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**BACTERIAL INFECTIONS IN PERSONS
INFECTED WITH THE HUMAN
IMMUNODEFICIENCY VIRUS TYPE-1 (HIV-1)**

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ABSTRACT

It has been more than three decades since the first cases of acquired immune deficiency were reported, groups at risk were defined, routes of transmission of the disease determined and the causative agent, the human immunodeficiency virus (HIV) was identified. The discovery of antiretroviral therapy (ARV) was a key moment in the history of the pandemic, transforming HIV from a fatal clinical condition in any case, to a chronic disease receiving a long-term care and an almost normal life expectancy. Since the discovery of zidovudine, the first pharmacologically active molecule against HIV, antiretroviral therapy had rapid and significant changes. However, opportunistic or common infections are relatively common in persons infected with HIV (PIH), which is today an important cause of morbidity and mortality, and problems remain related to prevention and curative therapy.

HIV-induced immunosuppression amplifies the risk of bacterial infections, tuberculosis and non-tuberculosis, often involving antibiotic-resistant strains, with severe and / or recurrent potential. Occurrence surrogate markers and bacterial infections spectrum are CD4 cell count and HIV-viral load. Clinical and biological manifestations are often atypical, and therefore requires a high index of suspicion for early diagnosis and medical management, prophylactic therapy or appropriate curative treatment.

By studying bacterial infections in immunocompromised patients with HIV, I tried to help improving prevention and diagnosis strategies of these infections in context of achieving an appropriate antibiotic standard for a cost-benefit effective treatment and for improving individual prognosis.

Key words: HIV, bacterial infections, tuberculosis

Objectives:

1. Evaluation of prevalence, incidence, mortality and bacterial infections spectrum tuberculosis (TB) and non-tuberculosis bacterial infections (BI) in PIH hospitalized in the Regional Center for Monitoring and Evaluation of HIV / AIDS in Craiova (Craiova R.C.).
2. Establishing the immuno-virological profile in PIH with bacterial coinfections
3. Comparative analysis of bacterial infections, tuberculosis and non-tuberculosis (epidemiology, clinical features, bacteriology) in PIH versus patients (Px) without HIV infection
4. Analysis of the general context of developing bacterial respiratory infections in PIH

Material and methods - general considerations:

The study group included PIH cases on record in Craiova R.C., which monitors and evaluates such cases in Oltenia (Dolj, Olt, Gorj and Mehedinti). I subdivided scientific approach in three substudies to better highlight the particularities of bacterial infections in PIH.

For data processing I use programs MICROSOFT EXCEL, SPSS and Epi Info 2000. Quantitative characteristics were described by average, standard deviation and median, and the qualitative indicators frequency and structure, depending on the type of the variable, the comparison was performed by Student -t test tests, χ^2 or Fischer. Mortality was assessed by calculating and comparing the rate of death. Survival data were described graphically by Kaplan-Meier curves, compared between the various interest groups by log-rank test. Differences were considered statistically significant for a threshold $p < 0.05$ and highly

statistically significant for $p < 0.001$, in a confidence interval (CI) of 95%. Univariate analysis: to estimate the time until the adverse event occurrence I used Kaplan-Meier method, the comparison being made with the log-rank test at a statistical significance level $p < 0.05$.

Substudy I had a mixed character: retrospective between 01/01/2000-31/12/2006 and prospective between 01/01/2007-31/12/2011, on a group of 768 PIH in Craiova R.C. and followed epidemiological, clinical and etiologic issues of bacterial infections other than tuberculosis and tuberculosis, as well as data on the immune and virologic status in PIH with bacterial co-infections.

Results of study I were as follows:

Bacterial co-infections (tuberculosis and non-tuberculosis bacterial infections) were recorded at 337 PIH (43.75%). The presence of non-tuberculosis bacterial infections was recorded in 189 PIH (24.60%), the majority of PIH -116 (15.01%) presented a single bacterial infection (BI 1). The presence of tuberculosis was confirmed at 209 PIH (27.21%), the majority of PIH-176 (22.92%) had TB1.

Chronological evolution of annual incidence showed that both non-tuberculosis bacterial infections and tuberculosis had an upward trend.

Among the 337 PIH with bacterial coinfections were noted 85 deaths (25.22%). The presence of non-tuberculosis bacterial infections PIH influenced survival, without reaching the statistical difference threshold ($p > 0.05$). The average duration of survival in PIH without non-tuberculosis bacterial infections would be of 16.19 years. The presence of these infections reduce the duration of 15.30 years ($p < 0.05$). The presence of tuberculosis in PIH has been noted to reduce significantly ($p < 0.05$) the survival of PIH.

