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ORIGINAL ARTICLE

Clinical predictors of the leading pathogens in human immunodeficiency virus-infected adults with community-onset bacteremia in the emergency department: The importance of transmission routes

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KEYWORDS
bacteremia;
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Abstract *Background/Purpose:* To investigate the clinical characteristics and pathogens of community-onset bacteremia among human immunodeficiency virus (HIV)-infected adults as well as to establish the clinical predictors of the major microorganisms.
Methods: An observational cohort study was conducted retrospectively between January 2007 and December 2012. Demographic characteristics and pathogens determined from chart records were analyzed.

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Salmonella enterica;
Staphylococcus aureus

Results: Of the 121 eligible HIV adults with bacteremia, there was a male predominance (106 patients, 87.6%); elderly individuals (age $\geq$ 65 years) accounted for only 2.5% of the study population (3 patients). Of the total microorganisms isolated ($n = 123$), *Staphylococcus aureus* (55, 44.7%) and *Salmonella enterica* (17, 13.8%) were the common pathogens. In a multivariate analysis, the leading two significant predictors of *S. aureus* infection were infective endocarditis (odds ratio, 11.49; $p = 0.001$) and transmission risk with injection drug users (IDUs; odds ratio, 6.22; $p = 0.001$). In addition, transmission risk with men who have sex with men (MSM; odds ratio, 37.49; $p = 0.001$) was the leading clinical predictor of *S. enterica* infection. In further analyses, a strong linear-by-linear correlation between *S. aureus* infection and IDU ($\gamma = 0.94$, $p = 0.02$) as well as between *S. enterica* infection and MSM ($\gamma = 0.96$, $p = 0.01$) was evidenced.
Conclusion: Focusing on the two key pathogens in HIV-infected adults with community-onset bacteremia, IDU was one of independent predictors associated with *S. aureus* infection, whereas MSM was the leading risk factor of *S. enterica* infection. Although the proposed predictive model of these pathogens has been not established, a scoring system involving the transmission risk of HIV may be of use for the early identification of these patients for clinicians.

Introduction

Bacteremia is a serious, life-threatening condition that is associated with high morbidity and mortality, and human immunodeficiency virus (HIV)-infected patients have an increased risk of bacteremia compared with HIV-seronegative patients.[1] Previous reports have indicated that high morbidity and mortality are associated with bacteremia in HIV-infected patients, with estimates indicating rates up to 21.5%.[2]

In Taiwan, the first cases of HIV infection and acquired immunodeficiency syndrome were reported in 1984.[3] Given the increased prevalence of HIV-infected patients worldwide, there was a corresponding increase in the number of patients diagnosed with HIV infection over the next two decades in Taiwan. A total of 31,231 HIV cases have been reported as of August 2015, with a prevalence of 0.13% among Taiwan population.[4] It is thus reasonable to assume that this prevalence may have led to the increased frequency of emergency department (ED) visits among HIV-infected patients. In addition, community-onset bacteremia constitutes the majority of bacteremic episodes in the ED.[5] As a result, ED clinicians were faced with the increasing challenge of managing HIV-infected patients with community-onset bacteremia. Previous studies on HIV-infected population dealt with clinical characteristics as well as the outcome and incidence of bacteremia[1,6,7]; additionally, the characteristics of bacteremia due to specific pathogens, such as nontyphoidal *Salmonella*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were reported in some studies.[7–9] However, none of these studies established the clinical predictors of these pathogens among HIV-infected patients with bacteremia. Thus, to assist the ED physicians to treat HIV-infected adults suspected to have community-onset bacteremia, we aimed to analyze the clinical characteristics and the distribution of bacteremia, to determine the leading causative microorganisms, and to establish the clinical predictors of the major pathogens.

Materials and methods

Study design and population

An observational cohort study was conducted retrospectively between January 2007 and December 2012 at four medical centers in North and South Taiwan. The local institutional review board approved the study protocol. Of the patients with blood culture sampling in the ED, age, sex, comorbidities, and the results of blood cultures with bacterial growth were screened based on a computer database. The study initially included all HIV-infected individuals with growth of microorganism(s) in blood culture but then excluded patients with contaminated blood cultures, those with fungemia or mycobacteremia, those with hospital-onset bacteremia, or those with bacteremia diagnosed prior to visiting the ED. Moreover, we also excluded patients lacking CD4 count measurement within 4 weeks before or 2 weeks after the bacteremic onset and those without an identified transmission route of HIV.

