Fatal Mycobacterium tuberculosis Bloodstream Infections in Febrile Hospitalized Adults in Dar es Salaam, Tanzania

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The isolation of pathogens normally regarded as nonopportunistic from HIV-infected patients in industrialized countries has been well documented [1, 2]. Gilks et al. in Nairobi were the first to describe the importance of bloodstream infections (BSIs) in African adults infected with HIV-1 [3]. Two subsequent studies that investigated BSIs in HIV-positive patients in Rwanda [4] and the Ivory Coast [5] suggested that infections due to non-typhi Salmonella species and Streptococcus pneumoniae were important causes of mortality and morbidity in this patient population. Although a few of the blood cultures performed in the Ivory Coast yielded mycobacteria and fungi [5], lysis-centrifugation was not used to look specifically for or to optimize recovery of these organisms. In this study, methods varied (e.g., with regard to inclusion criteria and patient exclusions), blood culture positivity rates ranged from 10% to 24%, and contamination rates were quite high.

In Tanzania, the etiology of fever in hospitalized patients is often obscure. Although a high prevalence of HIV-1 infection has been demonstrated among patients with deep bacterial infections admitted to Muhimbili Medical Centre in Dar es Salaam, Tanzania [6], little is known about the nature of the organisms causing BSI in febrile adults, regardless of their HIV status, or about the susceptibilities of these organisms to available antimicrobials. The true causes of community-acquired BSI in Tanzania remain largely unknown, especially with regard to mycobacteria and fungi. We therefore conducted a study to (1) assess the prevalence and etiology of BSI in this population; (2) estimate the prevalence of HIV-1 infection in this population; (3) assess the role of HIV-1 infection regarding the presence of BSI; and (4) estimate the prevalence of malaria parasitemia in febrile adults admitted to the medical center.

Methods

Patients

This was a prospective study of febrile adults consecutively admitted to the medical wards at Muhimbili Medical Centre, which has >1,000 beds and is the largest hospital as well as the main medical referral center in Tanzania. There are, on average, 25 admissions to the medical service per day; >50% of these patients are febrile. For each 24-hour period from 18 February through 16 April 1995 (study period), all febrile (axillary temperature, ≥37.5°C) adults (≥15 years of age) admitted to the adult medical unit in the Mwaisela Block at Muhimbili Medical Centre were seen by one of the principal investigators. After a physical examination was performed and a detailed history and informed consent were obtained but before antimicrobial treatment was commenced, 25 mL of venous blood was drawn for culture, HIV-1 serology, and malaria parasitemia testing, after skin cleansing with povidone iodine.
and isopropyl alcohol. HIV ELISA tests were repeated on patients with one positive result.

The ward was notified as soon as an organism was isolated from the blood and again when the organism was identified. Doctors and other ward staff were given advice on antimicrobial regimens when appropriate. Malaria blood films were obtained from a control group of 150 afebrile trauma patients in the orthopedic ward who did not have clinical manifestations of sepsis. These control patients were matched for age and sex with randomly selected patients from the febrile study group.

**Laboratory Methods**

**Blood cultures.** Ten mL of venous blood was inoculated at the bedside into a Septi-Chek (Becton Dickinson Microbiology Systems [BDMS], Cockeysville, MD) biphasic bacterial blood culture bottle, to which an agar slide paddle (BDMS) was attached in the laboratory. The blood culture bottle was then momentarily inverted so that the contents covered the agar paddle. An additional 10 mL of blood was added to an Isolator tube (Wampole Laboratories, Cranberry, NJ) for lysis and centrifugation within 8 hours of venepuncture. A portion of the lytic centrifugation concentrate was inoculated into a Myco-Chek (BDMS) biphasic mycobacteria blood culture bottle containing Middlebrook 7H9 broth, to which acid-fast bacilli (AFB) culture supplement was added and to which an AFB agar paddle (BDMS) was attached in the laboratory.

