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RESEARCH ARTICLE

Co-prevalent infections in adults with HIV-associated cryptococcal meningitis are associated with an increased risk of death: a nested analysis of the Advancing Cryptococcal meningitis Treatment for Africa (ACTA) cohort [version 1; peer review: awaiting peer review]

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Abstract

Background: HIV-associated cryptococcal meningitis accounts for 15% of AIDS related deaths globally. In sub-Saharan Africa, acute mortality ranges from 24% to 100%. In addition to the mortality directly associated with cryptococcosis, patients with HIV-associated cryptococcal meningitis are at risk of a range of opportunistic infections (OIs) and hospital acquired nosocomial infections (HAIs). The attributable mortality associated with co-prevalent infections in cryptococcal meningitis has not been evaluated.
Methods: As part of the Advancing Cryptococcal meningitis Treatment for Africa (ACTA) trial, consecutive HIV-positive adults with cryptococcal meningitis were randomised to one of five anti-fungal regimens and followed up until 10-weeks. We conducted a retrospective case note review of ACTA participants recruited from Queen Elizabeth Central Hospital in Blantyre, Malawi to describe the range and prevalence of OIs and HAIs diagnosed, and the attributable mortality associated with these infections.
Results: We describe the prevalence of OIs and HAIs in 226

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participants. Baseline median CD4 count was 29 cell/mm^3, 57% (129/226) were on anti-retroviral therapy. 56% (127/226) had at least one co-prevalent infection during the 10-week study period. Data were collected for 187 co-prevalent infection episodes. Suspected blood stream infection was the commonest co-prevalent infection diagnosed (34/187, 18%), followed by community-acquired pneumonia (32/187, 17%), hospital-acquired pneumonia (13/187, 7%), pulmonary tuberculosis (12/187, 6%) and confirmed blood stream infections (10/187, 5%). All-cause mortality at 10-weeks was 35% (80/226), diagnosis of an OI or HAI increased the risk of death at 10 weeks by nearly 50% (HR 1.48, 95% CI 1.01-2.17, p=0.04).
Conclusion: We demonstrate the high prevalence and broad range of OIs and HAIs occurring in patients with HIV-associated cryptococcal meningitis. These co-prevalent infections are associated with a significantly increased risk of death. Whether a protocolised approach to improve surveillance and proactive treatment of co-prevalent infections would improve cryptococcal meningitis outcomes warrants further investigation.

Keywords
cryptococcal meningitis, opportunistic infections, hospital acquired infections, nosocomial infections, HIV/AIDS, Africa

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Introduction

Cryptococcal meningitis is the commonest neurological complication in patients with advanced HIV disease, accounting for 15% of AIDS related deaths globally[1]. In sub-Saharan Africa, mortality ranges from 24%[2] to 100%[3]. Even in the context of clinical trials with delivery of rapidly fungicidal amphotericin-based regimens, case fatality is 24–45%[4]. We hypothesise therefore that in addition to the mortality directly associated with cryptococcal meningitis, patients with HIV-associated meningitis are also at risk of a range of opportunistic infections (OIs) and hospital acquired infections (HAIs) resulting from the prolonged hospitalization required for current treatment regimens. Co-prevalent human herpesvirus viraemias (2–28%)[5] and nosocomial bacteraemias (15%)[6] in cryptococcal cohorts have previously been reported, and there are reports of cryptococcal meningitis coinfection with tuberculosis[7–9] (including TB meningitis[10]), and pneumocystis pneumonia[11]. However, the overall morbidity and mortality associated with OIs and HAIs in patients undergoing treatment for HIV-associated cryptococcal meningitis has not been ascertained. Understanding this impact may aid design of enhanced infection screening and treatment interventions to reduce mortality.

As part of the Advancing Cryptococcal meningitis Treatment for Africa (ACTA) trial[4], we described the range and prevalence of OIs and HAIs in patients undergoing treatment for cryptococcal meningitis, and the attributable mortality associated with these infections.

Methods

The ACTA trial was a multi-centre randomised controlled trial which investigated the optimal treatment of HIV-associated cryptococcal meningitis in resource limited settings (ISRCTN45035509)[4]. From January 2013 to November 2016, 721 consecutive HIV-positive adults with cryptococcal meningitis were randomised to one of three treatment strategies: oral fluconazole plus flucytosine for two weeks, one-week Amphotericin B (AmB)-based therapy, and standard two weeks AmB-based therapy. Those in the AmB arms were further randomized to flucytosine or fluconazole in a 1:1 ratio, as the partner drug given with AmB. Patients received consolidation fluconazole therapy after the two-week induction period: 800 mg until anti-retroviral therapy (ART) initiation or switch at 4 weeks and 400 mg to 10 weeks. ART was prescribed according to national guidelines, naïve patients were commenced on ART at week 4. The primary endpoint was all-cause mortality at two-weeks and follow up was until 10-weeks.

