Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Original Research

Bacterial etiology and antibiotic resistance pattern of septicemia in HIV and non-HIV patients admitted to tertiary care hospitals, Shiraz, South of Iran

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Received July 10, 2017; **Accepted** September 11, 2017; **Published** September 30, 2017

Doi: http://dx.doi.org/10.14715/cmb/2017.63.9.20

Abstract: The present study aimed to determine the bacteriological etiology and antibiotic susceptibility pattern of sepsis in HIV infected and HIV uninfected patients, and related risk factors to introduce an appropriate therapy. This cross-sectional study was conducted from January 2014 to January of 2015 enrolling patients with sepsis associated with or without HIV infection admitted to Shiraz teaching hospitals, South of Iran. Blood and urine cultures were performed and standard microbiological methods were followed for isolation and identification of the bacteria. HIV antibody testing and CD4+ lymphocyte count were done for HIV-infected patients. Antimicrobial susceptibility tests were performed using the disk diffusion method in accordance with CLSI recommendations. Totally, 140 patients with sepsis including 30 HIV-positive, and 110 HIV-negative were enrolled. Our finding showed 26.7% and 20% blood and urine culture positivity in HIV-positive and 20.9% and 14.5% positivity in HIV-negative patients. *Staphylococcus aureus, Salmonella* spp. and coagulase-negative staphylococci (CoNS) each with frequency of 25% were detected as the most prevalent isolates in samples of HIV patients. In contrast, the main etiology for sepsis in HIV-negative patients was CoNS (47.8%), followed by *Escherichia coli* (17.4%). The median of CD4+ lymphocyte count and viral load in HIV patients were estimated 10.15 cells/mm3 and 68019.48 copies/mL, respectively. The results of the present study revealed that the main cause of sepsis in the studied hospitals was nosocomial pathogens. These findings highlighted the importance of infection control policies for preventing the emergence and spread of nosocomial infections.

Key words: Septicemia; HIV/AIDS; Antimicrobial susceptibility; Iran.

Introduction

Sepsis is defined as a complex systemic host response to an infectious agent that result in organ dysfunction (named “severe sepsis”) and hemodynamic instability (named “septic shock”) (1). Generally sepsis related mortality is 20 - 60% and these rates enhance due to sepsis severity, averaging 7% in systemic inflammatory response syndrome to 46% in septic shock (2). The prevalence of people living with HIV-infection in Iran has been reported 24,000, but recent estimates from UNAIDS claim that this rate is more than 90,000 (3). It has been reported that approximately 12-31% of the occurrence of sepsis in intensive care units (ICUs) belong to HIV-positive patients. Although the sepsis rate among patients with chronic diseases is 700 cases per 100,000 patients, this rate reaches 1,000 cases per 100,000 patients in HIV-infected peoples (4).

AIDS is a complicated disease that often needs intensive care support; however, the life expectancy of HIV-infected patients has improved with expansion of highly active antiretroviral therapy (HAART) (5). There are several factors that make the HIV-infected patients susceptible to bacterial infections such as abnormalities in humoral and cell mediated immunity, phagocytic cell dysfunction, skin and mucous membrane defects and low CD4+ lymphocyte count (6,7).

Despite the high importance of sepsis outcomes in hospitalized mortalities, HIV/AIDS patients have been neglected from sepsis studies. To the best of our knowledge, there is no previous study on etiology of bacterial sepsis in HIV-infected patients in Iran. The present study aimed to determine the bacteriological causes of sepsis and their sensitivity pattern in HIV-infected and HIV-uninfected patients, and quantification of viral load and CD4+ lymphocyte counts of HIV-infected patients in teaching hospitals of Shiraz, South of Iran.

Materials and Methods

Study design and setting

This cross-sectional study was carried out on HIV-positive and HIV-negative patients diagnosed with sepsis, hospitalized during 1 year from January 2014 to January 2015 at teaching hospitals (Namazee (Hospital

A), Shahid Faghihi (Hospital B)), South of Iran.

