GRAM-NEGATIVE BACILLI INFECTIONS IN HIV INFECTED PATIENTS

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Abstract: *The epidemiology of bacterial infections during HIV (human immune deficiency virus) infection changed after the introduction of HAART (highly active antiretroviral therapy) and of the prophylaxis programmes addressing the associated infections, which led to an increased prevalence of some of them. Despite the relatively low incidence, the gram-negative bacilli (GNB) infections must be suspected in the case of bacterial complications in these patients, considering the severe potential of respiratory and systemic infections caused, and also the variable susceptibility to antibiotics. The study targets the peculiar etiologic and clinical aspects of GNB infections in seropositive patients vs. seronegative ones, the characterization of germs from the antibiotics sensitivity point of view and the connection with the severity of the immune suppression. The data are analyzed and the results are presented in a comparative manner with those obtained from non-infected HIV patients. The retrospective study supports the implication of deep immune suppression in causing the severe GNB infections, the role of HAART in preventing the respiratory complications caused by these germ and also the recommendation of the antibiotherapy uninfluenced by the seropositivity status.*

Cuvinte cheie: *HIV, bacili Gram negativi, infecție*

Rezumat: *Epidemiologia infecțiilor bacteriene în cursul infecției HIV (virusul imunodeficienței umane) s-a schimbat consecutiv introducerii HAART (terapie antiretrovirală înalt activă) și a programelor de profilaxie adresate infecțiilor asociate, determinând creșterea prevalenței unora dintre ele. În ciuda incidenței relativ scăzute, infecțiile cu bacili Gram-negativi (BGN) trebuie suspectate în cazul complicațiilor bacteriene la acești pacienți, având în vedere potențialul marcat de severitate al infecțiilor respiratorii sau sistemice determinate și susceptibilitatea variabilă la antibiotice. Studiul vizează aspectele particulare etiologice și clinice ale infecțiilor cu BGN la seropozitivi vs seronegativi, caracterizarea germenilor referitor la sensibilitatea la antibiotice și corelarea cu severitatea imunodepresiei. Datele sunt analizate și rezultatele sunt prezentate comparativ cu cele obținute la pacienți neinfectați HIV. Studiul retrospectiv efectuat susține implicarea imunodepresiei profunde în determinarea infecțiilor severe cu BGN, rolul HAART în prevenirea complicațiilor pulmonare cu acești germeni, cât și recomandarea unei antibioterapii neinfluențată de statutul de seropozitivitate HIV în acest tip de infecții.*

INTRODUCTION

The epidemiology of bacilli infections during HIV infection changed after the introduction of HAART and of the prophylaxis programmes addressed to the associated infections, which led to the growth of prevalence in some of them. GNB infections must be suspected in HIV seropositive patients, considering the severe potential of the respiratory or systemic infections they can cause and also the variable susceptibility to antibiotics.

PURPOSE

The general objective of this study was the identification of certain aspects of GNB infections in HIV immunosuppressed infected patients, compared to immune-competent patients or non-HIV immune suppressed. The purpose of the research was a). The identification of main gram-negative bacilli involved in the infections occurred in seropositive HIV patients; b). The evaluation of certain evolutive aspects of the determined clinical picture; c). The description of isolated germs from the antibiotic sensitivity point of view; d) Linking the clinical aspects with the immune status of the patient.

METHODS

We performed a retrospective study on a group of 59 patients admitted at the No. I Infectious Diseases Clinic from Tîrgu Mureș between 01.02.2011 – 31.01.2012, who presented gram-negative bacilli infections other than gastroenteritis; the stool isolated gram-negative patients were excluded. Regarding the seropositive HIV patients, the collection of data was made using the observation sheets and the HIV infection monitoring and treatment files.