For the eligible patients, medical records were reviewed retrospectively for collection of clinical data. Data on clinical characteristics, comorbidities, severity of bacteremia (Pitt bacteremia score), severity of comorbidity (McCabe classification), microbiological results, HIV viral load, and CD4 count (measured within 4 weeks before or 2 weeks after the bacteremic onset), the source of bacteremia, further hospitalization, and laboratory data collected within 24 hours after bacteremic onset (i.e., ED arrival) were obtained using a predetermined case record form. As previously described,[5] multiple bacteremic episodes in a

single patient were considered as distinct events if separated by at least 7 days or if different causes were listed for the respective ED visits.

Microbiological studies

Nurses performed blood sampling to collect two sets of blood cultures from each patient. Each set of blood samples routinely consisted of one bottle for aerobic culture and another for anaerobic culture, with approximately 5 mL to 8 mL of blood in each bottle. Following blood collection, the culture bottles were immediately transported to the clinical laboratory department, loaded into the BACTEC 9240 system [Becton Dickinson and Company (BD), Franklin Lakes, NJ, USA], and incubated for 5 days or until the instrument detected bacterial growth. The culture bottles that exhibited bacterial growth were Gram stained, and the contents of the bottles were subcultured onto plates with blood agar (Trypticase soy agar II with 5% sheep blood; BD), Levine eosin—methylene blue agar (BD), chocolate agar, or Centers for Disease Control and Prevention (CDC) anaerobic blood agar (BD) for further identification. Biochemical tests and automatic identification systems were used for the final pathogen identification.

Definitions

HIV-infected patients were defined as having documented HIV serologic positivity. 'Bacteremia' was defined as two separate blood cultures growing the same microorganism or as a single blood culture associated with a clinically identified source growing the same microorganism(s). Blood culture samples with potential contaminating pathogens (e.g., coagulase-negative *Staphylococcus*, *Micrococcus*, *Propionibacterium acnes*, *Peptostreptococcus*, or *Bacillus* species) were considered contaminated, in accordance with the previously described criteria.[10] Polymicrobial bacteremia was defined as the isolation of more than one microbial species from a single bacteremic episode. Community-onset bacteremia indicated that the place of onset of the bacteremic episode was the community, including long-term health-care facility- and community-acquired bacteremia, as previously described.[11] Underlying malignancies included both hematological malignancies and solid tumors; comorbidities were defined as previously described.[12] The sources of bacteremia were classified as lower respiratory tract infections, urinary tract infections, skin and soft-tissue infections, intra-abdominal infections, or primary bacteremia, according to CDC definitions.[13]

Septic shock was defined as the presence of systemic inflammatory response syndrome and systolic blood pressure not higher than 90 mmHg after a crystalloid-fluid challenge of 20 mL/kg to 30 mL/kg body weight over a 30-minute period, or a blood lactate concentration of 4 mmol/L or higher.[14] Severe sepsis was defined as the coexistence of sepsis and at least one of the following signs or symptoms of acute organ dysfunction or hypoperfusion: metabolic acidosis, arterial hypoxemia [partial pressure arterial oxygen (PaO_2) $<$ 75 mmHg or ratio of partial pressure arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) $<$ 250], oliguria ($<$0.03 L/h for 3 hours or 0.7 L/24 h), coagulopathy (increase in prothrombin time or a drop of platelet count by 50% or to $<100 \times 10^7$ L), or encephalopathy (Glasgow coma score $<$ 14).[15] The severity of bloodstream infection at the time of blood sampling was assessed using the Pitt bacteremia score, a validated scoring system based on vital signs, mental status, mechanical ventilation, and the presence of cardiac arrest.[16] The estimated prognosis of pre-existing underlying diseases was described using the classification system of McCabe and Jackson.[17]

Data analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, Chicago, IL, USA), version 20.0. Continuous variables were expressed as the means $\pm$ standard deviations or interquartile ranges, and compared using Student *t* test. Categorical variables, expressed as numbers and percentages, were compared using a Chi-square test or Fisher exact test. All significant variables ($p < 0.05$) in the univariate analysis were incorporated into a hierarchical logistic regression model. Pearson correlation coefficient (γ) was used to measure the strength of the association between two continuous variables. A *p* value less than 0.05 was considered statistically significant.