Totally, 140 patients with sepsis diagnosis made by association of at least two of the following modification: temperature>380C, Heart rate >90/min, respiratory rate >20/min or PaCO2 <32 mm Hg, and white blood cell count >12 000/mm3 or <4000/mm3 or >10% immature band were included (8). Following the approval of the study protocol by Ethics Committee of Shiraz University of Medical Sciences, informed consent was obtained from patients' parents (IR.sums.REC.1394.S271). Exclusion criteria included antibiotic use in the previous 10 days and lack of written informed consent.

Collection and processing of specimens

The blood was drawn after cleansing of the skin with isopropyl alcohol and povidone iodine for aerobic blood culture (10 mL) and anaerobic blood culture (10 mL) as well as for complete blood count, and HIV antibody testing. Urine was collected in a clean container as soon as possible. Blood cultures of HIV-positive and HIV-negative patients with systemic inflammatory response syndrome (SIRS) were done systematically; 5-10 mL was inoculated into aerobic Bactalert vials and anaerobic Bactalert vials and processed by BACTEC 9240 system (Becton-Dickinson, Sparks, MD, USA). The blood samples were incubated for 2-14 days according to the standards of the World Health Organization (WHO) (9). After that, by using a sterile syringe, 0.1 mL of the sample was drawn and plated out on MacConkey, blood and chocolate agar plates. Duplicate plates were inoculated for each of the samples and incubated at 37 ^{0}C for 18-24 hours. The chocolate agar plates were incubated in CO2 incubator for the possible isolation of microaerophiles.

The identification of bacterial isolates was based on standard microbiological tests including Gram-positive isolates mentioned here such as catalase test, growth on mannitol salt agar, DNase production, and hemolytic activity on blood agar plates, and for Gram-negative isolates we used Voges-Proskauer (VP), triple sugar iron (TSI), citrate utilization, indole, urease, oxidase and hydrogen sulphide production. To confirm the identification of Gram-negative isolates, we also used API 20E or 20NE identification kits (API-bioMérieux, France).

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing for all bacterial isolates was performed by disc diffusion method on Mueller-Hinton agar (Oxoid) according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI) (10). The antibiotics tested for Gram positive isolates were Teicoplanin (TEC) (30µg), Rifampin (RIP) (5µg), Tetracycline (TET) (30µg), Gentamicin (GEN) (10µg), Synercid (SYN) (15µg), Erythromycin (ERY) (15µg), Cotrimoxazole (SXT) (1.25/23.75µg), Fosfomycin (FOF) (200µg), Clindamycin (CLI) (2µg) and Ciprofloxacin (CIP) (5 µg). For Gram negative isolates the antibiotics tested were Meropenem (MEM) (10µg), Ampicillin (AMP) (10µg), Piperacillin (PIP) and Piperacillin/Tazobactam (TZP) (10/100µg), Ceftazidime (CAZ) (30µg), Gentamicin (GEN) (10µg), Imipenem (IPM) (10µg), Nitrofurantoin (NIT) (300µg) and Ciprofloxacin (CIP) (5µg). E-test strip (Lioflichem, Italy) was applied to determine the minimum inhibitory concentrations (MICs) of vancomycin toward Gram-positive and imipenem for Gram-negative isolates as described by CLSI recommendation.

HIV diagnosis

HIV rapid test (ABON®) was used for serological diagnosis of HIV antibodies in serum samples obtained from the sepsis patients. HIV-positive patients were also evaluated for CD4+ lymphocyte count, and plasma HIV- 1 RNA load.

RNA extraction and Real Time PCR

The total RNA was extracted using the Invisorb Spin Plant RNA Mini Kit (Invisorb®). One-step real time quantitative RT-PCR was carried out in a 20 µL volume reaction amplification using RT-PCR kit (Altona, Hamburg, Germany) with ABI Prism 7500 Real Time PCR System (Applied Biosystems, USA).

Flow cytometry

The lymphocyte subsets were analyzed by using a four-color flow cytometer instrument (FACSCalibur; BDBiosciences, San Jose, CA) with anti-CD4 APC, anti-CD8 PE and anti-CD3 FITC (BD pharmingen). Furthermore, the percentages of CD8+ and CD4+ T cells were measured throughout the gated CD3+ cells. The data were analyzed by FlowJo software, version 7.6.1 (Tree Star, Ashland, OR).

