VIRULENCE
2016, VOL. 7, NO. 3, 320–328
http://dx.doi.org/10.1080/21505594.2016.1158359

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REVIEW

Bloodstream infections in HIV-infected patients

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ABSTRACT

In the combined antiretroviral therapy era, HIV-infected patients remain a vulnerable population for the onset of bloodstream infections (BSI). Worldwide, nontyphoid salmonellae, *Streptococcus pneumoniae, Escherichia coli, Staphylococcus aureus* and coagulase negative staphylococci are the most important pathogens. Intravenous catheter associated infection, skin-soft tissue infection and endocarditis are associated with Gram-positive bacteremia. Among the Gram-negative, nontyphoidal *Salmonella* have been previously correlated to sepsis. Other causes of BSI in HIV-infected patients are mycobacteria and fungi. Mycobacteria constitute a major cause of BSI in limited resource countries. Fungal BSI are not frequent and among them *Cryptococcus neoformans* is the most common life-threatening infection. The degree of immunosuppression remains the key prognostic factor leading to the development of BSI.

ARTICLE HISTORY
Received 23 September 2015
Revised 6 February 2016
Accepted 21 February 2016

KEYWORDS
AIDS; bacteriemia; bloodstream infection; BSI; fungemia; Gram negative; Gram positive; HIV; mycobacteria; sepsis

Introduction

Despite the dramatic reduction of AIDS-related deaths and opportunistic infection rate after the introduction of combined antiretroviral therapy (cART), infection with the human immunodeficiency virus (HIV) remains a cause of increased risk of bloodstream infection (BSI).[1-4] HIV-infected patients remain a "fragile" population, even after achieving an acceptable immunological status, as their mortality decreases to levels comparable to the general population only after 6–10 y of immune-recovery and HIV-RNA suppression.[5,6] Many factors appear to predispose HIV-infected patients to invasive bacterial and fungal infections; in particular, altered cell-mediated immunity, B-cell dysfunction with consequent lack of serum opsonins as well as qualitative and quantitative deficits of neutrophils.[7] HIV-infected patients are not fully immune until the CD4+T (CD4) cell count increases to >750 cells/μL.[8] In HIV-infected patients with CD4 cell count >500 cells/μL the risk of infectious diseases and even of AIDS-defining infections (e.g. recurrent pneumonia and extra-pulmonary tuberculosis) are higher compared to the general population.[8] The recent START-INSIGHT trial demonstrated that the CD4 cell count is crucial to define a patient's immunological status and to establish the timing of cART initiation. Indeed, patients who started cART early had a significantly lower probability of AIDS and non-AIDS events (e.g., bacterial infections), even when their baseline CD4 cell counts was >500 cells/μL.[9]

Two main factors influence the epidemiology of BSI in HIV-infected patients; the availability of cART, which has determined a reduction of incidence and a change of clinical characteristics of BSI in industrialized countries; [10] and the geographic distribution of some pathogens.[3] BSI are associated with increased mortality rate, length of hospital stay and intensive care unit (ICU) admission rate.[11] BSI are now a more frequent cause of ICU admission than *Pneumocystis jiroveci* pneumonia in HIV-infected patients.[12,13] Nontyphoid salmonella, *Streptococcus pneumoniae, Escherichia coli* and *Staphylococcus aureus* are the most important pathogens of BSI. Fungal and mycobacterial infections are less frequent but can have considerable clinical and economic impact. Among the pathogens responsible for BSI, *Mycobacteria* spp., *Cryptococcus neoformans* and recurrent nontyphoid salmonella constitute AIDS-defining conditions.[14]

This review describes the main characteristics of BSI in HIV-infected patients, focusing on the etiology, risk factors and outcome. A major scientific database[15] was searched, with the search string (HIV or AIDS) and (bloodstream infection OR sepsis OR fungemia OR bacteremia).

