Pulmonary Cryptococcosis in the Immunocompetent Host*

Therapy With Oral Fluconazole: A Report of Four Cases and a Review of the Literature

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Isolated pulmonary cryptococcosis (IPC) is an infrequently diagnosed infection, the management of which is not well defined. In past years, IPC traditionally has not been treated in the immunocompetent host, given its perceived benign and self-limited course and the toxicity associated with amphotericin B. However, some patients manifest prominent and disabling symptoms, and infection occasionally may disseminate. Fluconazole is active against Cryptococcus neoformans, is easily administered, and has an excellent safety profile. We present four healthy hosts with IPC who were treated with oral fluconazole for 6 to 8 weeks. A review of the literature was conducted to identify other cases of IPC in healthy hosts who were also treated with fluconazole. Our results and the limited experience reported in the literature suggest that fluconazole may be an appropriate choice for the treatment of IPC in the immunocompetent host. Indications for treatment are not defined, but symptomatic patients, those with multiple nodules or extensive infiltrates on chest radiographs, and/or those testing positive for serum cryptococcal antigen might be potential candidates for therapy. (CHEST 2000; 118:527–534)

Key words: antifungal therapy; cryptococcosis; Cryptococcus neoformans; fluconazole; pneumonia

Abbreviations: CSF = cerebrospinal fluid; CXR = chest radiograph; IPC = isolated pulmonary cryptococcosis; SCA = serum cryptococcal antigen

Although the respiratory tree is the normal portal of entry for Cryptococcus neoformans, pulmonary cryptococcosis is often clinically “silent.” Less than 10% of patients with disseminated cryptococcal infection have clinically apparent pulmonary involve-
lution of the infection. As such, careful clinical observation without specific antifungal therapy usually has been advocated for healthy hosts with no evidence of extrapulmonary disease, a decision previously made easier by the lack of therapeutic options to parenteral amphotericin B with its associated toxicities.

With the current availability of oral triazoles with their excellent antifungal activity against \( C\) \( neoformans \) and their low potential for toxicity, impediments to therapy of cryptococcal pulmonary disease in healthy hosts seemingly have decreased. In fact, Dismukes\(^4\) has suggested that many investigators now advocate fluconazole therapy for all patients with pulmonary cryptococcosis, regardless of their underlying disease status. He does, however, acknowledge that no controlled clinical trials have been conducted to evaluate that management approach. Accordingly, it would appear appropriate to readdress the issue of therapy for IPC in the nonimmunocompromised host, especially in regard to indications (if any) for treatment and the role of oral agents, such as fluconazole, in management of the infection.

We report four cases of IPC in seemingly healthy hosts, each of whom was successfully treated with oral fluconazole. Additionally, a literature review was conducted to identify other reported cases of IPC in healthy hosts who were treated with fluconazole over the past decade.

CASE REPORTS

Case 1

A 61-year-old man, previously in good health, was found to have bilateral nodular lesions on a chest radiograph (CXR) that was performed during evaluation for a possible cerebrovascular accident. He had no active respiratory symptoms, but he did report a recent “flu-like” illness with cough and yellowish sputum production that had lasted for 1 week. Routine laboratory studies were unrevealing. A chest CT scan confirmed the presence of multiple bilateral pulmonary lesions with ill-defined margins (Fig 1). The suspicion of malignancy prompted the performance of a transthoracic needle aspiration biopsy. Histology demonstrated granulomatous inflammation and intracellular yeast within histiocytes and multinucleated giant cells. A culture of the aspirate was positive for \( C\) \( neoformans \). The results of the lumbar puncture were unremarkable, and blood, urine, and cerebrospinal fluid (CSF) cultures failed to grow yeast. The result of an HIV serum antibody test was negative. Since the result of a serum cryptococcal antigen (SCA) test was positive at a titer of 1:32, treatment with fluconazole, 400 mg/d orally, was initiated. The patient completed a 6-week course of therapy with no significant side effects. At the end of treatment, the SCA titer was 1:4 and the pulmonary lesions were much improved on follow-up CXR. Now, 3 years after therapy, the patient remains well with no clinical or radiographic evidence of relapsing disease (Table 1).

