Predictive Value of Laboratory Markers in HIV-Positive Patient Diagnosed With Severe Sepsis

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Nowadays opportunistic infections are not the only threat in the case of HIV-infected patients, being upstaged by microbial or fungal severe infections, especially after the introduction of ultimate generation antiretroviral therapy. The aim of this study is to investigate the factors that are predictive for an unfavourable prognosis and the causality of severe sepsis in HIV-immuno-depressed hosts. The study included 42 HIV-seropositive patients, found out in the evidence of HIV/AIDS Regional Centre from Iasi, that have been diagnosed with severe sepsis with confirmed etiology between the January 2012 and December 2016. The study group was subdivided in two subgroups: the first batch represented by twenty patients HIV-infected in childhood (pediatric cohort) and the second batch represented by 22 patients HIV-infected in adulthood. The medium age at the time of the sepsis diagnosis was significantly lower in the first group compared to the second one (25.0±2.58 vs 34.9±11.8). The lowest CD4 cells levels were noted in the case of patients infected in childhood, being in C2/C3 disease stage. The bacterial etiology was variate in both studied subgroups, with the predominance of Escherichia coli (33.3%), Staphylococcus aureus meticilino-rezistent (26.2%) and Streptococcus pneumoniae (19%) strains. The liver and kidney disfunctions were frecvently present in HIV-infected patients with severe sepsis (n=28 respectiv 31). A high percentage of patients associated criptocococcosis meningoencephalitis (33.3%), the most affected were those from the second subgroup (40.9%). Systemic infections in HIV-seropositive patients presumes an additional risk of unfavourable outcome, especially in the context of non-adherence and non-compliance to ARV-therapy and a long-term HIV infection history.

Keywords: Severe sepsis, HIV Immunodepression, Antibiotherapy

In the last two decades, the evolution of HIV infection was definitely influenced by the introduction and accelerated development of highly active antiretroviral therapy (HAART), which led to a strong emprouvement of life quality in infected people, similar to non-infected population [1,2]. On the other hand, according to international statistics, the number of persons who contract HIV infection increases every year and this phenomenon is observable in underdeveloped countries. It is also known that patients HIV-seropositive are at risk for developping other types of infection [3,4]. Although the incidence of *Pneumocystis jiroveci* pneumonia and other opportunistic infections decreased because of HAART, sepsis still remains an important cause of acute pathology in HIV-infected patient [1,2,4]. More than 33% of these cases are found in developed countries [5,6]. The same situation was detected in tropical areas, regardless of the HIV-infection's stage [5,7]. It seems that human immunedeficiency virus influences directly the functionality of the immune system during the septic process. One of the main immune constituent is the complement system, whose deficiency usually leads to a marked alteration of the host organism's responsivity to a septic factor's aggresion and also to an unfavourable outcome in majority of cases [5,7,9]. Another important aspect is that related to the age at which the patient was HIV-infected and the precocity of HAART initiation, adherence and compliance and others preexistent comorbidities. All these anterior mentioned factors create a propitious foundation for pathophysiological changes specific for systemic infections [3,7,10]. Some studies showed an increasing incidence for bacterial infections in HIV-seropositive patients, independently from the antiretroviral therapy scheme's efficiency [11].

Despite the fact that septic pathology in HIV-positive population is associated with high severity, the number of studies centered on this theme didn't record a significant growth, so that an approach to the subject could be necessary [8,12].

The cellular immunity dysfunctions present in case of HIV infection predispose to a higher risk of infections determined by intracellular or encapsulated germs [13,14]. This types of infection became frequent also because of antibiotic misuse and the consequences are multidrug-resistant strains selection [12,15]. International statistics showed severe sepsis influences short and long-term in-hospital mortality for patients with HIV infection, which varies from 28 to 56% [4,15,16].

