

Sepsis in HIV-positive patients. What is the scale of the problem and how to approach it?

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Abstract

In the antiretroviral therapy (ART) era, human immunodeficiency virus (HIV)-positive patients are admitted to the hospital in a critical state for various reasons, with a decrease of hospitalizations due to opportunistic infections. About 12-31% of hospitalizations of HIV-infected patients in the intensive care unit (ICU) are due to sepsis. HIV-positive patients with sepsis have a higher mortality rate than HIV-negative patients. Although there are no specific recommendations on how to treat septic HIV-positive patients, it is important to remember which pathogens are the most common causes of infection in this group of patients. More attention should be drawn to nosocomial infections mainly caused by Gram-positive cocci and Gram-negative rods. According to the European AIDS Clinical Society Guidelines (EACS) 2015, ART should be introduced in all HIV-positive patients, regardless of the CD4 cell count. The recommendations do not contain information on treatment of patients with HIV with sepsis. The introduction of ART in HIV-positive patients in a critical state is still debatable due to the drug-drug interactions and route of administration. Though ART in critically ill patients may not affect the hospital survival, it has long-term benefits such as fewer AIDS-related events. The aim of this article was to provide physicians with an overview of recent information on patients with HIV who develop sepsis.

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Introduction

According to the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3), set in February 2016, sepsis should be defined as 'life-threatening organ dysfunction caused by a dysregulated host response to infection' [1]. Sepsis incidence in the United States increased from 621 000 in the year 2000 to 1 141 000 in 2008 [2]. According to some other data, it is estimated that sepsis incidence is about 150-300 cases per 100 000 inhabitants. The incidence increases up to 700/100 000 in patients with chronic diseases and up to 1000/100 000 in patients with human immunodeficiency virus (HIV) [3]. The incidence of septic shock is estimated to be about 11 cases per 100 000 inhabitants. Mortality rates are considered to be up

to 50% for sepsis and 80% for septic shock. One in 1000 people in developed countries suffer sepsis each year. There are no data about sepsis in developing countries [4]. One percent to 10% of patients with sepsis have HIV/AIDS and about 12-31% of admissions of HIV-infected patients to the intensive care unit (ICU) are due to sepsis [5, 6].

HIV and sepsis

There are numerous causes of admission of HIV-positive patients in a critical state to a hospital. They can be either HIV-related (opportunistic) or not (trauma, acute infections). With antiretroviral therapy (ART) becoming more popular, sepsis has become a more frequent diagnosis in HIV-positive

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patients. A prospective study conducted by Casalino *et al.* between 1995 and 1999 in Paris showed that after the introduction of ART (in 1997), AIDS-related admissions to the ICU decreased from 57.7% to 37%, and the opposite trend was seen in septic admissions: the percentage of patients with HIV and sepsis admitted to the ICU increased from 16.3% to 22.6% [7]. Even though opportunistic diseases are a decreasing cause of patient hospitalization, respiratory diseases still play a substantial role. In a retrospective study conducted by Turtle *et al.* on 43 HIV positive patients admitted to the ICU between 2001 and 2006, the majority were admitted due to respiratory disease [8].

The frequencies of bacteria causing pulmonary infections differ between countries and hospitals, but in general the most common pathogens are considered to be *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The latter occurs especially in patients with a low CD4 cell count. Fungal (especially caused by *Pneumocystis jirovecii*) and mycobacterial pneumonias also occur. There has been an increase in hepatic (especially in patients co-infected with HCV), renal and cardiovascular causes of admission of HIV-positive patients [9].

