MAJOR ARTICLE

Bacteremic Disseminated Tuberculosis in Sub-Saharan Africa: A Prospective Cohort Study

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Background. Disseminated tuberculosis is a major health problem in countries where generalized human immunodeficiency virus (HIV) infection epidemics coincide with high tuberculosis incidence rates; data are limited on patient outcomes beyond the inpatient period.

Methods. We enrolled consecutive eligible febrile inpatients in Moshi, Tanzania, from 10 March 2006 through 28 August 2010; those with *Mycobacterium tuberculosis* bacteremia were followed up monthly for 12 months. Survival, predictors of bacteremic disseminated tuberculosis, and predictors of death were assessed. Antiretroviral therapy (ART) and tuberculosis treatment were provided.

Results. A total of 508 participants were enrolled; 29 (5.7%) had *M. tuberculosis* isolated by blood culture. The median age of all study participants was 37.4 years (range, 13.6–104.8 years). Cough lasting >1 month (odds ratio [OR], 13.5; $P < .001$), fever lasting >1 month (OR, 7.8; $P = .001$), weight loss of >10% (OR, 10.0; $P = .001$), lymphadenopathy (OR 6.8; $P = .002$), HIV infection (OR, undefined; $P < .001$), and lower CD4 cell count and total lymphocyte count were associated with bacteremic disseminated tuberculosis. Fifty percent of participants with *M. tuberculosis* bacteremia died within 36 days of enrollment. Lower CD4 cell count (OR, 0.88; $P = .049$) and lower total lymphocyte count (OR, 0.76; $P = .050$) were associated with death. Magnitude of mycobacteremia tended to be higher among those with lower CD4 cell counts, but did not predict death.

Conclusions. In the era of free ART and access to tuberculosis treatment, almost one half of patients with *M. tuberculosis* bacteremia may die within a month of hospitalization. Simple clinical assessments can help to identify those with the condition. Advanced immunosuppression predicts death. Efforts should focus on early diagnosis and treatment of HIV infection, tuberculosis, and disseminated disease.

Disseminated tuberculosis is a major health problem in countries where generalized human immunodeficiency virus (HIV) infection epidemics coincide with high tuberculosis incidence rates [1]. Disseminated tuberculosis often causes rapidly fatal illness in patients with immunologically advanced HIV disease and has persisted as a public health problem even since the expansion of HIV care and treatment programs [2, 3]. Because the median survival of patients with bacteremic disseminated tuberculosis following admission to hospital may be very short [3–5], early recognition and treatment are likely to be important to avert mortality [6]. However, the clinical diagnosis of disseminated tuberculosis may be challenging in areas with limited laboratory services [7, 8], as patients may present with nonspecific symptoms and signs, and classic radiographic features of pulmonary or miliary tuberculosis may be absent [4, 5, 9]. Consequently, the diagnosis is often overlooked and is a frequent postmortem finding among HIV-infected patients in areas

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with high rates of tuberculosis [1]. Where laboratory services are available, disseminated tuberculosis may be strictly defined as isolation of *Mycobacterium tuberculosis* from blood or bone marrow, from a liver biopsy specimen, or from specimens from ≥2 noncontiguous organs in a single patient [10, 11].

M. tuberculosis was first recognized as a cause of bloodstream infection almost a century ago [12, 13]. Today, when sought using mycobacterial blood culture techniques, *M. tuberculosis* is a leading cause of community-acquired bloodstream infection among febrile hospitalized patients in sub-Saharan Africa [4, 14–18] and Asia [5, 9]. In-hospital case fatality rates for bacteremic disseminated tuberculosis in the era before the widespread availability of antiretroviral therapy (ART) approached 50% [4]. Unfortunately, the median time to positivity for *M. tuberculosis,* even in continuously monitored blood culture systems, exceeds 3 weeks, limiting its value for clinical management [19, 20]. *M. tuberculosis* nucleic acid amplification tests (NAATs) following extraction of large volumes of whole blood show promise for more rapid diagnosis, but they need refinement to improve sensitivity and adaptation for low-resource settings [21]. Although patient survival after *Mycobacterium avium* complex bacteremia was established for HIV-infected persons during the 1990s [22], little is understood about the natural history of *M. tuberculosis* bacteremia beyond the inpatient period or during the era of widespread availability of ART in endemic countries.