Results

Study population and demographics

During the 7-year study period, 134 HIV-infected patients with the growth of microorganisms on blood culture were identified at the ED. After exclusion of one patient due to lack of CD lymphocyte count measurement close to the bacteremic onset, two with health-care acquired infections, five with contaminant sputum culture (e.g., 3 episodes of coagulase-negative *Staphylococcus* and 2 episodes of *Bacillus* species), three with *Cryptococcus neoformans*, and two with mycobacteremia, 121 HIV-infected adults with community-onset bacteremia were identified as being eligible for the study.

The mean age of these 121 patients was 41.8 years with a male predominance (106 patients, 87.6%). Those aged 65 years or older (elderly patients) only accounted for 2.5% of the patient group (3 patients). Most patients (110, 90.9%) visited the ED from the community, but 11 patients were transferred from the EDs of other hospitals. Comorbidities included chronic hepatitis (67 patients, 55.4%), liver cirrhosis (17, 14.0%), diabetes mellitus (16, 13.2%), hypertension (9, 7.4%), chronic kidney disease (7, 5.8%), malignancy (5, 4.1%), old stroke (1, 0.8%), congestive heart failure (1, 0.8%), chronic obstructive pulmonary disease (1, 0.8%), and coronary artery disease (1, 0.8%); by contrast, 42 patients (34.7%) did not present with any comorbidity. Risk factors for HIV infection included being an injection drug user (IDU; 63 patients, 52.1%) or men who have sex with men (MSM; 12, 9.9%). The mean CD4 count was 355.6 cell/mm^3 (interquartile range, 83.5—518.0), and 61 patients (50.4%) received highly active antiretroviral treatment prior to their ED visit.

Distribution of microorganisms and port of entry

As there were four episodes of bacteremia with more than two ports of entry, there were a total of 126 sources of bacteremia. The most common source of bacteremia was infective endocarditis (24, 18.8%), followed by urinary tract infection (17, 13.3%), primary bacteremia (17, 13.3%), pneumonia (17, 13.3%), osteomyelitis (16, 12.5%), soft-tissue infection (16, 12.5%), intra-abdominal infection (12, 9.4%), central nerve system infections (3, 2.3%), septic arthritis (2, 1.6%), liver abscess (2, 1.6%), endophthalmitis (1, 0.8%), and biliary tract infection (1, 0.8%).

As there were two episodes of polymicrobial bacteremia, there were a total of 123 microorganisms. *S. aureus* (55, 44.7%) and *Salmonella enterica* (17, 13.8%) were the leading two pathogens, followed by *Streptococcus* species (14, 11.4%), *Escherichia coli* (13, 10.6%), *Klebsiella pneumoniae* (8, 6.5%), *Proteus* species (4, 3.3%), *P. aeruginosa* (4, 3.3%), *Aeromonas* species (2, 1.6%), *Serratia* species (2, 1.6%), *Enterobacter cloacae* (1, 0.8%), *Burkholderia pseudomallei* (1, 0.8%), *Enterococcus faecalis* (1, 0.8%), and *Chryseobacterium indologene* (1, 0.8%). Of note, methicillin-resistant *S. aureus* (MRSA) only accounted for 7.3% (4 isolates).

Clinical characteristics, severity, pathogen distribution, and outcome among various categories of HIV transmission risk

All eligible patients were categorized into three groups: IDU, MSM, and others. Demographic data, comorbidities, prior highly active antiretroviral therapy (HAART), various categories of CD4 lymphocyte count, major bacteremia-causing microorganisms, and source of bacteremia were compared among the transmission groups (Table 1). In the univariate analysis, only age, HIV viral load, various categories of CD4 lymphocyte count, the proportion of prior non-HAART treatment, comorbidities with chronic hepatitis, bacteremia due to *S. aureus* or *S. enterica*, and bacteremia due to bone and joint infections or due to skin and soft-tissue infection were different among the transmission groups. Furthermore, initial ED presentation and severity of bacteremic onset or comorbidity, length of hospital stay, and clinical outcome were also compared among these transmission groups. Of note, the severity of bacteremia or comorbidity and clinical outcome were similar but the length of total hospital stay and ICU stay were different among the transmission groups.