Bacterial BSI

The type and incidence of bacterial BSI in HIV-infected patients depend on the historical period (pre-cART or cART era), the geographic area (developed or

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Table 1. Frequencies of causative agents of bloodstream infections and characteristics and outcomes of patients according to the literature.

Causative Agent	Mean frequence % (range)	Setting of transmission %		Mean number of CD4+ (% of patients)		Outcome (mean crude mortality %)	References
		Community	Nosocomial	Any	<200		
Bacteria							
S. aureus	12 (2-28)	67	33	N.A.	N.A.	12	11,32–35,42,54
CONS	7 (0-26)	59	41	N.A.	N.A.	10	11,32–34,41,42,54
S. pneumoniae	13 (0-43)	77	23	41	59	9	4,11,19,24,25,32–35,41,42,54,57,58
NTS	15 (0-46)	80	20	30	70	34	4,14,32–35,42,49,50,53,54,57,58
E.coli	8 (0- 31)	65	35	N.A.	N.A.	15	10,32–35,42,54,57
P.aeruginosa	6 (0-30)	50	50	N.A.	N.A.	32	10,33–35,42,54
Others	24 (10-60)						
Total Bacteria	70 (16-100)					20	4,10,11,13,32–34,42,54,57
Mycobcateria							
M. tuberculosis	17 (0-54)	100	0	0	100	48	4,34,42,54,57,58,60
NTM	6 (0-17)	100	0	0	100		34,42,54,57,58
Total Mycobacteria	20 (0-63)					48	4,34,42,54,57,58,60
Fungi							
Criptpcoccus spp	5 (0-21)	89	11	N.A.	N.A.	26	4,33,34,42,54,64
Candida spp	1 (0-3)	23	77	26	84	41	33,34,54,64,69,70
Total fungi	10 (0-44)					35	4,33,34,42,54,57,64,69,70
Total		78	22	5	95	30 (12-68)	4,10,11,13,31–35,41,42,54

Note. CONS: coagulase negative staphylococci; NTS: non typhoidal salmonella; NTM: non tubercular mycobacteria; N.A.: not available.

resource-limited countries) and the clinical setting (community or hospital). Table 1 summarizes the frequency and the principal etiologies of bacterial BSI.

Gram-positive bacteria

Streptococcus pneumoniae

Invasive pneumococcal disease (IPD) is an important cause of bacteremia in HIV-infected patients throughout the world. Incidence rates of IPD can be up to 100-fold higher in HIV-infected individuals compared to a non-HIV population with more frequent recurring invasive disease.[16,17] The relative risk of IPD in HIV-infected patients was estimated to be 24.4 (95% confidence interval, 23.7–25.1) in a recent study.[18] The main risk factors for IPD in the current study were male gender, intravenous drug use, smoking, detectable HIV-RNA and low CD4 cell count.[18] By contrast, the use of cART and a pneumococcal conjugate vaccine have been associated with protection.[18,19]

The mortality rate observed in HIV-infected patients with pneumococcal bacteremia in the pre-cART era was lower compared to the non–HIV-infected population. This lower mortality rate might be related to several factors, including younger age, lower prevalence of associated comorbidities and decreased inflammatory response, leading to a lower incidence of septic shock.[13,20,21] Neither the incidence of BSI sustained by *S. pneumoniae* in the cART era, nor the mortality rate, decreased significantly.[19] The most important factors related to high mortality rate remain low CD4 cell count and the severity of pneumococcal disease (e.g. intensive care unit admission and sepsis).[19,22] In the cART era, however, HIV-infected patients are aging and this constitutes an independent risk factor for IPD.[18] Moreover, the advanced age of these patients implies an increasing incidence of comorbidities, including kidney diseases, diabetes and cardiovascular disease, which are well-known risk factors for pneumococcal infection in the general population.[18,19,21,23–25] The lack of improvement in the mortality rate with the introduction of cART underlines the need for an effective preventive vaccination strategy but data on the 23-valent pneumococcal vaccine are scarce.[14] The vaccine antibody response appears to be related to the CD4 cell count, with a lower response rate at a CD4 count $<$ 200 cells/μL.[26] A multicenter case-control study showed a reduction of IPD ratio only in patients who received vaccination when their CD4 cell count was $>$500 cells/μL.[27] Conversely, a study in Uganda when cART was not widely available demonstrated an unexpected increase of IPD in patients vaccinated with the 23-valent vaccine.[28]

