TJUH ADHERENCE TO IDSA GUIDELINES FOR THE TREATMENT OF CRYPTOCOCCAL MENINGITIS

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Introduction

Cryptococcal meningitis is an infectious complication of immune compromised states that carries a high rate of mortality or relapse. Although Infectious Disease Society of America (IDSA) guidelines outline the recommended treatment regimen for cryptococcal meningitis, clinicians take a heterogenous clinical approach. This study examines the use of antifungal regimens in treating cryptococcal meningitis at a tertiary care hospital.

Objectives

The primary endpoint was to determine the percentage of patients who received antifungal treatment that was backed by the highest Sobel class recommendation (i.e., "A1") from the most recent IDSA-endorsed guidelines. Secondary endpoints were mortality and clinical relapse.

Methods

After review of TJUH fungal culture data from 2003 to 2007, this study included patients who had either:

1. A positive cerebrospinal fluid culture (CSF) for *C. neoformans* (12 patients)
2. A positive blood culture with signs/symptoms of meningitis (1 patient)

After appropriate patients were identified, chart reviews were performed to obtain pertinent demographic, laboratory and treatment data (see Table 1). Treatment strategies were then compared to the most recent IDSA-endorsed practice guidelines.¹

For HIV+ patients, the class A1 recommendation for the treatment of cryptococcal meningitis involves all of the following:

1. "Induction" – 2 weeks of amphotericin B (0.7-1 mg/kg/d) + flucytosine (100mg/kg/d in divided doses), followed by
2. "Consolidation" – 10 weeks of fluconazole 400 mg/d, followed by
3. "Maintenance" – lifelong fluconazole at 200 to 400 mg/d

For HIV negative patients, two endorsed regimens exist. The first is identical to that for HIV+ patients except maintenance therapy is not needed, and the second regimen is simply extended induction therapy for six to ten weeks without either consolidation or maintenance.

Results

Of the eleven HIV+ patients identified with cryptococcal meningitis, two (18%) were treated with a regimen consistent with the IDSA-endorsed class A1 recommendations. Of the two

Table 1. Patient baseline characteristics at presentation.

Patient Characteristics	1st presentation N = 13 pts total
Age, Years [Median (Min, Max)]	42 (37, 58)
Sex - Male	12
Ethnicity	
Caucasian	1
African-American	12
Recent Antifungal Therapy	0
Comorbidities	
Diabetes Mellitus	1
Corticosteroid Therapy	0
Concurrent Bacterial Infection	3
HIV seropositive ¹	11
CD4+ count [Median (Min, Max)]	14 (2, 155)
Viral load [Median (Min, Max)]	146,642 (<75, >750,000)
HAART	2
<i>Pneumocystis jiroveci</i> prophylaxis	1
MAI prophylaxis ²	1
Concurrent cryptococcal fungemia	7
CSF	
WBC count [Median (Min, Max)]	32 (1, 635)
Protein [Median (Min, Max)]	101 (41,855)
Glucose [Median (Min, Max)]	40 (4, 63)
HAART: Highly Active Antiretroviral Therapy, MAI: Mycobacterium avium-intracellulare complex, CSF: Cerebrospinal Fluid, WBC: White Blood Cell	

HIV negative patients with cryptococcal meningitis, one was treated with an endorsed regimen (see Table 2).

For the HIV + subset, the most common deviations from the guidelines were as follows (note multiple deviations were present in some patients):

- 1) Flucytosine use during induction
 - a. Failure to use – 4 patients
 - b. Insufficient duration – 4 patients
 - c. Insufficient dose – 1 patient
- 2) Insufficient duration of amphotericin B – 2 patients
- 3) Insufficient duration of fluconazole during consolidation – 2 patients

For the secondary endpoint analysis, all five observed instances of death or clinical relapse were in patients who had non-endorsed induction regimens (see Table 2).

Table 2. Clinical outcomes by treatment categories.

Treatment Group	# of pts with relapse or death /# of pts treated
HIV (+) patients	
Induction therapy	
Appropriate Regimen	0 / 3
Inappropriate Regimen	5/ 8
Consolidation therapy	
Appropriate Regimen	0 / 2
Appropriate After Inappropriate Induction	4/ 7
Inappropriate Regimen	1 / 2
HIV (-) patients	
Induction therapy	
Appropriate Regimen	1 / 1
Inappropriate Regimen	1 / 1

Conclusion

The vast majority of patients diagnosed at TJUH with cryptococcal meningitis from 2003 to 2007 were not treated with the IDSA-endorsed regimen. Despite a small sample size, a significantly lower rate of mortality and relapse was seen in patients who received the IDSA-endorsed regimen.

Practitioner barriers to guideline adherence need to be further studied, and likely involve fear of antifungal side effects, logistical complexity of the overall treatment regimen and the belief that amphotericin B monotherapy during induction is non-inferior. With specific regard to the lack of clinician adherence to flucytosine recommendations, it is worthwhile to note that no outcome-based study exists that directly compares amphotericin B monotherapy (at currently recommended doses) to flucytosine combination therapy; the current recommendation to use combination therapy is based on a high quality study that demonstrated more rapid CSF sterilization.² Perhaps completion of such a randomized trial that demonstrates improved clinical outcomes with flucytosine addition would change future clinical practice.

References

1. Saag, ML (2008). "Practice Guidelines for the Management of Cryptococcal Disease." *Clinical Infectious Diseases* 30: 710-718.
2. Bennett, JE (1979). "A Comparison of Amphotericin B alone and combined with Flucytosine in the Treatment of Cryptococcal Meningitis." *New Engl J Med* 301(3):126-31.

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