Clinical predictors of *S. aureus*

For all enrollees, the association between several clinical variables and *S. aureus* infection among the HIV-infected adult patients is examined (Table 2). The following were significantly positively associated with *S. aureus* infection: transmission risk with IDU, prior non-HAART treatment, comorbidity with chronic hepatitis, and bacteremia due to bone and joint infections and infective endocarditis. By contrast, CD4 lymphocyte count less than 200 cell/mm^3, undetectable HIV viremia (indicated as HIV viral load $<$ 50 copies/mL), severe comorbidity based on McCabe classification and bacteremia due to pneumonia, urinary tract infection, and intra-abdominal infections were significantly negatively associated with *S. aureus* infection. Only the following variables were identified by the multivariate analysis as being significant (Table 4): transmission risk with IDU, severe comorbidity based on McCabe classification, bone and joint infections, and infective endocarditis. Of importance, a strong association between IDU and *S. aureus* infection was discovered.

Clinical predictors of *Salmonella* bacteremia

The association between several clinical variables and bacteremia due to *S. enterica* infection among the HIV-infected patients with community-onset bacteremia was examined in a univariate analysis (Table 3). *S. enterica* was also more frequently associated with patients having a CD4 lymphocyte count less than 200 cell/mm^3, transmission risk with MSM, and primary bacteremia; it was less frequently associated with patients having comorbidity with chronic hepatitis, undetectable HIV viremia (indicated as HIV viral load $<$ 50 copies/mL), transmission risk with IDU, and bacteremia due to infective endocarditis. However, only three significant variables were identified by the multivariate analysis, which are as follows (Table 4): transmission risk with MSM, CD4 lymphocyte count less than 200 cell/mm^3, and primary bacteremia.

The trends of major pathogens and HIV transmission routes regarding the increasing CD4 counts

All HIV-infected adults were categorized by CD4 lymphocyte count as follows: less than 100 cell/mm^3, 100—200 cell/mm^3, 201—350 cell/mm^3, 351—500 cell/mm^3, and over 500 cell/mm^3. The increasing CD4 lymphocyte count was not significantly correlated with the increasing proportion of two major bacteremia-causing microorganisms (i.e., *S. aureus* and *S. enterica*) and varied transmission risks (e.g., IDU, MSM, and others), as shown in Figure 1. However, a strong linear-by-linear correlation between *S. aureus* infection and IDU ($\gamma = 0.94$, $p = 0.02$) as well as between *S. enterica* infection and MSM ($\gamma = 0.96$, $p = 0.01$) was observed.

Discussion

In this study, the proportion of age, various categories of CD4 lymphocyte count, chronic hepatitis, major causative pathogens, and source of bacteremia were different among the various transmission groups (e.g., IDU, MSM, and others), but bacteremia severity, comorbidity severity, and clinical outcome were similar among the transmission groups. Notably, *S. aureus* and *S. enterica* were the two leading pathogens. Transmission risk with IDU was one of independent predictors associated with *S. aureus* infection, whereas transmission risk with MSM was the leading independent predictor associated with *S. enterica* infection. In further analysis, a strong correlation between *S. aureus*

Table 1 Clinical characteristics, comorbidity, comorbidity severity, causative microorganism, source of bacteremia, bacteremia severity and clinical outcome among 121 HIV-infected patients with community-onset bacteremia, as categorized by potential transmission routes.[a]