Staphylococcus aureus

S. aureus infections occurs widely in Asia, Europe and the United States, but causes few cases of BSI in Africa.[4,10,11,29,30–35] Intravenous catheter, skin-soft tissue infection and endocarditis are significantly associated with Gram-positive BSI.[34] *S. aureus* epidemiology is influenced by the historical era; *S. aureus* was the most important pathogen of BSI in a case-control study using all cases of community-acquired BSI identified prospectively in US in the pre-cART era.[30] *S. aureus* was the

principal nosocomial BSI pathogen in a Center for Diseases Control multicenter study in which it accounted for 35% of all etiologies.[36] Data for the cART era are controversial. In a prospective study in US, *S. aureus* was the third most frequent isolate after *E. coli* and *S. pneumoniae*,[11] while in a single-hospital study in Spain reporting 67 episodes of Gram-positive BSI (36% of total BSI), *S. aureus* (10.7%) and coagulase-negative staphylococci (8.6%) were the 2 most frequent pathogens.[34] Definitive positioning is not possible, owing to the paucity of studies available on this topic.

Methicillin-resistant staphylococcus aureus

Among people living with HIV, the transmission of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) is an emerging epidemic, with higher prevalence in healthcare settings.[37] It is documented that the majority of isolates in the largest cohort of HIV-infected patients presenting with *S. aureus* BSI were CA-MRSA (54%). Moreover, CA-MRSA was associated with increased probability of endocarditis and increased risk of death compared to other *S. aureus* strains.[38] Studies suggested HIV-infected patients to be at increased risk of CA-MRSA because of overlapping community networks as well as the high prevalence of intravenous drug use (IVDU). IVDU, hemodialysis and CD4 cell count <200 cells/μL are independent risk factors for CA-MRSA.[39] Recent data from a study by Kempkerr *et al.* suggest an association with advanced age, black ethnicity and AIDS.[40]

Coagulase-negative staphylococci

In a recent European study reporting the results of a 10 y survey of BSI in HIV-infected patients, coagulase-negative staphylococci were the principal isolated pathogens.[41] In this study, among 54 episodes of sepsis, 26% were caused by coagulase-negative staphylococci, 20% by *Streptococcus pneumoniae* and 13% by *Enterococcus* spp. The most frequent diagnoses in this group were catheter-related BSI and pneumonia. Prior AIDS diagnosis, nadir of CD4 <200 cell/μL and a current CD4 cell count <200 cell/μL were the risk factors. Notably, 56% of these episodes were nosocomial. The 1 and 6 month mortality were 17% and 28%, respectively.[41] Moreover, the Spanish single-hospital study mentioned above reported *S. aureus* (10.7%) and coagulase-negative staphylococci (8.6%) as the most frequent causative agents of 67 Gram-positive BSI (36% of total BSI).[34] Other studies report lower rates of BSI due to coagulase-negative staphylococci, ranging from 0%–6%.[11,32,33,42]