The remainder of the concentrate was inoculated onto Middlebrook 7H11 agar, heated blood (chocolate), and Inhibitory Mold Agar slants (BDMS). The bacterial and mycobacterial blood culture bottles and agar slants were incubated aerobically at 35°C. The Septi-Chek bacterial culture bottles were examined twice for signs of growth in the first 24 hours following incubation and then daily for the next 7 days. Broth from bottles that remained clear after 7 days was terminally subcultured onto sheep blood agar plates.

Preliminary identification of organisms was made in Tanzania with use of standard microbiological tests. If an enteric organism was suspected on initial microbiological analysis, a standardized inoculum of the organism was incubated in the BBL Crystal enteric/nonfermenter identification system (BDMS) for identification according to recommended procedures. All bacterial and fungal isolates were suspended in trypticase soy broth with calf serum and frozen to −70°C. The Myco-Chek blood culture bottles were inverted and rotated daily to cover the agar paddle during the first week, and then once weekly for 8 weeks or until growth was observed.

Mycobacteria isolates were frozen to −70°C in freezing media (7H9 broth with 10% sucrose) and also stored on Middlebrook 7H11 agar slants. All frozen isolates were transported to the Clinical Microbiology Laboratory at Duke University Medical Center (Durham, NC), where the identities of all bacteria, mycobacteria, and fungi isolates were confirmed. Mycobacteria were typed with use of gene probes and biochemical tests. Strains of *Mycobacterium tuberculosis* were characterized by restriction fragment length polymorphism (RFLP) assays.

**Malaria.** For each study patient, one thick and two thin blood smears were prepared with Fields stain and examined quantitatively for malaria parasites. Malaria blood films were prepared for the control group of 150 afebrile patients from the orthopedic ward.

**HIV-1 serology.** Serum samples were labeled with a randomly generated code number and the age and sex of the patient. At the end of the study, the sera were assayed in batches by ELISA (Vironostika HIV-1 Microelisa System; Organon Teknika Corporation, Durham, NC) for HIV-1 antibody. The code was then broken and the ELISA results correlated retrospectively with the patients’ study records.

**Antimicrobial susceptibility testing.** Antimicrobial susceptibility tests and interpretations were performed at Duke University Medical Center, according to the recommendations and guidelines proposed by the National Committee for Clinical Laboratory Standards [7, 8]. The antimicrobial panel chosen included affordable drugs readily available to patients in Muhimbili Medical Centre. Susceptibilities of gram-negative organisms to the selected antimicrobials were tested with the Microscan Walkaway (Baxter Diagnostics, Deerfield, IL). Other susceptibilities were tested with disk-diffusion procedures (Kirby-Bauer test). The Etest (AB BIODISK, Culver City, CA) was used to test the susceptibility of *Streptococcus pneumoniae* to penicillin. Susceptibility of *M. tuberculosis* isolates was tested by the BACTEC radiometric method (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD).

**Statistical Analysis**

An Epi-Info computer package (version 6.02) [9] was used to calculate the population sample size for the study, on the basis of published prevalence rates of BSI in studies conducted in Kenya, Rwanda, and the Ivory Coast [3–5]. The χ² test with Mantel-Haenszel and Yates’ correction and Fisher’s exact test, where appropriate, were used to compare groups. Odds ratios, relative risks, and 95% confidence intervals were calculated.

