Nosocomial Bloodstream Infection in Human Immunodeficiency Virus-Infected Patients in Taiwan: Descriptive Epidemiology and Risk Factors for Mortality

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Background and Purpose: Nosocomial bloodstream infection (NBSI) is common in patients with human immunodeficiency virus (HIV) infection. This study evaluated the incidence, causative pathogens, and outcome of NBSIs in hospitalized HIV-infected patients at a university hospital in Taiwan.

Methods: The medical records of all HIV-infected patients who developed NBSIs from June 1994 to June 2003 were retrospectively reviewed. A standardized case record form was used to collect demographic, clinical, laboratory, and microbiologic data.

Results: During the study period, 57 episodes of NBSIs occurred in 51 HIV-infected patients whose median age was 37 years (range, 23 to 60 years). All of the patients were at HIV infection stage C. The incidence of NBSIs was 2.3 per 1000 person-days of hospitalization (41.4 per 1000 discharges). More than three-fourths of the 57 episodes (77.2%) were classified as primary NBSIs. Other infection foci included respiratory tract (6 episodes), urinary tract (3), surgical site (2), and skin (2). *Staphylococcus* species were the leading pathogens (42.1%). The crude and attributable mortality rates in patients with NBSIs during the study period were 38.6% and 26.1%, respectively. Multivariate analysis using a logistic regression model revealed that shock and hypoalbuminemia at the onset of NBSIs were the 2 factors predictive of mortality.

Conclusions: NBSIs in hospitalized patients in the late stage of HIV infection were associated with a high attributable mortality rate. *Staphylococcus* species were the leading pathogen responsible for NBSIs. Presentations of shock and hypoalbuminemia were predictive of mortality.

Key words: AIDS-related opportunistic infection; Cross infection; HIV infection; Risk factors; Septicemia

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Since the first case of human immunodeficiency virus (HIV) infection in Taiwan in 1984, the number of cases of newly diagnosed HIV infection has increased at a rate of 15 to 20% yearly and more than 5000 cases have been diagnosed over the past 2 decades.[1] Acquired immunodeficiency syndrome (AIDS) was diagnosed in more than 1500 of these cases according to the 1993 expanded surveillance case definition for AIDS among adolescents and adults.[2] Many HIV-infected patients are hospitalized during the course of illness. During the hospital stay, nosocomial infections become another problem in this unique group of patients.[3]

Previous studies revealed that the nosocomial infection rates of HIV-infected patients, ranging from 6 to 10.5%, were higher than those of the general population, and that bloodstream infections (BSIs) were the most frequent infection by site, ranging from

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23.9 to 36% of all nosocomial infections.[3–6] These findings differ from HIV-negative patients, in whom urinary tract infection is the leading cause of nosocomial infection. The reasons for this discrepancy may include immune defects in neutrophils, frequent use of an indwelling central venous catheter (CVC), intravenous drug use, relatively infrequent use of urinary catheterization and mechanical ventilation, and a higher rate of skin colonization and infections.[5,7]

In addition to prolonged hospitalization and increased medical costs, nosocomial BSIs (NBSIs) are often associated with a higher mortality rate and a higher attributable mortality.[8–11] Although etiologic agents were well described in previous studies, analysis of risk factors for mortality in HIV- infected patients with NBSIs has been limited. This study investigated the causative pathogens and risk factors for mortality in HIV-infected patients who developed NBSIs.

Methods

Patients and data collection

National Taiwan University Hospital (NTUH) has been a major referral hospital for HIV and AIDS care in Taiwan. Highly active antiretroviral therapy (HAART) has been used at NTUH since April 1, 1997. From June 1994 to June 2003, a total of 912 HIV-infected patients were treated and followed at NTUH. During the past 9 years, there were 1359 admissions of HIV-infected patients at NTUH. All of the medical and microbiologic records of these patients were retrospectively reviewed to identify patients with bacteremia or fungemia who were hospitalized during the study period. A standardized case record form was used to collect the following demographic and clinical data: CD4 lymphocyte counts; HIV infection stage according to the Center for Disease Control (CDC) classification[2] for the period within 3 months of development of NBSIs; white blood cell (WBC) count; serum albumin level; severity of systemic inflammatory responses[12]; presence of CVCs; active opportunistic infection; organ failure at the onset of NBSI; and outcome.