Case 2

A 65-year-old man with a history of lung carcinoma that had been treated with right upper and middle lobe lobectomies was found to have bilateral ill-defined nodular lesions on a routine follow-up CXR. A chest CT scan confirmed the presence of multiple lesions measuring 10 to 15 mm in diameter that were located adjacent to the pleura and were predominantly in the left lung. The patient denied any acute respiratory symptomatology, although he did describe an occasional cough that was productive of small amounts of white sputum. A CT-guided transthoracic needle aspiration biopsy was performed to rule out recurrent cancer. Histologic examination revealed granulomatous inflammation and yeast within phagocytic cells. Cultures yielded \( C\) \( neoformans \). To assess the possibility of CNS extension of the infection, a lumbar puncture was performed; the result of the CSF cryptococcal antigen test was negative, as were the results of CSF cultures. Two blood cultures and a urine culture were also negative for cryptococci. The result of the test for SCA was positive at a titer of 1:2. Given the number of pulmonary lesions and the positive result of the SCA test, it was decided to treat the patient with oral fluconazole, 400 mg/d. Tolerance to treatment was excellent, and after 6 weeks of therapy the result of the SCA test was negative. A CXR at that point showed progressive clearing of the pulmonary lesions. On follow-up 3 years after completing therapy, the patient continues to do well from a clinical perspective. His most recent CXR reveals only stable nodularity in the left apex (Table 1).

Case 3

A 65-year-old man with a 5-week history of nonproductive, disabling cough was found to have a large density in the right lower lobe on CXR (Fig 2, top). A 10 × 10.5 × 8.5-cm dense opacity was confirmed by chest CT scan. A transthoracic needle aspiration biopsy was performed, revealing granulomatous inflammation and cryptococcal-like organisms. The result of the SCA test was positive at a titer of 1:64. The patient had no neurologic symptoms and refused to undergo a lumbar puncture. The result of the HIV antibody test was negative. Treatment with fluconazole, 400 mg/d orally, was initiated. Subjective improve-
Case 4

A 55-year-old woman presented with a 5-day history of achiness, profound malaise, and night-sweats. A review of systems was significant for a 40-lb weight loss with weakness and anorexia over the previous 2 months. A CXR revealed patchy infiltrates and consolidation of the right middle lobe and the superior segment of the right lower lobe. Empiric treatment for bacterial pneumonia was begun, but the patient’s condition worsened over the next few days, and she developed low-grade fevers and a persistent nonproductive cough. Bronchoscopy with BAL then was performed but findings were nondiagnostic. A follow-up CXR demonstrated increased consolidation of the right middle and lower lobes. Specimens from a transbronchial biopsy that was performed during a repeat bronchoscopy revealed granulomatous inflammation with multinucleated giant cells containing budding yeast that were consistent with Cryptococcus spp. The result of the SCA test was positive at a titer of 1:16. A lumbar puncture revealed no evidence of CNS involvement. The result of the HIV antibody test was negative. Treatment with fluconazole, 400 mg/d, was initiated. The fevers remitted, and the patient experienced subjective improvement within the first few days of therapy. Clinical improvement continued, and, by the sixth week, the result of the SCA test was negative. An 8-week course of therapy was completed, at the end of which a follow-up CXR demonstrated marked improvement in the previous infiltrates; persisting shadows at the right base were thought to represent parenchymal scarring. More than 2 years after completing her therapy, the patient remains well with no evidence of recurrence of her IPC. Her most recent CXR revealed only a stable parenchymal scar in the right mid-lung field (Table 1).

Literature Review

Since controlled clinical trials evaluating the efficacy of oral triazoles in the treatment of healthy hosts with IPC have not been performed, to our knowledge, easily retrievable data on patients receiving fluconazole as therapy for IPC are difficult to obtain (Table 2). Relatively few case reports or case series on the topic have been published, and most of those provide incomplete information on the immune status of patients, the type of infection (isolated pulmonary vs pulmonary plus extrapulmonary) being treated, and the dosage and duration of fluconazole therapy. Thus, meaningful data are limited.

