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MORTALITY AFTER CLINICAL MANAGEMENT OF AIDS-ASSOCIATED CRYPTOCOCCAL MENINGITIS IN KENYA

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ABSTRACT

***Background*: Cryptococcal meningitis (CM) is an increasingly prevalent infection among HIV/AIDS patients and is becoming a leading cause of morbidity and mortality in Africa. The short-term prognosis and management of patients with CM may be improved by identifying factors leading to mortality in patients with CM.**
***Objective*: To assess the clinical management and mortality associated with cryptococcal meningitis (CM) in patients with acquired immunodeficiency syndrome (AIDS) in Kenya.**
***Design*: A retrospective study.**
***Setting*: Kenyatta National Hospital and Mbagathi District Hospital, between August 2008 and March 2009.**
***Subjects*: Seventy six HIV-infected patients confirmed to be CM positive.**
***Results*: Results show that 30 (40%) of 76 patients diagnosed with CM died during hospitalisation after a median hospital stay of ten days (range, 2-73 days). Significant predictors of mortality in the univariate model were Mycobacterium tuberculosis (TB) co-infection (P = 0.04), having been diagnosed with a co-morbid condition such as diabetes mellitus, oral candidiasis and hypertension (P = 0.01), and a low median CD4+ T lymphocyte count (P < 0.001). The multivariable model revealed that male sex, previous or current anti-retroviral therapy (ART) at admission and CD4+ T lymphocyte count less than 50 were significant predictors of mortality. Conversely, a minimum of two weeks of amphotericin B treatment (P < 0.001), initiation of ART (P = 0.007) and monitoring of creatinine and electrolyte levels (P = 0.02) were significantly associated with survival in the univariate model.**
***Conclusions*: CM-associated mortality in Kenya is high; there is an opportunity to improve the management and the short-term outcomes of hospitalised HIV positive patients with CM in Kenya.**

INTRODUCTION

Immunosuppressed individuals are particularly susceptible to Cryptococcus neoformans infection and development of cryptococcal meningitis (CM) (1). In regions of the world that are heavily burdened by the acquired immunodeficiency syndrome (AIDS) epidemic, the incidence rate of AIDS-associated CM is remarkably high (2). An estimated 720,000 individuals are infected with CM each year in sub-Saharan Africa (2).The short-term prognosis of patients with CM is poor, and the disease is becoming a leading cause of morbidity and mortality among AIDS patients (3-4). Even with the most effective treatment, mortality typically occurs at a proportion of 9-70% within 3 months of diagnosis, and in-hospital mortality in sub-Saharan Africa occurs at a rate of 25% (2-5).

This study focused on assessing the management of patients with CM in Kenya, where 1.4 million people were living with human immunodeficiency 4 East African Medical Journal July 2014 virus (HIV) infection in 2008, the national prevalence of HIV was estimated at 7.8% for adults aged 15-49 years and the CM-associated mortality was high (2-6).

The overall prevalence of HIV (approximately 1.2 million adults aged 15-64 years) in this population has decreased nationally to 5.6% in 2012 (6). Current guidelines for sub-Saharan Africa recommend 1 mg/ kg/d amphotericin B (AmB) for two weeks as induction therapy or, if unavailable, fluconazole (FLC) 800 mg for four weeks (7). This is followed by fluconazole (FLC) 400 mg/d alone for eight weeks and 200 mg/d thereafter for life. Since antifungal medication is limited in these regions, other predictors of mortality must be identified to ease the burden of CM.

Most studies in Africa that evaluated antifungal therapy for CM were carried out in South Africa or Uganda (8). Considering that treatment for CM is similar throughout sub-Saharan Africa, we expected the clinical outcomes in Kenya to be comparable to those found in previous studies. This study was conducted to elucidate factors associated with mortality in CM in patients with HIV at two public hospitals in Nairobi, Kenya. Given the limited resources in developing areas, the identification of modifiable factors associated with mortality will be helpful in improving in-hospital CM management.

MATERIALS AND METHODS

Study design: A retrospective review of 76 patient medical records who were admitted to Kenyatta National Hospital (KNH) or Mbagathi District Hospital (MDH) between August 2008 and March 2009 was conducted. Patients considered for this study had to be HIV and CM positive. CM diagnosis had to be confirmed by India ink staining and/or cryptococcal antigen testing.

Study settings and participants: KNH is the oldest and largest referral and teaching hospital in Kenya with a 1,800 bed capacity. It serves as the primary hospital for the four million residents in the capital city, Nairobi. MDH is a 169-bed public hospital that serves as the tuberculosis referral centre for Nairobi. Study participants included HIV positive patients aged 13 years and older admitted at the two hospitals with a diagnosis of CM. Ethical approval and permission for this study was obtained from the University of Alabama at Birmingham Institutional Review Board (IRB) and the Kenyatta National Hospital Ethics and Research Committee.