In order to improve approaches to the clinical recognition of disseminated tuberculosis, to enhance our understanding of the natural history of the disease in the context of timely use of tuberculosis treatment and ART, and to improve identification of patients at greatest risk for death, we enrolled and followed up consecutive patients with *M. tuberculosis* bacteremia identified at 2 hospitals in Tanzania, a country experiencing a generalized HIV epidemic and high incidence of tuberculosis.

METHODS AND MATERIALS

Setting

Moshi (population, >144 000) is the administrative center of the Kilimanjaro Region (population, >1.4 million) in northern Tanzania and is situated at an elevation of approximately 890 meters above mean sea level. Malaria transmission intensity is low [23]. National adult HIV seroprevalence was estimated at 7.0% in 2003–2004 [24] and has since declined; national tuberculosis incidence was estimated at 297 cases per 100 000 persons in 2007 [25]. Kilimanjaro Christian Medical Centre (KCMC) is a consultant referral hospital with 458 inpatient beds serving several regions in northern Tanzania, and Mawenzi Regional Hospital (MRH), with 300 beds, is the regional hospital for Kilimanjaro. Together KCMC and MRH serve as the main providers of hospital care in the Moshi area. In 2008, KCMC admitted 22 099 patients and MRH admitted 21 763 patients.

Participants

Participants were prospectively identified from among adult and adolescent inpatients at KCMC and MRH from 10 March 2006 through 28 August 2010. As described elsewhere, all admitted patients aged ≥13 years and with oral temperatures of ≥38.0°C were invited to participate in the study [2]. From 31 August 2008, enrollment was restricted to those who also had HIV infection, subjective fever for >1 month, and weight loss of >10%. A standardized clinical history was taken and physical examination was performed on consenting patients by a trained clinical officer who was a member of the study team. Following cleansing of the skin with povidone iodine and isopropyl alcohol, blood was drawn for aerobic blood culture (10 mL) and for up to 3 simultaneous mycobacterial blood cultures (5 mL each) as well as for complete blood count, examination for blood parasites, and HIV antibody testing. For patients found to be HIV seropositive, CD4-positive T-lymphocyte count (CD4 cell count) was also measured. A chest radiograph was ordered for all patients and was reported using a standardized form by a radiologist. The results of all study investigations were provided immediately to the hospital clinical team to inform patient management. A discharge form was completed at the time of discharge from hospital that captured whether the patient died in hospital. Participants with *M. tuberculosis* bloodstream infection were referred for immediate initiation to tuberculosis chemotherapy and asked to return for follow-up by the study team monthly for 12 months. Those who did not return for follow-up visits were contacted by telephone and, if necessary, sought at home by a field worker. Deaths were recorded and standardized verbal autopsies were performed for outpatient deaths. Those with HIV infection were referred to an HIV care and treatment center. The timing of initiation of ART was at the discretion of the clinical team, although national guidelines recommended that patients with immunologically advanced HIV disease and tuberculosis start ART with stavudine, lamivudine, and efavirenz as early as 2 weeks after the initiation of the intensive phase of tuberculosis treatment [26].

Laboratory Methods

Complete blood count and differential were performed using the CellDyn 3500 automated hematology analyzer (Abbott Laboratories, Abbott Park, Illinois). Manual differentials were performed when necessary on blood films stained with Giemsa.

Blood culture bottles were assessed for volume adequacy by comparing the weight before and after inoculation with blood. BacT/ALERT standard aerobic (SA) and mycobacterial (MB)

bottles were loaded into the BacT/ALERT 3D automated microbial detection system (bioMérieux, Durham, North Carolina) where they were incubated for 5 and 42 days, respectively. BACTEC Myco/F Lytic bottles (Becton Dickinson, Franklin Lakes, New Jersey) were incubated at 35°C for 42 days; bottle bottoms were examined for fluorescence daily using a Wood lamp. ISOLATOR10 lysis-centrifugation tubes were centrifuged and processed using the Wampole ISOSTAT/ISOLATOR Microbial System (Inverness Medical, Princeton, New Jersey), plated to Middlebrook 7H10 agar, and incubated at 35°C in 5% carbon dioxide for 42 days. An aliquot of the blood-broth mixture was removed from bottles flagged positive by the instrument or by inspection of the bottom, using a 1-mL tuberculin syringe for SA and 5-mL syringe with 19-gauge needle for MB and Myco/F Lytic. A portion was examined by Gram stain, Kinyoun stain (MB and Myco/F Lytic), and India ink stain when yeast-like morphology was observed. Aliquots were plated to solid medium according to stain results. Nonmycobacterial plates were examined daily for growth and subsequent isolation and identification according to standard techniques. Mycobacterial plates were examined weekly for growth. AccuProbe Culture Identification Test MTB and MAC kits (Gen-Probe, San Diego, California) were used to identify members of *M. tuberculosis* complex and *M. avium* complex; other *Mycobacterium* species were identified by a reference laboratory [27, 28]. Colonies growing on lysis-centrifugation plates were counted and colony-forming units per milliliter of blood were calculated.

