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Clinical characteristics and outcome of *Pneumocystis carinii* pneumonia in HIV-infected and otherwise immunosuppressed patients

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ABSTRACT: The factors contributing to unequal mortality rates following *Pneumocystis carinii* pneumonia (PCP) in different groups at risk are poorly understood. We therefore compared the first episodes of PCP without prophylaxis in human immunodeficiency virus infected (HIV) and otherwise immunosuppressed patients in this retrospective study.

A total of 58 HIV-infected and 16 otherwise immunosuppressed patients were analysed. The comparison included epidemiological, clinical, laboratory, radiological and microbiological data, as well as therapy and clinical course. A prognostic analysis was performed using a logistic regression model.

The mortality was significantly different in the two groups (HIV group 17 *versus* non-HIV group 50%). Renal transplant patients had a higher survival rate as compared to malignancy or collagen vascular disease as underlying diseases at risk. Acute respiratory failure was more common in the non-HIV group. Variables found to be significantly associated with lethal outcome in univariate analysis were alveolar to arterial pressures difference for oxygen ($P_{(A\text{-}a),O_2}$), haemoglobin, platelet count, total protein, serum albumin, and γ-globulins in the HIV-group, and serum albumin in the non-HIV group. In the multivariate analysis of the HIV group, platelet count and γ-globulins remained independent prognostic factors.

In conclusion, in the HIV-group, mortality is closely related to the severeness of PCP as well as to the severeness of the acquired immune deficiency syndrome (AIDS) disease. In the non-HIV group, malignancy and collagen vascular disease as underlying conditions at risk account for the high mortality rate. Its severeness was mainly reflected by serum albumin, which represented the only variable found to be significantly associated with death in both groups.

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During the last decade, *Pneumocystis carinii* pneumonia (PCP) has emerged as an important cause of morbidity and mortality in human immunodeficiency virus (HIV) infected patients [1] and in other conditions associated with immunosuppression [2–7]. The overall survival following PCP in acquired immune deficiency syndrome (AIDS) patients has generally improved, reaching more than 90% of cases [8–10]. On the other hand, no comparable progress could be achieved in the treatment of non-HIV-related episodes [11]. In view of the high mortality rate of up to 50% in non-HIV patients, reports of an increasing frequency of PCP in this group at risk are of considerable concern [7]. Furthermore, recent reports of a higher mortality of PCP in the growing number of patients with previously unknown HIV-serostatus [12] have renewed the interest in prognostic factors relevant for outcome.

We therefore compared the first episodes of PCP in HIV-infected patients and in patients with other conditions associated with immunosuppression. Special emphasis was placed on an analysis of prognostic factors that might contribute to different outcomes in both groups.

Materials and methods

Our institution represents a teaching hospital with two departments for Internal Medicine of about 200 beds in total. Since 1985, 325 haemophiliac patients of the Bonner Hemophiliac Treatment Center have been treated at our institution, who were HIV-infected as a result of exposure to contaminated coagulation factor concentrates [13, 14].

The clinical charts of patients with proven PCP diagnosed at our institution from 1985 until 1992 were reviewed. A diagnosis of PCP was based on demonstration of the organisms in Giemsa and Grocott stains as described previously [15]. All data of initial investigations refer to the 24 h before diagnosis of PCP. Data were extracted manually, recorded on study forms and entered into a computerized database. In detail, the analysis included the following parameters: 1) epidemiological data (age, sex, risk factor for acquisition of PCP, history of AIDS-defining opportunistic infections, and immunosuppressive treatment); 2) data from history (cough, dyspnoea, fever, duration of symptoms prior to diagnosis, and loss of weight in the last 3 months prior to diagnosis); 3) clinical examination (height, weight, body mass index); 4) laboratory data (haemoglobin,haematocrit, leucocyte count, relative and absolute neutrophils and lymphocytes, platelet count, glutamic oxalo-acetic transaminase (GOT), glutamic-pyruvic trans-aminase (GPT), γ-glutamyltransferase (γ-GT), alkaline phosphatase (AP), bilirubin, total protein, albumin, fractions of electrophoresis, lactate dehydrogenase (LDH), and creatinine; 5) immune status (CD3, CD4, CD8 (within 3 months prior to diagnosis); 6) capillary blood gases (oxygen tension (P_{O_2}), carbon dioxide tension (P_{CO_2}), calculated alveolar to arterial pressure difference for oxygen ($P_{(A\text{-}a),O_2}$)); 7) May-Grünwald differential cytological stains of bronchoalveolar lavage (BAL) specimens; and 8) microbiological (medium of diagnosis of PCP, co-infections).