In a study conducted by Greenberg *et al.* of 990 patients with sepsis, 136 (13.7%) of them had HIV. Of the latter, 22% were on ART prior to hospitalization. There were 194 acute infections with 112 nosocomial/health care-associated infections, 55 AIDS-related, and 27 community-acquired infections. The most common pathogen of the community-acquired infections was *Streptococcus pneumoniae*. Fifty-one percent of the AIDS-related infections were *Pneumocystis jirovecii* pneumonia (PCP), whereas the nosocomial infections were caused mainly by Gram-positive cocci and Gram-negative rods. Patients with nosocomial/healthcare-associated or AIDS-related infections had lower CD4 counts and were less likely to be on ART ($p < 0.05$). The in-hospital mortality rate was 42%, and it was more associated with acute illness severity than with markers of immunodeficiency [10]. Due to immunosuppression, recurrent antibiotic treatment and more frequent exposure to invasive procedures, HIV-positive patients have a higher risk of nosocomial infections than HIV-negative patients. The incidence of nosocomial infections in HIV-positive patients is estimated to be 7.9-15 per 100 admissions. The main source of infection is through the intravascular catheter [11].

Interestingly, according to Mrus *et al.*, based on a study of discharge abstracts of 74 020 patients with sepsis in the year 1999 (10.3% of them had HIV/AIDS), patients with sepsis and HIV/AIDS were less likely to be admitted to the ICU (37% vs. 56%), but had greater mortality rates than those without HIV/AIDS (29% vs. 20%). The comparison of characteristics of the groups of patients with sepsis showed that those with HIV/AIDS and sepsis were younger on average (41.9 years vs. 49.9 years), were less likely to have other comorbidities (39% vs. 51%), but were more likely to be male (66% vs. 54%), and more likely to have respiratory and opportunistic infections than those without HIV/AIDS (53% vs. 9%) [12].

Similar results were demonstrated in an observational data analysis done by Akgun *et al.* Here, 539 HIV-positive patients and 375 seronegative patients with organ dysfunction were compared. Patients with HIV were younger and less frequently had hypertension, congestive heart failure, COPD and diabetes. They more frequently had pneumonia and other infectious diseases (21% vs. 12%), more frequently had mechanical ventilation (17% vs. 9%) and had a higher mortality rate (18.6% vs. 11.2%) than other patients in a critical state without HIV [13].

Another study, done in the Instituto de Pesquisa Clinica Evandro Chagas (IPEC) in Brazil between 2006 and 2008, showed a significantly different hospital mortality of HIV-positive patients with and without sepsis (66% vs. 34%, $p = 0.002$). The most common sites of infections were: lungs (52%), primary bloodstream (38%), venous catheter-related (7%) and urinary tract (3%). Ninety percent of the infections were nosocomial. The leading pathogens were: *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* sp., *Escherichia coli*, *Acinetobacter*, *Serratia marcescens*, *Staphylococcus* sp., and *Mycobacterium tuberculosis*. By using a Cox proportional hazards regression, a 4 times higher risk of death at 28 days was obtained in septic patients than for non-septic patients [5].

In a consecutive prospective analysis, by Silva *et al.*, even though the severity of sepsis of patients with HIV was similar to that in non-HIV patients and the prognostic scores did not differ much between the two groups, the risk of death at 28 days and at 6 months of follow-up was again higher for HIV-positive patients. The two groups also varied in the etiologies of sepsis – in HIV-positive patients it was mainly fungal and mycobacterial pulmonary or abdominal infections, while in the non-HIV ones it was mainly Gram-positive cocci and Gram-negative rods. Respiratory (77.8%), cardiovascular (75%) and neurological (52.8%) were the main organic dysfunctions in HIV-positive patients, in contrast with cardiovascular (72.7%), renal (63.6%) and lactic acidosis (29.1%) in the non-HIV septic patients [11].

In a retrospective study by Medrano *et al.*, HIV-positive patients in the ICU had a higher frequency of sepsis than the control group (non-HIV and non-HCV patients), 57.7% vs. 39.4%. HIV-infected patients had a higher mortality than the control group, independently of sepsis. The HIV/HCV-coinfected patients had a higher mortality rate regardless of the presence of sepsis at days 7 and 30, but not 90 [14].

Continue, stop or introduce ART in a HIV-positive patient with severe sepsis?