We conducted a retrospective case note review of all ACTA participants recruited from Queen Elizabeth Central Hospital in Blantyre, Malawi between November 2016 and July 2018. This site was the largest contributor to the trial and detailed OI and HAI information was only collected at this site. Patient demographics, clinical history, laboratory investigations, and outcome data were collected as part of the trial. Case notes were reviewed and details recorded regarding the nature, timing, diagnosis and treatment for incident OIs and HAIs.

Categorisation of opportunistic infections

Diagnoses were ascribed by the study physician based on standard clinical case definitions and investigations and treatment were according to the Malawian National Clinical Care guidelines. Routinely available investigations included: haematology and biochemistry blood tests, chest radiography, ultrasonography, sputum microscopy and Xpert MTB/RIF for investigation of TB, malaria rapid diagnostic test and blood smear, urine microscopy, culture and sensitivity (MC&S), blood cultures and cerebrospinal fluid MC&S. Due to resource constraints, markers of sepsis were limited to those which could be assessed clinically or through simple laboratory tests. Suspected blood stream infection (sBSI) was ascribed when at least two of the following criteria were met: (i) temperature < 35°C or >38.3°C; (ii) respiratory rate >20 breaths/minute; (iii) pulse >90 beats/minute; (iv) white cell count >12 or $<4\times10^9$ cells/l, but where no causative organism was identified at blood culture as per previous modified sepsis criteria used in our setting[12]. Data were collected on all physician diagnosed OIs and HAIs during the study period (Table 1). The following diagnoses were pre-specified as major co-prevalent infections associated with high risk of acute inpatient mortality: (1) pulmonary tuberculosis (PTB); (2) extra-PTB; (3) confirmed blood stream infection (cBSI); (4) sBSI; (5) acute respiratory illness (ARI), which included community- or hospital-acquired pneumonia and aspiration pneumonia.

Statistical analysis

Descriptive data used counts and percentages for categorical variables, and medians and interquartile ranges (IQR) for continuous variables. Time from randomisation to death due to any cause was analysed using survival analysis based on the Cox Proportional Hazard (PH) model with time-varying covariates. Hazard ratio (HR) of death and its corresponding 95% confidence interval (CI) for number of major OIs was estimated. To control possible confounding, the Cox model was adjusted for the following predictors; sex, age, anti-fungal regimen, ART use, baseline haemoglobin and quantitative cryptococcal fungal burden. Number of OIs was included in the survival model as a time-varying co-variate, to incorporate that fact that these illnesses were not all present at baseline but presented at variable times (0–2 weeks and/or 2–10 weeks) during the study period. The Cox PH assumption was assessed by testing the interaction between each predictor variable and time (log-scale). Analysis was conducted using R software version 3.4.4, and all tests were performed at 5% significance level.

Ethics

The ACTA trial protocol was approved by the London School of Hygiene and Tropical Medicine Research Ethics Committee (REC) (8854 – 5) and the University of Malawi, College of Medicine Research Ethics Committee (COMREC) (P.11/11/1149). Written informed consent was obtained from all participants. This analysis was part of the pre-specified aims of the ACTA protocol and the trial remained open during the data extraction for this study.

Table 1. Range and prevalence of opportunistic infections diagnosed in patients undergoing treatment for HIV-associated cryptococcal meningitis. 187 opportunistic infections (OIs) were diagnosed in 226 patients during the study period. 39% (89/226) had a single OI diagnosed, 11% (26/226) had two OIs, 4% (8/226) had three OIs and 1% had either four or more OIs diagnosed. A wide range of infections were diagnosed; suspected blood stream infection was the commonest opportunistic infection diagnosed (18%), followed by community acquired pneumonia (17%), aspiration pneumonia (8%), hospital acquired pneumonia (7%).