Experimental part

Material and methods

This retrospective study included 42 HIV-positive patients in different disease stages admitted in the Clinical Universitary Infectious Diseases Hospital St. Parascheva from Iasi, between January 2012 and December 2016. The inclusion criteria were: age>18 years, confirmed HIV infection/AIDS, at least two of the following: temperature>38°C or <36p C, leukocytosis>12 000/mm^3 or leucopenia<4000/mm^3, heart rate>120 beats/min, respiratory rate>24 respirations/min and the objectification of one or more organ dysfunctions. Septic shock was defined as sepsis with persistent arterial hypotension associated (systolic blood pressure measured values under 90 mm Hg), refractory to vascular filling maneuvers. Consensual definitions established by *Surviving Sepsis*

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Campaign Conference 2015 were used. Sepsis etiology was confirmed through blood cultures detection, collected in the first 24 h from hospital admission and doubled by others pathological products culture detection (cerebrospinal fluid, urine, tracheal aspirate, sputum, ascites liquid, pleural fluid). At least two blood cultures taken from different veins before antibiotic therapy initiation were collected. The identification of each isolated bacterial strain was achieved by biochemical characteristics (API galleries, BioMerieux). The antibiotic susceptibility was tested by disk diffusion method and minimum inhibitory concentration (MIC) calculated by E-test and the interpretation was made using CLSI (*Clinical Laboratory Standard Institute*) and EUCAST (*European Comitee on Antimicrobial Susceptibility Testing*). CD4 lymphocytes blood count was calculated by flow cytometry on FacsCount Becton-Dickinson analyzer. Plasma HIV viremia was performed by qPCR method on Real-Time PCR analyzer (Cobas-TaqMan Roche).

In this study we took up the actual age of the patients, also the age at which HIV infection occurred, the stage of the disease, the degree of immunosuppression quantified by CD4 lymphocytes blood count at the moment of sepsis diagnosis, HIV replication degree objectified by viremia levels, the presence and severity of septic , organ dysfunctions, the mortality rate registered in these category of patients. For a better understanding of the pathological context that predisposes to severe sepsis in HIV-infected patients, the study group was subdivided in two subgroups: batch one formed up by 20 patients with HIV infection childhood-acquired (so called pediatric cohort) and the second batch made up by 22 patients infected in adulthood. We also took in count parameters such as patients adherence and compliance to HAART.

Statistical analysis

The statistical processing of data was made with the help of statistical function SPSS 18.0, with a significance threshold of 95%. We used χ^2 as a qualitative nonparametric test to compare frequency distributions. Tracing ROC curve (Receiver Operator Characteristic) permitted sensitivity/ specificity balance evaluation. For this purpose we used Excell MedCalc version 9.6. and we also utilized derivatives indicators described by ANOVA test: mean, median, modulus, minimum/maximum values, standard deviations, standard error, variation coefficient.

Results and discussions

Among the 2037 HIV-infected patients admitted in the HIV/AIDS Regional Center during the mentioned period, only 42 met severe sepsis criteria. Among them, 20 patients were infected in childhood and 22 were framed in the category of people infected in adulthood. The percentage distribution showed a predominance for female in both studied groups (70% *vs* 68.2%, p=0.899) (table 1). Sixty percent of the patients from pediatric cohort came from the urban environment, while 59.1% of the patients infected in adulthood were originated from the rural area. The average age at the moment of sepsis diagnosis was significantly lower in the first group (table 1).

Fifty percent of the patients from the first batch and 68.2% of those from the second batch were in C3 disease stage (p=0.524) (fig.1).

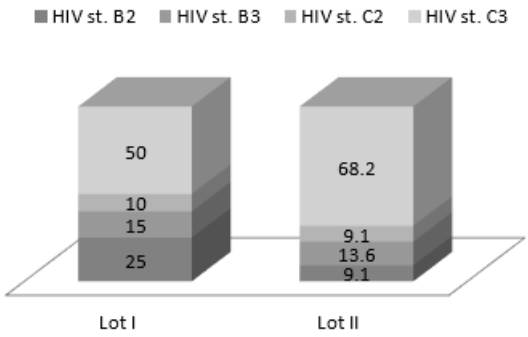

Fig.1. HIV infection stages in patients with severe sepsis

Regarding immunosuppression level's quantification by CD4 lymphocytes blood count, we noticed that the lowest average values were registered in the first batch found in C3, respectively C2 disease stage. We have also remarked that the patients from the second subgroup, in C3, respectively C2 disease stage had the lowest CD4 average level, without any statistical significant differences in comparison to group I and the series values variance was very ample (p=0.142) (table 2).