**Results**

Over the study period, 1,425 patients ≥15 years of age were consecutively admitted to the medical service at Muhimbili Medical Centre. Of these, 517 (36%) met the study criteria and were enrolled in the study. There were 280 males (54%). The median age in the study population was 38 (range, 15–95) years. During the study period, 15 patients died within the first 6 hours of admission, before investigators were notified or blood could be drawn. One hundred and forty-five patients (28%) had a BSI. One hundred and fifty-five clinically important organisms were isolated (table 1). Of the 517 study
Table 1. Blood culture pathogens isolated from HIV-1-positive and HIV-negative febrile patients.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. of patients</th>
<th>HIV-positive (n = 282)</th>
<th>HIV-negative (n = 235)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>0</td>
<td>1</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>7</td>
<td>5</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>non-typhi Salmonella</td>
<td>23</td>
<td>6</td>
<td>3.4 (1–10)</td>
<td></td>
</tr>
<tr>
<td>Salmonella typhi</td>
<td>0</td>
<td>1</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Shigella dysenteriae</td>
<td>0</td>
<td>1</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Shigella flexneri</td>
<td>3</td>
<td>0</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td><strong>Other gram-negative bacilli</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter lwoffii</td>
<td>1</td>
<td>0</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Alcaligenes xylosoxidans</td>
<td>1</td>
<td>0</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>1</td>
<td>0</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>0</td>
<td>0</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Serratia plymuthica</td>
<td>0</td>
<td>1</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Xanthomonas maltophilia</td>
<td>1</td>
<td>0</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td><strong>Gram-positive organisms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus casseliflavus</td>
<td>0</td>
<td>1</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>5</td>
<td>8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>6</td>
<td>5</td>
<td>NS</td>
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</tr>
<tr>
<td>Streptococcus group A</td>
<td>1</td>
<td>0</td>
<td>*</td>
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</tr>
<tr>
<td>Streptococcus group G</td>
<td>2</td>
<td>0</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td><strong>Yeasts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida lusitaniae</td>
<td>0</td>
<td>1</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>10</td>
<td>0</td>
<td>Undefined</td>
<td></td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>1</td>
<td>0</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td><strong>Mycobacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>57</td>
<td>3</td>
<td>12 (4–34)</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>0</td>
<td>1</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td><strong>Total no. of patients with blood pathogens</strong></td>
<td>118</td>
<td>27</td>
<td>6 (3–9)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. NS = not significant. * Numbers too small to calculate a test statistic.

1 Ten patients had two organisms isolated from their blood: 1 with Shigella flexneri and M. tuberculosis, 2 with Salmonella species and M. tuberculosis, 1 with Salmonella typhimurium and S. aureus, 1 with Burkholderia cepacia and Salmonella species, 2 with Salmonella species and S. pneumoniae, 1 with Citrobacter freundii and Serratia plymuthica, 1 with Salmonella species and Cryptococcus neoformans, and 1 with group A Streptococcus species and E. coli.

Patients, 282 (55%) were HIV-1-seropositive, and of the 145 patients with BSI, 118 (81%) were HIV-1-seropositive. HIV-1-positive patients were significantly more likely than HIV-1-negative patients to have a BSI (OR = 6; 95% CI, 3–9; P < .0001). Ten patients had polymicrobial BSI (>1 pathogen); 8 (80%) of these 10 patients were HIV-1-infected.

Sixty-one (42%) of the 145 patients with BSI had mycobacteremia. The median time to isolation of mycobacterial species by means of the lysis-centrifugation system, followed by inoculation into biphasic media, was 25 days. Biochemical and gene-probing techniques identified one of the mycobacterial isolates as Mycobacterium avium complex; the remaining 60 (98%) were M. tuberculosis complex. RFLP analysis of M. tuberculosis complex isolates demonstrated 44 different fingerprint designations among the 60 isolates. Fifty-nine (97%) of the 61 patients with mycobacteremia were HIV-1-seropositive (the M. avium complex isolate was also from an HIV-1-infected patient).

M. tuberculosis complex was the most frequently isolated pathogen (43%), followed by non-typhi Salmonella species (20%); Table 2 shows the six most frequently isolated organisms. These six organisms alone or in combination accounted for 135 (87%) of the 155 pathogens isolated. Of the 29 non-typhi Salmonella species isolates, 14 were Salmonella enteritidis, 10 were Salmonella typhimurium, and 5 belonged to other Salmonella serogroups. There were 4 Shigella species isolates: 3 Shigella flexneri and 1 Shigella dysenteriae.

The isolation rate for non-typhi Salmonella species was significantly higher in the HIV-1-seropositive patients than in the seronegative patients (P < .01) (Table 1). S. typhi was isolated once, in a culture of blood taken from a patient who was HIV-1-negative. There was no difference in the prevalence of
S. pneumoniae BSI among HIV-positive and HIV-negative patients. However, the infections due to other Streptococcus species (two group G and one group A) all occurred in HIV-positive patients. All 10 Cryptococcus neoformans isolates were from HIV-positive patients.