Treatment of HIV-positive patients with sepsis does not differ much from treatment of HIV-negative patients with sepsis. In both cases the medical staff should follow the international “Surviving Sepsis Campaign (SSC) Guidelines for Management of Severe Sepsis and Septic Shock” revised in 2012 (the 2016 version will appear soon) [15]. According to the new French 2013 Guidelines for Antiretroviral Ther-

apy of HIV-1 Infection in Adults as well as of the European AIDS Clinical Society Guidelines 2015, ART should be initiated in any HIV-positive person, regardless of the CD4 cell count [9, 16]. The limitation to this recommendation is that patients in a critical state are not always able to take the antiretroviral drugs orally and only zidovudine can be administered intravenously. The EACS guidelines do not specify the treatment of an HIV-positive patient with severe sepsis.

Lanoix *et al.* in the article “Antiretroviral therapy in intensive care” list other issues that need to be taken into consideration when using ART in a patient in a critical state. Namely, the drug interactions, risk of immune reconstitution syndrome (especially when ART is introduced in patients with a CD4+ T-cell count < 100 cells/ μ l and with a viral load >100 000 copies/ μ l) and drug kinetics in patients on mechanical ventilation and/or with gastric tubes [17]. According to Masur, due to the interactions of ART with other drugs metabolized by the cytochrome P-450 enzyme system, and due to the unpredictable pharmacokinetics of ART in severely ill patients (due to poor enteral absorption), in most situations it is best to stop the ART at the admission to the patient and consult an experienced pharmacokineticist and infectious disease specialist [18]. However, stopping the treatment suddenly may greatly increase the immunosuppression of the patient [8].

Casalino *et al.* compared the survival rates of HIV-infected patients before the ART era and after (between 1995 and 1999). The data showed no difference in ICU mortality between those two eras, whereas the long-term survival rate has increased substantially in the ART era [7]. According to van Lelyveld the 1-year mortality decreased from 71% in the pre-HAART era to 50% in the recent period ($p = 0.06$). The 5-year mortality decreased from 87% in the pre-HAART era to 59% in the early-HAART period ($p = 0.005$) [19].

On the other hand, a retrospective study by Dickson *et al.* did not show a better outcome in patients receiving ART (although in this study no patient began ART at admission) [20]. Similarly, a prospective study conducted by Japiassu *et al.* showed that ART use did not affect hospital survival, leaving the mortality rate at 50% both in those who received ART and those who did not [5]. A Taiwanese univariable analysis of hospital mortality for HIV-positive patients showed no difference between survivors and non-survivors with respect to ART use prior to the hospital admission ($p = 0.5$) or to the introduction of ART at admission ($p = 0.9$) [21]. Similar results were obtained by Meybeck *et al.* in a retrospective cohort study where 85 HIV-infected patients in the ICU were diagnosed. There was no significant difference in the ICU survival or the 6-month survival in patients on ART or not. But the prescription of ART during hospital stay was associated with less frequent AIDS-related events [22]. The reduction of frequency of progression of AIDS was also noted in a study by Zolopa *et al.*, when patients received the ART immediately rather than after opportunistic infection treatment was completed [23]. A more recent study conducted between 2011 and 2013 by Orsini *et al.*

did not question long-term benefits of the use of ART but again did not show any short-term benefits of such therapy [24]. The use of ART did not affect the mortality rate in patients in a critical state. The limitation of both Chiang's and Orsini's studies on the use of ART and the survival rate of patients was that patients' adherence to the therapy prior to hospital admission was not taken into consideration, nor was the prevalence of the mutations responsible for antiretroviral drug resistance.

Conclusions

Sepsis is still an important global burden. The incidence of sepsis increases in patients with HIV and increases the mortality rate in HIV patients. Since there are no additional recommendations on how to treat HIV-positive patients with sepsis, it is important to remember which pathogens are more often found in those patients. Special attention should be paid to nosocomial infections. Numerous articles analyze the benefits and disadvantages of introducing ART in patients in intensive care units. While there is no conclusive result on whether ART brings immediate, short-term benefits, it is agreed that it brings long-term benefits and should be introduced cautiously. Interactions between antiretroviral drugs and other drugs, as well as kinetics, need to be taken into account. Guidelines on treatment of HIV-positive septic patients are needed.

Conflict of interest

The author's declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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