HIV type 1 (HIV-1) antibody testing was performed on whole blood using both the Capillus HIV-1/HIV-2 (Trinity Biotech, Bray, Ireland) and Determine HIV-1/2 (Abbott Laboratories) rapid HIV antibody tests. The Capillus test was replaced with the SD Bioline HIV-1/2 3.0 (Standard Diagnostics, Kyonggi-do, Korea) on 4 March 2008 after a change in Tanzania Ministry of Health HIV testing guidelines. If rapid tests were discordant, the sample was tested with an enzyme-linked immunosorbent assay (ELISA; Vironostika Uni-Form II plus O Ab, bioMérieux). If the ELISA was negative, no further testing was done. If the ELISA was positive, a Western blot (Genetic Systems HIV-1 Western Blot kit, Bio-Rad, Hercules, California) was done to confirm [29]. The CD4 cell count was measured using the FACSCalibur system (Becton Dickinson).

During the study, the laboratory participated successfully in external quality assurance programs of the College of American Pathologists for serology, bacteriology, mycology, mycobacteriology, blood parasites, rapid HIV, and India ink; the Viral Quality Assurance program of the AIDS Clinical Trials Group for HIV-1 RNA polymerase chain reaction; and the United Kingdom National External Quality Assessment Service for flow cytometry.

Statistics

Data were entered using the Cardiff Teleform system (Cardiff, Vista, California) into an Access database (Microsoft Corp, Redmond, Washington). For continuous responses, analysis of variance was used to assess treatment difference between groups. For categorical data and binary responses, Cochran-Mantel-Haenszel test was performed to compare groups. Descriptive statistics for demographics and patient characteristic baseline were obtained for baseline comparability. A logistic regression analysis was performed to identify risk factors associated with death with bacteremic disseminated tuberculosis. An estimate of survival curve using the Kaplan-Meier method was computed. The log-rank test was performed to compare difference between 2 survival distributions. The Kendall τ correlation was used to measure the association between 2 groups. All statistical tests performed were 2-sided at the 5% level of significance. Statistical analyses were performed with SPSS software, version 12.0 (IBM SPSS, Chicago, Illinois).

Research Ethics

This study was approved by the KCMC Research Ethics Committee, the Tanzania National Institutes for Medical Research National Research Ethics Coordinating Committee, and an institutional review board of Duke University Medical Center.

RESULTS

Of 508 participants enrolled during the total study period, 29 (5.7%) had *M. tuberculosis* bacteremia and 25 (4.9%) had both *M. tuberculosis* bacteremia and complete clinical data available. Of the 29 with *M. tuberculosis* bacteremia, 9 (31.0%) had both a positive lysis-centrifugation blood culture and CD4 cell count available. Of the 25 with complete clinical data, 12 (48.0%) were identified during the period of unrestricted enrollment. The median age of all study participants was 37.4 years (range, 13.6–104.8 years) and 281 (56.2%) were female; 236 (46.5%) of the participants were HIV seropositive. Of HIV-infected patients, the median CD4 cell count was 111 cells/μL (range, 1–1105 cells/μL), 69 (29.2%) were taking trimethoprim-sulfamethoxazole prophylaxis, and 84 (35.6%) were receiving ART. Of all participants, 403 (79.3%) were enrolled during the period of unrestricted enrollment and 12 (2.9%) of these had *M. tuberculosis* bloodstream infection. The characteristics of these patients have been described elsewhere [2]. An additional 105 participants (20.7%) were enrolled during the period of restricted enrollment after 31 August 2008.