Seven (1.3%) of the 517 blood cultures yielded organisms that were considered contaminants (3 Staphylococcus epidermidis, 2 diphtheroids, 1 Micrococcus species, and 1 Bacillus cereus). There was no significant difference between the contamination rates of the cultures of blood taken from the HIV-seropositive patients (1.8%) and the HIV-seronegative ones (0.9%). Moreover, there was no significant difference between the contamination rates of blood cultures that yielded significant growth and those that were truly negative.

Forty-nine (9.5%) of 517 study patients had malaria parasitemia; there was no significant difference in comparison with the incidence in the afebrile control group (8.0%). Five (10.2%) of these 49 patients with parasitemia also had a BSI. Twenty (41%) of the 49 patients with malaria parasitemia were HIV-1-positive, suggesting that in our study population febrile HIV-1-negative patients were probably more likely than HIV-positive patients to have a positive malarial blood film on admission ($P < .05$).

Antimicrobial susceptibility tests suggested that chloramphenicol was the most effective of the available antimicrobials against Staphylococcus aureus and S. pneumoniae. Four (40%) of 11 S. pneumoniae isolates were resistant to penicillin. Chloramphenicol was also the most effective antimicrobial against Salmonella species. Fifty-seven (95%) of 60 M. tuberculosis isolates were susceptible to ethambutol, isoniazid, rifampin, and streptomycin; 2 (3.3%) were resistant to isoniazid and streptomycin and 1 (1.7%) was resistant to isoniazid only.

The median age of the 60 patients with M. tuberculosis BSI was 35 (range 15–65) years. Thirty-seven (62%) of these patients had a family history of cough and presented with shortness of breath, hemoptysis, and chronic symptoms (i.e., cough, diarrhea, or weight loss for $\geq$1 month) or had clinical signs of pleural effusion and consolidation on physical examination. Only 10 persons (17%) with mycobacteremia had sputum smears examined for AFB; the results of these sputum smears were not available. Moreover, the prevalences of chronic symptoms, pleural effusion, consolidation, and lymphadenopathy were similar in patients with and without M. tuberculosis BSI.

There were no symptoms or signs that were predictive of the presence of mycobacteremia. Twenty-three patients (38%) with M. tuberculosis BSI had no respiratory symptoms or physical signs suggestive of pulmonary pathology. Chest radiographs were not available for the majority of these patients. Twenty-seven (45%) of the 60 patients with M. tuberculosis BSI died before discharge from the hospital.

### Discussion

The results of our study indicate that the prevalence of BSI among febrile adults admitted to the largest referral hospital in Tanzania was 28% and that M. tuberculosis complex was the most common cause of community-acquired BSI. Non-typhi Salmonella species were the second most frequent organisms recovered, followed by S. aureus, Escherichia coli, S. pneumoniae, and C. neoformans, respectively (table 2). Moreover, 55% of febrile adults admitted to this hospital were HIV-1-seropositive.

The finding that M. tuberculosis was the most common bloodstream pathogen was unexpected, especially as previous studies in the Ivory Coast, Rwanda, and Kenya had suggested otherwise, i.e., that non-typhi Salmonella species and S. pneumoniae were the predominant causes of BSI in sub-Saharan Africa [3–5]. The heterogeneity of strains of M. tuberculosis demonstrated by RFLP suggests that our findings were due to neither an outbreak of M. tuberculosis BSI at Muhimbili Medical Centre nor inadvertent contamination of specimens in the microbiology laboratory.

In the United States and other developed countries, M. tuberculosis BSIs in both HIV-1-seropositive [10–13] and HIV-seronegative patients [14] have been recognized and reported. Moreover, M. tuberculosis BSIs have been reported in 15%–56% of HIV-infected patients clinically suspected to have extrapulmonary tuberculosis [10, 12, 13, 15–17]. Although the association between HIV-1 infection and tuberculosis has been well documented in Africa [18–21], few blood culture studies to detect mycobacteremia have been performed there [14]. In Western countries, M. tuberculosis BSIs are less common than M. avium complex BSIs, which are more frequently observed in patients with advanced HIV infection [11, 22, 23]. In contrast, M. avium complex BSIs are uncommon in sub-Saharan Africa [18, 24]. Previous studies in sub-Saharan Africa that attempted to culture mycobacteria in blood isolated M. tuberculosis in small numbers only [5, 18, 25]; M. avium complex was rare [26] or absent [25] in HIV-1-infected individuals.

