageal candidiasis at a mean of 11 ± 2 weeks (range, 3–36 weeks) after their initial posttreatment endoscopy; the median time to recurrence was 9 weeks. The two patients without recurrence were followed up for 12 weeks (the patient died) and 18 weeks (the patient moved from Los Angeles); phone contact with the latter patient 12 weeks later showed no symptoms of esophageal disease or oral thrush. Each of the two patients without recurrence had a T4 cell count at entry of 11/mm$^3$, whereas the mean T4 count of those with recurrent disease was 62 ± 16/mm$^3$ (difference not significant).

There were 31 total cases of recurrent esophageal candidiasis identified in the 19 patients occurring at a mean of 9 ± 1 weeks (range, 2–36 weeks) after documented resolution of their prior episode of esophageal candidiasis. Twenty-five of the 31 recurrent cases (81%) occurred within 10 weeks after the prior episode. Repeat clinical and endoscopic examination was performed after treatment in 22 cases of recurrent disease: 16 with symptoms and six without symptoms. Symptoms resolved after treatment in all 16 symptomatic cases, and 21 of the 22 cases (95%) of recurrent disease had endoscopic cure of esophageal candidiasis with antifungal therapy. In one case, symptoms resolved after 3 weeks of treatment but endoscopic evidence of esophageal candidiasis persisted (cultures showed both *Candida albicans* and *Candida glabrata*) during the last 2 months of life despite a double dose of fluconazole (200 mg/day) in the last 5 weeks.

Twenty-two of the 31 episodes (71%) of recurrent esophageal candidiasis were associated with esophageal symptoms, and only nine (29%) were associated with oral thrush. Recurrent symptoms occurred 25 times in 16 patients; *Candida* was the cause in 22 cases (88%), cytomegalovirus in two cases, and idiopathic esophageal ulcer in one case.

## Discussion

The results of our study indicate that almost all patients with AIDS and successfully treated esophageal candidiasis will develop a recurrence. Subsequent episodes of esophageal candidiasis tend to occur relatively soon after therapy is halted (Figure 1); 81% of all cases of recurrent esophageal candidiasis occurred within 10 weeks. Approximately two thirds of these recurrences were symptomatic, and less than one third were associated with oral thrush. Subsequent episodes of esophageal candidiasis also responded well to oral antifungal therapy; symptoms resolved in all patients, and endoscopic resolution occurred in 95% of cases.

Esophageal candidiasis is the most common cause of esophageal symptoms in patients with AIDS,[2–4] but it frequently occurs in the absence of symptoms as well.[4,5,8] Bianchi Porro et al. routinely performed endoscopy on their hospitalized patients with AIDS and found that 25 of their 52 evaluable patients (48%) had esophageal candidiasis, but only 60% of the patients with *Candida* infection were symptomatic.[4] Laine et al. found that 19 of 44 patients (43%) with esophageal candidiasis treated with ketoconazole who had resolution of symptoms still had endoscopic evidence of esophageal candidiasis.[5] Thus, our finding that recurrence of esophageal candidiasis was documented endoscopically in the absence of symptoms about one third of the time is not surprising.

Oral thrush was reported to be an excellent predictor for the presence of esophageal candidiasis early in the AIDS era.[9] However, other reports suggest a somewhat

less striking association.[2,8] In the largest evaluation of patients with human immunodeficiency virus infection and esophageal symptoms, Bonacini et al.[2] found that 30 of 57 symptomatic patients (53%) with esophageal candidiasis had oral thrush; the positive predictive values of thrush and no thrush for esophageal candidiasis were 77% and 38%, respectively. Our results show that less than one third of cases of recurrent esophageal candidiasis after antifungal therapy had associated oral thrush. The widespread use of antifungal medications may contribute to a decrease in the association of oral and esophageal candidiasis.

Almost 90% of cases with recurrent esophageal symptoms in our study were due to *Candida* infection. Therefore, we believe that patients presenting with recurrent symptoms after a prior episode of esophageal candidiasis should receive empiric therapy with an antifungal agent rather than have an immediate diagnostic endoscopy.

Continuous suppressive therapy is sometimes given to patients with frequent recurrences of oral thrush, and the question of similar therapy for esophageal candidiasis needs to be addressed. Long-term antifungal therapy is relatively expensive, and the possibility that long-term suppressive therapy will increase a patient's risk of developing resistant organisms must also be considered.[10] Therefore, the use of suppressive therapy would have to be clearly shown before its routine use could be recommended. Once a week antifungal therapy has been reported to significantly decrease recurrent oropharyngeal candidiasis[11]; weekly therapy certainly is attractive from the point of view of cost, but whether it would be as effective as more frequent dosing and whether it carries a lower risk of resistant esophageal candidiasis is unknown. Unlike patients with chemotherapy-induced neutropenia, patients with AIDS are generally not at risk of developing systemic candidiasis.[12] Furthermore, safe and effective oral therapy is available to treat esophageal candidiasis,[4-6] and our results indicate that subsequent episodes of esophageal candidiasis will respond to repeat therapy. For these reasons, we do not recommend long-term suppressive treatment to prevent recurrent esophageal candidiasis. However, future randomized controlled trials will be helpful in delineating the appropriate treatment strategy for patients after successful eradication of esophageal candidiasis.

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