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Original Article

Epidemiology of Bloodstream Infections and Predictive Factors of Mortality among HIV-Infected Adult Patients in Thailand in the Era of Highly Active Antiretroviral Therapy

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SUMMARY: Few studies have described the pattern of bloodstream infections (BSI) among HIV-infected patients in the highly active antiretroviral therapy (HAART) era, particularly in resource-limited settings. A retrospective cohort study was conducted among 140 HIV-infected patients who had a positive blood culture from 2004–2008. Of the 140 patients, 91 (65%) were male with a mean (SD) age of 38 (9.1) years and a median (IQR) CD4 cell count of 32 (9–112) cells/mm^3. Community-acquired infection was detected in 89% of patients. The blood cultures contained Gram-negative bacteria, 40%; fungi, 24%; *Mycobacterium* spp., 20%; and Gram-positive bacteria, 16%. Common causative pathogens were *Cryptococcus neoformans*, 21%; *Salmonella* spp., 15%; and *Mycobacterium tuberculosis*, 12%. Common focal sites of infection were the central nervous system, 24%; respiratory tract, 20%; and gastrointestinal tract, 18%. CD4 cell count (OR, 0.61 per 50 cells/mm^3 increment; 95% CI, 0.39–0.96; P = 0.031) was the only factor associated with mycobacterial or fungal BSI. The crude mortality was 21%. HAART (OR, 0.23; 95% CI, 0.01–0.77; P = 0.017), focal infection (OR, 0.31; 95% CI, 0.10–0.97; P = 0.044), and complication (e.g., shock) (OR, 9.26; 95% CI, 3.25–26.42; $P < 0.001$) were the predictive factors of mortality. In conclusion, opportunistic infections are still the leading causes of BSI among HIV-infected patients in the HAART era.

INTRODUCTION

Thailand began producing generic antiretroviral drugs in 2002 (1). Since then, the Thai government has supported the free provision of antiretroviral drugs to human immunodeficiency virus (HIV)-infected patients who are enrolled in the universal coverage health program. Highly active antiretroviral therapy (HAART) has significantly improved prognosis and prolonged AIDS-free survival worldwide (2–5). However, more than half of newly diagnosed Thai HIV-infected patients have advanced HIV disease and are unaware of their HIV status (6). Morbidity and mortality in HIV-infected patients is due to opportunistic infections caused by various microorganisms even in the HAART era (7,8).

HIV infection is associated with an increased risk of bloodstream infections (BSI) (9–11). *Streptococcus pneumoniae* and *Escherichia coli* were the most common Gram-positive and Gram-negative organisms isolated from the bloodstream of hospitalized HIV-infected patients in the United States in 2001 (12). The presence of BSI is associated with increases in mortality rate, length of hospital stay, and the intensive care unit (ICU) admission rate (12). Another recent prospective study in Spain showed that BSI in HIV-infected patients were often caused by Gram-positive pathogens (13,14).

Epidemiology of BSI in HIV-infected patients may differ across geographic areas, and may depend on the availability of HAART in that region. HAART has led to a significantly reduced incidence of bacteremia and a modification of its characteristics (14). Studies on BSI in HIV-infected patients before (9) and after (11) the widespread use of HAART in resource-limited settings have been reported. However, there are few studies published in English that surveyed BSI among HIV infected-patients in Thailand, and some of these were conducted prior to the HAART era (15,16). One study reported that *Salmonella* spp. was the most common pathogen, followed by *E. coli* and *Staphylococcus aureus* (16). In contrast, a recent study on BSI among HIV-infected outpatients in Cambodia, Thailand, and Vietnam showed that *Mycobacterium tuberculosis* accounted for 54% of infections, followed by fungi and bacteria (17).

Few studies have described the pattern of BSI and their clinical manifestations, which may have changed, among HIV-infected patients in the HAART era in resource-limited settings. We aimed to determine the epidemiology of causative pathogens and the clinical characteristics of HIV-infected patients with BSI in Thailand. Factors associated with mycobacterial or fungal BSI and mortality were determined. These results may help health care providers prevent BSI and empirically select antimicrobial therapy while blood culture

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results are pending.