Statistical analysis

Analysis was performed by using SPSS 21.0 (IBM Corp., USA). Continuous variables that showed skewed distribution were assessed by Mann_Whitney test for comparing two groups. Also, student T-test was used for continuous variables with normal distribution. Categorical variables were analyzed by Chi-square or Fisher's exact test. All statistical tests were two-tailed, with a significance level of 0.05.

Results

Demographic and clinical data

Over the 1 year study period a total of 140 patients with sepsis including 30 (21.4%) HIV-positive and 110 (78.6%) HIV-negative, which were admitted to Shiraz teaching hospitals, southwest of Iran enrolled. Totally, 119 patients were hospitalized in ICUs and 21 patients in internal wards. The detailed demographic and clinical characteristics of patients are presented in Table 1. Regard to sepsis severity in HIV negative patients, sever sepsis (46.4%) and sepsis (23.6%), were significantly higher than SIRS and septic shock ($P< 0.001$). On the other hand although severe sepsis and sepsis in HIV positive patients were high, significant differences were not observed. Respiratory tract were the most common site of infection for both groups, 6/30 (20.0%) of HIV/AIDS patients and 23/110 (20.9%) of non-HIV patients.

Paraclinical findings

The septic HIV patients showed significantly lower blood sugar (BS), hemoglobin (Hb), blood urea nitrogen (BUN), alanine transaminase (ALT) and aspartate aminotransferase (AST) levels, and higher C-reactive pro-

Table 1. Demographic and clinical characteristics of 140 patients with sepsis.

Variable	Characteristic	HIV-positive (n=30)	HIV-negative (n=110)
Age	MeanYears ± SD	44 ± 14.5	70.5 ± 15.5
Gender	Male	24 (80%)	66 (60%)
	Female	6 (20%)	44 (40%)
Hospital	Hospital A	8 (26.7%)	82 (74.5)
	Hospital B	22 (73.3%)	28 (25.5%)
Sepsis Severity	SIRS	2 (6.7%)	16 (14.5%)
	Sepsis	11 (36.7%)	26 (23.6%)
	Sever Sepsis	11 (36.7%)	51 (46.4%)
	Septic Shock	6 (20.0%)	17 (15.5%)
Site of infection	Respiratory Tract	6 (20.0%)	23 (20.9%)
	Urinary Tract	0 (0)	9 (8.2%)
	Soft tissue/skin, Bone	0 (0)	0 (0)
	Cardiovascular system	0 (0)	0 (0)
	Gastrointestinal tract	0 (0)	0 (0)
	Unknown	24 (80%)	68 (70.9%)
	Carcinoma	0 (0)	8 (7.3%)
	Meningitis	0 (0)	4 (4.1%)
	Liver	7 (23.3%)	4 (3.6%)
	Others	17 (56.7%)	62 (56.3%)
Positive blood culture		8 (26.7%)	23 (20.9%)
Positive urine culture		6 (20%)	16 (14.5%)
	Hematological and Biochemical		
	Mean (SD)	**Mean (SD)**	**P value**
WBC	6.54 (4.91)	10.01 (5.53)	0.80
CRP	151.94 (178.70)	103.21(98.60)	0.04
ESR	75.79 (35.23)	53.33 (40.34)	0.61
BS	106.95 (60.89)	184.01 (145.90)	0.005
Hb	9.67 (2.37)	11.05 (2.65)	0.02
BUN	20.29(12.80)	34.77 (23.58)	0.01
ALT	52.81 (53.54)	151.44 (355.41)	0.02
AST	73.67 (59.05)	178.00 (171.94)	0.001

Table 2. Bacteriological profile of positive blood and urine cultures in septic HIV positive and HIV negative patients.