Characteristics of Participants With and Without Bacteremic Disseminated Tuberculosis

The characteristics of participants enrolled from 17 September 2007 through 31 August 2008 during the period of unrestricted

Table 1. Characteristics of Participants With and Without Bacteremic Disseminated Tuberculosis, Kilimanjaro Christian Medical Centre and Mawenzi Regional Hospital, 2007–2008

Characteristic	No. (%) of Participants[a]			OR	(95% CI)	*P* Value[b]
	All (n = 403)	Disseminated Tuberculosis (n = 12)	No Disseminated Tuberculosis (n = 391)			
Age, years, median (range)	37.0 (13.6–95.5)	39.0 (21.2–55.7)	36.1 (13.6–95.5)	…	…	.935
Female sex	217 (53.8)	9 (75.0)	208 (53.2)	2.6	(.70–9.9)	.150
Ever treated for tuberculosis	39 (9.7)	2 (16.7)	37 (9.5)	1.9	(.40–9.1)	.413
Symptoms						
Cough	261 (64.8)	10 (83.3)	251 (64.2)	2.8	(.60–12.9)	.190
Cough >1 month	80 (19.9)	9 (75.0)	71 (18.2)	13.5	(3.6–51.2)	<.001
Fever >1 month	88 (21.8)	8 (66.7)	80 (20.5)	7.8	(2.3–26.5)	.001
Hemoptysis	22 (5.5)	2 (16.7)	20 (5.1)	3.7	(.76–18.1)	.105
Dyspnea	45 (11.2)	3 (25.0)	42 (10.7)	2.8	(.72–10.6)	.138
Weight loss >10%	99 (24.6)	9 (75.0)	90 (23.0)	10.0	(2.7–37.9)	.001
Signs						
Body mass index, median (range)	21.0 (13.5–41.8)	19.1 (15.5–33.3)	21.1 (13.5–41.8)	…	…	.489
Lymphadenopathy	42 (10.4)	5 (41.7)	37 (9.5)	6.8	(2.1–22.6)	.002
Systolic blood pressure, median (range), mm Hg	112 (60–200)	110 (84–146)	112 (60–200)	…	…	.874
Diastolic blood pressure, median (range), mm Hg	70 (20–128)	70.0 (51–103)	70.0 (20–128)	…	…	.255
Respiratory rate, breaths/minute, median (range)	25 (14–137)	28 (18–40)	25 (14–137)	…	…	.562
Oxygen saturation, %, median (range)	96 (71–100)	95 (88–99)	96 (71 100)	…	…	.514
Abnormal breath sounds	165 (40.9)	7 (58.3)	158 (40.4)	2.1	(.64–6.6)	.223
Crepitations	178 (44.2)	8 (66.7)	170 (43.5)	2.6	(.77–8.8)	.124
Absent breath sounds	6 (1.5)	0 (0.0)	6 (1.5)	[c]	[c]	>.999
Bronchial breathing	57 (14.1)	4 (33.3)	53 (13.6)	3.2	(.93–11.0)	.066
Pleural rub	15 (3.7)	1 (8.3)	14 (3.6)	2.5	(.30–20.3)	.407
Splenomegaly	15 (3.7)	0 (0.0)	15 (3.8)	[c]	[c]	>.999
Hepatomegaly	32 (7.9)	1 (8.3)	31 (7.9)	1.1	(.13–8.5)	.959
Abdominal mass	9 (2.2)	0 (0.0)	9 (2.3)	[c]	[c]	>.999
Glasgow coma score, median (range)	15.0 (3.0–15.0)	15.0 (14.0–15.0)	15.0 (3.0–15.0)	…	…	.010
Neck stiffness	20 (5.0)	1 (8.3)	19 (4.9)	1.8	(.22–14.5)	.590
Kernig sign positive	0 (0.0)	0 (0.0)	0 (0.0)	[c]	[c]	>.999
Skin lesion	17 (4.2)	0 (0.0)	17 (4.3)	[c]	[c]	>.999
BCG scar	368 (91.3)	12 (100.0)	356 (91.0)	Und	Und	.611
Laboratory findings						
HIV infection	157 (39.0)	12 (100.0)	147 (37.6)	Und	Und	<.001
CD4 cell count, cells/μL, median (range)	105 (1–1400)	41 (3–179)	112 (1–1400)	…	…	<.001
Hemoglobin level, g/dL, median (range)	8.3 (5.0–16.0)	8.3 (6.0–11.0)	8.0 (5.0–16.0)	…	…	.561
Lab test results						
Hematocrit level, %, median (range)	25 (14–45)	25 (18–33)	27.40 (14–45)	…	…	.482

Table 1 continued.