Patient data collection: A data abstraction sheet was used to collect data from each patient's medical records. Variables abstracted included demographic characteristics, duration of illness, previous use of antifungal drugs, CM treatment, general questions on CM management (e.g. rehydration and supplementing of potassium chloride, therapeutic lumbar puncture (LP), fundoscopy, computed tomography (CT) scan, biochemical tests for creatinine, potassium, and blood glucose, haemoglobin and use of anaelgesics) and clinical status of HIV infection. Date of HIV diagnosis, CD4 cell counts, HIV viral load, co-morbidities (neurological disorders, chronic conditions and microbial infections), discharge status (alive or dead) and treatments were also obtained from patient records.

Statistical analysis: Categorical variables are presented as frequencies and percentages, and continuous variables as means and medians. Clinical presentation and outcome were compared using $\chi 2$ test and Fisher's exact test for categorical variables, and student t test and z test for continuous variables. Correlation analyses were performed to detect multicollinearity between independent variables. Multivariable logistic regression analyses using a significance level of <0.05 was used to determine factors associated with CM outcomes. Variables that were statistically significant at $p<0.05$ on the bivariate model and those known to be associated with clinical outcomes of CM based on previous studies were entered into the multivariable model using the backward stepwise method. Odds ratios (OR) and 95% confidence intervals (CI) were generated as measures of association for all variables entered into the model. Data analysis was conducted using SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Patient characteristics: Characteristics of the patient cohort are summarised in Table 1. Of the 76 patients diagnosed with CM, 36 (47%) were seen at KNH and 40 (53%) at MDH. All patients were confirmed to be HIV positive. Median age of the patients was 35 years and 61% were males. TB co-infection was reported in approximately one-third (33%) of the patients. At the time of admission for CM, 26 patients (34%) were known to be infected with HIV, and 19 (25%) were currently or previously on ART. The remaining 50 (66%) patients were diagnosed with HIV while being treated in the wards. The median CD4+ T lymphocyte count of the patients with CM patients was 31 (Range: 1- 468) cells/mm3. In addition to CM, other AIDS-defining illnesses diagnosed in the cohort included tuberculosis (33%), Kaposi's sarcoma (1 patient), and candidiasis (1 patient).

Treatment profiles: As indicated in Table 1, 51% of the patients with CM received and completed the WHO recommended AmB and FLC combination therapy. More than 90% of the patients with CM received some form of antifungal therapy (i.e. combination AmB and FLC, AmB alone, or FLC alone) and antibiotics for July 2014 East African Medical Journal 5 treatment of CM and bacterial infections other than TB

respectively. Most patients received co-trimoxazole and/or benzylpenicillin to treat and prevent bacterial infections. The majority (79%) of the patients also received at least one anaelgesic, the most common of which was paracetamol (53%).

In-hospital Mortality Profile: A comparison of the short-term outcome of inpatients is given in Table 2. Overall, 39% (30/76) of the patients confirmed to have CM died, with a median time to death of ten days after admission. The two-week mortality was 29% (22/76). Univariate analysis revealed that mortality was associated with concomitant TB infection (P=0.04), having a co-morbid condition such as diabetes mellitus, oral candidiasis and hypertension (p=0.01), and measuring baseline creatinine and electrolyte once (P<0.001). Patients who died had significantly lower CD4+ T lymphocyte counts compared with those who survived (P<0.001). All but two patients discharged alive at KNH had their creatinine and electrolyte levels measured more than once. Of the ten patients who had creatinine and electrolyte levels measured only once, the six who received AmB all died (data not shown). A multivariate analysis showed that male sex (OR= 1.9, CI 1.0-3.7, P=0.06), previous or current ART at the time of admission (OR= 3.5, CI 1.2-10.6, P=0.03), and CD4+ T lymphocyte count <50 (OR= 4.3, CI 1.5-12.6, P=0.01) were independently associated with mortality.