The radiographs of the chest were reviewed by one of the research team (AP), who was otherwise blinded for clinical information. Fifty seven radiographs (46 survivors/11 deaths) were available for analysis. The distribution of the infiltrates was evaluated, dividing the chest by a vertical line and two horizontal lines originating above and below the hilus, respectively, resulting in six areas. Patterns of parenchymal infiltrates were graded as: absent (0); reticular or reticular-nodular (1); ground-glass (2); or airspace filling (3). A severity score was calculated by multiplying the type of the parenchymal infiltrate and the number of areas affected.

The protocol of the therapeutic regimens and dosages were recorded. The clinical course was judged with regard to improvement and cure or death. Death associated with PCP was assumed when it occurred during anti-pneumocystic treatment and no evidence of another secondary underlying diagnosis could be established. The assessment of adverse effects of antipneumocystic treatment included a search for all known reported toxicities and complications. Leucopenia was defined as a leucocyte count <2.0 cells$\times 10^9 \cdot L^{-1}$, thrombocytopenia as a platelet count <50 platelets$\times 10^9 \cdot L^{-1}$. Elevations of serum transaminases of at least twofold above normal were regarded as significant.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows. Time-to-event distributions were estimated using the method of KAPLAN and MEIER [16]. Univariate analysis was performed using the Chi-squared test for categorial variables and the Fisher's exact test in case of small expected frequencies. Continuous variables were tested for normal distribution by calculation of the skewness. If the variable did not exceed 1 the Student's two-tailed t-test was used. Otherwise, the nonparametric Mann-Whitney U-test was used. Descriptive statistics for continuous variables are expressed as the mean±the standard deviation. In all cases, two-sided p-values were used, considering values of less than 0.05 as significant.

The prognostic analysis was performed using a stepwise forward logistic regression model, with p-value of less than 0.05 as a limit for entering new terms. All variables were entered as categorial variables. Optimal cut-offs were determined by univariate logistic regression analysis. Variables reaching an alpha-error of less than 0.05 were included in the multivariate model.

Results

Study population

A total of 74 clinical records of first episodes of PCP without prophylaxis were entered into the analysis. Fifty eight cases represented manifestations of AIDS, and 16 cases had other conditions associated with immunosuppression (table 1).

Table 1. – Epidemiological features of patients studied

	PCP HIV (n=58)	PCP non-HIV (n=16)	p-value
Age yrs*	37±12 (15–67)	48±16 (16–75)	<0.005
Sex M/F	53/5	11/5	NS
Risk factors n			
Haemophiliac	34	-	
Homo/Bisexual	19	-	
i.v. drug abuser	3	-	
Other	2	-	
Cadaveric renal transplantation	-	5	
Malignancy+	-	5	
Collagen vascular disease++	-	4	
Other+++	-	2	
Immunosuppressive treatment n			
Steroids + cytotoxic therapy	-	14	
Steroids only	-	2	
Immune status			
CD4 mm^3	49±56	ND	

*: mean±SD, and range in parenthesis. +: small cell lung cancer, limited disease, during prophylactic radiation of the central nervous system; acute lymphatic leukaemia FABL2 in remission during induction therapy; chronic lymphatic leukaemia RAI IV; multiple myeloma stage IIIA Durie and Salmon; gastrointestinal non-Hodgkin's lymphoma. ++: lupus erythematosus with extensive systemic vasculitis; acute dermatomyositis; Wegener's granulomatosis; bullous pemphigoid. +++: immunoglobulin A (IgA)-nephritis; traumatic cerebral oedema. PCP: *Pneumocystis carinii* pneumonia; HIV: human immunodeficiency virus; M: male; F: female; NS: nonsignificant; ND: no data.