Characteristics	Patient number (%)			*p*
	IDU, $n = 63$	MSM, $n = 12$	Other, $n = 46$	
Sex, male	55 (87.3)	12 (100)	39 (84.8)	0.36
Age, y (mean ± SD)	40.0 ± 7.9	34.8 ± 10.9	46.0 ± 12.5	0.001
HAART naïve	41 (65.1)	5 (41.7)	14 (30.4)	0.001
HIV viral load, 10^3 copies/mL (mean ± SD)[b]	43.8 ± 76.7	217.0 ±245.2	248.2 ± 527.2	0.02
Category of CD4 count (cell/mm^3)				<0.001
<100	5 (7.9)	8 (66.7)	19 (41.3)	
100–200	7 (11.1)	0 (0)	6 (13.0)	
201–350	12 (19.0)	2 (16.7)	9 (19.6)	
351–500	16 (25.4)	1 (8.3)	2 (4.3)	
>500	23 (36.5)	1 (8.3)	10 (21.7)	
Major comorbidities				
Chronic hepatitis	44 (69.8)	4 (33.3)	19 (41.3)	0.003
Liver cirrhosis	9 (14.3)	0 (0)	8 (17.4)	0.30
Diabetes mellitus	6 (9.5)	1 (8.3)	9 (19.6)	0.27
Hypertension	4 (6.3)	0 (0)	5 (10.9)	0.40
Malignancy	3 (4.8)	1 (8.3)	1 (2.2)	0.59
Chronic renal insufficiency	1 (1.6)	2 (16.7)	4 (8.7)	0.07
Severity of comorbidity (McCabe classification)				0.85
Ultimately and rapidly fatal disease	7 (11.1)	2 (16.7)	6 (13.0)	
Nonfatal	56 (88.9)	10 (83.3)	40 (87.0)	
Major microorganism				
Staphylococcus aureus	42 (66.7)	3 (25.0)	10 (21.7)	<0.001
Methicillin-resistant *S. aureus*	5 (7.9)	0 (0)	0 (0)	0.09
Non-*Salmonella* Enterobacteriaceae	12 (19.0)	2 (16.7)	14 (30.4)	0.32
Klebsiella pneumoniae	3 (4.8)	0 (0)	5 (10.9)	0.28
Escherichia coli	5 (7.9)	2 (16.7)	6 (13.0)	0.55
Proteus species	1 (1.6)	0 (0)	3 (6.5)	0.29
Streptococcus species	7 (11.1)	0 (0)	7 (15.2)	0.34
Salmonella enterica	1 (1.6)	7 (58.3)	9 (19.6)	<0.001
Major source of bacteremia				
Infective endocarditis	15 (23.8)	2 (16.7)	7 (15.2)	0.52
Bone and joint infection	14 (22.2)	0 (0)	2 (4.3)	0.009
Skin and soft-tissue infection	13 (20.6)	0 (0)	3 (6.5)	0.04
Primary bacteremia	6 (9.5)	3 (25.0)	8 (17.4)	0.26
Intra-abdominal infection[c]	6 (9.5)	1 (8.3)	8 (17.4)	0.42
Urinary tract infection	5 (7.9)	3 (25.0)	9 (19.6)	0.12
Pneumonia	5 (7.9)	2 (16.7)	8 (17.4)	0.30
Severity-of-illness marker at bacteremia onset (ED arrival)				
Hospitalization through the ED	56 (88.9)	11 (91.7)	43 (93.5)	0.71
Admission to intensive care unit	8 (12.7)	3 (25.0)	5 (10.9)	0.43
Pitt bacteremia score ≥ 4 points	3 (4.8)	2 (16.7)	4 (8.7)	0.33
Initial presentation at ED				
Severe sepsis	18 (28.6)	5 (41.7)	15 (32.6)	0.65
Septic shock	8 (12.7)	2 (16.7)	5 (10.9)	0.86
Clinical outcome				
28-d mortality	5 (7.9)	1 (8.3)	5 (10.9)	0.87
1-y mortality	17 (27.0)	1 (8.3)	13 (28.3)	0.35
Length of stay, day, mean ± SD				
Total hospitalization	21.7 ± 16.2	22.1 ± 20.0	12.6 ± 10.0	0.005
Intensive care unit	0.9 ± 3.2	3.8 ± 9.7	0.3 ± 1.0	0.02

[a] Data are expressed as case numbers (percentages), unless specifically indicated.
[b] Fourteen patients without HIV viral load measurement within 4 weeks before or 2 weeks after the bacteremic onset and 26 with undetectable viremia (indicated as <50 copies/mL) were excluded.
[c] Including liver abscess and biliary tract infection.
ED = emergency department; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; IDU = injection drug users; MSM = men who have sex with men; SD = standard deviation.

Table 2 Univariate analyses of risk factors of *Staphylococcus aureus* among HIV-infected adults with community-onset bacteremia.

