Lumbar puncture drainage with intrathecal injection of amphotericin B for control of cryptococcal meningitis

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Summary
Cryptococcal meningitis is a disease with high mortality and refractory to intravenous antifungal treatments with agents such as amphotericin B and fluconazole. We investigated lumbar puncture catheter drainage with an intrathecal injection of amphotericin B as a treatment for cryptococcal meningitis. All of the 14 patients enrolled in the treatment group survived with no evidence of relapse during 1-year follow-up. Complications included lumbosacral nerve root irritation in seven patients and urinary retention in seven patients. This study demonstrated that the technique used was effective in controlling the symptoms. The major complications disappeared after discontinuation of intrathecal injection of amphotericin B or with low-dose therapy. Therefore, this technique could be an effective and safe method for the treatment of cryptococcal meningitis.

Introduction
Cryptococcal meningitis is a potentially fatal disease caused by infection with Cryptococcus spp., especially Cryptococcus neoformans. High intracranial pressure is responsible for symptoms such as headache, cranial damage and hernia. The main therapy is the intravenous injection of antifungal agents, such as amphotericin B, as induction treatment followed by maintenance treatment (Saag MS et al., Clin Infect Dis 2000; 30: 710–8), whereas with conventional antifungal drug methods, high intracranial pressure is difficult to control. The mortality rate is high even if the patient is treated with a combination of two or more antifungal drugs. Our study showed lumbar drainage with intrathecal injection of amphotericin B is an effective method to control cryptococcal meningitis.

Cases
General data
Fourteen cryptococcal meningitis patients were enrolled in this study and were treated using the lumbar drainage method in our department between February 2003 and February 2007. Patients included eight men and six women whose age ranged from 16 to 56 years (mean, 34.2 years; median, 35.5 years). All the patients were HIV negative and otherwise healthy. The interval between the occurrence of first symptoms and time point of diagnosis varied from 13 days to 70 days, with a median of 32 days.

Clinical presentation
All 14 patients experienced headaches. 10 had irregular fever (temperature ranging from 38 °C to 40 °C) and nine patients were admitted with signs of meningeal irritation. Two patients were unconscious on arrival at the hospital. Two patients experienced diplopia and three had ear noises. The details are described in Table 1.

Detection of cranial spinal fluid
The intracranial pressures (ICP) varied from 200 mmH2O to more than 400 mmH2O, and in five
cases, an ICP of more than 400 mmH2O was detected. India ink examination of cranial spinal fluid (CSF) was positive and pathogen was identified as *Cryptococcus neoformans* by culture and API test (bioMérieux) in all patients. Yeast count in the CSF varied from 4 to 170 × 10^6/l and the titres of cryptococcal latex agglutination test (LAT; Immuno Mycologics, Inc, Norman, OK, USA) for CSF of patients were between 1 : 160 and 1 : 2560 on admission.

### Treatment protocol

**Intravenous use of antifungal agents.** The patients were treated with amphotericin B intravenously or intrathecally. Amphotericin B was administered intravenously for more than 8 weeks, beginning at 1 mg day\(^{-1}\) and gradually increased to 35 mg day\(^{-1}\) (0.5–0.7 mg kg\(^{-1}\) day\(^{-1}\)) over 4 days, in combination with oral 5-flucytosine (100 mg kg\(^{-1}\) day\(^{-1}\)). Two patients were treated with intrathecal amphotericin B because of adverse reactions to intravenous administration, including bone marrow depression and liver dysfunction. After about 8 weeks of induction treatment, all patients were given itraconazole (400 mg day\(^{-1}\)) or fluconazole (150 mg day\(^{-1}\)) plus itraconazole for over 6 months. In addition, 20% mannitol solution was given intravenously one to four times per day to decrease the ICP.