Gram-negative bacteria

Among the Gram-negative bacteria, nontyphoidal *Salmonella* (NTS) is correlated to HIV infection. NTS refers to infections caused by all serotypes of *Salmonella* except *typhi* and *paratyphi* A, B and C. NTS transmission can occur via the consumption of food or water contaminated with animal feces and, less frequently, through direct contact with infected animals and/or directly between humans. *Salmonella* infection can have a wide spectrum of clinical presentations: from a self-limiting enterocolitis to a bacteremia with metastatic foci, involving bones, joints, liver, spleen and the meninges.[43] From the beginning of the HIV pandemic, an increased incidence of NTS bacteremia in HIV-infected patients compared to the general population, was described.[44-46] Indeed, recurrent *Salmonella* bacteremia was included among the AIDS-defining conditions.[14] Furthermore, NTS bacteremia have high mortality and a tendency to relapse in HIV-infected patients.[47] A prospective study conducted in Malawi in adult patients hospitalized for NTS found that 99% of them were HIV-positive. The inpatient mortality rate was 47%, and 43% of the survivors had a recurrence.[47] Nevertheless, the burden of NTS bacteremia among AIDS-related opportunistic infections has changed over time. Before the introduction of cART, NTS were a major source of BSI and were associated with increased mortality.[48] After 1996, the incidence of recurrent NTS bacteremia decreased significantly among patients who achieved favorable immune-virological response after receiving cART. Hung *et al.* followed up 93 patients who received a diagnosis of NTS bacteremia from June 1994 to June 2006 in Taiwan.[49] They found that patients who received cART had an incidence of recurrent NTS bacteremia that was significantly lower compared to patients enrolled in the pre-cART era. In particular, the incidence of recurrent NTS bacteremia was 2.56 cases per 100 person-years in the cART era versus 70.56 cases per 100 person-years in the pre-cART era ($P < 0.001$). Recurrent NTS bacteremia occurred mostly in patients with a low CD4 cell counts in both the pre-cART and the cART era (median CD4 cell count, 8 cells/mL and 20 cells/μL, respectively).[49] Nevertheless, this epidemiologic trend in developed and developing countries is not homogenous. Studies in Africa found NTS is the most frequent Gram-negative isolate, followed by *E. coli*.[4,50–52] A study in Tanzania showed a high prevalence (7.6%) of NTS bacteremia among febrile HIV adult patients admitted at a tertiary hospital compared to non-HIV patients (0.5%), proving NTS BSI to be a common occurrence in this setting.[52] A similar scenario was observed in Asia.[33,53,54] In a study of BSI in HIV-infected persons in 2006–2008 in Southeast Asia, Varma *et al.*

found NTS to be the most common bacterial cause of BSI.[53] Likewise, Kiertiburanakul *et al.* described the pattern of BSI among HIV-infected patients in the cART era in Thailand and found Gram-negative bacteria were the first cause of BSI (39.6%) and, among them, *Salmonella* spp was the most frequent pathogen (15.6%).[54]

By contrast, *E. coli* and *P. aeruginosa* are the dominant species among Gram-negative pathogens in Europe and US, and there is a lower rate of *Salmonella* spp. infections.[11,30,33]

Escherichia coli and pseudomonas aeruginosa

In the nosocomial setting, Gram-negative bacteria are a minor source of BSI compared to Gram-positive.[55,11,33] In a 12 months multicenter prospective study of patients with advanced HIV infection, Petrosillo et al. found Gram-negative organisms accounting for approximately one-fifth of all BSI and 12.9% of catheter-related BSI. *E. coli* and *P. aeruginosa* were the most frequent Gram-negative isolates.[55] Afessa et al. found that Gram-negative bacteria caused 31% of nosocomial bacteremia in hospitalized HIV-infected patients, with *P. aeruginosa* as the most common pathogen.[11] Similarly, in a retrospective study by Ortega *et al.*, Gram-negative bacteria caused 31% of nosocomial BSI both in the pre-cART and in the cART era. *P. aeruginosa* and *E. coli* were the most frequently isolated microorganisms in these studies.[33]

