An Expanded Role for Therapeutic Lumbar Punctures in Newly Diagnosed AIDS-Associated Cryptococcal Meningitis?

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(See the HIV/AIDS Major Article by Rolfes et al on pages 1607–14.)

Keywords. cryptococcosis; lumbar puncture; intracranial pressure.

For decades, clinicians have debated the role of repeated lumbar punctures (LPs) in the management of increased intracranial pressure (ICP) among patients with cryptococcal meningitis. After the initial diagnosis of cryptococcal meningitis, most experts agree that repeated LPs are appropriate for the following reasons: first, in the management of increased ICP through the removal of cerebrospinal fluid (CSF); second, to follow the mycologic and inflammatory response to antifungal therapy; and third, to look for evidence for persistent or relapsing disease and the development of immune reactivation in inflammatory syndrome. Among these indications, management of increased ICP is the most common reason for performing repeated LPs among patients with newly diagnosed cryptococcal meningitis.

These so-called “therapeutic LPs” have been endorsed by several groups, including the Infectious Diseases Society of America (IDSA), the South African Medical Society and the World Health Organization (WHO), and are performed in lieu of more invasive procedures, such as the placement of a lumbar drain or temporary ventriculostomy [1–3]. Indeed, the IDSA guidelines for the management of cryptococcal meningitis go so far as to recommend daily LPs in situations that dictate a more aggressive approach to controlling persistently elevated ICP (>250 mm of CSF), in an effort to improve overall survival, prevent neurologic consequences, such as sudden blindness, deafness, and/or other cranial nerve abnormalities, and improve symptom control [1]. To our knowledge, no randomized controlled trials have explored the optimal frequency of therapeutic LP, the amount of CSF to be removed at each interval, or important parameters that inform the clinician if and when to place a permanent ventricular shunt. There are even fewer data on such temporary interventions as lumbar drains and external ventriculostomy drains. Thus, our current recommendations are based on large data sets, smaller observational studies, and anecdotal experience.

It is undeniable that outcomes are worse among human immunodeficiency virus-infected patients with newly diagnosed cryptococcosis in the developing world than among those in the industrialized world [4–7]. Factors contributing to these poorer outcomes are complicated, but certainly they include limited access to care and resources, including antifungal and antiretroviral therapy, and logistical challenges [5–8]. Much effort has been expended to help improve access to antifungal therapy for patients in greatest need [9, 10]; less attention has been given to the importance of therapeutic LPs in the management of cryptococcal meningitis. Why is this important? Because many investigators have demonstrated that poorer outcomes in these patients are due not only to limited access to rapidly fungicidal drugs, such as amphotericin B and flucytosine, but also to inadequate management of increased ICP [11]. The relative influences of these 2 factors on the poor outcomes among these patients are difficult to determine, but most investigators agree that they are inextricably linked.

In this issue of Clinical Infectious Diseases, Rolfes and colleagues [12] provide more observational data supporting the use of therapeutic LPs among patients...
with newly diagnosed AIDS-associated cryptococcal meningitis. Most of these patients were enrolled in the recently published Cryptococcal Optimal ART Timing (COAT) trial, which demonstrated a survival advantage for patients with deferred (5 weeks) versus early (1–2 weeks) antiretroviral therapy among those with newly diagnosed cryptococcal meningitis [13]. In the current study [12], clinicians were encouraged to perform therapeutic LPs among patients with high initial opening pressures and/or among those experiencing symptoms consistent with increased ICP. The primary end point was mortality rate at 11 days, so all the data concern acute mortality. When these data were adjusted for patient weight, CSF fungal burden, and Glasgow coma score, the authors observed significantly improved short-term survival among patients who underwent ≥1 therapeutic LP after the initial diagnostic LP. What is surprising is that these observations occurred independent of initial opening ICP. These data are both interesting and important because they argue for a much more careful look at the indications for performing therapeutic LPs in the acute management of cryptococcal meningitis. There are several plausible explanations for these observations, but the most likely is that ICP may increase over the days after an initially normal measurement, with or without symptoms, and that the reduction in ICP after LP is beneficial. This “preemptive” approach to therapeutic LPs seems to have had a significantly reduced mortality rates.

This study has its shortcomings. It was not a randomized trial, and the sample was relatively small. Moreover, various factors influence the decision to perform LPs, including physician preference and patient acceptability, and these confounders are difficult to measure. Nonetheless, these data provide more insights into the value of therapeutic LPs in the acute setting among patients with cryptococcal meningitis and emphasize that the baseline opening ICP and/or the development of symptoms of increased ICP may not be the only indications for repeated LP. Indeed, ICP is such a dynamic process among these patients that a single measurement at the time of diagnosis is not always reflective of significant changes in ICP over time. In essence, these data raise a question: Should all these patients undergo another LP early (eg, within ≤3 days) after the initial diagnosis of cryptococcal meningitis?

There are several barriers to the standard use of therapeutic LPs in the developing world, particularly in sub-Saharan Africa. Not the least of these is limited access to proper manometers and sterile LP needles. Some groups have recently called for governmental and WHO initiatives to provide readier access to LP kits that include LP needles and manometers. An alternative to standard manometers are makeshift manometers using disposal intravenous tubing attached to a metered stick [14]. This alternative has not been validated on a large scale but must be considered because of reduced cost.

Education for healthcare providers is another potential barrier, but I have learned that most providers caring for these patients are keenly aware of the message contained within the treatment guidelines. Specifically, most can provide a fairly detailed understanding of the need for repeated LPs for therapeutic purposes. The challenge is more to make therapeutic LPs a priority in the management of these patients. Imagine that you are a physician working in a medical facility in sub-Saharan Africa (or any other part of the developing world), charged with the responsibility of caring for the 10–15 patients you admitted within the last 24 hours. You also have 60–80 patients to see in the clinic today. Without additional support from other providers, the performance of a repeated LP to improve symptoms and possibly improve the outcome in a patient with cryptococcal meningitis becomes a low priority, given the expense of the procedure, the time commitment, and the competing demands of other patients with similarly critical issues.

The other important barrier is cultural. Indeed, patients in sub-Saharan Africa are generally reluctant to undergo initial LP for diagnosis and management of cryptococcal meningitis, much less repeated LP, because of a perception that LPs are unnecessary and dangerous and may lead to death. Indeed, cryptococcal meningitis and death are closely linked in sub-Saharan Africa, and the cause of death is often mistakenly attributed to LP. Convincing an individual with few symptoms to undergo repeated LP in this setting is very challenging.

Despite these challenges, I believe that data from the current study [12] and previous observations provide sufficient evidence to warrant a prospective evaluation of the influence of routine therapeutic LPs on morbidity and mortality in the acute management of cryptococcal meningitis. The design of such a trial would be challenging, but it would be worth the effort. In the meantime, healthcare providers must continue pushing for expanded access to LP needles and manometers for these highly vulnerable patients. This important and simple intervention has tremendous potential impact on short-term mortality and morbidity rates, but it must be studied and validated before becoming a part of routine practice. If the practice of routine repeated LP is validated, then this approach must be accepted by busy clinicians and presented to patients in a way that emphasizes both the importance and safety of the procedure.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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