MATERIALS AND METHODS

Patients and population: A retrospective cohort study was conducted at Ramathibodi Hospital (a 1,000-bed university hospital in Bangkok, Thailand). Patients with a positive blood culture were identified from the database of the microbiology laboratory in the Department of Pathology between January 2004 and June 2008. The study was approved by the institutional review board. Inclusion criteria were as follows: (i) ≥ 15 years of age, (ii) documented HIV infection, (iii) a diagnosis of BSI, which was defined as an isolated true pathogen in one or more blood cultures with clinically apparent signs and symptoms of infection. Patients were excluded if there was any evidence of blood culture contamination, which was defined as a single blood culture yielding one of the following organisms: coagulase-negative staphylococci, *Corynebacterium* spp., *Bacillus* spp., *Propionibacterium* spp., *Peptostreptococcus* spp., *Clostridium* spp., or unidentified Gram-positive rods, or if the clinician did not initiate treatment, believing that it was not a true pathogen.

Data collection: Medical records were retrieved and reviewed. The following variables were collected, (i) clinical characteristics, including gender, age, route of HIV acquisition, prior opportunistic infections, underlying conditions, and antiretroviral therapy, (ii) BSI, including causative pathogen, type and site of infection, hospitalization, co-infection, complications, and outcome, (iii) laboratory-related data, including complete blood count, blood chemistry, CD4 cell count, HIV RNA, hepatitis B virus, and hepatitis C virus (HCV) profile. Community-acquired infection was defined as a positive blood culture that developed within 48 h of admission, and nosocomial infection was defined as an infection that developed after 48 h of hospitalization or within 14 days of a previous hospitalization.

Statistical analysis: Chi-square test or Fisher's exact test and Student's *t* test or Mann-Whitney U test were used to compare categorical variables and continuous variables between the two groups, respectively. Logistic regression was used to determine the factors associated with mycobacterial or fungal BSI and mortality. The odds ratio (OR) and 95% confidence interval (CI) were estimated. Variables with $P < 0.10$ were considered in the multivariate logistic regression model after assessment of multicollinearity of variance inflation factors. Variables were selected from a multiple logistic regression model with backward stepwise selection, and those that attained a level of significance were retained in the model. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata statistical software version 10.0 (Stata Corp., College Station, Texas, USA).

RESULTS

A total of 140 patients were included in the analysis. Their mean (standard deviation [SD]) age at BSI diagnosis was 38 (9.1) years; 91 (65%) patients were male, 91 (65%) patients had heterosexual risk of HIV acquisition, and 83 (59%) patients had a prior AIDS-defining illness (tuberculosis was the most common at 43%). Overall, 7.1% and 12.8% of patients were positive for HBsAg and anti-HCV, respectively, and 13.6% of patients had another underlying condition. Only 51

Table 1. Clinical characteristic of 140 HIV-infected patients who had bloodstream infection

Characteristic	n = 140
Mean (SD) age, years	38 (9.1)
Male gender, no. (%)	91 (65)
Route of HIV acquisition, no. (%)	
Heterosexual	91 (65)
Unknown or other	49 (35)
Prior AIDS defining illness, no. (%)	83 (59.3)
Tuberculosis	49 (43)
Pneumocystis jiroveci pneumonia	24 (21)
Cryptococcosis	13 (11.4)
Cytomegalovirus disease	6 (5.3)
Malignancy	4 (3.5)
Others	18 (15.8)
Antiretroviral therapy, no. (%)	51 (36.4)
NNRTI-based HAART regimen	40
PI-based HAART regimen	11

Some patients had more than one prior opportunistic infection. HAART, highly active antiretroviral therapy; NNRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SD, standard deviation.

Table 2. Characteristic of bloodstream infection among 140 HIV-infected patients

Characteristic	n = 140
Causative pathogen, no. (%)[1)]	
Gram-negative bacilli	57 (39.6)
Fungus	35 (24.3)
Mycobacterium spp.	29 (20.1)
Gram-positive cocci and rod	23 (16.0)
Causative pathogen, no. (%)[1)]	
Cryptococcus neoformans	30 (20.8)
Salmonella spp.	21 (14.6)
Mycobacterium tuberculosis	17 (11.8)
Escherichia coli	14 (9.7)
Non-tuberculous mycobacteria	12 (8.3)
Staphylococcus spp.	12 (8.3)
Klebsiella pneumoniae	4 (2.7)
Penicillium marneffei	4 (2.7)
Streptococcus pneumoniae	2 (1.4)
Other *Streptococcus* spp.	3 (2.1)
Histoplasma capsulatum	1 (0.7)
Others	23 (16)
Focal site of infection, no. (%)	115 (82.2)
Central nervous system	34 (23.8)
Respiratory tract	29 (20.3)
Intra-abdomen or gastrointestinal tract	26 (18.2)
Bone marrow	16 (11.2)
Lymph node	12 (8.4)
Urinary tract	11 (7.7)
Skin and soft tissue	10 (7)
Catheter-related	3 (2.1)
Bone and joints	2 (1.4)

[1)]: Some patients had more than one organism recovered from blood culture.