Table 1

Baseline charactristics of patients with cryptococcal meningitis admitted at Kenyatta National Hospital and Mbagathi District Hospital between August 2008 and March 2009

Variable	Frequency n=76(%)
Age, median years (range)	35(20-53)
Sex	
Females	30(40)
Males	46(60)
Time to discharge: median days (range)	22(5-68)
Time to death: median days (range)	10(3-74)
TB co-infection	25(33)
HIV-seropositive at admission	26(36)
ART, current or previous	19(25)
CD4+ T lymphocyte count in cells/mm^3	
Not measured	22(29)
≤25	19(25)
25-99	24(31)
100-249	9(12)
≥250	2(3)
Median(range)	31(1-468)
Viral load, median HIV-1 RNA copies/µl (range)	605,000(207-6,000,000)
CSF protein/glucose levels	
Not measured	39(51)
High CSF protein levels	24(32)
Low CSF glucose levels	33(42)
Complete blood count	
Not done	29(38)
Low hemoglobin levels	15(20)
Low white blood cells count	13(17)
Baseline creatinine and electrolytes	
Not measured	41(54)

Measured	35(46)
Measured more than once	25(33)
Creatinine, median μmol/L (range)	91(42-153)
Antifungal therapy	
None 5(7)	
AmB and FLC	39(51)
AmB alone	23(30)
FLC alone	9(12)
ART initiated	8(11)
Analgesics	
None	16(21)
Paracetamol	40(53)
Tramadol	13(17)
Brufen	14(18)
Diclofenac	13(17)
Antibiotics	
None	4(5)
Co-trimoxazole	54(72)
Benzylpenicillin	48(63)
Ceftriaxone	32(42)
Chloramphenicol	32(42)

Table 2
In-hospital mortality profile of HIV positive patients with CM in Kenya, August 2008- March 2009

Variable	Alive n = 46 (%)	Dead n = 30 (%)	P-value
Hospital			
Kenyatta National Hospital	16 (40)	14 (39)	0.58
Mbagathi District Hospital	24 (60)	16 (61)	
Outcome after two weeks of admission	54 (71)	22 (29)	0.07
Age, median years (range)	35.0 (20-46)	35.5 (25-53)	1.00
Sex			
Females	18 (39)	12 (40)	1.00
Males	28 (61)	18 (60)	
Antifungal therapy			
None	1 (2)	4 (13)	0.08
AmB and FLC	27 (59)	12 (40)	0.26
AmB alone	13 (28)	10 (34)	0.80
FLC alone	5 (11)	4 (13)	0.73
ART			
Current or previous	14 (30)	5 (17)	0.28
Initiated	8 (17)	0 (0)	0.007
TB co-infection	10 (22)	15 (50)	0.04

Co-morbidity present	15 (33)	22 (73)	0.01
Viral load, median HIV-1 RNA copies/μl (range)	604,924 (207-6,000,000)	604,746 (93,053-3,536,282)	0.87
CD4+ T lymphocyte count, median cells/mm^3 (range)	49 (1-468)	14 (3-214)	<0.001
Antibiotics administered			
Any	44 (96)	27 (90)	0.30
None	1 (2)	3 (10)	0.32
Co-trimoxazole	36 (78)	18 (60)	0.35
Benzylpenicillin	32 (70)	16 (53)	0.38
Ceftriaxone	21 (46)	11 (37)	0.55
Chloramphenicol	18 (39)	14 (47)	0.62
Metronidazole	2 (4)	3 (10)	0.38
Baseline creatinine and electrolytes			
Not measured	25 (54)	16 (53)	0.95
Measured	21 (46)	14 (47)	0.84
At least six times	8 (17)	0 (0)	0.02
At least four times	18 (39)	2 (7)	0.002
At least twice	20 (43)	5 (17)	0.02
Once	1 (2)	9 (30)	<0.001

Values in bold are statistically significant at p<0.05
Chi square and student t-test were used for categorical and continuous variables, respectively.

Co-morbidity include ; TB , hepatitis B, brain abscess, Kaposi's sarcoma, gastroenteritis, hypertension, diabetes, cerebral atrophy, subarachnoid hemorrhage, epilepsy, ulcer, psychosis, pellagra, respiratory tract infection, and oral candidiasis.

DISCUSSION

This study reveals that there is high mortality associated with CM in patients with HIV/AIDS in public hospitals in Kenya and discusses some aspects of CM management that can be improved. The study identified predictors of mortality among patients with CM and highlighted the need to address the existing gaps in the management of this disease in Kenya.

CM associated mortality in our inpatient population, both at two weeks (29%) and overall (39.5%) is consistent with previously published studies from Africa (9,10). We found that the majority of the deceased patients (73%) died during the first two weeks of admission. This may be attributed to late presentation of patients as evidenced by low CD4+ T lymphocyte counts and high viral loads at admission. As expected, patients with CD4+ T lymphocyte count < 50 fared worse than their counterparts. Our study also revealed that patients who had previously received or were currently receiving ART at the time of admission were four times more likely to die. This may be attributed to advanced HIV/AIDS stage at presentation to hospital. A recent cost-effectiveness study supported routine cryptococcal antigen (CRAG) screening for patients beginning ART since detection is possible three weeks before CM clinical symptoms manifest (11). In limited resource settings, early screening and appropriate FLC prophylaxis could potentially ease the burden of CM in patients with AIDS.

