Cryptococcus neoformans Meningitis at 2 Hospitals in Washington, D.C.: Adherence of Health Care Providers to Published Practice Guidelines for the Management of Cryptococcal Disease

Shmuel Shoham, Cameron Cover, Nancy Donegan, Eric Fulnecky, and Princy Kumar

1Georgetown University School of Medicine, and 2Washington Hospital Center, Washington, D.C.

Meningitis due to Cryptococcus neoformans may be associated with elevated intracranial pressure (ICP), but management of this complication is often overlooked. We retrospectively analyzed 39 consecutive patients with cases of culture-proven, community-acquired meningitis and ascertained adherence to Infectious Diseases Society of America (IDSA) practice guidelines for management of cryptococcal meningitis. Of these 39 patients, 26 (67%) had infection due to C. neoformans. Cerebrospinal fluid opening pressure had been measured for 13 (50%) of these 26 patients, and major deviations from the guidelines with respect to ICP management were observed in the care of 14 (54%). Seven (50%) of these 14 patients developed neuropathies during therapy, compared with 1 of the 5 patients whose care had minor or no deviations from the guidelines (P = .024). Major departures from the IDSA guidelines for management of ICP due to C. neoformans meningitis are common and can be associated with neurological injury during therapy.

Cryptococcus neoformans is a major cause of meningitis in immunocompromised patients [1]. Cryptococcal meningitis is frequently associated with elevated intracranial pressure (ICP). Pressures of ≥250 mm H2O correlate with a higher pathogen burden, a higher incidence of neuropathies, and decreased survival [2]. Elevated ICP can be managed with removal of CSF by lumbar puncture and, in refractory cases, by placement of a CSF shunt [3–5]. Delays in diagnosis and treatment of hydrocephalus associated with cryptococcal meningitis are associated with poor outcomes [6]. Optimal treatment of cryptococcal meningitis requires antifungal therapy and management of elevated ICP.

Practice guidelines for the management of cryptococcal disease have been published by the Infectious Diseases Society of America (IDSA) [7]. The present study sought to assess the level of adherence with the guidelines and to describe the impact that deviation from these recommendations may have on clinical outcomes.

Methods. All cases of CSF culture–proven, community-acquired meningitis that occurred from 1 October 2000 to 31 December 2002 at the 2 tertiary care facilities in Washington, D.C. (Washington Hospital Center, which has 907 beds, and Georgetown University Hospital, which has 609 beds) were evaluated retrospectively. The institutional review boards of both hospitals approved the study, and the requirement for informed consent was waived. All CSF specimens had been cultured on blood and chocolate agar and thioglycolate broth. Fungal and viral cultures had not been routinely performed. Patients were identified by review of clinical-laboratory, infection-control, and infectious diseases–consultation databases.

Hospital records of patients ≥18 years of age who had CSF cultures that yielded C. neoformans were identified, and data was abstracted regarding each patient’s demographic characteristics and risk factors for disease, the antibiotic therapy used, the measurements of CSF opening pressure, and the subsequent management of ICP. Patients with multiple positive cultures were considered to have a single case of disease. For patients with multiple hospital admissions for cryptococcal meningitis, data from a single presentation were used. The management of each case was compared with IDSA treatment guidelines for cryptococcosis [7]. Two investigators jointly evaluated the records, and decisions with respect to consistency with the guidelines were made by consensus.

Deviations from the guidelines were defined as follows: (1) failure to measure the opening pressure at the initial CSF assessment; (2) failure to attempt to lower the ICP by daily lumbar drainage or by placement of an external drain; and (3) failure to perform a follow-up lumbar puncture after 2 weeks of therapy, to document clearance. The published IDSA guidelines recommend daily drainage of CSF to reduce the pressure until the ICP is controlled [7]. Because strict adherence may be difficult, drainage within 36 h after the previous CSF sam-

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Reprints or correspondence: Dr. Shmuel Shoham, Section of Infectious Diseases, Washington Hospital Center, 110 Irving St. NW, Washington, DC 20010 (shmuel.shoham@medstar.net).

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plunging was considered to meet the recommendation of the guidelines. Presence of a lumbar drain or shunt was considered to meet this recommendation. Assessment of CSF after 1 week was considered to meet expectations. Major deviations from the guidelines were defined as failure to measure the opening pressure at the time of the initial CSF assessment and/or failure to attempt to lower the ICP within 72 h after the CSF pressure was measured to be ≥350 mm H2O. All other deviations from the guidelines were considered minor. Failure to measure the initial CSF opening pressures of patients who were subsequently found to have normal ICP was not considered a major deviation.

The incidence of adverse neurologic events during therapy was determined. Neurologic events included new or worsening cranial nerve deficit, confusion, hallucinations, or obtundation. Blurred vision and seizures were not considered adverse events if they represented a continuation of symptoms present before the institution of therapy and that had not worsened in frequency or severity.