Blood					Urine				
Isolate	**Total No.**	**HIV positive (N = 8/30)**	**HIV negative (N = 23/110)**	**P value**	**Isolate**	**Total No.**	**HIV-positive (N = 4/30)**	**HIV-negative (N =16/110)**	**P value**
Gram-positive	**20**	**5 (62.5)**	**15 (65.2)**		**Gram-positive**	**8**	**2 (50.0)**	**6 (37.5)**	
CoNS	13	2 (25.0)	11 (47.8)		Yeast	1	1 (25.0)	0	
S. aureus	5	2 (25.0)	3 (13.0)	0.32	*S. aureus*	1	1 (25.0)	0	0.04
Non-hemolytic streptococci	1	1 (12.5)	0		Enterococci	6	0 (0)	6 (37.5)	
Enterococci	1	0	1 (4.3)						
Gram-negative	**11**	**3 (37.5)**	**8 (34.8)**		**Gram-negative**	**12**	**2 (50.0)**	**10 (62.5)**	
Pseudomonas spp.	3	0	3 (13.0)		*Enterobacter* spp.	2	0	2 (12.5)	
Stenotrophomonas maltophilia	1	0	1 (4.3)						
E. coli	4	0	4 (17.4)		*E. coli*	10	2 (50.0)	8 (50.0)	0.99
Acinetobacter baumannii	1	1 (12.5)	0	0.02					
Salmonella spp.	2	2 (25)	0						

tein (CRP) level compared to HIV-negative patients ($P < 0.05$).

The mean of CD4+ lymphocyte count, CD8+ lymphocyte count, and HIV-1 viral load in HIV infected patients were 7.2, 18.6, and 68019.5, respectively. Meanwhile, 12 (40%) of HIV patients were co-infected with hepatitis C virus (HCV).

Microbiologic data

From the totally 140 blood cultures, 31 (22.1%) shown bacterial growth, of which 8 (26.7%) were obtained from HIV patients and 23 (20.9%) from HIV-negative patients. Meanwhile, from 140 urine cultures, 22 (15.7%) were positive for bacterial growth, 6 (20%) from HIV patients and 16 (14.5%) from HIV-negative patients. The predominant isolates in blood cultures of HIV infected patients were *Staphylococcus aureus*, *Salmonella* spp. and coagulase-negative staphylococci (CoNS) each with frequency of 25%, and in HIV uninfected patients was CoNS (47.8%) followed by and *E. coli* (17.4%). (Table 2). The predominant urine isolates in both groups were *E. coli* with a frequency of 50%. Moreover, in order to investigate the association of CD4+ lymphocyte count, CD8+ lymphocyte count, CD4/8+ lymphocyte count and absolute CD4+ lymphocyte count with the blood and urine positivity, we used Mann-Whitney test and the results are presented in Table 3.

Table 3. CD4, CD8, CD4/CD8 and absolute CD4 level of septic HIV patients in comparison to blood and urine culture positivity.

Culture type	Variable	Positive culture Median (IQR)	Negative culture Median (IQR)	P-value
Blood culture	CD4	2.16 (8.45)	4.88 (9.01)	0.29
	CD8	3.4 (11.63)	12.05 (27.69)	0.19
	CD4/CD8	0.68 (1.62)	0.33 (2.7)	0.82
	Absolute CD4	6.76 (11.68)	3.88 (12.7)	0.89
Urine culture	CD4	7.77 (12.62)	3.03 (8.89)	0.59
	CD8	4.13 (8.27)	12.05 (21.2)	0.41
	CD4/CD8	0.85 (2.41)	0.28 (2.28)	0.56
	Absolute CD4	6.64 (9.05)	3.93 (15.12)	0.85

Antimicrobial resistance pattern

The MIC50/MIC90 of vancomycin and imipenem toward isolates obtained from samples of HIV patients and HIV-negative patients were 0.5/1 mg/mL and 0.5/>0.32 mg/mL, and 0.75/1 mg/mL and 0.94/>32 mg/mL, respectively.

The full results of antibiotic resistance patterns of Gram-positive and -negative bacteria in septic HIV positive and HIV-negative patients are presented in Table 4, and Table 5, respectively. In overall, *Staphylococcus* spp. as commonest Gram positive isolates collected from samples were mostly susceptible to synercid and teicoplanin, and mostly were resistance against erythromycin and tetracycline. Enterobacteriaceae species were the most detected Gram-negative isolates, which showed high resistance toward ciprofloxacin and ampicillin. Also, the susceptibility of the Enterobacteriaceae species were varied to the meropenem, imipenem, piperacillin and ceftazidime.