HIV infection had been diagnosed by enzyme-linked immunosorbent assay (ELISA), immunofluorescence and/or Western blot analysis prior to the diagnosis of PCP in 55 cases. Thus, three cases represented PCP as the first manifestation of AIDS with previously unknown HIV serostatus. Overall, PCP was the first AIDS-defining manifestation in 45 out of 58 cases, the second in 12 out of 58 and the third in 1 out of 58 cases. The underlying diseases of the non-HIV group are presented in table 1.

PCP was diagnosed by BAL in 57 out of 58 patients of the HIV group and in all cases of the non-HIV group. One case was diagnosed by induced sputum. An additional histological diagnosis by transbronchial lung biopsy was performed in five HIV-infected patients. Autopsy further confirmed the diagnosis in four cases of the non-HIV group.

The incidence of PCP during 1985–1988 and 1989–1992 was 24 and 34, respectively, in the HIV group, as opposed to 10 and 6, respectively, in the non-HIV group.

The mean age was significantly higher in patients without HIV infection (table 1).

Clinical symptoms and performance

The frequency of clinical symptoms, such as fever, shortness of breath and cough, did not differ between the groups. The mean duration of symptoms prior to diagnosis of PCP was about 9 days longer in HIV-infected patients, but this did not reach statistical significance (20.4±19.2 *vs* 11.4±8.2 days; p=NS).

The mean body mass index was significantly lower in the HIV group (20.7±3.1 *vs* 23.0±2.6 $kg \cdot m^{-2}$; p<0.04). The mean loss of weight within three months prior to diagnosis was not different in both groups (7.4±7.9 *vs* 5.8±6.0 kg; p=NS). The analysis of blood gases revealed nonsignificant differences in the severeness of hypoxaemia $P_{(A\text{-}a),O_2}$ (45±21 *vs* 58±16 mmHg); p=NS.

Laboratory values

The mean values of the following parameters were found to be significantly lower in the non-HIV group: haemoglobin (116±2 *vs* 101±16 $g \cdot L^{-1}$; HIV group and non-HIV group respectively p<0.03); platelet count (221±106 *vs* 147±109 platelets$\times 10^9 \cdot L^{-1}$; p<0.04); total protein (72±10 *vs* 58±9 $g \cdot L^{-1}$; p<0.0001); serum albumin (33±7 *vs* 29±4 $g \cdot L^{-1}$; p<0.01); and γ-globulins (17±7 *vs* 8±7 $g \cdot L^{-1}$; p<0.0001). The mean value for LDH was higher in the non-HIV group, but did not reach statistical significance (451±273 *vs* 630±691 $U \cdot L^{-1}$; p=NS).

The cytological patterns of BAL smears uniformly revealed an elevated mean percentage of lymphocytes (18±23 *vs* 28±16%) and neutrophils (13±19 *vs* 12±11%) without significant differences in both groups.

Co-pathogens

A bacterial pathogen could be cultured from BAL in 19 out of 40 (48%) HIV patients. Evidence for a bacterial pulmonary co-infection could only be established in two cases (*Streptococcus pneumoniae* (by significant growth in culture) and *Mycoplasma pneumoniae*). Three of 10 cultures of BAL and none of 11 transbronchial biopsies proved positive for cytomegalovirus. In addition, two patients had concomitant systemic infections as proven by blood cultures, one with *Pseudomonas aeruginosa* (due to sinusitis) and one with *Candida albicans* (as a central-line infection).

Accordingly, 4 out of 14 (29%) patients in the non-HIV group revealed a bacterial growth in cultures of BAL, but none was considered significant. However, two patients (with chronic lymphatic leukaemia and lupus erythematosus) had a concurrent systemic infection (*Pseudomomas aeruginosa* and *Acinetobacter calcoaceticus* plus *Klebsiella pneumoniae*, respectively, as proven by blood cultures). The latter patient was demonstrated to have a concomitant cytomegalovirus-pneumonia at postmortem.