Table 3. Clinical characteristic of 140 HIV-infected patients who had bloodstream infection stratified by causative pathogen (mycobacteria or fungus versus bacteria)

Variable	Mycobacteria or fungus (n = 64)	Bacteria (n = 76)	P
Clinical characteristics			
Mean (SD) age, years	35.7 (7.2)	39 (10)	0.021
Male gender, no. (%)	40 (62.5)	51 (67.1)	0.597
Heterosexual risk, no. (%)	46 (71.9)	45 (59.2)	0.155
Prior AIDS defining illness, no. (%)	41 (64.1)	42 (55.3)	0.306
Had underlying condition, no. (%)	6 (9.4)	13 (17.1)	0.221
Antiretroviral therapy, no. (%)	22 (34.4)	29 (38.2)	0.725
Community-acquired infection, no. (%)	64 (100)	61 (80.3)	<0.001
Had focal site of infection, no. (%)	61 (95.3)	54 (71)	<0.001
Had co-infection, no. (%)	8 (12.5)	15 (19.7)	0.360
Had complication of infection, no. (%)	22 (34.4)	37 (48.7)	0.122
Laboratory investigations			
Median (IQR) total leukocyte, cells/mm^3	5,330 (4,065–8,880)	6,480 (3,300–10,600)	0.325
Median (IQR) total neutrophil, %	77 (68–86)	79 (69–86)	0.904
Median (IQR) total lymphocyte, %	13 (6–19)	11 (7–24)	0.861
Median (IQR) hemoglobin, mg/dL	9.4 (7.8–11.2)	9 (7.8–10.6)	0.824
Median (IQR) AST, U/L	48 (34–98)	52 (34–87)	0.818
Median (IQR) ALT, U/L	48 (34–69)	51 (36–80)	0.593
Median (IQR) alkaline phosphatase, U/L	146 (96–284)	122 (91–304)	0.464
Median (IQR) albumin, mg/dL	29.3 (22.8–34.8)	31.4 (23.2–36.6)	0.435
Median (IQR) creatinine, mg/dL	1 (0.8–1.3)	1.2 (0.9–2.1)	0.004
Median (IQR) CD4 cell count, cells/mm^3	20 (8–60)	54 (12–191)	0.010
Median (IQR) HIV RNA, log copied/mL	4.8 (2.1–5.9)	4.2 (1.7–5.0)	0.090
Positive HBsAg	5 (13.9)	5 (11.4)	0.747
Positive anti-HCV	4 (12.5)	14 (35)	0.032

SD, standard deviation; IQR, interquartile range; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

(36%) patients were receiving HAART at the time of BSI diagnosis with a median (interquartile range [IQR]) CD4 cell count of 32 (9–112) cells/mm^3 and median (IQR) HIV RNA of 4.4 (1.7–5.2) log copies/mL (Table 1).

Community-acquired infection was detected in 125 (89%) patients. Blood cultures revealed: Gram-negative bacteria, 39.6%; fungi, 24.3%; *Mycobacterium* spp., 20.1%; and Gram-positive bacteria, 16%. Common causative pathogens were *Cryptococcus neoformans*, 20.8%; *Salmonella* spp., 14.6%; and *M. tuberculosis*, 11.8%. A total of 23 (16.2%) patients had more than 1 pathogen isolated. Among the 115 (82.2%) patients who had focal sites of infections, the most common sites were the central nervous system, 23.8%; respiratory tract, 20.3%; and intra-abdomen, 18.2% (Table 2).