Mycobacteria

The isolation of a mycobacterium from a blood culture represents a manifestation of disseminated mycobacterial infection. It can be caused by both tubercular (MTB) and non-tubercular (NTBM) mycobacteria and is typical of immuno-compromised patients. In Western countries BSI caused by mycobacteria are uncommon. Conversely, they are frequent in limited resource settings, like some South-East Asiatic and sub Saharan African countries, where mycobacteria constitute a major cause of sepsis and account for high percentages of positive blood cultures in HIV-infected patients. A mycobacterial infection should be always suspected in HIV-infected patients coming from high prevalence countries. The mycobacteria account for a number of BSI ranging from 17% to 54% of all etiologies in studies performed in endemic areas (Table 1).[42,50,53,56-58] This high prevalence may depend on the high frequency of tubercular disease in these geographic areas, as nearly one quarter of the new MTB cases worldwide are estimated to occur in sub-Saharan Africa.[59] In addition, advanced HIV disease may play a role. In many countries, especially in those with difficult access to care, HIV infection is often diagnosed in advanced stages, when the number of CD4 cell is extremely low. In the above-mentioned studies, patients diagnosed with mycobacterial BSI had a CD4 cell count <100 cells/μL in most cases with a range of median values between 15 and 129 cells/ μL.[53,42,54] In this setting, mycobacterial BSI are relatively frequent, not only in cases of overt BSI, but also when the symptoms are less severe, even when pulmonary tuberculosis is considered improbable. In a recent study performed in Malawi, all HIV-infected patients with a CD4 cell count <250 cells/μL and with chronic fever and/or weight loss, but negative smear for mycobacteria, were investigated.[56] Among 469 patients, 61 had a positive blood culture and mycobacteria accounted for 24% of all isolated (11 cases of MTB and 4 NTBM). On the other hand, MTB BSI may present as severe sepsis, in which the differential diagnosis between bacterial and mycobacterial origin is challenging. In a study performed in Uganda, nearly 1 in 4 HIV-infected patients hospitalized with severe sepsis had MTB bacteremia.[42] In this study, MTB was the commonest etiology of BSI (23.4% of cases), while NTBM constituted 4% of isolates. Several attempts have been made to outline the profile of the typical patients at risk for mycobacterial BSI. They are usually less likely to receive cART,[42] with significantly lower median CD4 cell counts,[42,54,60] higher HIV RNA,[54] fever and cough lasting for $>$ 1 month,[60] weight loss of >10 %[60] and presence of lymphadenopathies.[60] Moreover, they were more likely to have community-acquired infections, were younger compared to patients with bacterial BSI[54] and their hemoglobin values were below the median levels.[56] Jacob *et al.* even proposed a score based on male sex, increased heart rate, low CD4 cell count, absence of cART, fever, low serum sodium and low hemoglobin.[42] Score higher than 21 points corresponded to a probability of having a diagnosis of MTB bacteremia greater than 70% in the study, but the characteristics considered were not specific, because many of them are present in non-controlled HIV infection also in absence of BSI. Thus, the possibility of such a diagnosis must always be taken into account and cultures for mycobacteria should always be performed, regardless of scores, especially in patients with low CD4 cell count or if there is no response to antibiotic therapy. The majority of mycobacteria infection are caused by TBM, but in patients with very low CD4 cell count (<50 cells/ μL) atypical mycobacteria are also possible and in particular organisms of the *Mycobacterium avium complex* (MAC).[61] Likewise to TBM, MAC BSI are associated with high plasma HIV-RNA levels, but also with previous opportunistic infections and colonization of the respiratory or gastrointestinal tracts.[61] The etiological diagnosis is not possible until the result of cultures become positive, but their median time of response exceeds 3 weeks, limiting their role for immediate clinical management.[62] The outcome of this kind of infection is poor, and the tubercular etiology of BSI has been found to be a

predictive factor of mortality itself in univariate logistic regression among patients with sepsis.[54] The 30-day mortality rate has been estimated higher than those seen in other BSI in HIV-infected patients,[42] with a mortality rate of about 50% during the hospitalization.[60,63]