Although the patients who completed AmB treatment fared well, it should be noted that 20 patients who were started on AmB, either alone or in combination with FLC, died. Based on the univariate analysis, we suspect that the inadequate monitoring of creatinine and electrolyte levels may also have contributed to these deaths. Ideally, AmB should be stopped if significant nephrotoxicity develops (7-9). All the six patients who were not tested for renal function after AmB treatment was started died. Although this may be due to patients dying before they could be monitored properly, we found a protective effect from being tested even once after treatment. Specifically, of the 24 patients who were treated with AmB and had creatinine and electrolyte levels monitored at least once after treatment initiation, only five died. Although AmB is the most effective antifungal available for patients with CM, our results show the benefit of treatment is blunted without

proper assessment of renal function. Even in areas of limited resources, adequate monitoring should be feasible.

Since patients at MDH must wait for their families to procure AmB, which can be costly (USD 200), FLC was sometimes given as the first-line of treatment. This is unfortunate since AmB is known to clear cryptococcal infections more rapidly than FLC (12). While mortality was not significantly associated with any of the three combinations of antifungal therapy (AmB, FLC, AmB and FLC) in our study, the unavailability of AmB may be negatively impacting the health of patients with CM. Even though AmB is given as soon as it becomes available, at which time FLC is stopped, this delay may be as long as one week. Consideration should be given to increasing the availability of AmB in public hospitals (13).

Few studies on CM have evaluated the impact of co-morbidity, which is often present in immuno-compromised patients and likely contributes to mortality. We found that the survival for the patients co-infected with TB was only 40%, significantly lower in comparison with the proportion of patients without TB. Of note, rifampicin, a mainstay of anti-TB therapy, was previously shown to hasten the elimination of FLC from the body (14,15). The clinical impact of this interaction is still unknown. To our knowledge, no clinical trial has included patients with CM and TB as a separate treatment group. Further studies should determine the prevalence of concomitant TB and compare the clinical presentation, treatment, and outcome of these patients to those solely infected with CM. As evident from the data, several antibiotics, including co-trimoxazole, chloramphenicol, benzylpenicillin, and ceftriaxone are widely used in the management of CM in the two hospitals but the association of these drugs with clinical outcome is unknown.

We found that initiation of ART during the induction phase of antifungal treatment was associated with survival. Currently available data do not provide a consensus on when to initiate ART in patients who have received AmB treatment (16). With the increasing access to ART in sub-Saharan Africa and other developing areas, research efforts should focus on making recommendations for the timing of ART initiation in patients with CM. In particular, there is a concern that CM relapse, which often occurs as a result of immune reconstitution inflammatory syndrome (IRIS) secondary to starting ART after AmB treatment, may lead to increased mortality (17,18). We were unable to follow up patients for development of cryptococcal IRIS, normally seen after 30 days of ART initiation (17).

There are several limitations to this study. First, mortality or survival was our only endpoint. CSF culture status after two weeks of treatment would have been a useful measure of success of treatment, but the standard of care at these hospitals did not include regularly scheduled follow-up lumbar punctures. Although therapeutic lumbar punctures are known to have been carried out, patient records do not reflect such management for intracranial pressure. Also, we could not ascertain the cause of death of the patients, and therefore, other AIDS-related complications may have contributed to mortality, especially in individuals who died several weeks after CM diagnosis. Finally, the study data were exclusively collected from inpatient files and we could not investigate long-term survival or factors associated with relapse.

In conclusion, this study found that the in-hospital mortality is high. Although the poor prognosis may be partly explained by late stage of disease at presentation, mortality can be reduced by adjusting modifiable factors. For instance, all patients receiving AmB must be regularly monitored to detect possible nephrotoxicity, at which point treatment may be changed. Also, CRAG testing of patients receiving ART may lead to early, improved CM management. Long-term goals for CM management should be to determine optimal treatment regiments for patients with comorbidities such as TB. Improving the survival of these patients alone would largely improve outcomes among patients with CM. Resistance of C. neoformans to FLC, which has been reported in Kenya, and its effect on clinical outcomes, will require further studies (18). Finally, there is a pressing need to improve access to the most effective antifungal drugs in Kenya. The problem of AmB availability in resource-limited settings cannot be overemphasised.

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