The following data was selected and processed: 1). Demographical data: the patients' age and gender, their environment; 2). Their HIV seropositive status; 3). Their cell immunity status determined by the number of T CD4 and T CD8 lymphocytes; 4). The clinical status of the HIV infection; 5). Clinical data: clinical manifestations/signs of acute infection,

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severity signs, associated diseases; 6). Bacteriological examinations: blood cultures, urine culture, sputum, ear secretion, pharynxes exudate, nose secretion, wound or skin collections secretion; 7). DST of isolated germs; 8). Duration of antibiotic treatment; 9) Mortality rate.

Based on the inclusion criteria, we selected a study group which contained a total of 59 GNB infected patients. According to the seropositive HIV status, demonstrated through 2 ELISA and a Western – Blot tests, the patients were divided in 2 batches:

-batch A, including 24 HIV infected patients,

-batch B, including 35 HIV negative patients,

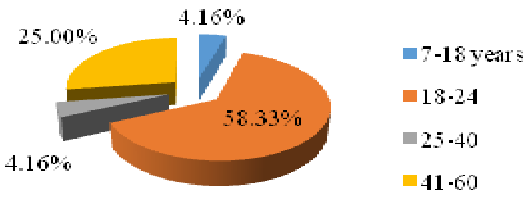
RESULTS

Demographical data. The repartition of the patients by gender showed an almost equal distribution among the two batches, with most cases being women: 15 and, respectively 24 patients, compared to men, with 9 patients in each batch, the women/men proportion being 1.66 in batch A and 2.66 in batch B. As for the seropositive batch, this aspect is in correlation with the higher number of female patients in the Mureş Centre records.

In batch A, 16 patients (72%) are from the countryside and 8 (31.43%) from an urban environment; in batch B, 7 patients (20%) are from the countryside and 28 (80%) from an urban environment.

The medium age in batch A was much lower than in batch B: 27.95 years, and 45.8 years respectively. We think this aspect is due to the fact that in Mureş, there are more patients with horizontal infections developed in their childhood, between 1987 and 1992, argumentation sustained by the positioning of the patients in age groups in this study: 18-24 years old - 14 patients (58.33%), 41-60 years old - 6 patients (25%), and 2 patients each (4.16%) in the 7-18 year old and 25-40 year old groups (figure no. 1).

Figure no. 1. Patients' distribution per age groups in batch A



The age group distribution of the patients from batch B is more heterogeneous, with a majority in the over 60-year-old group: 13 patients (37.14%); 25-40 years old: 10 (28.50%), 41-60 years old: 6 (17.14%); 2 cases each (5,70%) in the 0-6-year-old group, 7-18 and 18-24-year-old groups (figure no. 2). The distribution is explicable by the cluster of risk factors in the elderly: metabolic conditions (diabetes) and cardio-circulatory conditions (heart failure, venous circulatory failure), which can favour GNB infections.

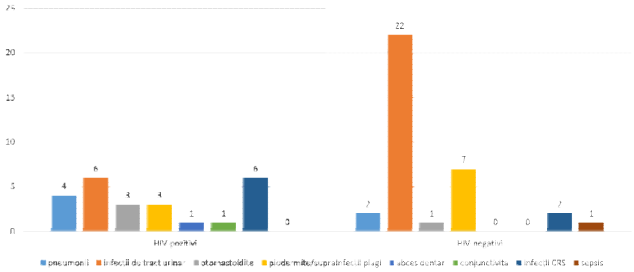
The immune status. The HIV seropositive patients were classified in the CDC Atlanta 1993 study as follows: 18 (77%) immune stage 3,4 (14%) in the second stage and 2 (9%) in the first stage.

The clinical status of HIV infection. When they were diagnosed with GNB infection, 22 patients (91.66%) were in clinical status C (AIDS).

Clinical report. The main pathology in batch A was constituted by urinary tract infections (UTI) and infections of the higher respiratory tract (CRS) (angina, acute adenoids, sinusitis, bronchitis), equally diagnosed, 6 each (25%). We counted 4 cases of pneumonia (16.66%). Three patients (12.5%) were diagnosed with otomastoiditis and another 3 with over infected GNB plagues. We diagnosed one case (12.85%) with conjunctival infection and also one with dental apical suppuration (figure no. 2).