A more recent study in Nairobi revealed mycobacteremia in patients with advanced HIV infection [26]; of 14 cases of mycobacteremia, 3 (21%) were due to M. avium complex and 11 (79%) to M. tuberculosis. This was the first published report...
that disseminated *M. avium* complex infection occurs in patients with advanced HIV infection in sub-Saharan Africa. Our study supports the finding that *M. avium* complex BSIs are relatively uncommon in that region.

The Septi-Chek bacteria biphasic system has been previously used in Africa to investigate nonmycobacterial bacteremia [5]. Although this system does not require specialized equipment, which would be impractical in a country with limited resources, it is expensive relative to lysis-centrifugation. Mattar et al. [27], using lysis-centrifugation, inoculated concentrate onto various media selective for mycobacteria, including 7H9 broth, and demonstrated that lysis-centrifugation is easy to perform, with a relatively high yield of AFB.

Ours is the first study in Africa in which the concentrate from lysis-centrifugation was inoculated directly into a biphasic bottle containing media selective for AFB. Our data confirm previous findings that liquid media enhance the recovery of small numbers of mycobacteria from clinical specimens [28].

The Myco-Chek AFB bottle is a biphasic system that combines a paddle containing Middlebrook 7H11, modified egg-based, and chocolate solid media with a bottle containing 20 mL of 7H9 broth and an internal CO2 source. This mycobacterial culture system was chosen because it has been shown to have significantly greater sensitivity, compared with that of conventional solid media, for the recovery of all mycobacteria from clinical specimens [29, 30].

Wasilauskas and Morrell demonstrated that the lysing anticoagulant in the Isolator tube inhibited the growth of *M. avium* complex [31]; Doern and Westerling subsequently reported optimum recovery of *M. avium* complex from blood, using a small volume of Isolator concentrate (0.2 mL) to inoculate the BACTEC 12B broth [32]. In our study, we used 1 mL of concentrate to inoculate the Myco-Chek 7H9 broth. Although this likely optimized our recovery of AFB, the *M. avium* complex and *M. tuberculosis* yield might have been improved further by the use of a smaller Isolator-concentrate inoculation volume. A study comparing the yield of *M. tuberculosis* from blood cultures using large and small Isolator concentrate volumes inoculated into a mycobacterial biphasic system has not yet been done.

This study had some limitations. First, only one blood culture specimen was drawn from each patient; two blood cultures would probably have yielded a larger number of organisms. It follows that the true rate of BSI in our cohort of febrile adult patients was probably higher than our observed rate of 28%. Second, blood cultures could not be repeated for some patients from whom *S. epidermidis*, *Micrococcus* species, and *Bacillus* species were isolated, because these patients died before the organisms were identified in the laboratory. The decision to treat these organisms as contaminants was based on work done in Nairobi suggesting that the presence of these organisms in the blood does not correlate with presentation and clinical state [3].

Third, ELISA HIV-1 results were not confirmed by western blotting. Data from Tanzania have shown that the use of two ELISAs to confirm the presence of HIV-1 antibodies produces results comparable to those of the western blot [33]. Thus, in a country with a high prevalence of HIV-1 infection and limited financial resources, western blot analysis is neither customary nor necessary. Fourth, we did not culture different body-site specimens and fluids for pathogens. We were therefore not able to correlate a BSI with the concurrent culture-positivity of a specimen from another site for the same organism. The fifth and final limitation was that HIV-2 antibody was not assayed for. To date, no HIV-2 infection has been found in Tanzania, despite a continuous search by workers at Muhimbili Medical Centre.