Chest radiographs

The radiographic score for the type of the parenchymal infiltrate was not significantly different for survivors and nonsurvivors in the two groups (chi-squared p=0.12 in the HIV group and p=0.6 in the non-HIV group). Neither did the severity score for type of infiltrates and number of areas involved reveal significant differences between the two groups (7.9±9.6 *vs* 7.4 ± 7.1), as well as for survivors and nonsurvivors of both groups (7.0±7.7 *vs* 8.0±6.9 for the HIV group; 7.9±9.6 *vs* 7.4±7.1 for the non-HIV group).

Treatment and adverse effects

No significant differences could be detected between the two groups in drug treatment regimens and dosing schedules. However, the non-HIV group received mechanical ventilation significantly more frequently (p<0.01) (table 2). The pulmonary co-infections and concomitant systemic infections diagnosed *in vivo* could be successfully treated in both groups.

Adverse effects of therapy with co-trimoxazole were more common in HIV-infected patients, including cutaneous reactions (19 *vs* 0%), leucopenia (40 *vs* 17%) and elevations of GPT (37 *vs* 17%) and GOT (15 *vs* 13%), but no differences in frequencies of adverse reactions reached statistical significance. In both groups, one patient had severe pancreatitis during pentamidine mesylate.

In the HIV group, three patients received mechanical ventilation, one as a result of acute respiratory failure and cardiopulmonary resuscitation on the fourth day of therapy, two due to progressive respiratory failure after 14 and 18 days of therapy, respectively. In the non-HIV group, five patients received mechanical ventilation, three presenting with acute respiratory failure 3 and 4 days after the initial symptoms, and two being diagnosed during mechanical ventilation. The difference in the incidence of acute respiratory failure was significant (p<0.03).

Outcome

The outcome was significantly more favourable in the HIV group (mortality 17 *vs* 50%; log rank p<0,01)

Table 2. – Treatment of PCP in both groups

	HIV group (n=58)	Non-HIV group† (n=16)	p-value
First-line therapy			
Co-trimoxazole (100 mg·kg^{-1} sulphamethozole, 20 mg·kg^{-1} trimethoprim)	54	14	ns
Pentamidine mesylate (2mg·kg^{-1})	2	1	ns
Pentamidine isethionate (4 mg·kg^{-1})	2	-	
Change of therapy*			
Pentamidine mesylate (2 mg·kg^{-1})	1	-	ns
Pentamidine isethionate (4 mg·kg^{-1})	2	-	
Eflornithin (300 mg·kg^{-1})	1	-	ns
Other therapeutic modalities			
Adjunctive steroids** (1–2 mg·kg^{-1})	41	12	ns
Mechanical ventilation	3	5	<0.01

*: change because of treatment failure (2 patients) and severe adverse effects (2 patients) of co-trimoxazole; **: given for symptomatic therapy of severe dyspnoea since 1986, and regularly since 1990 in case of severe hypoxaemia (oxygen tension (P_{O_2}) <8 kPa (<60 mmHg) on room air with oxygen supplementation), also given for therapy of allergic rashes. †: One patient in the non-HIV group died the day after the diagnosis of PCP and was not treated. For abbreviations see legend to table 1.

(fig. 1). Time distribution of death was comparable in the two groups: 60% of nonsurvivors of the HIV group died during the first 10 days after diagnosis, as compared to 50% of the non-HIV group. In both groups, all patients on mechanical ventilation died.

Death was due to treatment failure in 7 out of 10 cases in the HIV group. Other reasons of lethal outcome included acute necrotizing pancreatitis during therapy with intravenous pentamidine-mesylate, uncontrolled oesophageal variceal bleeding with underlying chronic hepatitis C and liver cirrhosis, as well as suicide after 21 days of therapy. Co-infections were not relevant cofactors for mortality. The number of prior AIDS manifestations had no influence on mortality.

Six out of 8 deaths in the non-HIV group were due to treatment failures. One patient died because of a protracted septic shock after staphylococcal sepsis diagnosed prior to PCP, another (small cell lung cancer) died the day after the diagnosis. Documented co-infection may have contributed to death in one case with cytomegalovirus-pneumonia.

All five patients with cadaveric renal transplantation as risk factor survived, whereas 4 of the 5 with malignant neoplastic disease and 3 of the 4 with collagen vascular disease did not survive. This difference in survival was significant (p<0.01).