Discussion

In the recent years, there has been an increasing rate of mortality associated with increasing incidence of sepsis (11). The burden of sepsis on healthcare is important in HIV-positive patients and recent studies indicate a shift towards etiology of infections and mortality in these patients (12). Therefore, routine surveillance to determine the etiology of sepsis is necessary in HIV infected population (4). Although, for definitive diagnosis of the etiologic agents of sepsis, blood culture are considered as the “gold standard", there are some problems such as being time-consuming, low sensitivity, and contamination possibility especially with commensal bacteria (13).

Table 4. Antimicrobial resistance pattern of Gram-positive isolates in both groups.

	HIV negative				HIV positive			
Antibiotic	MSSA	MSCoNS	MRCoNS	Enterococci	MSSA	MSCoNS	MRCoNS	NHS
Number	3	2	9	7	3	1	1	1
GEN	50	25	33.3	100	0	0	100	0
TEC	0	0	0	0	0	0	0	-
ERY	66.6	100	66.7	100	66.6	100	66.6	100
TET	33.3	100	66.7	100	33.3	100	66.6	0
CIP	33.3	0	44.4	100	33.3	0	44.4	0
CLI	33.3	0	100	57.1	33.3	0	100	100
SXT	0	100	0	0	0	100	0	0
RIP	0	100	44.4	57.1	0	100	44.4	0
SYN	0	0	0	100	0	0	0	-
VA	0	0	0	71.4	0	0	0	0

Abbreviations: MSSA: Methicillin-susceptible *S. aureus*; MSCoNS: Methicillin-susceptible coagulase-negative staphylococci; MRCoNS: Methicillin-resistance coagulase-negative staphylococci; NHS: Non-hemolytic streptococci.

Table 5. Antimicrobial resistance pattern of Gram-negative isolates in both groups.

	HIV negative				HIV positive		
Antibiotic	*Entrobacter spp.*	*E. coli*	*Pseudomonas spp.*	*Stenotrophomonas maltophilia*	*E. coli*	*Salmonella spp.*	*Acinetobacter baumannii*
Number	2	12	3	1	2	2	1
CIP	50	50	33.3	0	100	0	100
MEM	0	0	33.3	-	0	-	100
IPM	0	0	66.7	-	0	-	100
AMP	50	33.3	66.7	-	50	0	100
CAZ	50	16.7	33.3	0	50	0	100
TIG	-	-	0	-	-	-	0
GEN	50	25	33.3	-	50	-	100
NIT	50	16.7	66.7	-	50	-	100
PIP	50	16.7	33.3	-	0	-	100
TZP	50	8.3	33.3	-	50	-	100
SXT	0	33.3	-	0	-	0	-

In accordance with previous survey in our region, a higher frequency of HIV infection was seen in male patients; however, the observed differences was not statistically significant (14). The present study indicated that the primary source of infection was mostly respiratory in both HIV-infected and -uninfected individuals (20% vs. 20.9%). The prevalence of respiratory tract infection as a cause of sepsis had been reported in other studies (4,15,16). Moreover, it has been demonstrated that severe sepsis emerged as a common cause of hospital admission for those living with HIV/AIDS and non-HIV patients (17-19).

In the case of bacteremia, the clinical relevance of CoNS when isolated from blood cultures is essential to determine the true infection rather than contamination (13). Recent studies indicated that to predict the true infection, the concentrations of CRP can be used (20). Our findings regarding association of CRP level and blood culture positivity were in accordance with those studies indicated that systemic inflammatory response to bacterial infections can induce septic shock in both HIV patients and non-HIV patients (4). Indeed, reports from different countries indicate that, it seems that immunosuppression has no significant effect on the acute phase response to severe infections (11).

The results of our positive blood cultures in HIV patients were in agreement with other studies such as Cambodia (19%), Tanzania (17%) and Malawi (23%) (21-23). However, the results are lower compared to other studies such as Uganda (31%) and USA (89.6%) (24,25). Also, the results of HIV-uninfected patients were similar to those of Uganda (23%) and lower than Macedonia (34.2%) and USA (30%) (26-28). Recent Iranian studies similar to our findings, reported low rates of blood cultures positivity ranging from 5.7% to 15.1% (29, 30). The possible reasons for difference in isolation rates might be the limited number of study participants and the studied region. Also, patients might have received clinical care or self-medication with antibiotics before referring to the healthcare settings.