A percentage of 63.6% (no=28) of the studied patients showed neither compliance nor adherence to antiretroviral medication. This phenomenon was more frecquent in the case of the patients adulthood-infected (86.3%, n=11) than those from pediatric cohort (65%, n=13).

In a similar way, the highest plasma HIV viremia was present in patients who are in C2 or C3 disease stage, independently of the origin group (p=0.028 *vs* p=0.019) (table 3).

The bacterial etiology of severe systemic infections in HIV-infected persons was varied including both Gram-positive (*Staphylococcus aureus meticilino-rezistent* - MRSA, *Streptococcus pyogenes, Streptococcus pneumoniae*) and Gram-negative germs (*Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Serratia marcescens* and *Acinetobacter baumannii*) (table 4). The most common causative agents of severe sepsis in patients from the first subgroup was *E. coli* (45%), followed up by MRSA (20%) and *S. pneumoniae* (20%) and in the second subgroup the etiology was represented by similar microorganisms, but with different percentages MRSA (31.8%), *E.coli* (22.7%) and *S. pneumoniae* (18.2%) (table 4).

Organ dysfunction was present in the evolution of infectious process in both categories of patients, without any significant statistical differences between them (p>0,05). Sixty percent of the individuals from the first batch associated liver failure and 75% of them developped kidney failure (table 5). We have also noticed a higher incidence of criptococcal meningitis in patients infected at maturity age (40.9% *vs* 25%; p=0.272).

Characteristic	Group I	Group II	P
No	20	22	-
Female/Male	14/6	15/7	0.899
Urban/Rural	12/8	9/13	0.215
Average age±SD (min-max), years	25.0±2.58 (20-32)	34.9±11.8 (18-72)	**0.001**

Table 1
DEMOGRAPHIC CHARACTERISTICs

Table 2

CORRELATIONS BETWEEN CD4 VALUES AND HIV STAGING

HIV	No	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Batch I (p=0.05)								
std. B2	5	105.00	69.689	31.166	18.47	191.53	55	201
std. B3	3	116.00	39.345	22.716	18.26	213.74	80	158
std. C2	2	88.50	95.459	67.500	-769.17	946.17	21	156
std. C3	10	62.30	44.749	14.151	30.29	94.31	6	148
Total	20	83.65	56.045	12.532	57.42	109.88	6	201
Batch II (p=0.142)								
std. B2	2	113.00	131.522	93.000	-1068.68	1294.68	20	206
std. B3	3	160.00	61.441	35.473	7.37	312.63	115	230
std. C2	2	311.50	235.467	166.500	-1804.08	2427.08	145	478
std. C3	15	95.73	110.741	28.593	34.41	157.06	1	356
Total	22	125.68	126.932	27.062	69.40	181.96	1	478

Table 3

CORRELATIONS BETWEEN HIV VIREMIA AND HIV-INFECTION STAGING

HIV	No	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Batch I (p=0.028)								
std. B2	5	582816	1110550	496653	-796114	1961746	14502	2562000
std. B3	3	244167	281662	162618	-455521	943854	25500	562000
std. C2	2	2868375	3832696	2710125	-31567028	37303778	158250	5578500
std. C3	10	1437024	1376300	435224	452478	2421570	29500	3652100
Total	20	1187678	1582810	353927	446900	1928456	14502	5578500
Batch II (p=0.019)								
std. B2	2	66175	76120	53825	-617736	750086	12350	120000
std. B3	3	383247	342179	197557	-466772	1233265	12540	687000
std. C2	2	922365	1226342	867155	-10095884	11940614	55210	1789520
std. C3	15	2009502	1501020	387562	1178265	2840739	175500	4524100
Total	22	1512243	1475156	314504	858196	2166290	12350	4524100