Reviews by Dromer et al and Yamaguchi and colleagues focus on fluconazole monotherapy as an alternative to amphotericin B for cryptococcosis in HIV-negative patients. Each study includes immunocompetent and immunocompromised patients as well as patients with meningitis. Neither study provides specific details about the cases of IPC that occurred in healthy hosts. In the study by Dromer et al, antifungal therapy was chosen in a nonrandomized fashion on the basis of primary physician preference. Fluconazole was utilized in the therapy of 40 patients, 15 of whom did not have meningeal involvement. However, on the basis of the data presented, it cannot be ascertained what proportion of those 15 patients were healthy hosts and what pro-

Figure 2. Top: posteroanterior chest radiograph revealing dense right lower lobe opacity in a 65-year-old man with cryptococcal pneumonia. Bottom: follow-up posteroanterior chest radiograph, which was obtained 11 months after the completion of a 6-week course of therapy with oral fluconazole, revealing a residual scar in the right lower lobe.

ment in the cough was noticed promptly thereafter. The patient received a 6-week course of therapy without side effects. A CXR after treatment showed improvement of the infiltrate. The titers of SCA decreased progressively and became negative 11 months after the initiation of treatment. A follow-up CXR revealed only a residual scar (Fig 2, bottom). Now, > 2 years after completing therapy, the patient remains well with no clinical evidence of relapsing cryptococcosis (Table 1).
### Table 1—Overview of Cases*

<table>
<thead>
<tr>
<th>Case No. Age, yr/Sex</th>
<th>Symptoms</th>
<th>CXR</th>
<th>Chest CT</th>
<th>Lung Biopsy</th>
<th>CSF</th>
<th>Other Cultures</th>
<th>SCA Titer</th>
<th>HIV Serology</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/61/M</td>
<td>None</td>
<td>Bilateral nodules</td>
<td>Multiple bilateral nodules</td>
<td>Yeast in histiocytes; Cx → <em>C neoformans</em></td>
<td>Neg Ag and Cx</td>
<td>Blood Cx Neg, Urine Cx Neg</td>
<td>1:32</td>
<td>Neg</td>
<td>Flu, 400 mg/d × 6 wk</td>
<td>Cure (&gt; 3-yr follow-up)</td>
</tr>
<tr>
<td>2/65/M</td>
<td>None</td>
<td>Bilateral nodules</td>
<td>Multiple 10 × 15-mm nodules adjacent to pleura</td>
<td>Yeast in phagocytes; Cx → <em>C neoformans</em></td>
<td>Neg Ag and Cx</td>
<td>Blood Cx Neg, Urine Cx Neg</td>
<td>1:2</td>
<td>ND</td>
<td>Flu, 400 mg/d × 6 wk</td>
<td>Cure (&gt; 3-yr follow-up)</td>
</tr>
<tr>
<td>3/65/M</td>
<td>Intractable nonproductive cough</td>
<td>RLL density</td>
<td>Dense opacity in RLL</td>
<td>Yeast present; no Cx done</td>
<td>ND</td>
<td>ND</td>
<td>1:64</td>
<td>Neg</td>
<td>Flu, 400 mg/d × 6 wk</td>
<td>Cure (&gt; 2-yr follow-up)</td>
</tr>
<tr>
<td>4/55/F</td>
<td>Weight loss, malaise, fever, night sweats, cough</td>
<td>RML and RLL patchy infiltrates and consolidation</td>
<td>ND</td>
<td>Yeast within multinucleated giant cells; no Cx done</td>
<td>Neg Ag and Cx</td>
<td>ND</td>
<td>1:16</td>
<td>Neg</td>
<td>Flu, 400 mg/d × 8 wk</td>
<td>Cure (2-yr follow-up)</td>
</tr>
</tbody>
</table>

* M = male; F = female; RML = right middle lobe; RLL = right lower lobe; ND = not done; Cx = culture; Neg = negative; Ag = antigen; Flu = fluconazole.

### Table 2—Literature Review*

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Patients Treated With Cryptococcosis, No./Patients Treated With Fluconazole, No.</th>
<th>Healthy Hosts With IPC, No.</th>
<th>Fluconazole Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dromer et al/1996</td>
<td>83/40 Unknown Unknown</td>
<td>200–400 6</td>
<td>93% (14/15) cure rate for nonmeningeal disease</td>
<td></td>
</tr>
<tr>
<td>Yamaguchi et al/1996</td>
<td>44/44 22 Unknown Unknown</td>
<td>200–400 &gt; 4</td>
<td>86% (19/22) cured or improved</td>
<td></td>
</tr>
<tr>
<td>Yew et al/1996</td>
<td>4/4 4 4</td>
<td>600 then 400 4–5 then 10–12</td>
<td>100% cure rate (but all patients treated initially with amphotericin B)</td>
<td></td>
</tr>
<tr>
<td>Liaw et al/1995</td>
<td>8/4 6 6</td>
<td>NS 8–12</td>
<td>100% cure rate for those treated with fluconazole</td>
<td></td>
</tr>
<tr>
<td>Robinson/1995</td>
<td>1/1 1 1</td>
<td>NS NS</td>
<td>Patient died despite therapy with amphotericin B and fluconazole</td>
<td></td>
</tr>
</tbody>
</table>