Based on our findings the number of positive urine cultures was 22 (15.7%) out of 140 urine cultures 6 (20%) of were HIV-positive and 16 (14.5%) were HIV-negative patients. These results were closest to other studies such as Iran (13.2%), Ethiopia (14%) and different from USA (25%) (28,31,32). The probable reasons for these variations may be because of different risk factors and detection criteria of urinary tract infections (UTIs) in previous studies. In accordance with the aforementioned studies there was not any significant relationship between the percentage of positive urine culture and gender in the present current study.

In the current study, Gram-positive isolates were found as 20% of sepsis etiology, whereas the Gram-negative bacteria were found in 16.4% in both groups. Nevertheless, the present data was different from other studies reported where Gram-negative bacteria were the commonest isolated bacteria than Gram-positive such as in Uganda (53.2 % and 38.3 %) (33). The microbial etiology that led to sepsis in the HIV/AIDS and non-HIV patients were different. In the HIV/AIDS patients, among blood isolated, *S. aureus*, *Salmonella* spp. and CoNS were the major cause of sepsis. Similar to the findings of previous studies, *S. aureus* was the main cause of sepsis in Ethiopia (42%) (34) and *Salmonella* was the major cause of sepsis in Kenya (46%) and Thailand (26%) (35,36). In the non-HIV patients, CoNS and *E. coli* were the main pathogens. The importance of CoNS should be considered, when detected from blood culture; while, in most studies contamination was considered (33, 37). Nowadays, CoNS are potentially considered as opportunistic pathogens and their incidence has been increased (38, 39). In the present study, *E. coli* with the frequency of 50% were found as major cause of UTIs in both groups, same as previous studies (31,39,40).

In most of previous studies, in accordance with our results, Glycopeptides antibiotics were a highly active drugs against Gram-positive organisms (23,41-44). In the present study, accordance to several previous reports, Gram-negative microorganisms were more resistant than that Gram-positive microorganisms (45,46,47). In present study carbapenems and tigecycline showed to be promising *in vitro* effects, which can be recommend for the treatment of Gram-negative isolates related infections. These findings are consistent with those of the previous studies (47,48).

Finally, our study had some limitations; first, we had limited access to more specific microbiological tests;

for example, mycobacterial cultures were not performed. Second, no information was available on some important data prior to ICU admission, for example previous antimicrobials usage, time between the onset of symptoms and clinical presentation which may play important roles in developing antimicrobial resistance. Third, as preliminary study in our region, the sample size was low and we could not match HIV/AIDS and non-HIV septic groups.

In summary, the results of the present study revealed that the main cause of sepsis in the studied hospitals was nosocomial pathogens. Several factors can be mentioned for such observation including poor hand hygiene by both staff and patients, cross-contamination via environmental sources, inappropriate antibiotic usage, and immunity status of hospitalized patients. These findings highlight the importance of infection control policies for preventing the emergence and spread of nosocomial infections. Additionally, due to the variable etiological agents of septicemia and their antibiotic susceptibility patterns, the results of regional assessments, provide useful information for prescription of more effective empirical therapy and epidemiological comparison.

Acknowledgments
The authors would like to thanks all participants for their friendly cooperation. This study was supported by Shiraz University of Medical Sciences grants No. 93-7531 and 93-5, and is related to MSc thesis of Farzaneh Ghassabi. The authors would like to thank Mr. J. Moayedi and Ms. Z. Mousavi for their technical assistance and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

Conflict of Interest Statement
None declared.

Author's contribution
Study concept and design: N. Hadi, T. Hashempour, M. Moghadami and M.A Davarpanah; acquisition of data and sampling: F. Ghassabi and Mehrdad Halaji and N. Chatrabnous; analysis and interpretation of data: H. Raeisi Shahraki and Mehdi Kalani; drafting of the manuscript: F. Ghassabi; critical revision of the manuscript for important intellectual content: T. Hashempour and N. Hadi; study supervision: N. Hadi and T. Hashempour.

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