**Lumbar drainage and intrathecal injection of amphotericin B.** A lumbar catheter was inserted in the L4/L5 disc space and connected to a CSF drainage device. With the patient in a supine position, the device’s manometer was set at 20 cm above the line of the bilateral acoustic duct. Over 200 ml of CSF was drained per day for the first 4 days and subsequently, the amount of CSF drained was gradually decreased. Amphotericin B was diluted into the drained CSF and slowly injected back into the subarachnoid space through the lumbar catheter. The injection was administered slowly, with not more than 5 ml CSF dilution of amphotericin B per 20 min. The dose of amphotericin B used intrathecally was 0.1 mg day\(^{-1}\) for the first injection, and then increased 0.1 mg each time thereafter to 1.0 mg day\(^{-1}\). The injection was given once a day during the CSF catheter drainage, and then once every 2 days for the following weeks. The duration of the treatment was 5–21 days (median 14 days). After the catheter was pulled out, the lumbar puncture could be adopted for intrathecal injection every 2–3 days.

### Outcome

The two unconscious patients recovered after lumbar drainage; the diplopia experiences by two patients and the ear noises experiences by three patients disappeared after 3–7 days’ treatment.

After 2 weeks, the yeast count in the CSF decreased to 1–20 × 10^6/l. After 4–8 weeks, the symptoms were no longer evident and mycological cultures of CSF from all patients were negative, although the CSF yeast counts remained between 1 and 8 × 10^6/l. All the patients were then given oral antifungal agents for at least 6 months. The titres of LAT decreased to 1 : 8 to 1 : 156, and the CSF yeast counts were 1–8 × 10^6/l after over 1-year of follow-up. To date, no relapse of symptoms has occurred.

### Complications

The main complications of intrathecal injection of amphotericin B were lumbosacral nerve root irritation (manifested as lumbar or leg pain) and urinary retention (Table 2). No catheter-related infection occurred in our study. The complications disappeared after the dosage of intrathecal amphotericin B decreased.

### Discussion

In this study, we demonstrate that the lumbar drainage and lumbar intrathecal injection of amphotericin B is an effective and safe alternative to repeated lumbar punctures in the treatment of cryptococcal meningitis. The incidence of catheter-related bacterial meningitis was low. The main complications included lumbosacral nerve root irritation and urinary retention, which were mild and manageable. None of the

<table>
<thead>
<tr>
<th>Intrathecal dose (mg)</th>
<th>Complication</th>
<th>Numbers of patients</th>
</tr>
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<tbody>
<tr>
<td>0.6</td>
<td>Lumbosacral nerve root irritation</td>
<td>3</td>
</tr>
<tr>
<td>0.8</td>
<td>Lumbosacral nerve root irritation</td>
<td>4</td>
</tr>
<tr>
<td>0.9</td>
<td>Retention of urine</td>
<td>4</td>
</tr>
<tr>
<td>1.0</td>
<td>Retention of urine</td>
<td>3</td>
</tr>
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</table>
patients in our study received prophylactic antibiotics during lumbar drain process and no nosocomial infection occurred.

The mechanism of increased ICP in patients with cryptococcal meningitis is not well understood. It was postulated to be a result of the increment of vascular permeability and cerebral oedema resulting from cytokine-induced inflammation (Graybill JR et al., Clin Infect Dis 2000; 30: 47–54). It is also proposed that arachnoid villi and lymphatic vessels plugged with fungal cells may be a key factor in leading to significant impairment of the reabsorptive function resulting in elevated CSF pressure (Denning DW et al., Am J Med 1991; 91: 267–72; Malezza R et al., Clin Invest 1994; 72: 1020–6). Thus, it is very important to eliminate the pathogenic yeast in the central nerve system to control the ICP and other symptoms of meningitis.

There are several methods to manage high ICP, such as ventriculoperitoneal or ventriculoatrial shunt. Manosuthi W et al. (Int J STD & AIDS 2008; 19: 268–71) retro-analysed their work on temporary external lumbar drainage for reducing ICP in patients with cryptococcal meningitis, proposing temporary external lumbar drainage to be an important and safe method for reducing the high ICP, but did not use amphotericin B intrathecally, and only 81.5% of their patients were alive after 3 months of follow-up.