The incidence of nosocomial infection in all hospitalized patients was obtained from the database maintained by the Infection Control Center of NTUH.

Definitions

NBSI was defined as proposed by the CDC,[13] which required more than one culture of blood specimens yielding bacteria or fungi, which were obtained in the presence of fever (body temperature ≥ 38°C) developing at least 48 hours after admission and not attributable to other causes. Cases for which a single blood culture yielded coagulase-negative staphylococci, *Corynebacterium* species, *Bacillus* species, or *Propionibacterium acnes* were excluded from further analysis.[14,15]

CVC-related BSI was defined as isolation of the identical species of microorganism from a semiquantitative culture of the vascular catheter tip (15 colony-forming units/mL or more using the Maki roll-plate technique[16]) with the same antibiotype as the microorganism isolated from peripheral blood specimens[17]; or as the microorganism isolated from the skin exit site of the CVC with signs and symptoms of infection.[9] Primary BSI was defined as a BSI without an infection focus or as a BSI classified as CVC-related.

The severity of NBSI at onset was classified as sepsis, septic syndrome, septic shock, and refractory septic shock according to the criteria of severity for systemic inflammatory syndrome.[12] Mortality was defined as death within 30 days after the onset of NBSIs.

Statistical analysis

All statistical analysis was performed with SPSS version 10.0 (SPSS, Chicago, Illinois, USA). Continuous variables were compared with t test. Categorical variables were compared by using chi-squared test. Logistic regression model was used for univariate and multivariate analyses to determine the independent predictive factors of mortality. In addition, incidence rates (events per unit of person-time) were compared with normal-theory test manually. A p value < 0.05 was considered significant.

Results

During the 9-year study period, 51 HIV-infected inpatients had 57 episodes of NBSIs, and 6 patients had 2 episodes of NBSIs. The incidence of NBSIs was 2.3 per 1000 person-days of hospitalization or 41.4 per 1000 discharges. During the same study period, the incidence of NBSIs in all hospitalized patients at NTUH was 18.7 per 1000 discharges.[18] Before the introduction of HAART, the incidence of NBSIs in HIV-infected inpatients was 1.4 per 1000 person-days of hospitalization or 31.5 per 1000 discharges. After the introduction of HAART, the incidence increased to 2.7 per 1000 person-days of hospitalization ($p = 0.054$) or 43.6 per 1000 discharges ($p = 0.338$). The duration of hospital stay of HIV-infected inpatients before and after HAART was 23.5 ± 23.2 and 16.0 ± 20.2 days ($p < 0.001$), respectively. However, the duration of hospital stay of HIV-infected inpatients who developed NBSIs before and after HAART was 58.4 ± 23.5 and 53.1 ± 51.9 days ($p = 0.640$), respectively.

The demographic, clinical, and laboratory data of the patients with NBSIs are shown in Table 1. Their

Table 1. Clinical characteristics of HIV-infected patients who developed nosocomial bloodstream infections (NBSIs) and univariate analysis of prognostic factors.