Statistical analyses were performed using SPSS software, version 10 (SPSS), and EPI Info, version 6 (Centers for Disease Control and Prevention). The Mann-Whitney U test or χ² analysis was used to compare patient characteristics and neurologic outcomes for patients with and patients without major deviations from the guidelines for management of cryptococcosis.

Results Thirty-nine patients with cases of culture-proven, community-acquired meningitis were identified. For 26 of these patients, culture of CSF was positive for C. neoformans. Pathogens identified in the other patients were Streptococcus pneumoniae (in 4), Listeria monocytogenes (in 3), Neisseria meningitidis (in 2), and Mycobacterium tuberculosis, Staphylococcus aureus, Escherichia coli, and Enterobacter cloacae (in 1 each). Of patients with cryptococcal meningitis, 19 had AIDS; 5 of these 19 were newly discovered to be seropositive for HIV. For the other patients, risk factors were solid-organ transplantation (4 patients), diabetes mellitus (4), and leukemia (1), and 1 patient had no discernible risk factor. Patients whose illness was managed according to the guidelines did not differ significantly from patients whose care deviated from the guidelines with respect to age, HIV status, CSF glucose level, CSF India ink positivity, or median value for first measured CSF pressure (265 vs. 325 mm H2O) (differences not statistically significant by Mann-Whitney U test).

Five patients received management in accordance with IDSA guidelines [7]. For the other 21 patients, the greatest deviations were observed with regard to management of CSF pressure. Major deviations were noted in the care of 14 patients. The most common variance, observed in the care of 13 patients, was a failure to measure the CSF opening pressure at baseline, during the initial CSF evaluation. For 9 patients, the recommendation to perform additional, serial lumbar puncture(s) to manage elevated ICP was not followed within the time frame set by the guidelines [7]. For 7 patients, surveillance CSF sampling after initiation of therapy was not performed. All patients received initial antifungal therapy in accordance with the recommendations of the guidelines [7]. Of the 14 patients whose care had major deviations from the guidelines, 7 (50%) developed new neurologic abnormalities during therapy, including cranial nerve deficits and visual and auditory changes. New neurologic deficits developed in 1 of the 5 patients who received management according to the guidelines and in 0 of the 7 patients whose care had minor deviations.

Discussion Elevated ICP is a common feature of cryptococcal meningitis. Patients may develop this complication before diagnosis or while receiving therapy. The precise mechanisms are not known, but it has been hypothesized that elevated subarachnoid pressure is caused by impairments of CSF outflow due to the accumulation of fungus and shed polysaccharide capsules in the arachnoid villi and subarachnoid spaces [2, 8]. Cerebral edema induced by the yeast itself, by polysaccharide antigen, and, possibly, by fungus-derived mannitol likely contributes to elevated ICP [9, 10]. Increasing headache, as well as papilledema, blindness, hearing loss, cranial neuropathies, and even death can occur in patients with elevated ICP [2, 8, 11–13]. Reduction of CSF pressure by mechanical drainage can provide rapid relief of symptoms and is associated with improved outcomes [2, 14, 15].

Patients with cryptococcal meningitis should have their CSF pressure measured as part of the initial evaluation. The IDSA guidelines recommend that, for patients with elevated CSF pressure, lumbar drainage should remove enough CSF to reduce the pressure to 200 mm H2O or 50% of the initial opening pressure, and that, initially, drainage should be performed daily to maintain the pressure in the normal range [7]. In recalcitrant cases, a lumbar drain may be used.

In our series, the majority of patients did not have their disease managed according to IDSA guidelines. Failure to measure the opening CSF pressure was the most common deviation. We speculate that many clinicians are unaware of the role of C. neoformans in the epidemiology of meningitis. In addition, practitioners involved in the initial care of these patients may have not realized the importance of ICP management in this disease. Failure to perform serial lumbar punctures (or to place a drain) for management of elevated ICP was another common departure from the guidelines. Frequent CSF sampling or placement of a drain may have been sufficiently arduous to discourage compliance with this recommendation. The guidelines are general and may not apply in every instance. For a given patient, deviations in management may be minor and/or necessary. However, we found that, when treatment deviated from the guidelines, especially with respect to management of ICP,
neurological outcomes tended to be worse. Major deviations were observed in the management of ICP in 88% of patients whose neurological status deteriorated. The better outcomes for patients treated according to the guidelines likely reflect the beneficial effect of aggressive management of elevated ICP. Given the high rate of cryptococcosis in our series, we suggest that, in treatment settings with a high prevalence of immunosuppression, measurement of ICP be performed for all patients evaluated for meningitis.

Our ability to draw conclusions from this study regarding the overall scope of deviation from the guidelines and the impact that such departures have upon clinical outcomes is limited by the small number of patients, the retrospective nature of the study, and the limited follow-up period. However, our study suggests that major deviations from the recommendations may be common and can be associated with adverse neurologic outcomes. Therefore, we advocate increased awareness of the recommendations and caution when electing to depart from them.

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