Amphotericin B is the treatment of choice for cryptococcal meningitis (Saag MS et al., Clin Infect Dis 2000; 30: 710–8), but it is difficult for amphotericin B to permeate into CSF (Zhang X et al., J Drug Target 2003; 11: 117–22). This may explain why cryptococcal meningitis patients respond poorly to intravenous amphotericin B treatment, however, intrathecal injection could elevate the amphotericin B concentration in CSF significantly. The benefits of lumbar drainage were not only to increase the concentration of antifungal agents in CSF, but also to reduce the ICP and yeast burden in the central nervous system, thereby ameliorating symptoms. The severe complication of this technique, such as nosocomial infection, did not appear in our study with strict aseptic techniques.

The overall mortality associated with cryptococcal meningitis is approximately 25% in Thai patients with AIDS (Jongwutiwes U et al., Curr HIV Res 2007; 5: 355–60; Manosuthi W et al., J Med Assoc Thai 2006; 89: 795–802). Intrathecal use of amphotericin B (through lumbar puncture or lumbar drainage) significantly reduced mortality in our study, i.e. all 14 patients survived. However, more clinical data are required to confirm this finding. The symptoms also improved more quickly as shown in a previous study using lumbar puncture (Chen J et al., Acad J Sec Mil Med Univ 2005; 26: 456–57). In this article, Chen J and his co-workers reported 46 cases of cryptococcal meningitis treated with amphotericin B intravenously and through lumbar puncture injection. The symptoms, such as headache (all 46 cases) and diplopia (11/46), improved after 23–40 days treatment. While in our study, most of patients’ condition improved after 1–2 weeks treatment.

According to the Practice Guidelines for the Management of Cryptococcal Disease by National Institute of Allergy and Infectious Diseases Mycoses Study Group, standard therapy consists of amphotericin B, 0.7–1 mg kg⁻¹ day⁻¹, plus flucytosine, 100 mg kg⁻¹ day⁻¹, for 6–10 weeks for otherwise healthy patients with CNS cryptococcal infection. An alternative to this regimen is amphotericin B (0.7–1 mg kg⁻¹ day⁻¹) plus 5-flucytosine (100 mg kg⁻¹ day⁻¹) for 2 weeks, followed by fluconazole (400 mg day⁻¹) for a minimum of 10 weeks (Saag MS et al., Clin Infect Dis 2000; 30: 710–8). In our series, the amphotericin B was given at the dosage of 0.5–0.7 mg kg⁻¹ day⁻¹ because patients always had severe adverse reaction when amphotericin B was given intravenously at a higher dosage in China.

Because of its inherent toxicity and danger, lumbar puncture was not regularly recommended, but this manipulation is relatively easy to perform if the medical staff are well trained, and the adverse reactions were generally mild and manageable. Previously, we used the lumbar puncture for amphotericin B injection to treat cryptococcal meningitis patients in our department, which also decreased the mortality but with less efficiency in the long term and more occurrences of lumbosacral nerve root irritation and urinary retention. In the study of Chen J et al. (Acad J Sec Mil Med Univ 2005; 26: 456–57), about 35% patients (16/46) had complication of acroanaesthesia and urinary retention. The frequency of neurotoxicities in our study was much lower. The possible reasons could be that intrathecal catheter was more convenient for doctors to inject amphotericin B slowly.

Overdrainage of CSF, reported in about 3% of cases (Samadani U et al., Neurosurgery 2003; 52: 148–51), is a rare but potentially serious complication of lumbar drains that can cause tentorial or tonsillar herniation (reported in 3 of 1198 procedures) or subdural haematoma if not recognised (Dagniew E et al., Neurosurgery 2002; 51: 823–9; Dardik A et al., J Vasc Surg 2002; 36: 47–50). Patients need careful
and frequent monitoring and follow-up, necessary examinations and urgent intervention should be taken.

In conclusion, the incidence of complications in lumbar catheter drainage method for intrathecal use of amphotericin B was low and manageable. The clinical symptoms of the patients treated with this method were controlled quickly and were stable in the long-term follow-up. We suggest that this procedure is safe and effective in the treatment of cryptococcal meningitis.

Acknowledgments

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