Variable	No. of NBSIs (%)	No. of deaths	Mortality (%)	Univariate analysis	
				p value	Odds ratio (95% CI)
Gender					
Female	2 (3.5)	0	0	0.793	0.001
Male	55 (96.5)	22	40		(0.000-1.3 x 10^{19})
CD4 lymphocyte count (x 10^6/L)					
< 100	51 (89.5)	20	39.2	0.780	1.290
≥ 100	6 (10.5)	2	33.3		(0.216-7.712)
Serum albumin level (g/L)*					
≤ 25	18 (39.1)	12	66.7	0.007	6.000
> 25	28 (60.9)	7	25.0		(1.634-22.033)
Active opportunistic infection					
Yes	44 (77.2)	16	36.4	0.525	1.500
No	13 (22.8)	6	28.2		(0.429-5.243)
Severity of NBSIs					
With shock	16 (31.4)	12	75.0	0.001	9.259
Without shock	41 (68.6)	10	24.4		(2.440-35.714)
WBC count (x 10^6/L)					
< 4000	28 (49.1)	8	28.6	0.130	0.429
≥ 4000	29 (50.9)	14	48.3		(0.143-1.284)
Platelet (x 10^6/L)					
< 150,000	36 (63.2)	14	38.9	0.953	1.034
≥ 150,000	21 (26.8)	8	38.1		(0.342-3.125)
Classification of NBSI					
Secondary	13 (22.8)	6	46.2	0.525	1.500
Primary	44 (77.2)	16	36.4		(0.429-5.243)
Delayed treatment					
Yes	13 (22.8)	8	61.5	0.060	3.429
No	44 (77.2)	14	31.8		(0.949-12.392)

* Data missing for 11 episodes of NBSI.
CI = confidence interval; WBC = white blood cells.

median age was 37 years (range, 23 to 60 years). Seven of the 51 patients had underlying comorbidity other than HIV infection as follows: 4 patients had chronic hepatitis B virus infection, 1 of whom had liver cirrhosis related to hepatitis B virus infection; 1 patient had chronic hepatitis C virus infection; and another 2 patients had chronic renal insufficiency. All of the patients with NBSIs were at HIV infection stage C with 51 episodes occurring in patients with CD4 lymphocyte counts of 100 x 10^6/L or less and 44 episodes in patients with active AIDS-defining opportunistic infections. Septic shock or refractory septic shock at the onset of NBSIs was noted in 16 episodes. Ten episodes of NBSIs led to organ failure, including respiratory failure in 7, renal failure in 3, heart failure in 1.

Forty four episodes of NBSIs were classified as primary, among which 19 episodes were CVC-related. The primary foci of the other 13 episodes included lower respiratory tract in 6, urinary tract in 3, surgical site in 2, and skin in 2. The causative pathogens of all episodes of NBSIs are shown in Table 2. The 3 leading pathogens were *Staphylococcus aureus*, coagulase-negative staphylococci, and *Pseudomonas aeruginosa*. Overall, Gram-negative bacteria accounted for 29 (50.9%) episodes, Gram-positive bacteria for 30 episodes (52.6%), and both Gram-negative and -positive bacteria for 4 episodes (7.0%). The causative pathogens of the 44 episodes of primary NBSIs are listed according to their CVC-related or non CVC-related association in Table 2. Of these 44 episodes of primary NBSIs, the leading 3 pathogens were *S. aureus*, coagulase-negative staphylococci, and non-typhoid *Salmonella*. Gram-positive bacteria were found in 25 episodes (56.8%), Gram-negative bacteria in 21 episodes (47.7%), and yeast in 1 episode (2.3%). In 3 (6.8%) of the 44 episodes of primary NBSIs, both Gram-positive and negative bacteria were found, and in 1 episode, 2 different Gram-negative bacteria were isolated at the same time.

In 22 episodes, the affected patients died of causes related to the NBSIs. The overall mortality rate was 38.6%. During the study period, the mortality rate of all HIV-infected inpatients during hospitalization was 12.5%. Therefore, the attributable mortality rate of NBSIs in HIV-infected patients was 26.1%. Considering the possible effect of introduction of HAART, the crude and attributable mortality rates of NBSI in HIV-infected patients before the introduction of HAART were 37.5% and 25.7%, respectively; after the

Table 2. Microbiology of the 57 episodes of nosocomial bloodstream infections (NBSIs) and the 44 episodes classified as primary NBSIs.