Infection category	Co-prevalent infection	N (%)
Total		187 (100)
Suspected/confirmed bloodstream infections	Suspected blood stream infection	34 (18)
	Confirmed bacteraemia	10 (5)
Respiratory infections/ tuberculosis (TB)	Community acquired pneumonia	32 (17)
	Hospital acquired pneumonia	13 (7)
	Aspiration pneumonia	15 (8)
	Pneumocystis pneumonia	1 (0.5)
	Pulmonary TB	12 (6)
	Extrapulmonary TB (unspecified)	8 (4)
	TB meningitis	5 (3)
	Disseminated TB	4 (2)
Sexually transmitted/ genitourinary infections[1]		22 (12)
Skin/soft tissue/mucosal/ ophthalmic infections[2]		11 (6)
Gastro-intestinal/ abdominal infections[3]		16 (9)
Other[4]		4 (2)

[1] Sexually transmitted/genitourinary infections included: genital ulcer disease, pelvic inflammatory disease, syphilis and urinary tract infections.

[2] Skin/soft tissue/mucosal/ophthalmic infections included: Kaposi's Sarcoma, skin abscess, tinea corporis, candidiasis and conjunctivitis.

[3] Gastro-intestinal/abdominal infections included: acute gastroenteritis, chronic diarrhoea and wasting, hepatic abscesses, splenic abscesses.

[4] Other = malaria

Results

In total, 226 out of 255 (89%) patients with HIV-associated cryptococcal meningitis recruited into the ACTA trial were included in the analysis; the remaining 29/255 patients were not included due to incomplete clinical data. The median age was 36 years (IQR 32–43 years), and 57% were male. All participants had advanced HIV; baseline median CD4 count was 29 cell/mm^3 (IQR 12–64 cell/mm^3), baseline haemoglobin was 11.1g/dL (IQR 9.8–12.3g/dL). At recruitment, 57% (129/226) were on ART. All-cause mortality at 10-weeks was 35% (80/226), median time to death was 14.5 days (IQR 3–29 days).

Out of the 226 patients, 127 (56%) patients had at least one OI or HAI diagnosed during the 10-week study period. A total of 39% (89/226) had a single co-prevalent infection diagnosed, 11% (26/226) had two, 4% (8/226) had three, and 1% had either four or more. Data were collected on a total of 187 co-prevalent infection episodes (Table 1). sBSI was the commonest co-prevalent infection diagnosed (34/187, 18%), followed by community-acquired pneumonia (32/187, 17%), aspiration pneumonia (15/187, 8%), hospital-acquired pneumonia (13/187, 7%), chronic diarrhoea (13/187, 7%), pulmonary TB (12/187, 6%) and cBSIs (10/187, 5%).

A range of bacterial pathogens were isolated from blood, including four multidrug resistant (MDR) bacteria: extended spectrum beta lactamase producing *Escherichia coli* (n=2), MDR *Salmonella typhi* (n=1), MDR *Salmonella typhimurium*

(n=4), *Methicillin-resistant Staphylococcus aureus* (n=1), *Streptococcus pneumoniae* (n=1), and *Klebsiella pneumoniae* (n=1).

A total of 134 infection episodes met the pre-defined criteria for a major co-prevalent infection; 30% (40/134) were diagnosed on study day one. The median time to diagnosis of a major co-prevalent infection was 9 days (IQR 1–27 days), 53% (71/134) of major co-prevalent infections were diagnosed at least two weeks after the commencement of anti-fungal therapy. Risk of all-cause mortality at 10 weeks was significantly increased (p = 0.04) if a participant was diagnosed with any one of the pre-specified major co-prevalent infections (HR 1.48, 95% CI 1.01-2.17). Results were similar for all pre-specified adjusted analyses, other than fungal burden which was an independent predictor of mortality.

Discussion

We show that co-prevalent OIs and HAIs are common in adults with HIV-associated cryptococcal meningitis with more than half of participants being diagnosed with at least one co-prevalent infection during the 10-week study period. We also demonstrate that diagnosis of a major co-prevalent infection (suspected or confirmed BSI, tuberculosis, or ARI (community- or hospital-acquired pneumonia and aspiration pneumonia)) was associated with nearly a 50% increased risk of death (HR 1.48, p=0.04) amongst our cohort. Whilst one third of these major co-prevalent infections were diagnosed at study entry, the median time to diagnosis was nine days, either indicating nosocomial acquisition or delayed diagnosis. It is essential therefore that physicians treating patients with HIV-associated cryptococcal meningitis remain vigilant for OIs and HAIs, and consider the sub-group of patients with co-prevalent infections as particularly high-risk of death.