Table 4

THE BACTERIAL ETIOLOGY OF SEVERE SEPSIS IN HIV-INFECTED PATIENTS

Causative agent		**Study roup**		**Total**
		Subgroup I	**Subgroup II**	
Escherichia coli	No	9	5	14
	%	45.0%	22.7%	33.3%
Staphylococcus aureus MR	No	4	7	11
	%	20.0%	31.8%	26.2%
Pseudomonas aeruginosa	No	0	3	3
	%	0.0%	13.6%	7.1%
Klebsiella pneumoniae	No	2	1	3
	%	10.0%	4.5%	7.1%
Streptococcus pneumoniae	No	4	4	8
	%	20.0%	18.2%	19.0%
Streptococcus pyogenes	No	1	0	1
	%	5.0%	0.0%	2.4%
Serratia marcescens	No	0	1	1
	%	0.0%	4.5%	2.4%
Acinetobacter baumannii	No	0	1	1
	%	0.0%	4.5%	2.4%
Total	No	20	22	42
	%	100.0	100.0	100.0

Hematological dysfunction objectified by low haemoglobin and hematocrit levels was present in all studied cases, regardless of the HIV-infection moment. We also found that 16.1% (no=7) had mild neutropenia (>1000/mmc and <1500/mmc), 28.5% (no=12), moderate neutropenia (>500/mmc and <1000/mmc) and 7.1% (no=3), severe neutropenia (<500/mmc) (table 6).

Table 5
ORGAN DYSFUNCTION IN HIV-POSITIVE PATIENTS WITH SEVERE SEPSIS

Organ dysfunction	Subgroup I (no=20)		Subgroup II (no=22)		P	RR	IC95%
	n	%	No	%			
Liver dysfunction	12	60.0	16	72.7	0.382	0.75	0.40-1.40
Kidney dysfunction	15	75.0	16	72.7	0.867	1.07	0.51-2.24

Table 6
HEMATOLOGICAL PARAMETERS IN HIV-POSITIVE PATIENTS WITH SEVERE SEPSIS

Laboratory markers	Subgroup I	Subgroup II	P
No	20	22	-
Haemoglobin, medie±SD (min-max), g/dl	10.09±1,05 (7.30-11.50)	9.55±1.41 (6.0-11.30)	0.175
Hematocrit, medie±SD (min-max), %	31.95±2.48 (27-36)	30.68±2.97 (25-36)	0.143
Leucocytes, medie±SD (min-max), no/mm^3	8006±5491 (1250-17520)	5425±4494 (1245-16500)	0.102
Neutrophils, medie±SD (min-max), no/mm^3	4983±4818 (750-13250)	2974±2377 (120-14500)	0.164

Characteristics	Subgroup I	Subgroup II	P
No(%)	5 (20%)	9 (40,9%)	-
Female/Male	2/3	3/6	0.804
Urban/Rural	4/1	3/6	0.086
Average age±SD (min-max), years	25.0±2.55 (21-27)	38.22±13.89 (21-72)	**0.050**

Table 7
MORTALITY RATE IN HIV-INFECTED PATIENTS WITH SEVERE SEPSIS

Table 8
PREDICTABILITY MODELS OF UNFAVOURABLE OUTCOME IN PATIENTS WITH HIV-INFECTION AND SEVERE SEPSIS

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	0.073(a)	0.005	-0.020	0.482	0.005	0.213	1	40	0.647
2	0.252(b)	0.064	0.015	0.473	0.058	20.424	1	39	0.128
3	0.252(c)	0.064	-0.010	0.480	0.000	0.000	1	38	0.993
4	0.527(d)	0.278	0.200	0.427	0.214	100.965	1	37	0.002
5	0.601(e)	0.361	0.273	0.407	0.084	40.722	1	36	0.036
6	0.748(f)	0.559	0.484	0.343	0.198	150.700	1	35	0.001
7	0.771(g)	0.594	0.510	0.334	0.035	20.920	1	34	0.097
8	0.885(h)	0.783	0.731	0.248	0.189	280.849	1	33	0.001

a Predictors: (Constant), Gender; b Predictors: (Constant), Gender, Age; c Predictors: (Constant), Gender, Age, Environment; d Predictors: (Constant), Gender, Age, Environment,Sepsis Diagnosis; e Predictors: (Constant), Gender, Age, Environment, Sepsis Diagnosis, Liver Dysfunction; f Predictors: (Constant), Gender, Age, Environment, Sepsis Diagnosis, Liver Dysfunction, Kidney Disfunction; g Predictors: (Constant), Gender, Age, Environment, Sepsis Diagnosis, Liver Dysfunction, Kidney Dysfunction, ATB-therapy period; h Predictors: (Constant), Gender, Age, Environment, Sepsis Diagnosis, Liver Dysfunction, Kidney Dysfunction, ATB-therapy period, Antifungal Therapy

The multivariate analysis revealed that in 20% of the cases with unfavourable outcome, the gender, the age, the origin environment and the causative agent were significantly correlated (p=0.002) (table 8).