Causative microorganisms	Number of NBSIs episodes		
	Primary NBSIs		Total NBSIs
	CVC-related	Non-CVC-related	
Gram-positive bacteria			
Staphylococcus aureus			15
Methicillin-susceptible			2
Methicillin-resistant	8	4	13
Coagulase-negative staphylococci	4	5	9
Enterococcus species	1	1	4
Corynebacterium species	0	1	1
Peptostreptococcus asaccharolyticus	0	1	1
Gram-negative bacteria			
Pseudomonas aeruginosa	2	2	7
Escherichia coli	1	0	5
Enterobacter cloacae	1	1	4
Non-typhoid *Salmonella*	0	4	4
Acinetobacter baumannii	1	5	6
Bacteroides species	0	2	2
Klebsiella pneumoniae	1	0	2
Stenotrophomonas maltophilia	1	0	1
Citrobacter freundii	0	1	1
Candida albicans	0	1	2
Candidia glabrata	0	0	1
Dual pathogen	1*	3†	9‡

* Including methicillin-resistant *Staphylococcus aureus* + *Pseudomonas aeruginosa* in 1 episode of central venous catheter-related bloodstream infection.
† Including methicillin-resistant *Staphylococcus aureus* (MRSA) + non-typhoid *Salmonella* in 1 episode of primary bloodstream infection (BSI), MRSA + *Acinetobacter baumannii* in 1 episode of primary BSI, and *A. baumannii* + non-typhoid *Salmonella* in 1 episode of primary BSI.
‡ Including methicillin-resistant *Staphylococcus aureus* (MRSA) + *Pseudomonas aeruginosa* in 1 episode, MRSA + non-typhoid *Salmonella* in 1, MRSA + *Candida glabrata* in 1, *Enterococcus* species + *Escherichia coli* in 2, *E. coli* + *P. aeruginosa* in 2, MRSA + *Acinetobacter baumannii* in 1, and *A. baumannii* + non-typhoid *Salmonella* in 1.
CVC = central venous catheter; BSI = bloodstream infection.

introduction of HAART, these were 38.8% and 26.2%, respectively.

In univariate analysis, shock and low serum albumin levels (≤ 25 g/L) at the onset of NBSIs were the predictive factors for mortality (Table 1). In multivariate analysis, shock and low serum albumin level at the onset of NBSIs remained the 2 factors significantly predictive of mortality, with odds ratios of 5.376 (95% confidence interval [95% CI], 1.211-23.810; $p = 0.027$) and 5.117 (95% CI, 1.278-20.491; $p = 0.021$), respectively.

Discussion

In this study, we found that hospitalized patients who were at the late stage of HIV infection had a higher risk for developing NBSIs, with an incidence rate of 2.3 per 1000 person-days of hospitalization. NBSIs were associated with a high crude mortality rate (38.6%) and attributable mortality rate (26.1%). The incidence of NBSIs did not change significantly after the introduction of HAART. The incidence of NBSIs in HIV-infected inpatients in this study was similar to those of previous reports (2.3 *vs* 1.32-2.45 per 1000 person-days of hospitalization).[5,9] Compared with the incidence of NBSIs in all hospitalized patients at NTUH (18.7 per 1000 discharges) during the same study period,[18] HIV-infected inpatients had a significantly higher rate of NBSIs (41.4 per 1000 discharges, $p < 0.001$).

The reasons why HIV-infected patients are at increased risk of developing NBSIs might be related to their compromised host status,[3,4] frequent use of a CVC, infrequent use of urinary catheterization and mechanical ventilation,[5] high burden of colonization and skin infection,[7] and multiple related intrinsic factors, such as intravenous drug use and Karnofsky performance score.[9] Of the 57 episodes of NBSIs in this series, 44 (77.2%) were classified as primary. This result is similar to previous reports (70.5- 82%).[9,10] Among these 44 episodes, use of a CVC was found to be causative in 19 episodes.