In the B batch, UTI was the main manifestation, diagnosed in 22 patients (62.80%), followed by plague over infections in 7 patients (20%). These were mostly leg ulcers or over infected forms of erysipelas. We have registered 2 cases of pneumonia (5.71%). The GNB isolation, in the context of CRS pathology, was extremely rare (2 cases, 5.70%). We found one case of sepsis (figure no. 2).

Figure no. 2. Distribution of patients by GNB determined clinical picture in A and B batches



Comparing the two batches, the absence of a dominant pathology in seropositive patients is apparent, in contrast with the non-HIV batch, in which the UTI is dominant. We noticed a predisposition in the HIV infected patients to develop over-infections in the ENT area. Pneumonia was more frequent in HIV infected patients, through the specific impact on immune deficiency organisms, but the seriousness of the episodes was uncommon in both batches, causing mortality; death occurred in a C3 status AIDS patient, without TARV antiretroviral treatment, which presented an extremely severe form of bronchopneumonia with Acinetobacter spp., with excavation tendencies, aggravated by pneumothorax; it evolved lethally. In the seronegative patients' batch, both bronchopneumonia episodes occurred in highly severe associated pathology patients: one patient under dialysis because of chronic renal insufficiency, diagnosed initially with Escherichia Coli sepsis; and in a CABG after extended infarction patient.

The only sepsis case in the batch was diagnosed in a non-infected HIV patient, immune suppressed through renal insufficiency, transplant rejection (renal transplant), insulin dependent diabetes, and systemic vasculitis with Escherichia Coli etiology.

We noticed the recurrent tendencies of GNB infections, through successive pneumonia episodes in 2 AIDS status patients, which were not on TARV: Klebsiella pneumonia, then Acinetobacter pneumonia, then successive Haemophilus influenza pneumonia (with bilateral diffuse injury, insidious onset) and Klebsiella, existing in skin and mucous infections: AIDS and vulvar carcinoma patient, trailing over-infections with Pseudomonas, E. Coli, Proteus.

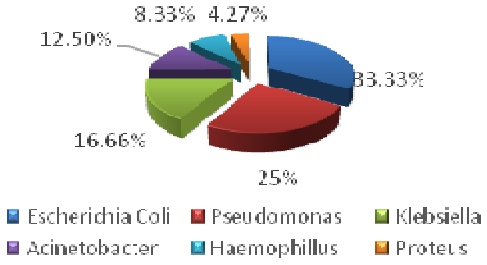
In seronegative patients, the recurrences were determined by filed factors: relapsing UTI in patients with diabetes and urinary catheters (3 patients with 2-3 episodes), recurrent skin infections in psoriasis and recurrent erysipelas patients, over infected, with varicose ulcers and post- thrombotic syndrome history.

Associated diseases. The dominant associated pathology in the HIV seropositive batch was chronic HIV hepatopathy in 9 patients (33%) and pulmonary tuberculosis in 4 (12.5%). Other links were: hypertriglyceridemia, Cryptococci meningoencephalitis and chronic mastoiditis (2 cases each), cerebral atrophy, viral chronic B hepatitis, bronchial asthma and chronic prostatitis – one case each. As a comorbidity factor, we identified 5 cases (20.83%) of chronic smoking.

In the B batch, the more frequent associated diseases were: ischemic heart disease, arterial hypertension and heart insufficiency in 12 (34.28%), 8 (22.85%) and 7 patients (20%); we registered diabetes in 7 patients (20%), psoriasis in 2 (5.71%) and systemic erythematous lupus and multiple sclerosis one case each (2.85%).