More than 48% of the patients with unfavourable outcome associated hepatic and kidney disorders, beyond age, gender, origin environment and etiologic agent (p=0.001) (table 8).

For more than 73% of the patients the unfavorable prognosis depended on gender, age, origin environment, etiologic agent, liver and kidney dysfunctions and the association of antibiotherapy with antifungal medication for the treatment of systemic mycosis (table 8).

The following biological markers had the role of good predictors for a bad evolution in the case of patients with HIV infection and severe sepsis: CD4 lymphocytes (AUC=0.866; IC95%: 0.745-0.987), hemoglobin (AUC=0.849; IC95%: 0.724-0.975), hematocrit (AUC=0.779; IC95%: 0.614-0.944), leucocytes (AUC=0.776; IC95%: 0.616-0.935) and neutrophils number (AUC=0.857; IC95%: 0.725-0.989) (fig.2).

26.2% of the total number of patients were HIV-infected mothers, without statistical significant differencies between the two studied subgroups (25% *vs* 27.3%; p=0.867). We didn't observe a higher mortality incidence in this category. A percentage of 64.2% of these individuals were neither compliant nor adherent to HAART and the phenomenon was more frequent in the first batch.

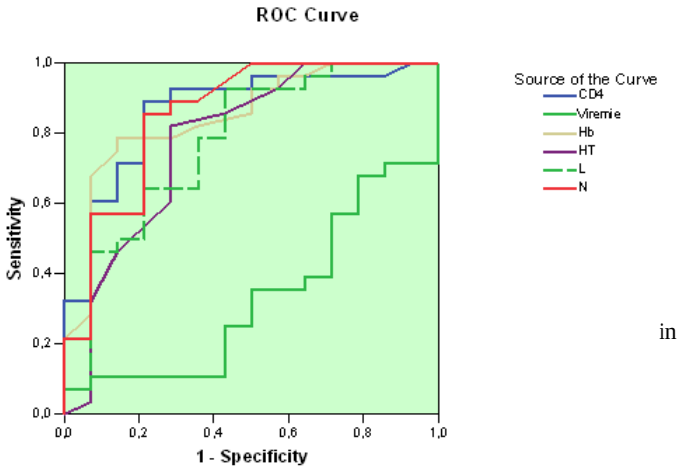

Fig.2. Specificity/sensitivity of biologic markers in unfavourable outcome prediction for HIV-seropositive patients with severe sepsis

Test Result Variable(s)	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CD4	0.866	0.062	0.000	0.745	0.987
HIV Viremia	0.332	0.087	0.078	0.162	0.502
Hemoglobin	0.849	0.064	0.000	0.724	0.975
Hematocrit	0.779	0.084	0.003	0.614	0.944
Leucocytes	0.776	0.081	0.004	0.616	0.935
Neutrophils	0.857	0.067	0.000	0.725	0.989

The test result variable(s): CD4, Hb, HT, N has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.a Under the nonparametric assumption. b Null hypothesis: true area = 0.5

Invasive bacterial infections represent a real threat to HIV-infected patients, especially in the context of a marked immunosuppression, confirmed by the presence of a low CD4 T lymphocytes values [1,5,16]. Although the ratio of severe sepsis number of cases in HIV seropositive patients and the total number of HIV-infection persons found out in the evidence of the HIV/AIDS Regional Center of Iasi is subunit, we could affirm that mortality rate is higher in the first mentioned category. According to several studies on this theme, approximately 2.8 million people with HIV infection had died in 2005, with the specification that the majority of deaths were registered in regions like Subsaharian Africa, where the possibilities of diagnosis and treatment are extremely limited [17]. It was found that HIV infection associated with malnutrition predispose to bacteremia development [5,8,18]. In SUA, sepsis is the main cause of mortality in HIV-seropositive patients who are admitted in the intensive care units [17,19]. The evolution of the pathological process from systemic inflammatory response syndrome (SIRS) to sepsis, severe sepsis and septic shock is accelerated in patients with cellular immunity deficiencies and the mortality in these cases reaches 15-45% [20].