Characteristic	No. (%) of Participants[a]			OR	(95% CI)	*P* Value[b]
	All (n = 403)	Disseminated Tuberculosis (n = 12)	No Disseminated Tuberculosis (n = 391)			
Lab test results						
Platelet count, 10^9 cells/L, median (range)	213 (27–887)	263 (168–887)	202 (27–515)	…	…	.179
Neutrophil count, 10^9 cells/L, median (range)	4.6 (0.1–88.2)	5.4 (0.7–9.8)	4.5 (0.1–88.2)	…	…	.119
Lymphocyte count, 10^9 cells/L, median (range)	1.1 (0.0–7.0)	0.8 (0.1–2.1)	1.2 (0.0–7.0)	…	…	.007
Chest radiograph						
Normal	15 (3.7)	3 (25.0)	12 (3.1)	10.5	(2.5–43.9)	.001
Parenchymal abnormality	14 (3.5)	3 (25.0)	11 (2.8)	11.5	(2.7–48.5)	.001
Nodular abnormality	5 (1.2)	1 (8.3)	4 (1.0)	8.8	(.91–85.3)	.061
Pleural abnormality	7 (1.7)	2 (16.7)	5 (1.3)	15.4	(2.7–89.4)	.002
Central structure abnormality	2 (0.5)	1 (8.3)	1 (0.3)	35.5	(2.1–604.3)	.014

Abbreviations: BCG, Bacille Calmette-Guérin; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; Und, undefined.

[a] Data are no. (%) of participants unless stated otherwise.

[b] The *P* value is based on an independent *t* test with equal valance not assumed for continuous variables, χ^2 test for categorical variables, and Fisher exact test for undefined OR.

[c] Numbers are too small to calculate a test statistic.

Figure 1. Survival curve of participants with bacteremic disseminated tuberculosis, Kilimanjaro Christian Medical Centre and Mawenzi Regional Hospital, 2006–2010 (n = 29).

enrollment with and without disseminated tuberculosis are shown in Table 1. All participants with *M. tuberculosis* bacteremia were HIV-infected. Cough lasting >1 month (odds ratio [OR], 13.5; $P < .001$), fever lasting >1 month (OR, 7.8; $P = .001$), weight loss of >10% (OR, 10.0; $P = .001$), lymphadenopathy (OR 6.8; $P = .002$), HIV infection (OR undefined; $P < .001$), and lower CD4 cell count and total lymphocyte count were associated with bacteremic disseminated tuberculosis.

Outcome of Participants With Bacteremic Disseminated Tuberculosis

The survival curve for all participants with bacteremic disseminated tuberculosis is shown in Figure 1. Of participants with bacteremic disseminated tuberculosis, 50% died within 36 days of enrollment. There was no significant difference in survival between those enrolled before and those enrolled after 31 August 2008, when enrollment was restricted ($P = .722$).

Predictors of Death Among Participants With Bacteremic Disseminated Tuberculosis

Table 2 shows risk factors for death among participants with bacteremic disseminated tuberculosis. Lower CD4 cell count (OR, 0.89; $P = .049$) and lower total lymphocyte count (OR, 0.76; $P = .050$) were associated with death from disseminated tuberculosis.

Relationship Between Degree of HIV-Associated Immune Suppression and Magnitude of Mycobacteremia

Figure 2 shows the relationship between CD4 cell count and the magnitude of mycobacteremia, measured directly as colony-forming units per milliliter. The Pearson product-moment correlation coefficient for the relationship is −0.0486 with a *P* value of .155, and the Kendall τ correlation coefficient for the relationship is −0.333 with a *P* value of .497.

Table 2. Predictors of Death Among Participants With Bacteremic Disseminated Tuberculosis, Kilimanjaro Christian Medical Centre and Mawenzi Regional Hospital, 2006–2010 (n = 20)