GNB infections etiology. In both batches, E. Coli prevailed: 8 patients (33.33%) in batch A and 14 patients (37.20%) in batch B. A high percentage of Pseudomonas strains were isolated - 6 patients (25%) and 6 patients (17%) respectively, followed by Klebsiella, in both batches: 4 patients (16.66%) in batch A and 6 patients (17%) in batch B. Other species of GNB were found in smaller numbers: Acinetobacter spp. in 3 patients for each group (representing 12.50% and 8.57%), Proteus in 1 patient (4.16%) in batch A and in 4 (11.40%) in batch B. In batch A, we isolated Haemophilus influenza in 2 patients (8,33%) and in batch B, Citrobacter (1 case - 2.85%) and species of Enterobacter (2 cases - 5.71%) (figure no. 3).

Figure no. 3. GNB species percentage distribution in isolated seropositive patients



Infection location. The most frequently isolated germ in urine culture in both batches was E. Coli: 6 cases in batch A, 12 cases in batch B; in seronegative patients other GNB-s were found: Proteus in 3 cases, Pseudomonas, Klebsiella, Enterobacter, 2 case each, and Citrobacter and Acinetobacter, 1 case each.

The pneumonia etiology in batch A was Klebsiella pneumonia (2 patients), and respectively Haemophilus and Acinetobacter (1 patient each), while in batch B was Acinetobacter and Pseudomonas.

In the seropositive patients, with pyoderma and over infected plague, 2 strains of Pseudomonas and one strain of E. Coli were isolated from the pustules. The plague over infections diagnosed in batch B had various etiologies: E. Coli, Proteus and Acinetobacter (1 case each), Pseudomonas (3 cases).

Regarding CRS infections in seropositive patients, we found Pseudomonas strains in 3 cases, Klebsiella, in 2 cases, and E.Coli, Haemophilus and Proteus one of each; in the seronegative patients' batches, there were mostly Klebsiella strains (3 cases).

The only positive blood culture was with E. Coli, in a severely non-HIV immune suppressed patient.

Isolated GNB antibiogram evaluation. We noticed a high susceptibility (95 %) to carbapenem (CBP) and 3rd generation aminoglycosides (Agl III) (85%); the sulphonamides resistance percent (SULF) (30.76%), and 3rd generation cephalosporin (Cef III) (30.43%) in seropositive patients (figure no. 4). In the seronegative patients' batch, the sensitivity for CBP was 85%; we identified resistance to beta lactamase inhibitors (IBL) (50%) and quinolones (CHN) (42%) (figure no. 5).

Figure no. 4. Isolated GNB antibiotics sensitivity evaluation in seropositive patients

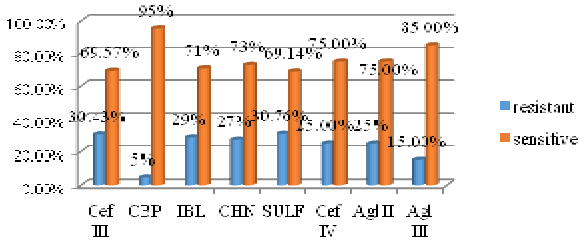
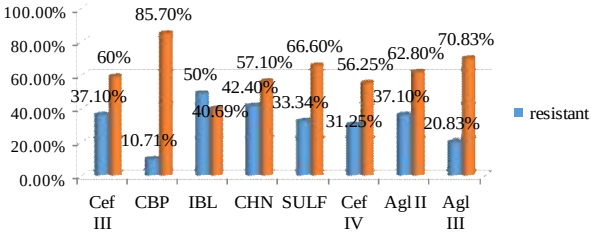


Figure no. 5. Isolated GNB antibiotics sensitivity evaluation in seronegative patients



The evaluation of the antibiotics susceptibility of the GNB strains proved excellent sensitivity to carbapenems in both batches, but also a significant difference between these and an important class of antibiotics, regarding the high sensitivity of the seropositive isolated strains to quinolones (73% vs. 57%), 4th generation cephalosporin (85% vs. 56%), betalactams with betalactamase inhibitors (71% vs. 50%), and, less remarkable but obvious, to aminoglycosides (83% vs. 70%) and 3rd generation cephalosporins (69.57% vs. 60%). As an explanation, we considered the frequent use of antibiotics, due to the relapsing non-HIV patients' infections, as a result of field factors; repeated cures of antibiotics in the hospital or at home, sometimes with self-medication, increases the risk of resistance induction and it could explain the constant susceptibility discrepancies. We noticed a high rate of sulphonamides resistance in both patient categories (33-39%).