Consistent with other cryptococcal meningitis studies in low resource, high HIV prevalence settings, the 10-week all-cause mortality was high in our cohort (35%)[13,14]. Deaths occurred throughout the study period with 50% of deaths occurring in the first 14 days. It has been postulated from previous HIV-associated cryptococcal meningitis trials[15], that acute deaths (≤2 weeks) are more likely to be attributable to cryptococcal meningitis, whilst after two weeks other HIV-related causes of death predominate. Although it is likely that cryptococcal meningitis was the primary cause of death for the majority of patients in our cohort, the time-distribution of deaths also supports our hypothesis that other co-prevalent infections contribute to the considerable mortality in this severely immunocompromised group. Post-mortem studies to ascertain autopsy prevalence of co-prevalent OIs and HAIs amongst patients with HIV-associated cryptococcal meningitis would be required to further test this hypothesis.

The prevalence of cBSI in our study population (3.5%) was lower than that described during the COAT (Cryptococcal Optimal Anti-retroviral therapy Timing), when a cohort prevalence of 15% was reported[11]. Whilst our study was not sufficiently powered to detect differential bacteraemia rates across the anti-fungal arms, it is possible that the shortened 1-week course of IV amphotericin (and the oral anti-fungal arm) trialled as part of the ACTA trial was associated with fewer nosocomial intravascular line HAIs compared with the prior gold standard of two-weeks of IV amphotericin as used in the COAT trial. cBSI was similarly associated with an increased risk of death in the COAT trial. 50% (4/8) of the isolates in our cohort were multi-drug resistant, highlighting the major challenge of increasing anti-microbial resistance and the risk of nosocomial infections.

The broad range of OIs diagnosed reflect the complexities in managing patients with advanced HIV and cryptococcal meningitis. Although co-prevalent infections were diagnosed throughout the 10-week study period, nearly one third of major co-prevalent infections were diagnosed on day one, symptoms of these may have contributed to hospital presentation. We therefore recommend that patients diagnosed with HIV-associated cryptococcal meningitis should be systematically screened for other OIs at hospital admission with targeted investigation thereafter. Additionally, the fact that around half of co-prevalent infections were diagnosed two weeks after antifungal initiation, demonstrates that patients with HIV-associated cryptococcal meningitis patients remain at high risk of co-prevalent infections following hospital discharge. Whilst we hypothesise that routine screening for key OIs and HAIs at both inpatient and outpatient assessments may facilitate early diagnosis and treatment, data on co-prevalent infections from other cryptococcal cohorts to inform design of an OI screening and prevention intervention are limited and more research is needed.

The need for a comprehensive approach to reducing infections in advanced HIV through early ART and targeted antimicrobial prophylaxis has been incorporated into World Health Organization guidelines for the management of advanced HIV[16]. The REALITY randomised controlled trial, evaluated an innovative multicomponent approach to reducing OIs and early mortality, demonstrating that enhanced antimicrobial prophylaxis (combined anti-bacterial, anti-fungal, anti-helminth, anti-protozoal) at ART initiation reduced early mortality in adults and children with a CD4 count <100 cell/mm^3. A similar multifaceted approach to reducing mortality in HIV-associated cryptococcal meningitis could be adopted. Whether a protocolised, goal-directed therapy approach including OI screening in addition to targeted anti-infectives and nutritional supplements would improve cryptococcal meningitis outcomes warrants further investigation.

This analysis has several limitations. Case notes were reviewed retrospectively following trial completion therefore there is a risk of incomplete case records and recall bias. The limited diagnostics available in Malawi may mean the overall prevalence of OIs and HAIs and in particular cBSIs could have been underestimated. This potential for under-ascertainment of exposure status may have led to an underestimation of the HR comparing mortality at 10-weeks between those with- and without major co-prevalent infections. Conversely it is possible that in the first few days after commencing treatment that cryptococcaemia-driven sepsis be classified as a sBSI leading to over ascertainment of sBSI.

Conclusion

In conclusion, we have demonstrated the high prevalence and broad range of OIs and HAIs that occur in patients with HIV-associated cryptococcal meningitis. Co-prevalent infections were associated with a significantly increased risk of death. We recommend that cryptococcal meningitis patients should be systematically screened for OIs and HAIs. Whether a protocolised approach to improve surveillance and proactive treatment of co-prevalent infections will further improve cryptococcal meningitis outcomes warrants further investigation.

Data availability

Figshare: WOR CM co-infections data file.xlsx, https://doi.org/10.6084/m9.figshare.13295858[17].

This project contains the following underlying data:

- WOR CM co-infections data file.xlsx This data file describes the range, frequency, timing and outcome of co-infections amongst study participants with HIV-associated cryptococcal meningitis

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