Patients with mycobacterial or fungal BSI were younger (P = 0.021), and were more likely to have community-acquired infection (P < 0.001), a focal site of infection (P < 0.001), a lower CD4 cell count (P = 0.010), and higher HIV RNA (P = 0.090) compared to patients with bacterial BSI. Patients with mycobacterial or fungal BSI also had lower creatinine levels (P = 0.004) (Table 3). By univariate logistic regression, age at BSI diagnosis (OR, 0.75 per 5 years increment; 95% CI, 0.60–0.92; P = 0.008), focal site of infection (OR, 8.28; 95% CI, 2.35–29.22; P = 0.001), and CD4 cell count (OR, 0.70 per 50 cells/mm^3 increment; 95% CI, 0.55–0.89; P = 0.031) were associated with mycobacterial or fungal BSI. By multiple logistic regression, CD4 cell count (OR, 0.61 per 50 cells/mm^3 increment; 95% CI, 0.39–0.96; P = 0.031) was the only factor associated with mycobacterial or fungal BSI.

Of the 140 patients, 123 (87.8%) required hospitalization and 49 (42.1%) had at least one complication, e.g., shock, ICU admission, acute kidney injury, acute respiratory distress syndrome, or disseminated intravascular dissemination. The overall mortality rate was 21.4%. The mortality rate did not differ significantly between patients with mycobacterial or fungal BSI and those with bacterial BSI, even though patients with mycobacterial or fungal BSI had a lower mortality rate (17.2% versus 25%; P = 0.305). The clinical characteristics of patients who were alive and dead were compared (Table 4). Patients who were dead were less likely to have received HAART, had community-acquired infection, had a focal site of infection, and were more likely to have complications and higher liver enzyme levels compared to living patients. Predictive factors of mortality as determined by univariate logistic regression were HAART (OR, 0.21; 95% CI, 0.07–0.63; P = 0.006), *Mycobacterium* spp. infection (OR, 0.22; 95% CI, 0.05–0.98; P = 0.047), and complication (OR, 8.57; 95% CI, 3.22–22.85; P < 0.001). By multiple logistic regression, HAART (OR, 0.23; 95% CI, 0.01–0.77; P = 0.017), focal infection (OR, 0.31; 95% CI, 0.10–0.97; P = 0.044), and complication (OR, 9.26; 95% CI, 3.25–26.42; P < 0.001) were the predictive factors of the mortality.

Table 4. Clinical characteristic of 140 HIV-infected patients who had bloodstream infection stratified by clinical outcome (alive versus dead)

Variable	Alive (n = 110)	Dead (n = 30)	P
Clinical characteristics			
Mean (SD) age at blood stream infection, years	38.2 (9.0)	37.4 (9.4)	0.599
Male gender, no. (%)	71 (64.6)	2 (66.7)	0.505
Route of HIV acquisition, no. (%)			0.193
Heterosexual	74 (67.3)	17 (56.7)	
Unknown or other	36 (32.7)	13 (43.3)	
Prior AIDS defining illness, no. (%)	65 (59.1)	18 (60)	0.551
Had underlying condition, no. (%)	17 (15.4)	2 (6.7)	0.174
Antiretroviral therapy, no. (%)	47 (42.7)	4 (13.3)	0.003
Community-acquired infection, no. (%)	101 (91.8)	24 (80)	0.070
Had focal site of infection, no. (%)	94 (85.4)	21 (70)	0.050
Causative pathogens, no. (%)			0.162
Mycobacterium spp.	27 (24.6)	2 (6.7)	
Fungus	26 (23.6)	9 (30)	
Gram-negative bacilli	40 (36.4)	14 (46.7)	
Gram-positive cocci and rod	17 (15.4)	5 (16.7)	
Had complication of infection, no. (%)	35 (31.8)	24 (80)	<0.001
Laboratory investigations			
Median (IQR) total leukocyte, cells/mm^3	7,553 (3,600–9,800)	6,065 (4,430–8,140)	0.757
Median (IQR) total neutrophil, %	78.5 (68–85)	81.5 (69.5–87)	0.345
Median (IQR) total lymphocyte, %	12 (6–20)	10 (6–20)	0.525
Median (IQR) hemoglobin, mg/dL	9.6 (7.8–10.6)	9.3 (8.4–11.6)	0.357
Median (IQR) AST, U/L	48 (32–81)	72 (44.5–155)	0.028
Median (IQR) ALT, U/L	49 (33–74)	55.5 (39–94)	0.256
Median (IQR) albumin, mg/dL	31.1 (24.8–36.4)	28.6 (21.8–34)	0.173
Median (IQR) creatinine, mg/dL	1.0 (0.8–1.4)	1.2 (0.9–1.9)	0.264
Median (IQR) CD4 cell count, cells/mm^3	37 (9–112)	28 (12–114)	0.994
Median (IQR) HIV RNA, log copied/mL	4.4 (1.7–5.2)	3.8 (1.7–5.9)	0.748
Positive HBsAg	10 (14.5)	0	0.207
Positive anti-HCV	14 (22.2)	4 (44.4)	0.152

Abbreviations are in Table 3.