Newly diagnosed cases with HIV / AIDS in at the diagnosis time of tuberculosis were recorded at PIH 67 (32.06%). Between 2001-2005 there was a decrease in the incidence of tuberculosis (20% -39%) in HIV-infected patients and then an upward trend for 2007-2010 (38% -46%).

The location of tuberculosis was pulmonary in most cases (59 PIH-88, 06%).

In PIH with TB1, CD4 lymphocytes recorded an average value of 179.89 cells / CMM and a median of 92 cells / CMM. In case of pulmonary tuberculosis, average CD4 cell count was 151.44 cells / CMM, and in case of extra-pulmonary tuberculosis, the average was 67.55 CD4 cells / CMM ($p < 0.05$). For HIV viremia in PIH with TB1 was an average value of 94486.08 copies / mL (4.97 lg). For PIH with TB2, CD4 lymphocytes recorded an average value of 94.73 cells / CMM, and HIV viremia recorded an average of 93700.22 copies / mL (4.97 lg). Immune and virologic status of PIH with TB3 showed that all PIH had a CD4 cell count < 50 cells / CMM and high values of HIV viremia (6.41 lg copies / mL, 6.28 lg copies / mL and 5.68 lg copies / mL).

The etiologic spectrum of non-tuberculosis bacterial infections has been dominated by triad *Staphylococcus aureus* (69 PIH-36.51%), *Escherichia coli* (31 PIH-16. 41%), and *Streptococcus pneumoniae* (28 PIH-14. 81%).

For PIH with BI 1, CD4 lymphocytes recorded an average value of $363.67 \pm$ cells / CMM, with different values depending on the etiology: *Ps.aeruginosa* and *Str.pneumoniae* infections were accompanied by severe levels of immunosuppression ($p < 0.05$) compared to any levels of immunosuppression observed in PIH with BI 1 of other etiologies. HIV viremia recorded an average of 21866.14 copies / mL, with different values depending on the etiology, the highest level of viral replication being found for PIH with staphylococcal BI 1 (56039.13 copies / mL).

For PIH with BI 2, CD4 lymphocytes recorded an average value of 316.45 cells / CMM, with different values depending on the etiology, as follows: average value of 196.21 cells / CMM for PIH with staphylococcal infection, 153,95 cells / CMM for PIH with

pneumococcal infections and 373.53 cells / CMM for PIH with *E.coli* infection. Severe immunosuppression observed in PIH staphylococcal and pneumococcal bacterial infections was significantly different ($p < 0.0002$) compared to level of immunosuppression observed in PIH with BI 2, with *E. coli*. HIV viremia recorded an average of 29544.29 copies / mL, with different values depending on the etiology BI 2 as follows: average of 68716.32 copies / mL for PIH with staphylococcal infections, of 21753.19 copies / mL for PIH pneumococcal infections and 1397.25 copies / mL for PIH with *E. coli* infections. The highest level of viral replication was found for PIH with staphylococcal BI2 was significantly different ($p < 0.0001$) compared to the levels of viral replication registered in BI 2 with *Str. pneumoniae* and *E. coli*.

Substudy II was comparative, prospective, analyzing features of bacterial infections in PIH and was held between 01/01/2007-31/12/2010, on four groups of patients: group A1 with 110 PIH over 16 years with tuberculosis, group A2 with 114 PIH aged 16, diagnosed with non-tuberculosis bacterial infections, group B with 1442 HIV seronegative adult Px with non-tuberculosis bacterial infections, group C with 3388 Px HIV seronegative adults with tuberculosis. From each group were excluded Px with malignant suffering. The results of this substudy were as follows:

Cumulative incidence of TB cases diagnosed during the study was 21.86% in group A1 and 0.68% in group C, registering a high risk for PIH, with statistically significant difference ($p = 0.000$; RR = 62.06; CI 95%). The number of deaths recorded in the first 12 months after diagnosis of tuberculosis was significantly higher in PIH-15 (13.63%) versus-307 Px non HIV (9.06%) ($p = 0.000$).

The location of tuberculosis was predominantly pleuropulmonary in both groups: 94 cases (85.45%) in group A1 versus 3159 cases (93.24%) in group C. Regardless of HIV status, the most common form of extrapulmonary tuberculosis was the node (9 PIH-56. 25% versus 73-31.87 % Px without HIV), but high risk for PIH (RR = 2.85, $p < .05$). At the time of TB diagnosis, 83 PIH (75.45%) in group A1 had a febrile onset versus 3027 Px (89.34%) in group C ($p < 0.0001$).