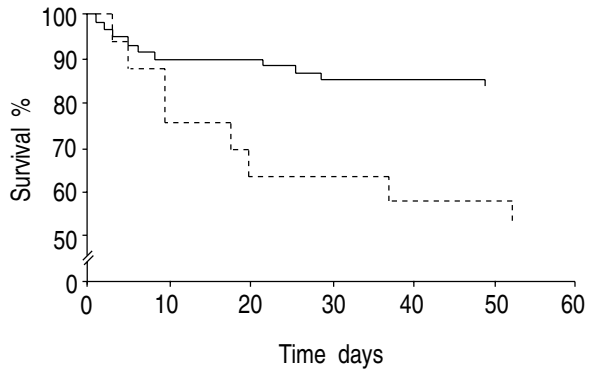

Fig. 1 – Survival Kaplan-Meier plot of human immunodeficiency virus (HIV) patients (———) and non-HIV patients (- - - - - -).

Mortality during the study period

Comparing the first and last 4 yrs of the study period, there was a significant decrease in mortality in the HIV group (33 *vs* 6%; p<0.02). The mean duration of symptoms did not change during these time periods (20.8±20.4 *vs* 20.1±18.9 days; p=NS). The fatality rate in the group treated without and with adjunctive steroids (20 *vs* 16%) was comparable. The only variable found to be significantly different for the two periods was the mean serum albumin (30±6 *vs* 35±6 g·L^{-1}; p<0.009). A corresponding trend of the mortality rate could not be observed in the non-HIV group (50% in both time periods).

Logistic regression analysis

Using a univariate logistic regression model for categorial variables, six parameters proved to be significantly associated with death in the HIV group: $P_{(A\text{-}a),O_2}$, haemoglobin, platelet count, total protein, serum albumin, and γ-globulins. Conversely, only serum albumin was found to be a significant parameter in the non-HIV group. Table 3

Table 3. – Results of the stepwise forward logistic regression analysis of prognostic factors

	Odds ratio	95% CI	p-value
HIV-group - Univariate			
$P_{(A\text{-}a),O_2}$ mmHg	15.9	1.6–161.9	<0.02
Haemoglobin g·L^{-1}	2.2	1.1–4.6	<0.03
Platelets ×10^9·mL^{-1}	4.5	1.4–14.9	<0.01
Total protein g·L^{-1}	5.4	1.6–18.7	<0.01
Serum albumin g·L^{-1}	6.3	1.2–31.9	<0.02
γ-globulins g·L^{-1}	3.2	1.2–8.8	<0.02
HIV-group - Multivariate			
Platelets ×10^9·mL^{-1}	9.9	2.2–44.9	<0.005
γ-globulins g·L^{-1}	7.0	1.8–26.8	<0.005
Non-HIV group - Univariate			
Serum albumin g·L^{-1}	4.2	1.1–15.9	<0.04
Chi-squared of the multivariate model = 0.0001.			
Categorial cut-offs:			
$P_{(A\text{-}a),O_2}$ mmHg	≤55=0,	>55=1	
Haemoglobin g·L^{-1}	≤100=1,	>100=0	
Platelets ×10^9·mL^{-1}	≤80=1,	>80=0	
Total protein g·L^{-1}	≤60=1,	>60=0	
Serum albumin g·L^{-1}	≤30=1,	>30=0	
γ-globulins g·L^{-1}	≤10=1,	>10=0	

95% CI: 95% confidence interval; $P_{(A\text{-}a),O_2}$: alveolar to arterial pressure difference for oxygen; HIV: human immunodeficiency virus.

summarizes these results, and also presents the odds ratios. In the multivariate approach, 43 sets of data including eight deaths were available. Only platelet count and γ-globulins remained independently associated with lethal outcome in the HIV group.

Discussion

Our data confirm the observation of previous studies reporting a different outcome of PCP in HIV-infected and otherwise immunosuppressed patients [11, 17]. Moreover, we observed a significant improvement of prognosis in the HIV group but not in the non-HIV group when comparing the first 4 yrs of the study (1985–1988) with the last 4 yrs (1989–1993).