Similar to the findings of previous reports, we found that microorganisms belonging to the *Staphylococcus* species were the major pathogens (42.1%) causing NBSIs in HIV-infected patients.[9,10] A higher rate of carriage of *S. aureus* among HIV-infected patients (34-52.9%),[19-21] compromised host immunity, and use of a CVC[22] might be causative.

The crude mortality rate (38.6%) and the attributable mortality rate (26.1%) in this study were similar to or higher than those described in previous reports (attributable mortality rate, 17.4 to 27%).[9,10] During the study period, the crude mortality rate of HIV-negative patients with NBSIs at NTUH was approximately 24% (Wang JT, unpublished data), which was similar to previous reports (18.8%-35%).[23-26] Therefore, the mortality rate for NBSIs was higher in patients with HIV infection than in other patients. The higher attributable mortality rate of our patients might have been due to the fact that all included patients had HIV infection in stage C, and the immunity of our patients was generally more severely compromised than in previous studies. During the study period, the crude mortality rate of non-HIV-infected patients with primary NBSIs was 20.9% (Wang JT, unpublished data), which was also lower than that of HIV-infected patients in the current study (16/44, 36.4%). Our findings support the results of Lark et al, who reported that HIV infection was a risk factor predictive of mortality in patients with NBSIs.[23,24] In addition to an increase of mortality, NBSI also led to prolonged hospital stay in periods before and after the introduction of HAART ($p = 0.003$ before HAART; $p < 0.001$ after HAART). However, the hospital stay of patients who developed NBSIs was similar before and after the introduction of HAART ($p = 0.640$).

Previous studies usually emphasized the risk factors for the development of NBSIs in patients with HIV infection, with less attention to the risk factors for mortality.[9,10] In this study, univariate analysis using a logistic regression model revealed that shock and severe hypoalbuminemia (≤ 25 g/L) at the onset of NBSIs in HIV-infected patients were predictive factors for mortality. Delayed initiation of effective treatment by more than 3 days was a predictive factor of mortality with borderline significance ($p = 0.060$). In the multivariate analysis, we again found that shock and severe hypoalbuminemia at the onset of NBSIs were the 2 factors that predicted the mortality of patients with NBSIs. Shock at the onset of NBSIs was indicative of more severe NBSIs and thus was a predictor of mortality.[24,25] Serum albumin levels are an indicator of the nutritional status of patients and have been reported to predict 1-month and long-term mortality of bacteremia.[27] Our study demonstrated similar results. Delayed treatment remained a borderline predictive factor for mortality ($p = 0.053$), which might have been related to the small case number of NBSIs in the present study. Recent CD4 lymphocyte count was not a predictive factor for outcome of NBSIs. This may have been due to the low CD4 T lymphocyte count (less than 100 x 10^6 cells/L in 51 episodes) in nearly all of our patients.

In this study, the mortality of NBSI was not affected by the introduction of HAART. This may be partially explained by the fact that patients treated before and after the introduction of HAART were in stage C of HIV infection and thus had similar host immune status regardless of whether they had received HAART or not. The incidence of NBSIs in HIV-infected patients appeared to be lower ($p = 0.054$) before the introduction of HAART at NTUH when calculated as episodes per 1000 discharges. However, the incidence was similar when calculated as episodes per 1000 person-days of hospitalization ($p = 0.338$). This might have been due to the longer duration of hospital stay before than after the introduction of HAART ($p < 0.001$). The longer hospital stay before HAART might reflect both lack of clinical experience for caring HIV-infected patients and lack of available effective treatment for HIV infection leading to more complicated clinical courses.

In conclusion, hospitalized patients at the late stage of HIV infection were at a higher risk of developing NBSIs than the general population and also had a higher attributable mortality rate for NBSIs. HIV-infected patients who developed NBSIs also had significantly prolonged hospital stay. *Staphylococcus* species were the leading pathogens of NBSIs. Presentation of shock and low serum albumin level at the onset of NBSIs were the 2 factors predictive of mortality in these patients.

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