Characteristics	*Staphylococcus aureus* bacteremia, *n* (%)		Odds ratio (95% confidence intervals)	*p*
	Yes, *n* = 55	No, *n* = 66		
Age ≥ 50 y	6 (10.9)	14 (21.2)	0.46 (0.16–1.28)	0.13
Sex, male	51 (92.7)	55 (83.3)	2.55 (0.76–8.52)	0.12
Pitt bacteremia score ≥ 4 points at ED	3 (5.5)	6 (9.1)	0.58 (0.14–2.42)	0.51
Transmission risk group				
Injection drug users	42 (76.4)	21 (31.8)	6.92 (3.08–15.55)	<0.001
Men who have sex with men	3 (5.5)	9 (13.6)	0.37 (0.09–1.42)	0.13
HAART naïve	34 (61.8)	26 (39.4)	1.59 (1.07–2.34)	0.01
Undetectable HIV viremia[a]	6/49 (12.2)	20/48 (34.5)	0.27 (0.10–0.73)	0.008
CD4 count < 200 cell/mm^3	14 (25.5)	31 (47.0)	0.39 (0.18–0.84)	0.02
Major comorbidities				
Chronic hepatitis	37 (67.3)	30 (45.5)	2.47 (1.17–5.19)	0.02
Hypertension	6 (10.9)	3 (4.5)	2.57 (0.61–10.80)	0.30
Liver cirrhosis	5 (9.1)	12 (18.2)	0.45 (0.15–1.37)	0.15
Diabetes mellitus	6 (10.9)	10 (15.2)	0.69 (0.23–2.02)	0.49
McCabe classification with ultimately and rapidly fatal disease	2 (3.6)	13 (19.7)	0.15 (0.03–0.72)	0.008
Major source of bacteremia				
Infective endocarditis	20 (36.4)	4 (6.1)	8.86 (2.80–27.99)	<0.001
Bone and joint infection	14 (25.5)	2 (3.0)	10.93 (2.36–50.59)	<0.001
Skin and soft-tissue infection	8 (14.5)	8 (12.1)	1.23 (0.43–3.53)	0.70
Primary bacteremia	7 (12.7)	10 (15.2)	0.82 (0.29–2.31)	0.70
Urinary tract infection	2 (3.6)	15 (22.7)	0.13 (0.03–0.59)	0.003
Intra-abdominal infection[b]	2 (3.6)	13 (19.7)	0.15 (0.03–0.72)	0.009
Lower respiratory tract infection	1 (1.8)	14 (21.2)	0.07 (0.01–0.54)	0.001

[a] Indicated as HIV viral load < 50 copies/mL, and 14 patients lacking HIV viral load measurement were excluded.
[b] Including liver abscess and biliary tract infection.
ED = emergency department; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus.

infection and IDU as well as between *S. enterica* infection and MSM was observed.

In the past years, several studies have evaluated the clinical characteristics of bacteremia in HIV-infected population.[1,6,7] However, the distribution of causative microorganisms varied geographically among the various studies. The two leading microorganisms in Taiwan, as reported previously, were non-typhoid *Salmonella* and *S. aureus*.[7] In New York, the leading microorganisms were *S. aureus* and coagulase-negative *Staphylococcus*,[18] whereas in San Francisco, *S. aureus* and *Streptococcus pneumoniae* were the leading microorganisms.[6] This geographical difference might be due to several affecting factors. However, in the literature, only three factors, namely, the source of bacteremia, the recipient of highly active antiretroviral therapy, and IDU, were reported.[19] Notably, based on our data, transmission risk of HIV was also one of determinants that lead to a change in the causative microorganism. Although the proposed predictive model of these pathogens has been not established, a scoring system involving the transmission risk of HIV may be of use for early identification of these patients for clinicians.

Focusing on the HIV-seronegative individual, *S. aureus* is the most relevant bacterial pathogen for IDUs; in particular, *S. aureus* is the main cause of soft-tissue infections and of severe infection such as endocarditis and bacteremia in IDUs.[20] Indeed, the relationship between *S. aureus* infection and transmission risk of IDU has been well discussed with regard to HIV-infected patients.[21] Similar to these previous studies,[20,21] the IDU was strongly associated with *S. aureus* infection in our population. However, in contrast to a previous study that reported a high proportion of MRSA (up to 68%) among *S. aureus* strains in HIV-infected individuals,[22] a low incidence of MRSA was discovered in our population.