In Romania, HIV infection has some particularities regarding the transmission path and also the disease evolution. Data provided by the HIV/AIDS Monitoring and Evaluation Department from Romania indicated the number or individuals diagnosed with such a disease between 1985-2016 was about 21 702 and the total of new diagnosed cases of HIV-infection during 2016 was 296 [21].

The 42 patients included in the study who were diagnosed with severe systemic infections represent a small percentage of those 2037 seropositive patients found out in the evidence of HIV/AIDS Regional Center Iasi, probably because the trigger of bacterial infectious process needs the meeting of certain criteria such as: a long-term HIV-infection evolution, the compromising of cellular immunity, low CD4 lymphocytes level, intense viral replication as a consequence of resistance to antiretroviral therapy or lack of adherence to the same type medication. The patients included in the pediatric cohort have a higher risk for developing sepsis during a life-time, mostly because HIV-infection childhood-aquired implies not only a prolonged exposure to the virus, but also a greater severity of the disease as a consequence of immune system's immaturity in that period [17,21]. This aspect is confirmed by our study, the average age at the moment of sepsis diagnosis being lower in this category. According to national data, there is an increased number of patients belonging to the pediatric cohort with a delayed establishment of HIV-infection diagnosis (sometimes more than 10-14 years), so that the absence of specific treatment stood at the base of marked immunosuppression and the appearance of severe microbial infections [23,24].

More than half of the patients included in our study were in C3 disease stage at the moment of the diagnosis and this is another important aspect which pleads for the incontestable role of immunosuppressive factors in the septic process's development. The low CD4 lymphocytes level (<200/mmc) met in both studied subgroups confirmed the anterior mentioned hypothesis.

A study centered on the direct HIV effect upon pathophysiological mechanisms described in sepsis pointed out that complement system's activation is produced during HIV infection evolution, the phenomenon being more amplified in the context of a systemic infection [1,7,24]. Here it appears that seropositive patients are more predisposed to develop severe forms of disease, with a more reserved prognosis. Considering the high mortality registered in our study, we could affirm that evolution towards severe sepsis and multiple organ dysfunction is a quick process as a result of immunity system alteration. Another surprising aspect is that related to a reduced number of deaths in the first subgroup, but the result is difficult to interpret in terms of a small number of studied cases.

The etiologic spectrum of bacterial infections in HIV seropositive patients differs in certain respects from that of those seronegative, as is apparent from a recent study

published in January 2014 [25]. The main infections appeared on an HIV immunosuppressive background in the pre-HAART were those caused by opportunistic microorganisms [1,15,26]. After the introduction of antiretroviral medication it was found that the opportunistic infection's incidence has significantly decreases, but the risk for developing microbial invasive infections (especially sepsis) remained unchanged [10,27]. These conclusions are sustained by a number of studies carried out on a representative batch of patients, before and after the initiation of antiretroviral therapy [25,28]. At the same time, some of the researchers pointed out that a adequate viro-immunological control of HIV-infection reduces the bacteremia risk in this population category [12,28].

Usually, bacterial microorganisms isolated from HIV-infected patient blood cultures varies from one geographical area to another, but it has been objectified a greater involvement of some pathogenic species like *Salmonella, S. pneumoniae, E. coli* and *S. aureus* [14,28]. Among Gram-negative germs we have observed a higher frequency of sepsis caused by *E.coli,* followed up by *P.aeruginosa, K. pneumoniae, S. marcescens* and *A. baumanii*. Gram-positive bacteria were mainly represented by methicillin-resistant *Staphylococcus aureus* (MRSA), followed by *S. pneumoniae* and *Streptococcus pyogenes.* According to international research, CA-MRSA (Community-Acquired MRSA) nasal colonization rate is higher in HIV population [15,18,29]. Petrosillo and the collaborators had noted a major implication of staphylococcal strains in the bacteremia etiology in HIV infected people and this aspect could be explained by the great number of carriers, so that in more than 80% of the cases, the appearance of staphylococcal bacteremia is secondary to nasopharyngeal colonization [4,21,29].