The reasons for this reduction of mortality in the HIV group from 33% during the first period to 6% during the last 4 years are complex. As the duration of symptoms prior to diagnosis was not different in both periods, an earlier diagnosis is unlikely to represent the factor responsible. The use of steroid therapy was also not different in the two periods. However, we found a higher mean serum albumin in patients in the second period, pointing to a better general performance status at diagnosis of PCP. This may be the result of antiviral treatment. The improving prognosis of HIV-associated PCP increases the difference in comparison to the poor prognosis of PCP in otherwise immunosuppressed patients.

We found that the otherwise immunosuppressed patients were also an nonhomogeneous population with regard to outcome. All patients with cadaveric renal transplantation as risk factor survived, whereas patients with haematological malignancies, solid tumours and collagen vascular diseases generally had an unfavourable course. Corresponding mortality rates of up to 50% have also all been reported for non-solid organ transplant risk groups [11, 17].

In agreement with other comparative studies, we found a significantly higher mean age in the non-HIV group [7, 11, 17]. However, we could not confirm age as an independent risk factor for lethal outcome within each group.

Since the initial comparative study, it was thought that PCP in HIV patients has a more insidious onset [17]. Indeed, the duration of symptoms was about 9 days longer in the HIV group. This difference, though not reaching statistical significance, corresponds to previous reports. On the other hand, the duration of symptoms was not significantly associated with death in both groups in the regression analysis. It therefore appears unlikely that a generally more acute onset or a delay in diagnosis determines the different outcome. However, one patient in the HIV group and three in the non-HIV group had an acute respiratory failure shortly after onset of therapy. This course is clearly different from that of all other deaths, in taking a "relentless downhill course" without improvements in blood gas determinations [18]. We consider this subgroup as a generally distinct entity of PCP-associated respiratory failure. There is evidence from our study that this course may occur more frequently in the non-HIV group.

The alveolar-arterial pressure difference for oxygen ($P_{(A\text{-}a),O_2}$) was not different in the two groups, thus making a generally more severe initial presentation in one group most unlikely. In contrast, consistent with other reports [10, 19, 20], a significant association with death could be found for a higher $P_{(A\text{-}a),O_2}$ in the HIV-group, and a corresponding tendency not reaching significance in the non-HIV group according to the regression analysis. This fact qualifies the degree of severity of PCP at presentation as a risk factor for lethal outcome independently of the group at risk.

In contrast to another study [10], only $P_{(A\text{-}a),O_2}$ but not type and extent of radiographic infiltrates or neutrophil counts in bronchoalveolar lavage could be confirmed as a significant prognostic variable. On the other hand, consistent with previous reports, haemoglobin [19] and serum albumin [17, 19, 20] were found to be risk factors for death in the HIV group in univariate regression analysis. In addition, platelet count and total protein, as well as γ-globulins, were identified as further risk factors. These variables, although nonspecific in nature, may primarily reflect an advanced stage of the AIDS disease rather than acute and reversible parainfectious effects on bone marrow, protein metabolism and (humoral) immunity. In multivariate analysis, only platelet count and γ-globulins remained independent prognostic factors. Thus, according to our results, these seemingly nonspecific parameters add important prognostic information to those more closely associated with PCP. The heterogenecity of the non-HIV group may have impeded the identification of a comparable set of significant prognostic parameters. Thus, only serum albumin was found to be significantly associated with an unfavourable outcome. The mean levels of LDH, reported to be of prognostic value in HIV-infected patients [20, 21], did not reach statistical significance in our study. In view of the wide range of data, statistical significance may have been achieved in a larger series.

In conclusion, malignancy and collagen vascular disease as underlying diseases accounted for the higher mortality in the non-HIV group. Acute respiratory failure was found to occur more frequently in these patients. Mortality was closely related to the severeness of PCP as reflected by oxygenation, as well as to the severeness of the AIDS disease as reflected by markers of bone marrow depletion and humoral immunity in the HIV group. Serum albumin represented the only variable found to be significantly associated with death in both groups. Further studies might attempt to identify other parameters specifically reflecting the severeness of maligancy and collagen vascular disease as risk factors for death of PCP. Finally, efforts should be made to improve understanding of the mechanisms of acute respiratory failure in these patients.

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