Disseminated infection with nontyphoidal *Salmonella* is recognized early in the HIV epidemic and this is also the main bacteria isolated from adult blood culture series in Africa[23] and Taiwan.[7] There are several considerations that support the strong relationship between *Salmonella* infection and MSM among HIV-infected adults with community-onset bacteremia. First, the frequency of diarrhea was increased in those HIV-infected patients who were homosexual or bisexual (80%) versus those who were heterosexual and/or IDUs (58%). Thus, the presence of diarrhea may simply be a consequence of a superimposed 'gay bowel syndrome in the former group'.[24] Second, it was recognized that sexually active homosexual men were at increased risk of infectious diarrheas due to *Salmonella*, even prior to the onset of the HIV epidemic worldwide. Finally, those homosexual men having many sexual partners and increased frequency of oral–anal contact with homosexual population are at greater risk of such infection.[25]

Table 3 Univariate analyses of risk factors of salmonellosis in HIV-infected adults with community-onset bacteremia.

Characteristics	Salmonellosis, *n* (%)		Odds ratio (95% confidence intervals)	*p*
	Yes, *n* = 17	No, *n* = 104		
Age ≥ 50 y	4 (23.5)	16 (15.4)	1.69 (0.49–5.85)	0.48
Sex, male	15 (88.2)	91 (87.5)	1.07 (0.22–5.23)	>0.99
Pitt bacteremia score ≥ 4 points at ED	1 (5.9)	8 (7.7)	0.75 (0.09–6.41)	>0.99
Transmission risk group				
Men who have sex with men	7 (41.2)	5 (4.8)	13.86 (3.71–51.84)	<0.001
Injection drug users	1 (5.9)	62 (59.6)	0.04 (0.005–0.33)	<0.001
HAART naïve	8 (47.1)	52 (50.0)	0.94 (0.58–1.53)	0.82
Undetectable HIV viremia*	0/15 (0)	26/92 (28.3)	—	0.02
CD4 count < 200 cell/mm^3	14 (82.4)	31 (29.8)	10.99 (2.95–40.97)	<0.001
McCabe classification with ultimately and rapidly fatal disease	2 (11.8)	13 (12.5)	0.93 (0.19–4.56)	>0.99
Major comorbidities				
Chronic hepatitis	6 (35.3)	61 (58.7)	0.39 (0.13–1.12)	0.07
Diabetes mellitus	2 (11.8)	14 (13.5)	0.86 (0.18–4.16)	>0.99
Hypertension	1 (5.9)	8 (7.7)	0.75 (0.09–6.41)	>0.99
Liver cirrhosis	1 (5.9)	16 (15.4)	0.34 (0.04–2.78)	0.46
Major source of bacteremia				
Primary bacteremia	9 (52.9)	8 (7.7)	13.50 (4.09–44.58)	<0.001
Intra-abdominal infection**	3 (17.6)	12 (11.5)	1.64 (0.41–6.56)	0.44
Lower respiratory tract infection	3 (17.6)	12 (11.5)	1.64 (0.41–6.56)	0.44
Urinary tract infection	2 (11.8)	15 (14.4)	0.79 (0.16–3.82)	>0.99
Infective endocarditis	0 (0)	24 (23.1)	NA	0.02
Bone and joint	0 (0)	16 (15.4)	NA	0.12
Skin and soft-tissue infection	0 (0)	16 (15.4)	NA	0.12

* Indicated as HIV viral load <50 copies/mL and 14 patients lacking HIV viral load measurement were excluded.
** Including liver abscess and biliary tract infection
ED = emergency department; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; NA = not available.

We interpreted our data considering several limitations inherent in the study design. First, the retrospective nature of the study may have limited the number of patients identified or the information obtained. Thus, a patient with a lack of CD lymphocyte count or risk of HIV transmission was excluded according to our study design. However, only one patient was excluded based on this criterion. Second, for privacy reasons, the screening test of HIV infection was not routinely performed in the study hospitals. Therefore, we only included HIV-seropositive patients in our analyses. It is not clear whether this would have affected the distribution of bacteremia. Third, although our study included all patients from four EDs of medical centers, the distribution of causative microorganisms should be cautiously

Table 4 Multivariate analyses of risk factors of *Staphylococcus aureus*/*Salmonella* bacteremia among HIV-infected adults with community-onset bacteremia.