The overall rate of blood culture contamination in this study was low (1.3%). True-positive blood cultures were not more likely than negative cultures to have a contaminant. This was achieved by ensuring that high aseptic standards were maintained before and during venipuncture, with use of both alcohol and povidone iodine for skin cleansing, by allowing the skin to dry properly before venesection, and by scrupulously cleaning the rubber diaphragms of blood culture bottles and Isolator tubes with isopropyl alcohol before inoculation with blood or other sterile solutions during every stage of microbiological processing and analysis.

Three of the organisms considered contaminants were identified only on terminal subculturing of clear blood culture broth onto sheep blood plates, after 7 days of incubation. Thus, these organisms could have been introduced into the inocula at the time of terminal subculturing and not at the initial venipuncture. Without microbiology facilities and appropriate blood cultures, the prevalence of BSI in the febrile Tanzanian study population would not have been determined. While the prevalence of BSI has probably been underestimated in febrile adults, malaria parasitemia may be overestimated as the underlying cause of fever. Tanzania already has an established mycobacteria reference laboratory. Thus, it might be more practical to develop existing blood culture facilities, particularly to detect mycobacteremia and fungemia. Surveillance in this area is vital, especially as our study has demonstrated that 95% of *M. tuberculosis* isolates remain susceptible to ethambutol, isoniazid, rifampin, and streptomycin.

Limited resources restrict the availability of antimicrobials in Tanzania and other sub-Saharan countries. Thus, identification of organisms isolated in blood cultures and antimicrobial susceptibility testing should promote appropriate antimicrobial prescribing. In this study, 40% of *S. pneumoniae* isolates were resistant to penicillin, and susceptibility testing suggested that chloramphenicol would have been the antimicrobial of choice for an infection caused by this pathogen. On the other hand, the number of bacterial isolates (including *S. pneumoniae*) tested for susceptibility to available antimicrobials was too small to allow specific conclusions regarding optimal choice of agents for specific infections in patients or to enable reasonable estimation of the prevalence of antimicrobial-resistant organisms in the community. We did not test susceptibilities of
isolates to panels of antimicrobials used for routine antimicrobial susceptibility testing in the United States because many of these agents are not routinely available in sub-Saharan countries, including Tanzania.

Although 37 (62%) of 60 patients with mycobacteremia had pulmonary disease revealed by history and physical examination, sputum smears for mycobacteria were available for only 10 (17%) of these individuals. Moreover, many patients did not undergo chest radiography during their hospital stay for various reasons, which included lack of clear clinical indication, inability of the patient to pay for the procedure, lack of hospital personnel, broken radiography machines, an overwhelmed radiology department, or death before a chest radiograph could be obtained.

It is possible that many of the 23 patients with mycobacteremia but no clinical evidence of pulmonary disease had occult pulmonary tuberculosis. However, because many of these patients did not undergo chest radiography on admission for the various reasons mentioned, the true number of patients with occult *M. tuberculosis* pulmonary or extrapulmonary disease remains unknown. A mortality rate of 45% among study patients with mycobacteremia suggests that further research needs to be conducted to determine the extent of occult *M. tuberculosis* disease in sub-Saharan Africa.

We recommend the following: (1) establish basic facilities to rapidly identify AFB, common gram-positive and gram-negative pathogens, and their susceptibilities to available antimicrobials; (2) expand microbiology capabilities to include lysis-centrifugation, which we have demonstrated to be feasible and within the capabilities of the microbiology staff at Muhimbili Medical Centre; and (3) encourage and train clinicians to actively seek mycobacterial infection in febrile patients clinically suspected of having HIV-1 infection. As has been the case in the United States for many years, it might be more appropriate to integrate mycobacteriology and bacteriology services rather than maintain them as separate entities, as is the case in so many countries in Africa. This study suggests that providing basic microbiology laboratory facilities in sub-Saharan Africa will have significant impact on patient care.

We conclude that (1) in lesser developed countries with high HIV prevalence, febrile adults should be evaluated for a wide spectrum of infectious agents, including mycobacteria, fungi, and bacteria; (2) there is a need to expand the capability of laboratories in these countries to diagnose a wide range of emerging pathogens; and (3) these data may help change policies for prophylactic or empirical antimicrobial therapy for febrile HIV-infected patients.

Acknowledgments

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References