Pulmonary Cryptococcosis in Normal Hosts

Treat or Observe?

Although it is accepted that the lung is the portal of entry for disseminated cryptococcosis, it remains unclear if disseminated disease results from reactivation of pulmonary disease since many patients have no evidence of pulmonary disease at time of diagnosis of disseminated disease. Treatment of cryptococcal pulmonary disease remains controversial. In fact, there is no consensus in the literature on what constitutes pulmonary infection vs colonization. The Infectious Disease Society of America (IDSA) guidelines for management of cryptococcal disease recommend that all symptomatic patients with positive respiratory culture findings be treated and have a lumbar puncture to exclude CNS infection; however, the management of patients without symptoms is less clear. The IDSA guidelines recommend that all asymptomatic patients with positive respiratory culture findings be considered for treatment, with the caveat that there are reports of immunocompetent patients with positive sputum culture findings who have done well clinically without treatment. The goal of treatment of isolated pulmonary cryptococcosis is to not only treat the infection but to prevent dissemination, particularly to the CNS.1,2

Nadrous and colleagues (see page 2143) from the Mayo Clinic conducted a retrospective review of 36 nonimmunocompromised patients with pulmonary cryptococcosis, 24 of whom were symptomatic, to address whether treatment is indicated and whether extensive workup for dissemination is necessary. It is unlikely that a prospective study of this entity will ever be performed given the small number of cases per year. In fact, these authors reviewed 26 years of records to identify 36 evaluable cases! Seventeen patients were observed without treatment, 12 patients received antifungal therapy, and an additional 7 patients underwent surgical resection. Follow-up information was available for only 25 patients, of whom 8 patients were not treated, 11 patients had received antifungal therapy, and 6 patients had surgical intervention.

One of the shortcomings of this review is what defines true infection vs colonization. The chest radiographic findings were abnormal in all 36 patients warranting further workup; however, one third of the patients were asymptomatic. It remains unclear what prompted asymptomatic patients to have a chest radiograph. Does this really represent cryptococcosis or was Cryptococcus neoformans an incidental finding? In addition, seven patients, including three asymptomatic patients, underwent surgical intervention to exclude malignancy. I question the clinical significance of isolated pulmonary nodules or cryptococcomas.

In a previous retrospective review,3 my colleagues and I described pulmonary cryptococcosis in HIV-seronegative patients. Our first challenge was to define infection vs colonization. The case definitions used in that report were as follows: (1) definite infection, the isolation of C neoformans in a respiratory specimen with radiographic evidence of disease and clinical symptoms without any other proven etiologies; (2) presumptive infection, the isolation of C neoformans in a respiratory specimen with radiographic evidence of disease, clinical symptoms, and concomitant respiratory pathogens or other noninfectious respiratory disease (bronchitis, aspiration pneumonia, bronchiectasis, interstitial pulmonary fibrosis, congestive heart disease, or connective tissue disease), so that one cannot solely attribute the patient’s presentation to cryptococcosis; and (3) col-

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onization, the isolation of *C neoformans* in a respiratory specimen with (a) a normal chest radiograph, or (b) an asymptomatic state with abnormal chest radiograph, or (c) a postmortem confirmation of another etiology without evidence of cryptococcal disease. A disseminated disease was defined as an isolation of *C neoformans* in the blood, in sterile body fluid, or at an extrapulmonary site.

In the report by Nadrous and colleagues, 12 of the 17 untreated patients were symptomatic. Follow-up was only available for six symptomatic and two asymptomatic patients for a median of 14 months. Using the definitions above, the two asymptomatic patients would be categorized as colonization. So, in essence, the authors’ recommendation that nonimmunocompromised patients with pulmonary cryptococcosis do not need treatment is based on the outcomes of only six symptomatic individuals. All six of those patients had “resolution,” which they defined as patients with no evidence of disease for at least 6 months after treatment or ≥ 1 month after no therapy. Given the indolent nature of cryptococcosis, I question whether 1 month is adequate follow-up to conclude that resolution occurred among patients who are asymptomatic and never treated.

In their report, the baseline serum cryptococcal antigen (sCRAG) was obtained in 22 patients and was positive in 3 patients. The IDSA guidelines clearly state “the presence of a positive serum cryptococcal antigen titer implies deep tissue invasion and a high likelihood of disseminated disease.” This is in agreement with experts in the field and numerous studies of cryptococcal antigen. Although false-positive results can occur (albeit rare), these patients had culture-positive evidence and clinical correlation to warrant that they indeed represent true positives. Two of the three patients were treated with fluconazole, and the untreated patient remained clinically well at 13.5 months of follow-up. Despite the apparent clinical outcome in this untreated patient, I believe clinicians should obtain sCRAG from all symptomatic patients with positive respiratory culture findings to seek evidence of disseminated infection. It is through testing of the antigen that one can then make a decision to do further “extensive follow-up.” I think the implications of a pulmonary isolate in a patient with symptoms and a positive serum cryptococcal antigen implies disseminated disease and thus is quite different from someone with a negative antigen. The expense of performing sCRAG is quite nominal compared with the cost of missing and thus not treating a disseminated infection. Cerebrospinal fluid (CSF) analysis including a cryptococcal antigen was performed in 11 patients, and it is unclear if these included the 3 patients with positive sCRAG.