Patient characteristics	Odds ratio	95% confidence intervals	*p*
Risk of *Staphylococcus aureus* bacteremia			
Source of bacteremia			
Infective endocarditis	11.49	2.70–48.91	0.001
Bone and joint infection	5.49	1.01–29.95	0.049
Urinary tract infection	0.21	0.04–1.14	0.07
Lower respiratory tract infection	0.08	0.04–1.14	0.03
Transmission risk with injection drug users	6.22	2.18–17.70	0.001
Ultimately and rapidly fatal disease	0.11	0.02–0.70	0.02
Risk of *Salmonella* bacteremia			
Men who have sex with men	37.49	4.34–323.49	0.001
CD4 count < 200 cell/mm^3	12.11	2.26–64.86	0.004
Primary bacteremia	10.52	2.11–52.34	0.004

HIV = human immunodeficiency virus.

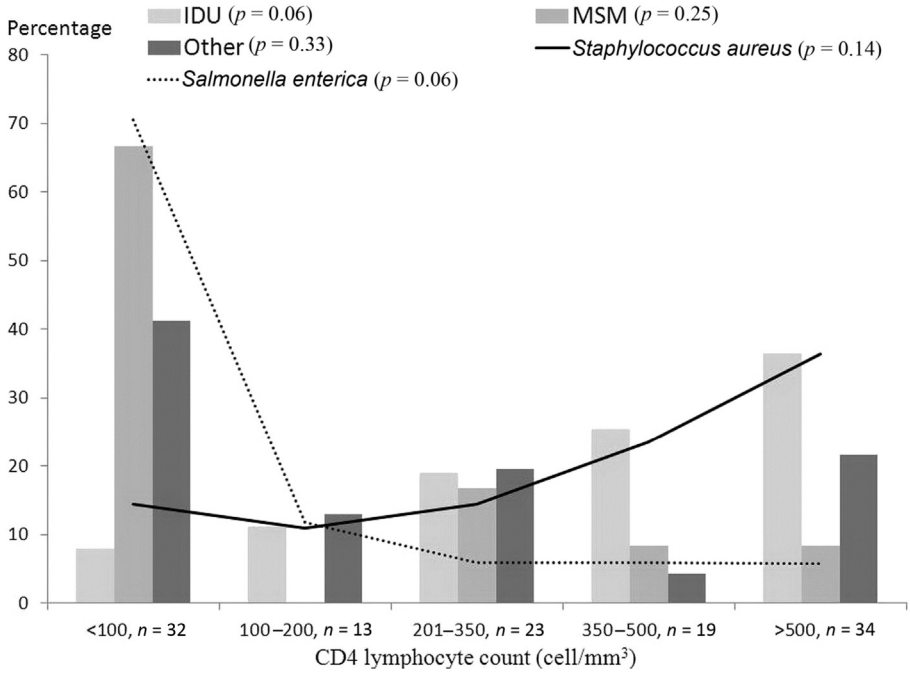

Figure 1. The trends of the leading two pathogens and human immunodeficiency virus (HIV) transmission routes among HIV-infected adults with community-onset bacteremia, with regard to the increasing CD4 counts. All *p* values were calculated using Pearson correlation. MSM, men who have sex with men.

interpreted. Because bacteremia can be caused by low-virulent pathogens, such as viridians streptococcus, the infection might have occurred in outpatient clinics, so the pathogen distribution in our study is not representative of all community-onset bacteremia. Finally, although we examined all bacteremic patients who visited the ED for a long period, this study was conducted in an area of high proportion of the transmission routine with IDU. Therefore, our findings may not be generalizable to other populations with low prevalence of IDU.

In conclusion, this study was the first investigation focusing on the predictors of key pathogens in HIV-infected patients with community-onset bacteremia. As far as the two leading microorganisms (*S. aureus* and *S. enterica*) are concerned, IDU was one of independent predictors associated with *S. aureus* infection and MSM was the most important risk factor of *S. enterica* infection. Therefore, based on transmission risk of HIV infection, a prospective study of a large population should be conducted in the future to test these clinical predictors in an effort to assist clinical physicians and improve the quality of care.

Conflicts of interests

The authors report no conflicts of interest.

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