Treatment period evaluation. The length of antibiotics treatment of GNB infections was 5 to 26 days (15.5 days medium) in the A batch, and 4 to 23 days (13.5 days medium) in the B batch.

Mortality rate. There were 3 deaths in the A batch and 1 in the B batch. The GNB infection: bronchopneumonia with Acinetobacter complicated with pneumothorax caused directly one death only, a patient with AIDS. The small number of cases did not allow a statistical analysis.

DISCUSSIONS

The present study presents the results of a retrospective one year research, conducted on patients admitted at No. I Infectious Diseases Clinic from Tîrgu Mureș, whose aim was to evaluate the GNB infections in HIV seropositive patients vs. seronegative ones; the seropositive patients are monitored by the Regional Centre of Surveillance and Monitoring the HIV/AIDS Infection Mureș.

Compared to the HIV uninfected patient batch, in the seropositive one we identified a grown prevalence of CRS with GNB infections (9/24 vs. 3/35); most studies worldwide indicate the CRS infections as the most frequent in HIV infected patients (54-55%).(1,2)

The most severe clinical manifestation in HIV seropositive patients was pneumonia. The features were: onset during the C3 stage of HIV infected patients, supporting the growing risk of GNB infections in severe immune suppressive conditions or AIDS stage;(3,4) the absence of TARV, which confirms the importance of correctly implementing it in order to reduce the rate of pulmonary complications.(5,6) The prevalence of GNB in bacterium caused pneumonia in seropositive patients varies according to geographical areas, from 5-15% to 53%, and even to 85% in Romania.(5,6,7,8,9) The Haemophilus influenza pneumonia had the particularities described in the immune suppressed.(10) The Acinetobacter pneumonia had likely nosocomial character in both groups, atypical radiological aspect, the germ acting like an opportunistic pathogen, responsible for morbidity and mortality rates in severe immune suppressive HIV or non-HIV patients.(11) Klebsiella pneumonia caused 2 cases in the seropositive batch; recent studies indicate the germ as an etiological agent in 20% of bacteria related pneumonia.(9) We noticed the relapsing character of GNB pneumonia in the seropositive batch, specific to the decreasing level of LT-CD4, at which the bacterial pneumonia constitutes itself a predictive factor of relapse.(7,12) We recorded one death out of the 4 cases of pneumonia, the mortality rate in bacterial pneumonia in HIV infections being around 10-15%.(13)

Sulphonamides account for the highest resistance percentage (over 30%); the literature indicates a growing percentage of GNB resistance for this class, around 50-61%. Unlike other study results, we identified a relatively high percentage of resistance to 3rd generation cephalosporins, betalactams and quinolones, due to the involvement of large spectrum betalactamase producing strains, fact that discourages us from sustaining their use as initial empirical therapy in severe GNB infection, locally, regardless of the HIV seropositive status.(14,15,16)

CONCLUSIONS

1. Severe immune suppression, characteristic to AIDS status, is favouring the GNB infections.
2. The distribution of GNB infections on age categories in seropositive patients respects proportionally their HIV infection affect.
3. The absence of TARV is influencing decisively the occurrence of GNB bacterial pneumonia.
4. GNB pneumonia in seropositive patients is extremely severe, regardless of the HIV immune suppressive status; in HIV seropositive patients, there is also a relapse tendency.
5. The susceptibility to antibiotics of GNB steams is higher in seropositive patients regarding the local epidemiological context, compared to the general population.
6. The length of the antibiotics treatment necessary in GNB infections is not generally influenced by the patients HIV seropositive status and the treatment is similar.

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