*NS = not stated.
portion had IPC. However, the overall cure rate for patients without meningitis receiving fluconazole was 93%. Among 44 patients treated with fluconazole by Yamaguchi and colleagues, 22 apparently had IPC. However, the percentage of patients who were healthy hosts is not specified (overall, 75% of patients had significant underlying diseases). Of those patients with IPC who received fluconazole, 19 of 22 (86%) were classified as cured or improved. Accordingly, Yamaguchi et al concluded that fluconazole was a promising agent for the treatment of cryptococcosis.

Four cases of IPC in immunocompetent hosts treated with fluconazole were described by Yew et al. One patient presented with chest pain and was found to have cavitary consolidation on CXR; IPC was an incidental finding in the other three patients (two with consolidation and one with a solitary cavitary lesion). All patients were initially treated with amphotericin B (average dose, 337.5 mg; dose range, 100 to 900 mg). Only after the patients developed adverse reactions to amphotericin B was fluconazole therapy initiated. The dosage of fluconazole was 600 mg/d orally for 4 to 5 weeks followed by 400 mg/d for 10 to 12 weeks. At the end of the treatment, follow-up CXRs revealed only minimal residual scarring, and all patients were relapse free during a follow-up period of 8 to 24 months. Unfortunately, prior administration of amphotericin B to those patients clouds the interpretation of the efficacy that is attributable to fluconazole, especially since radiographic findings were improving in each patient prior to the initiation of fluconazole therapy.

Several additional reports also contain references to patients with IPC who, purportedly, were treated with fluconazole, although the details in most of those reports are likewise limited. Liaw and colleagues, in investigating the diagnostic utility of direct determinations of cryptococcal antigen in transthoracic needle aspirates, identified seven immunocompetent patients with pulmonary cryptococcosis, six of whom had disease confined to the lung. Four patients were treated with oral fluconazole for 2 to 3 months (it is unclear which four patients) and had uneventful clearing of lesions from their chest radiographs. Robinson described a patient without meningitis receiving fluconazole in combination with miconazole or 5-flucytosine. Only Nakashima10 specified the dosage (400 mg/d) and duration (2 to 4 weeks) of the fluconazole therapy that was administered. Information regarding the responses to treatment for most patients is likewise limited. The results when fluconazole was used as monotherapy were described as “excellent,” “good in 2/5 and fair in 3/5 cases,” “clinical efficacy rate 100%,” “50–90% improvement of shadows,” and “improvement” or “marked improvement of CXR findings.” In the two cases of cryptococcal pneumonia, fluconazole was given in combination with other antifungal agents; the condition of one of the patients improved, but information on response of the other patient was not available.15

**Discussion**

Pulmonary infection with *C neoformans* may have several untoward clinical sequelae. Even though most pulmonary infections are viewed as being “clinically silent,”1–3,19 symptomatic disease can occur.1,20 On occasion, those symptoms may be severe and disabling (e.g., high fevers, refractory cough, or chest pain) and may last for days to weeks before a diagnosis is established19–20 or before resolution of the pulmonary process occurs.21,22,26 Perhaps of even greater import, pulmonary cryptococcosis occasionally can eventuate in severe pneumonia with respiratory failure or in extrapulmonic dissemination, particularly to the CNS.2,3,20

Although immunocompromised hosts are considered to be at greatest risk for the life-threatening complications of cryptococcal pulmonary infection, those complications also may occur in healthy hosts.2,3,20 Cases of overwhelming cryptococcal pneumonia with fatal outcome in immunocompetent patients, though unusual, have been reported.9,24 The dissemination of infection to the CNS in otherwise healthy hosts also occurs, even when the pulmonary process appears to be stable or resolving.3 However, there are few available studies to provide accurate information on the incidence of severe pneumonia or meningitis among healthy hosts with pulmonary cryptococcosis. In the retrospective review by Kerkering et al,17 17% of healthy hosts with untreated pulmonary cryptococcal infection devel-
oped CNS dissemination. More recently, Rozenbaum and Goncalves,27 in retrospectively studying 171 patients with cryptococcosis in Brazil, found that 69% of their 35 nonimmunosuppressed patients had concomitant pulmonary and CNS disease. Thus, the threat of CNS dissemination in healthy hosts with pulmonary cryptococcosis would appear to be very real.