Variable	OR	*P* Value
Age	1.0	.578
Sex	0.60	.583
Fever >1 month	0.00	>.999
Cough >1 month	0.00	.999
Diarrhea >1 month	[a]	[a]
Weight loss >1 month	[a]	[a]
Receipt of antituberculosis drugs since current illness started	0.00	>.999
Receipt of antiretroviral therapy since current illness started	1.3	.796
Receipt of cotrimoxazole prophylaxis since current illness started	0.60	.538
Years since first positive HIV test	0.59	.538
Past treatment for tuberculosis	0.00	.999
Years since first treated for tuberculosis	[a]	[a]
Temperature	0.91	.898
Body mass index	0.87	.318
Conjunctival pallor	0.45	.427
Oral candidiasis	6.7	.120
Lymphadenopathy	2.9	.287
Blood pressure, systolic	0.99	.681
Blood pressure, diastolic	0.99	.524
Respiratory rate	1.0	.812
Reduced oxygen saturation	1.4	.123
Abnormal breath sounds	[a]	[a]
Presence of ascites	0.80	.881
Hepatomegaly	1.3	.796
Splenomegaly	[a]	[a]
Glasgow coma score	[a]	[a]
Neck stiffness	[a]	[a]
Kernig sign positive	[a]	[a]
Presence of herpes zoster scar	0.70	.812
Presence of Kaposi sarcoma	0.00	>.999
Presence of BCG scar	[a]	[a]
Abnormal chest radiograph	0.42	.512
Presence of infiltrates on chest radiograph	1.0	1.000
Presence of nodules on chest radiograph	0.00	.999
Presence of cavities on chest radiograph	2.0	.638
Presence of pleural effusion on chest radiograph	0.80	.887
Presence of hilar lymphadenopathy on chest radiograph	[a]	[a]
Presence of pericardial effusion on chest radiograph	[a]	[a]
HIV infection laboratory confirmed	1.3	.881
CD4 cell count	0.89	.049
Positive cryptococcal antigen test	[a]	[a]
Hemoglobin level	1.2	.584
Hematocrit level	1.1	.499
Total lymphocyte count	0.76	.050
Platelet count	1.0	.226
Raised neutrophil count	1.1	.226
Blood culture time to positivity for *M. tuberculosis*	1.0	.720
M. tuberculosis bacteremia magnitude	1.1	.272

Table 2 continued.

For continuous variables, odds ratios are per unit increase in value.

Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

[a] Unavailable due to missing values, or the variable is constant for all data.

DISCUSSION

We describe the survival of patients with bacteremic disseminated tuberculosis over 12 months of follow-up in a setting where ART and tuberculosis treatment are readily available. In this context, we demonstrate that bacteremic disseminated tuberculosis is often rapidly fatal, with almost one-half of affected patients dying within a month of enrollment. We find that a range of clinical and laboratory features may assist with the identification of patients with bacteremic disseminated tuberculosis. Those patients with immunologically advanced HIV disease are at greatest risk of death and also experience the highest magnitudes of mycobacteremia.

Although almost one-half of participants with bacteremic disseminated tuberculosis had died by 1 month of follow-up, the fact that more than one-third of participants were still alive after 1 year is cause for some optimism. It is likely that earlier identification of patients with disseminated tuberculosis may increase the proportion of long-term survivors. We have previously demonstrated that mycobacterial blood culture plays an

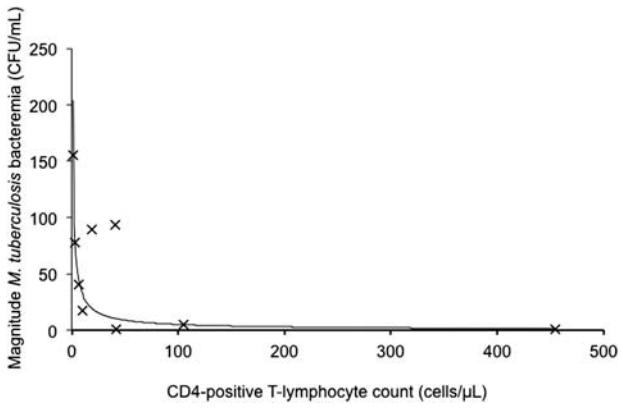

Figure 2. Number of *Mycobacterium tuberculosis* colony-forming units per milliliter by CD4-positive T-lymphocyte count among participants with bacteremic disseminated tuberculosis, Kilimanjaro Christian Medical Centre and Mawenzi Regional Hospital, 2006–2010 (n = 9). Abbreviation: CFU, colony-forming unit.

increasingly important role in the diagnosis of disseminated tuberculosis in the United States [11]. However, the median time to positivity for *M. tuberculosis* in continuously monitored blood culture systems exceeds 3 weeks [19, 20]. Because bacteremic disseminated tuberculosis is rapidly fatal in a substantial proportion of patients before a mycobacterial blood culture instrument signals positivity, alternative approaches to facilitate early diagnosis are needed. *M. tuberculosis* NAATs on whole blood can yield results within a day, but improvements to sensitivity are needed to detect low-magnitude mycobacteremia [21].