Fungi

In the cART era, consistent with the trend registered for bacterial infections, fungal BSI decreased significantly compared to the pre-cART era (Table 1).[34,64] They constitute a minority of BSI and are found almost exclusively in patients with advanced HIV. The predictive factors of fungal BSI are prior AIDS-defining illness, greater age, lower CD4 cell count and high HIV-RNA.[54,65] Different fungal species (including *Cryptococcus* spp, *Candida* spp., *Penicillium marneffei* and *Histoplasma capsulatum*) have been isolated in HIV-infected patients, with higher mortality rates compared to non HIV-infected patients.[54] Cryptococcosis is the most common life-threatening systemic fungal infection and extrapulmonary cryptococcosis is an AIDS-defining illness.[14] It occurs typically in patients with low compliance with routine medical care and with cART.[66,67] In a French surveillance study, 1644 cases of cryptococcosis in HIV-infected patients were reviewed. The total number of cases rose steadily until 1995, decreased sharply in 1996 and 1997, and reached a plateau thereafter.[66] In another 12 y study in a tertiary care hospital in Switzerland, 315 patients were diagnosed with fungemia. Among them, 12% were HIV-infected and 35% died within 6 months after fungemia. *Cryptococcus* spp. and *Candida* spp were the most frequently identified species.[64] In a retrospective cohort study in Thailand in 2004–2008, data were collected for 140 HIV-infected patients with BSI. *Cryptococcus neoformans* was the pathogen isolated most frequently (20.8% of cases). Other fungal pathogens, less frequently isolated, were *P. marneffei* (2.7%) and *H. capsulatum* (0.7%). Overall, a fungal etiology was proved in 35/140 cases (25%).[54] In the same study, 59% of patients were in CDC clinical stage C and only 36% were on cART. The predictive factors for fungal etiology were older age, focal site infection, kidney insufficiency, higher HIV-RNA and low CD4 cell count.[54] Candidemia in the pre cART era was a common nosocomial infection in HIV-infected patients hospitalized in ICU, or those with hematological malignancies and neutropenia.[64,68] In a single-hospital study from 1990 to 1995 in France, the overall mortality was 38% in 13 episodes of candidemia, which was considered a potentially lethal nosocomial complication during late-stage AIDS.[69] A retrospective case control study in the cART era highlighted a significant reduction in the incidence of all cases of hospital-acquired candidemia compared to the pre cART era. By contrast, the overall mortality rate was higher (59%).[70] Despite the use of cART, candidemia represents a severe complication in advance-stage AIDS.[70]

P. marneffei and *H. capsulatum* fungemia are common only in the respective endemic areas (Asia and South America) and they must be investigated as probable causative agents in people from those areas, including travelers.[31,64,71-74]

Conclusions

BSI in HIV-infected patients have a wide spectrum of possible etiologies, heavily influenced by the geographic area and by the availability of cART. The clinical manifestations are similar to those of control patients; however, the incidence and mortality of BSI are often higher in a HIV population. Higher HIV-RNA, low CD4 cell count and an AIDS-defining condition remain the predictive factors in this setting. Current guidelines recommend the 'test and treat' strategy for all HIV-infected people, independently of the CD4 cell count and the clinical stage.[75] Such an approach should result in an increasing HIV population with good immunological status, which will lead to a drop in AIDS-defining conditions. In this scenario, a reduction of BSI due to NTS, Mycobacteria and Cryptococci can be expected. Total disappearance of these conditions is hampered, however, by the 'late presenter' issue. Indeed, too many patients still have their HIV status diagnosed in an advanced stage of disease, when their CD4 cell count is already very low. Another factor that will probably have an impact on the rate of BSI in HIV infected patients is the fact that many of them have now the possibility to become older, thus risking the typical problems of elderly people, like cardiovascular disease, hypertension, diabetes mellitus, chronic kidney disease, osteopenia/osteoporosis and non-AIDS defining cancers. These patients, like their HIV-negative counterpart, are at risk of hospitalization and exposure to nosocomial infections; therefore, an increase of nosocomial BSI in HIV patients can be expected. We expect BSI will always be a serious disease with a heavy burden in terms of morbidity and mortality in HIV-infected patients; those with advanced diseases and those in care from a long time and aging with HIV infection represent the highest risk groups.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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