Heretofore, the approach to management of pulmonary cryptococcosis has been predicated on the widely accepted belief that spontaneous resolution of infection is the rule for the majority of patients, especially in the absence of host immunocompromise.1–3,20 As initially espoused by Hammerman and colleagues3 and subsequently more clearly delineated by Kerkering et al.,2 therapy generally has been withheld from healthy hosts with IPC with the expectation that infection will ultimately remit spontaneously without treatment and that severe infection including disseminated disease generally will not occur. As a consequence of the observations and recommendations of those authors, most healthy hosts diagnosed with IPC over the past several decades have not been treated.19,22,23,25,26

The recommendations of Hammerman et al3 and Kerkering et al2 notwithstanding, it would appear that selected healthy hosts with IPC might benefit from directed therapy, especially those patients with very prominent or disabling clinical symptoms (eg, our patients 3 and 4) or those patients potentially at risk for the development of severe disease. The rationale for treatment would, thus, be twofold: to promote the more rapid resolution of clinical symptoms and signs that may be disabling, and to prevent the development of potentially life-threatening complications such as diffuse pneumonia or CNS dissemination. Indeed, both Hammerman et al3 and Kerkering et al2 strongly assert that the morbidity and mortality from pulmonary cryptococcosis may be reduced if treatment is initiated before dissemination with meningeal involvement occurs.

Unfortunately, on the basis of the available data, it is difficult, if not impossible, to identify prospectively those healthy hosts with IPC who might benefit from “preemptive” therapy. Although it is logical to assume that treated patients with IPC would have a shorter duration of symptoms and signs than untreated patients, comparative data in that regard have not been published. In both of our symptomatic patients (patients 3 and 4), previously persistent and disabling symptoms such as fever and cough had largely resolved within 1 week of the initiation of fluconazole therapy. Unfortunately, the duration to time of resolution of the symptoms in untreated patients is not commented on by either Hammerman et al3 or Kerkering et al.2 Thus, there is no standard of comparison to assess the symptomatic benefit of antifungal therapy. As regards the identification of patients at risk for severe or disseminated disease, Hammerman and colleagues3 attempted to correlate the presence or absence of chest symptoms and the radiographic pattern of disease with the subsequent development of cryptococcal meningitis in surgically treated patients but could identify no correlation. Kerkering et al2 suggested that the presence of granuloma formation on lung histopathology was associated with a good prognosis and, thus, might speak against the need for therapy. However, the predictive value of that observation remains unproven, and tissue specimens from the lung are not available for all patients.

In the absence of well-defined clinical, radiographic, or pathologic criteria that might accurately identify patients at risk for debilitating symptoms, protracted disease, or severe infectious complications, the potential role for SCA titers in this setting as an aid to decision making is perhaps worthy of consideration. It is now well recognized that patients with IPC, presenting clinically either as pneumonic15,16,22,23,28,29 or with nodular lesions,23 may exhibit positive results in SCA tests. In the series by Yamaguchi et al,6 16 of 22 patients (73%) with IPC had positive results of SCA tests. Thus, in a patient with pulmonary cryptococcosis that is clinically confined to the lung, a positive SCA test result does not necessarily support a diagnosis of occult or evolving dissemination. However, in the patient with IPC, the SCA may serve as a marker of disease activity or overall organism burden. Therefore, it could be postulated that a positive SCA test result might reflect an increased risk for more severe local disease or for dissemination. At this point, however, that relationship remains unproven, and the utility of a positive SCA test result as a predictor of which patient with IPC might benefit from therapy is unknown.