Tuberculosis cases with positive bacteriology were more common in group C (1931 Px-56. 99%) versus group A1 (28 PIH-25. 46%) ($p = 0.000$). In group A1 was found a higher risk of hydrazide resistance (RR =30.85; $p < 0.05$), rifampicin resistance (RR = 175; $p = 0.000$), hydrazide and rifampicin resistance (in 2009 : RR = 6.21; $p > 0.05$ in 2010: RR = 30.85; $p < 0.05$) compared to group C. The cumulative incidence of non-tuberculosis bacterial infections during the study was 22.66% in group A2, compared with 8.7% in group B, with high risk for PIH compared to Px non HIV ($p = 0.000$; RR = 17. 23; CI95%). The frequency of death was low in both groups, but with increased risk ($p < 0.05$; RR = 4.05; CI95%) for PIH-6 (3.09%) – against non-tuberculosis bacterial infections, Px non HIV 11 (0.76%).

Febrile syndrome accompanied non tuberculosis bacterial infections in 1108 (76.84%) Px non HIV in group B versus 51 PIH (44.74%) in group A2 ($p = 0.0001$). Clinical spectrum was dominated by low/high urinary tract infections (UTI) and acute lower respiratory tract infections (ALRTI) in both groups, with significantly higher frequency in PIH ($p = 0.000$).

In case of *Str.pneumoniae* was a very high sensitivity to teicoplanin, linezolid, moxifloxacin and vancomycin, high for ceftriaxone, medium for erythromycin, regardless of HIV status ($p > 0.05$), and sensitivity to cotrimoxazole and rifampicin was reduced case of PIH compared with Px non-HIV ($p < 0.05$). *S.aureus* was very high sensitive to vancomycin, amikacin, clindamycin, linezolid, high for oxacillin and ciprofloxacin, medium for erythromycin, low for penicillin in both groups ($p > 0.05$), but lower for cotrimoxazole for PIH versus non HIV Px ($p < 0,05$). Sensitivity of *E.coli* was high meropenem, amikacin,

ceftriaxone, medium for gentamicin and low for amoxicillin-clavulanate in PIH and Px non HIV ($p > 0.05$). For ciprofloxacin there was a high sensitivity in Px non HIV and medium for PIH ($p < 0.05$).

Substudy III was comparative, retrospective, for the period 01/01/2005-31/12/2010 and prospective for the period 01/01/2011-31/12/2011, and included PIH in Craiova R.C., horizontally infected in early childhood, organized into three groups: group A1-31 PIH diagnosed with pulmonary tuberculosis during 01.01.2009-31.12.2010 with antiretroviral (ARV) at baseline, group A2-46 PIH without respiratory infections during 01.01.2005-31.12.2011, with ARV treatment group at baseline and group A3-21 PIH with bacterial pneumonia, bacteriologically documented and diagnosed during 01.01.2009-31.12.2010, with ARV treatment at baseline in the study.

I analyzed the risk factors for bacterial respiratory infections, clinical, biological and imagistic aspects of these infections and their relationship to immune status of PIH. The period 01.01.2009-31.12.2010, in which the bacterial respiratory were diagnosed was noted T3, the period 01.01.2007-31.12.2008 was noted T2 and 01.01.2005-31.12.2006 was noted T1, the time period of 6 months of diagnosis was noted T4 and the period of 12 months of diagnosis was noted T5. The results were as follows:

The value of body mass index at T1 and T2 were similar in the three groups ($p > 0.05$); at T3, T4 and T5, the body mass index was different ($p < 0.05$) between group A1 ($17.44 \pm 3.01 \text{ kg / m}^2$) versus group A2 ($22.11 \pm 4.18 \text{ kg / m}^2$) ($p > 0.05$) and similar in groups A2 and A3 ($21.17 \pm 3.12 \text{ kg / m}^2$).

CD4 cell count value at T1 was significantly lower ($p = 0.001$) in group A1 versus A2 (331.09 cells / CMM vs 658.09 cells / CMM), and there was no difference ($p = 0.126$) between group A2 versus A3 (658.09 cells / CMM versus 557.69 cells / CMM). The value of CD4 cell count at T2 was lower ($p < 0.001$) in group A1 versus A2 (173 cells / CMM vs. 634.22 cells / CMM) and between group A3 (437.88 cells / CMM) compared to group A2 (634.22 cells / CMM), $p = 0.039$. At T3, the CD4 lymphocytes in A1 (105.66 cells / CMM) and A3 (163.26 cells / CMM) was lower ($p < 0.0001$) than in group A2 (682.55 cells / CMM). At T1, the HIV viral load was higher in group A1 versus A2 (7893.23 copies / mL vs 2123.22 copies / mL), the difference being statistically significant ($p < 0.0001$); there was no difference ($p = 0.067$) between group A2 (2123.22 copies / mL) versus A3 (2413.34 copies / mL).

HIV viral load at T2 was higher in group A1 (24790.25 copies / mL) versus A2 (954.71 copies / mL), with statistically significant difference ($p < 0.0001$), but there was no difference ($p = 0.399$) between group A2 (954.71 copies / mL) versus A3 (1011.78 copies / mL). At T3, showed elevated HIV viral load ($p < 0.0001$) in group A1 (99520.97 copies / mL) and A3 (8563.11 copies / mL) compared to group A2 (78.43 copies / mL).