It seems that the incidence of invasive systemic infections in individuals with HIV- infection increases inversely proportional with the immunosuppression degree [16,18,29]. A study conducted in the USA regarding this topic identified CD4 lymphocytes low levels in every seropositive patient diagnosed with sepsis and Grant and his team described very low CD4 values, with an average<58 cells/μL in the context of septic pathology, toxoplasmosis and tuberculosis added to the preexisting health conditions [21,27,30]. In our study none of the patients did not have CD4 lymphocytes values> 500 cells/μL, but the lowest level was registered in the case of childhood-infected persons, most probably because of the long-term disease evolution and in some situations because of the belated placing under observation, when their immune-depression has already been in an advanced evolution phase. According to some other bibliographical sources, the CD4 lymphocytes deficit wasn't associated to a greater risk of systemic infections and the authors supposed that this result might be due to the protective effect of cotrimoxazole prophylaxis [17,22,30]. Still, this hypothesis seems to be contradicted by other similar studies in which the prophylactic administration of this antibiotic did not decrease the bacteremia risk, but on the contrary it influenced the etiologic microbial agents' resistance in a negative way [29,30]. There have been also significant differences between the infectious risk in the first three months after ARV-therapy initiation and that in the following period, when therapeutic effect should have already been consolidated [1,5,30].

Another important biological parameter that influences the response of an HIV-infected organism exposed to infection and also the therapeutic strategies in these situations is the neutrophils count [30,31]. Beyond the numerical deficit we can also discuss about neutrophil dysfunctions, with serious repercussions on chemotaxis and phagocytosis, free radical production and adhesion molecules expression [6,31].

We have noticed that more than half of the patients included in our study (51.7%) were neutropenic at the moment of the diagnosis and this aspect could partially explain the occurrence of sepsis in its severe forms and the unfavourable outcome. The mortality and morbidity associated to bacterial infections in HIV seropositive hosts are directly related to the presence of neutropenia, which represents an independent risk factor for bacteremia in this population group [5,28,31]. In addition to that, the infectious risk also depends on the neutropenia level, as it is apparent from extensive international studies [27.31]. We have drawn the same conclusion from our research by the fact that all the patients with severe neutropenia had died.

The mortality rate among studied patients was 33%, surpassing the European percentage (16-22%) [11,18,31]. Generally, the mortality in these situations is variable, being seized between 7 and 46% [15,32]. In Romania, more than 25% of HIV seropositive persons who associate systemic infections die by multiple organ dysfunction [33-36]. This phenomenon is determined by the late diagnosis establishment (membership in an disadvantaged social categories, the inadequate population informing in conjunction with a low level of risks comprehension) and, on the other hand by the lack of compliance to ARV-therapy, with bad consequences on the immune control, HIV viremia and resistant viral mutants [19,37]. The prognosis of HIV-infected patients is also influence by the association of tuberculosis with pulmonary localization, as well as extra-pulmonary localization (meningeal, osteoarticular, renal, oral) [38]. It has been demonstrated a higher incidence of smoking in this category of patients, which could explain the presence of severe respiratory dysfunctions in sepsis [39].

Conclusions

The prognosis of HIV seropositive patients who are diagnosed with severe sepsis at a certain moment depended on several factors: T CD4 lymphocytes values, viral load, neutropenia degree, hemoglobin and hematocrit values. Those who had CD4 blood count under 200cells/m^3, high HIV viremias, neutrophils blood count under 500 cells/mm^3 and diverse degrees of anemia associated an increased risk of bad evolution in comparison to those who did not met these criteria, most probably because of the immunological and hematological viral-induced decline. The prolonged antibiotic therapy was also present in the case of patients with unfavourable outcome. Cryptococcal meningitis represented another bad prognosis factor on one hand because of the opportunistic infections characteristic to an advanced immunosuppression stage and, on another hand to the microbial causative agent's aggresivity. Mortality rate in HIV infected persons was elevated, especially in the context of non-adherence and non-compliance to ARV-therapy.

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