Even if one accepts the premise that selected patients with IPC are deserving of therapy, firm guidelines for treatment are not available. However, with the availability of an easily administered and safe therapy, such as fluconazole, the indications for treatment of IPC perhaps should be reassessed. Certainly, on the basis of a limited number of uncontrolled studies,5,6 fluconazole appears to be effective in the treatment of cryptococcosis in non-HIV-infected patients. As such, several authors have suggested that fluconazole may be an appropriate therapy for IPC in healthy hosts.4,30 In fact, a retrospective review conducted by Pappas et al31 found that 49% of non-AIDS patients with pulmonary cryptococcosis were treated with fluconazole.
monotherapy even in the absence of published recommendations and guidelines.

A precise delineation of appropriate candidates for therapy has not yet been forthcoming. Kauffman\textsuperscript{30} recently has suggested that therapy with fluconazole may be indicated “for patients with pulmonary disease who have no meningeal or other organ involvement and who have mild to moderate symptoms.” That recommendation does not differentiate between healthy hosts and those with immunocompromise of host defenses. Our observations and clinical experiences would support the use of fluconazole for those healthy hosts with IPC who have disabling symptoms or who exhibit multiple nodules or extensive infiltrates on chest radiographs. If a positive SCA test result proves to be a predictor of severe or complicated disease in healthy hosts with IPC, that parameter also could be utilized as a criterion for therapy.

Notwithstanding the difficulties in identifying appropriate candidates for therapy, the optimal dosage of fluconazole and the duration of therapy are also undefined. In the series reported by Dromer et al.\textsuperscript{5} the majority of patients received 4 to 6 weeks of therapy with fluconazole. However, Yew et al\textsuperscript{6} extended therapy to a minimum of 14 weeks. Kauffman\textsuperscript{30} acknowledged that the optimal duration of treatment for pulmonary cryptococcosis was not currently known but suggested that therapy should be continued until the CXR abnormalities resolve; for many patients, she projected that the duration of required treatment would be 3 to 6 months. Our four patients received 6 to 8 weeks of therapy with fluconazole, a duration in keeping with that used in the therapy of cryptococcal meningitis in non-HIV-infected patients. At the end of treatment, all our patients had exhibited demonstrable improvement in CXR findings and significant declines in SCA titers. To date and to our knowledge, with > 2 years of posttreatment follow-up for all patients, no case of relapsing infection has been documented.

Just as the duration of therapy is not known, the optimal fluconazole dosage has likewise not been defined. Dromer et al\textsuperscript{5} and Yamaguchi et al\textsuperscript{6} both employed a daily fluconazole dose of 200 to 400 mg, whereas Yew et al\textsuperscript{6} utilized an “induction” dose of 600 mg for 4 weeks, followed by 400 mg for 10 to 12 weeks. Our patients all received fluconazole, 400 mg/d, the “usual” dose also advocated by Kauffman.\textsuperscript{30} Clearly, additional data will be needed before a consensus opinion on dosage can be developed.

In summary, our observations and a limited number of reports in the literature\textsuperscript{4–7} suggest that fluconazole may be an effective therapy for IPC in the healthy host. Since fluconazole is well tolerated and has an excellent safety profile, it would seem appropriate to consider fluconazole as a therapeutic option in patients who have healthy immune function and IPC, with the goals of therapy being to accelerate the recovery from symptomatic disease and to prevent the development of severe local or disseminated infection. Appropriate candidates for treatment remain to be clearly defined but might include patients with persistent and/or disabling symptoms, those with multiple nodules or extensive infiltrates on CXRs, and/or, possibly, those with positive SCA test results. However, additional studies will be needed to determine more precisely the role of fluconazole in the treatment of IPC in immunocompetent patients as well as the optimal dosage and duration of that therapy.

Aberg and colleagues\textsuperscript{32} recently conducted a retrospective review of their experience with pulmonary cryptococcosis in patients who were not infected with HIV and concluded that immunocompetent hosts who were asymptomatic did not require antifungal therapy. However, they did recommend therapy for symptomatic patients, for patients with a positive SCA test result, and for patients with underlying immunologic disorders. Although none of their healthy hosts with pulmonary cryptococcosis were treated with fluconazole, they expressed the opinion that azole therapy was probably sufficient in most cases. In an accompanying editorial, Sarosi\textsuperscript{33} questioned the wisdom of observing immunocompetent patients without therapy, especially when the estimated risk of dissemination may be 12.5%, and suggests that therapy with fluconazole should be strongly considered given its relative lack of toxicity and probable efficacy.

\textbf{References}

8. Liaw Y-S, Yang P-C, Yu C-J, et al. Direct determination of