Previous research has shown that a substantial group of patients with bacteremic disseminated tuberculosis may be identified by consistently applying a routine approach to tuberculosis clinical and laboratory diagnosis [6, 30]. However, a proportion of patients with disseminated disease will not be detected with a standard approach, and the size of this group appears to vary according to local clinical practices, laboratory services, and epidemiologic conditions [5, 6, 31, 32]. It is notable that a substantial minority of patients have a normal chest radiograph. We confirm that chronic cough and fever lasting >1 month, a history of weight loss of >10%, lymphadenopathy, and HIV infection [4, 17, 33] assist with the identification of patients with disseminated tuberculosis. Furthermore, among those patients with HIV infection, we demonstrate that lower CD4 cell count is a useful predictor of disseminated disease.

As far as we are aware, risk factors for death among patients with bacteremic disseminated tuberculosis have not previously been studied prospectively. Although the sample size was small, lower CD4 cell count and the related measure of lower total lymphocyte count were the only predictors of death identified among many evaluated by our study. Of interest, there was a trend of patients with bacteremic disseminated tuberculosis with immunologically advanced HIV disease having higher magnitudes of mycobacteremia. However, magnitude of mycobacteremia was not itself associated with increased risk for death. It is possible that host, organism, and clinical management factors not measured by our study could contribute to the outcome of survival. Although we did not study the role of *M. tuberculosis* genotype or antimicrobial resistance, the epidemiology of both has been described elsewhere among tuberculosis patients in northern Tanzania [34]. The most appropriate timing for initiation of ART among the subset of patients with bacteremic disseminated tuberculosis has not been specifically studied. However, randomized trials confirm that early initiation of ART is associated with improved outcomes in HIV and tuberculosis coinfected patients, with and without immunologically advanced disease [35–39]. Participants with tuberculosis identified in this study were recommended to have ART initiated 2 weeks after the start of treatment for tuberculosis [26], although clinician practices may have varied. It is not known whether *M. tuberculosis* bacteremia independently influences risk for the immune reconstitution inflammatory syndrome, and our study was not designed to answer this potentially important question.

The high case fatality rate of bacteremic disseminated tuberculosis underscores the importance of intervention earlier in the course of HIV infection and prior to the loss of immunologic control of tuberculosis among latently infected individuals or prior to dissemination in those with pulmonary infection. Provision and promotion of HIV counseling and testing services facilitates the early detection of HIV infection. Referral of HIV-infected individuals to healthcare services that identify and effectively treat active tuberculosis [40], treat latent tuberculosis infection [41], and initiate trimethoprim-sulfamethoxazole prophylaxis [42] and ART in a timely manner [43] may all contribute to a reduction in the number of persons presenting late with fatal disseminated tuberculosis. The use of empiric tuberculosis treatment in patients suspected to have disseminated tuberculosis can be considered and is an area where further research is needed [44].

Our study had a number of limitations. The number of patients with bacteremic disseminated tuberculosis identified was quite small, limiting our ability to identify minor risk factors. Nonetheless, our study was conducted over 4 years and likely represents one of the largest prospective studies on bacteremic disseminated tuberculosis yet reported. Although it was a component of the routine clinical care of study participants, the systematic collection of samples for routine diagnosis of pulmonary tuberculosis was not part of the study design, preventing assessment of sputum mycobacteriology as a predictor of disseminated tuberculosis. Our study was not designed to comprehensively evaluate host and organism factors associated with bacteremic disseminated tuberculosis. Future studies might build on our work by incorporating a pulmonary tuberculosis comparison arm, evaluating host genomic risk factors for extrapulmonary disease, and studying the role of *M. tuberculosis* genotype and antimicrobial resistance.

In conclusion, bacteremic disseminated tuberculosis is rapidly fatal in a large proportion of patients, especially those with immunologically advanced HIV disease. However, early recognition and consequently early initiation of potentially lifesaving treatment may be facilitated by careful clinical history, physical examination, and use of laboratory tests that are widely available at district hospitals in endemic areas [45]. Specific laboratory diagnosis can be augmented with mycobacterial blood culture, but assays yielding a more rapid result such as NAATs are needed to influence management in the first few days after presentation to a healthcare facility.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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