DISCUSSION

The results from this study demonstrated the clinical characteristics of HIV-infected patients who had BSI at a tertiary care university hospital during 5 years under the universal coverage health program with HAART supported by the Thai government. The majority of our patients were heterosexual males with a mean age of 38 years and advanced disease (Table 1). These patient characteristics were not different from those of a prior study in Thailand (9) and another recent large study in Southeast Asia irrespective of the HAART era (17).

Blood cultures from HIV-infected patients in the present study mostly contained Gram-negative bacteria, followed by fungi, *Mycobacterium* spp., and Gram-positive bacteria. The most frequently isolated BSI pathogens were *C. neoformans*, *Salmonella* spp., *M. tuberculosis*, *E. coli*, and non-tuberculous mycobacteria; these were similar to those reported by other studies in the same setting both before and after the HAART era (Table 2) (9,15–17). In these patients, advanced disease was associated with opportunistic infections. Infections with *Salmonella* spp. were the most common bacterial infections in HIV-infected patients, which is consistent with the results from other studies, and demonstrated that efforts are needed to prevent invasive salmonellosis in HIV-infected persons through improvements in food and water safety (18). However, in the Western world, the most frequent isolates were Gram-positive bacteria. *S. aureus* is also a major cause of bacteremia in AIDS patients in particular conditions, such as injection drug use and catheter-related septicemia (13,14,19–21).

Furthermore, *M. tuberculosis* remains one of the most common causes of BSI among HIV-infected patients; this finding is consistent with that of another study, and is particularly valid in resource-limited settings with a high incidence of tuberculosis (17). We found that the most common fungal infection was *C. neoformans* followed by *Penicillium marneffei* (Table 2). In contrast, in some other studies, *C. neoformans* and *Candida albicans* (and spp.) were found to be the most common causes of fungemia (13).

The predictive factors for mycobacterial or fungal BSI were older age, focal site infection, higher creatinine, lower CD4 cell count, and higher HIV RNA. We found that every 50 cells/mm^3 increment of the CD4 cell count was significantly associated with 39% lower odds of having mycobacterial or fungal BSI. These results may help health care providers to select empirical antimicrobial therapy while blood culture results are pending.

The crude mortality was 21% in our study, and was comparable to that of other studies (10,12). Antiretroviral therapy, community-acquired infection, focal site of infection, and complication were significantly associated with mortality. Early detection of focal site infection, getting rid of the source of infection, and correcting complications may minimize mortality among HIV-infected patients with BSI. In addition, only one-third of the patients in this study were receiving HAART at baseline or at diagnosis of BSI. Patients receiving HAART can contract BSI because they can still have very low CD4 cell counts. The median CD4 cell count at baseline was less than 50 cells/mm^3 in both groups (Table 3). Almost all patients should have received HAART before they developed BSI. HAART was lately initiated even in the era of HAART in Thailand. Furthermore, the Thai government should focus on fully supporting HAART to improve the immunologic state of HIV-infected patients.

A limitation of this study is that it was conducted at a single university hospital in Bangkok. HIV-infected patients in other urban areas and rural areas may have different clinical characteristics, and the distribution of causative pathogens may differ among particular areas. Despite this limitation, we believe that our study provides a potentially valuable insight into the epidemiology of BSI among HIV-infected patients in the HAART era in Thailand.

In conclusion, *C. neoformans*, *Salmonella* spp., and *M. tuberculosis*, so called opportunistic infections, are the leading causes of BSI among HIV-infected patients in the HAART era. These patients presented with very low CD4 cell counts, and high mortality was observed. These results suggest that HIV/AIDS prevention and scaling up of treatment are urgently needed in Thailand.

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Conflict of interest None to declare.

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