Relevant follow-up data were missing on 31% (11 of 36 patients) of their total cohort and 53% (9 of 17 patients) who were never treated. Therefore, I do not believe management recommendations can be derived from this small case series. But, I do agree with the authors that CSF examination in nonimmunocompromised hosts without CNS findings is unnecessary. However, I recommend sCRAG to rule out dissemination in symptomatic nonimmunocompromised patients. I do not feel it is necessary in asymptomatic nonimmunocompromised hosts who most likely have airway colonization.

I think the IDSA guidelines best reflect the current treatment approach, which in the absence of data supporting observation alone is to treat symptomatic nonimmunocompromised patients. Obviously, management decisions should consider the individual’s signs/symptoms and access to follow-up care. I agree with the authors’ statement that their study suggests that localized pulmonary cryptococcosis may not need antifungal therapy and decisions should be made on an individual basis. In the setting of acute cryptococcal pneumonitis, it may be safe to observe; however, most persistent fungal respiratory infections (> 3 weeks in duration), such as blastomycosis, coccidiodomycosis, and histoplasmosis, are treated with a short course of azoles. Considering risk vs benefit, I would offer treatment with oral fluconazole for persistent cryptococcosis in a nonimmunocompromised host.

In the previous study noted earlier, we identified 36 patients with pulmonary cryptococcosis, 18 of whom were not immunocompromised; 3 patients were categorized as definitive disease, 8 patients as presumptive, and 7 patients as colonized. One of the patients with definitive disease was treated with amphotericin B, and two of the “colonizers” had a surgical intervention to exclude malignancy. None of the 18 acquired progressive disease. These findings are consistent to those reported by Nadrous and colleagues. I concur with their statement that “we do not believe that extensive workup (with blood cultures, lumbar puncture) for possible dissemination is necessary in most nonimmunocompromised subjects with serum antigen-negative pulmonary cryptococcosis in the absence of suggestive or significant symptoms.” This study is not sufficiently powered to statistically prove this; however, it does support the prevailing clinical doctrine and the IDSA management guidelines formulated in the absence of conclusive data. This study also demonstrates that there continues to be a need for prospective studies to address with greater clarity which patients are at risk.
for developing disease, which patients should be offered therapy, and what therapeutic regimens are the most effective.

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REFERENCES

What Is the Prognosis for Using the Pneumonia Severity Index To Make Site-of-Care Decisions In Community-Acquired Pneumonia?

Starting in 1993, the approach to community-acquired pneumonia (CAP) changed dramatically with the development of management guidelines by a number of national societies.1,2 This process has continued for a decade, and the result has been a more organized approach to disease management and to defining the agenda for research in CAP. Although guidelines help to provide a framework for the care of patients, there are a number of controversies in management, and not all guidelines have approached these issues in the same way. One unresolved issue is deciding who should be admitted to the hospital, a decision that has a major impact on the cost of care for patients with CAP. The American Thoracic Society guidelines have stated that the admission decision is an “art-of-medicine” decision and that scoring systems, such as the pneumonia severity index (PSI), should be used as decision support tools for evaluating mortality risk.1 But, they also have stated that no rule can be used, by itself, to define the need for hospitalization.1 On the other hand, the Infectious Disease Society of America has endorsed the use of the PSI to guide the admission decision.2

In our current health-care environment, cost containment is an important goal, and the major driving factor in the cost of care for CAP patients is the site-of-care decision. In the United States, CAP affects 5.6 million patients annually, with a total cost of care of $8.4 billion.3 Although the majority of patients (4.5 million) are treated out of the hospital, the majority of cost ($8.0 billion) is attributed to patients admitted to the hospital. Inpatient costs can be curtailed in a number of ways, ranging from a reduction in length of stay (LOS) to avoiding hospital admission altogether, especially in patients who are at a low risk for poor outcome. Fine et al4 have examined the relationship between LOS and costs, and have estimated the financial impact of reducing LOS by 1 day to be $680, from a median of $5,942. The economic benefit of a reduction in LOS has no obvious negative clinical impact, since investigators have demonstrated that among different hospitals, there are no differences in outcome observed at sites with the shortest duration of hospitalization.5 This is probably related to the fact that most patients achieve clinical stability within 2 to 3 days of hospital admission yet are often kept in the hospital for several days after reaching this point.6 Interestingly, investigators also have demonstrated that costs are not evenly distributed throughout the hospitalization, with 32% of all costs being incurred on the first 2 days and daily costs declining thereafter.7 This can be explained because room costs are relatively constant, but pharmacy costs, emergency services, and radiologic/laboratory tests are greatest on the first day. Thus, reducing LOS can reduce costs, but maybe not as dramatically as avoiding hospitalization.

It is against this backdrop that the PSI was developed by Fine and colleagues,7 in what may be the most important investigation of CAP in the past decade. The PSI was developed using a derivation cohort of 14,199 inpatients with CAP, and was independently validated in 38,039 inpatients and outpatients prospectively enrolled in the Pneumonia Patient Outcomes Research Team cohort study.7 One limitation in the derivation of this rule was that it included mostly patients seen in a hospital emergency depart-