The adherence score of 95-100% to antiretroviral therapy recorded a linear aspect in group A2; in group A1, there has been downward trend in the 5 years before diagnosis of tuberculosis (T1-T3), then an upward trend in the first year after screening (T3-T5).

In 5 years before diagnosis of tuberculosis there were found AIDS- related clinical events in 12 PIH (38.71%) in group A1 versus 4 PIH (8.70%) in group A2, the difference being statistically significant ($p = 0.003$). In the group A3, there were found AIDS related clinical events in 2 PIH (9.53%), with no statistically significant difference ($p > 0.05$) comparative to group A2.

In patients with tuberculosis, fever occurred in 24 PIH (77.42%) at T3; in group A2 no PIH had fever during the monitoring period. In patients with bacterial pneumonia, 14 PIH (66.66%) had fever at the onset at T3.

In group A1, positive bacteriological examinations were found in 12 PIH (35.49%), visible acid-resistant bacilli (AFB) in 6 PIH (19.36%) and positive cultures for *M. tuberculosis* in 10 PIH (32.25%).

In group A3, the etiology of bacterial pneumonia was *Str.pneumoniae* (16 PIH-76.19%), *H. influenzae* (1 PIH-4.77%), *Klebsiella pn.* (1 PIH-4.77%), *S. aureus* (1 PIH-4.77%) and *Ps.aeruginosa* (2 PIH-9, 52%).

Radiological changes found were typical for pulmonary tuberculosis in 8 PIH (25.81%) and atypical in 15 PIH (48.38%). Normal radiologic appearance had 8 PIH (25.81%) with pulmonary tuberculosis. Radiological changes for bacterial pneumonia were atypical in 2 PIH (9.52%) and typical in 19 PIH (90.48%).

Two PIH deceased (6.45%) with tuberculosis. Unfavorable evolution of tuberculosis in PIH was noted for those with *M. tuberculosis* resistant to antibiotics ($p = 0.01$; RR = 3.56) and PIH non-adherent to treatment ($p = 0.03$; RR = 2, 79). Recurrent bacterial pneumonia was found in 3 PIH (14.29%). Multiresistant to antibiotic strains of *Str.pneumoniae* and *Ps.aeruginosa* presented 3 PIH (14.29%) with recurrent pneumonia.

Conclusions

1. Bacterial coinfection was present in about half of PIH (43.7%) and has a negative impact on their morbidity and mortality. During 2000-2011, in Craiova R.C., there was an upward trend of occurrence of new cases of tuberculosis in PIH, similar for non-tuberculosis bacterial infections.

2. Tuberculosis was a "primer" diagnosis in PIH, this being characterized by an ascending evolution over the last five years (2007-2011).

3. Compared to HIV-negative patients, bacterial infections were more common, with attenuated clinical manifestations and severe evolution in PIH. The most common location of tuberculosis was respiratory, in both PIH and Px non HIV. *M. tuberculosis* isolation rate was lower in PIH compared to Px non HIV. Etiologic spectrum of non tuberculosis bacterial infections was dominated by the triad *S.aureus*, *E.coli*, *Str.pneumoniae* in PIH versus *E.coli*, *Str.pneumoniae*, *Enterobacter* to Px non HIV.

4. Tuberculosis was accompanied by severe immunosuppression, higher in case of extrapulmonary forms, of relapses, the cases in which the diagnosis of HIV infection and tuberculosis coincided temporally and in high HIV viral replication. In case of non tuberculosis bacterial infections there was a moderate / severe immunosuppression and viral replication.

5. At PIH, the general context of developing bacterial respiratory infections was characterized by high degree of immunosuppression, high levels of viral replication of HIV, the presence of AIDS-related clinical events in terms of poor adherence to antiretroviral therapy. PIH with respiratory bacterial co-infections deviate from their classical presentation (clinical, biological and radiological).

6. HIV infection was associated with high risk of resistance of *M. tuberculosis* to hydrazide and rifampicin, *Str. pneumoniae* resistance to cotrimoxazole and rifampicin, *E. coli* resistance to ciprofloxacin and amoxicillin-clavulanate, *S.aureus* resistance to cotrimoxazole.

8. Severe evolution of tuberculosis was found in PIH non-adherent to antiretroviral treatment and *M.tuberculosis* resistance. Potential recurrent pneumococcal pneumonia was found in cases of multiresistant strains of *Str.pneumoniae*.

9. Only permanent interdisciplinary monitoring of patients with HIV infection may lead to the notification development context of occurrence of bacterial infections and allows active preventive interventions.

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