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Prognostic factors influencing the outcome in *Pneumocystis carinii* pneumonia in patients with AIDS

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Abstract

Background **– Studies attempting to identify the prognostic factors that influence the outcome of *Pneumocystis carinii* pneumonia (PCP) in patients with AIDS using a multivariate analysis are few. In order to identify those prognostic factors amenable to medical intervention, univariate and multivariate analyses were performed on 102 patients with AIDS suffering a first episode of PCP.**

Methods **– One hundred and two consecutive patients with AIDS (51% drug abusers, 45% homosexuals, and 4% with other HIV risk factors) admitted to our institution between 1986 and 1989 whose respiratory infection was diagnosed by bronchoalveolar lavage were studied prospectively.**

Results **– The overall mortality was 28%, rising to 79% in those patients who required mechanical ventilation. According to univariate analysis the following variables were related to a poor prognosis: age >35 years; risk factor for HIV infection other than drug abuse; an AIDS diagnosis confirmed before 1988; Pa_{O_2} <8 kPa at admission; severe acute respiratory failure on admission (Pa_{O_2}/FI_{O_2} <20 kPa); mechanical ventilation; antibiotic therapy for PCP other than trimethoprim-sulphamethoxazole; multiple microbial pulmonary infection; serum lactate dehydrogenase (LDH) >22·5 μkat/l on admission; serum albumin level <30 g/l. Multivariate analysis showed that only mechanical ventilation was independently associated with a poor outcome.**

Conclusions **– The mortality of AIDS patients presenting with a first episode of PCP before 1990 was high (28%). The main prognostic factor associated with poor outcome was the requirement for mechanical ventilation due to severe acute respiratory failure.**

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Keywords: *Pneumocystis carinii* pneumonia (PCP); AIDS; prognosis.

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Pneumocystis carinii penumonia (PCP) is one of the most frequent causes of morbidity and mortality in patients with AIDS. This pulmonary complication occurs in approximately 80% of those who do not receive primary prophylaxis.[1 2] Mortality in AIDS patients with PCP ranges between 10% and 40%[3–6] despite adequate antibiotic treatment with trimethoprim-sulphamethoxazole or pentamidine. Mortality increases from 50% to 100% in patients who develop acute respiratory failure requiring mechanical ventilation.[7–11]

Several studies have evaluated different clinical and physiological variables as indicators of the outcome of PCP in patients with AIDS. In a univariate analysis of prognosis, the severity of radiological abnormalities and an alveolar to arterial oxygen gradient (A–a Po_2) of >4 kPa on admission predicted a poor outcome.[6] Other studies have identified other factors associated with mortality such as serum lactate dehydrogenase (LDH) and albumin levels,[3 4] the existence of leucocytosis and, more recently, the presence of bronchoalveolar lavage fluid neutrophilia.[12] Studies of the prognosis of AIDS patients with PCP have generally used univariate statistical methods and only two reports[3 13] have used a multivariate statistical method.

The aim of the present study was to assess the prognostic factors influencing the outcome of the first episode of PCP in patients with AIDS diagnosed before 1990 using both univariate and multivariate statistical methods, to identify better those subsets of population amenable to medical intervention.

Methods

PATIENTS

One hundred and two patients with HIV infection consecutively admitted to the Hospital Clinic of Barcelona with a first episode of PCP were studied. The study was conducted prospectively between January 1985 (when the first case of AIDS was diagnosed in our institution) and December 1989.

DIAGNOSTIC CRITERIA

The diagnosis of AIDS was confirmed according to the CDC definitions.[14] The diagnosis of PCP was based upon the presence of characteristic cysts in Gomori's methenamine silver stain or the presence of trophozoites in a Giemsa stain from samples of bronchoalveolar lavage fluid.

Table 1 Demographic and clinical characteristics of the 102 patients

	No. (%)
Demographics	
Mean (range) age (years)	34 (18–70)
Sex (M:F)	95:7
Risk factors	
Drug abuse	51 (51)
Homosexuality	45 (45)
Other	4 (4)
Years of diagnosis	
1985–7	40 (39)
1988–9	62 (61)
AIDS indicator event	
PCP	64 (63)
Other	31 (30)
Kaposi's sarcoma	7 (7)
Clinical data	
Symptoms	
Fever	99 (97)
Cough	96 (94)
Chest pain	18 (18)
Dyspnoea	44 (43)
Weight loss	54 (53)
Mean (range) duration of symptoms (days)	21 (2–90)
Lung examination	
Normal	36 (35)
Crackles/rales	66 (65)
Chest radiographs	
Normal	9 (9)
Localised infiltrates	28 (28)
Bilateral infiltrates	63 (62)
Cavitation/pneumothorax	1 (1)
Mechanical ventilation	
Yes	19 (19)
No	83 (81)

VARIABLES STUDIED AND DEFINITIONS

In all patients the following variables were recorded: sex, age, risk factors for HIV infection, event indicator of AIDS, time since AIDS diagnosis, and the presence of the following clinical symptoms and their duration before admission: cough, haemoptysis, chest pain, dyspnoea, weight loss, and fever. Other analysed variables included auscultation of rales, antibiotic treatment for PCP, radiological appearance on admission (normal; unilateral or bilateral infiltrates; cavitation; pneumothorax), arterial blood gas tensions on admission, the need for mechanical ventilation and the following blood tests on admission: haematocrit (%), level of haemoglobin (g/dl), leucocyte, lymphocyte and CD4+ counts (cells $\times 10^9$/l), serum albumin (g/l), cholesterol (mmol/l) and serum lactate dehydrogenase (LDH) (μkat/l). Acute respiratory failure was diagnosed if the Pa_{O_2} was <8 kPa breathing room air. The A–a P_{O_2} was calculated using the alveolar gas equation[16] assuming the respiratory quotient (R) to be 0·8. Severe acute respiratory failure was considered present if the patient had a Pa_{O_2}/F_{IO_2} <20 kPa.

In this study all HIV infected patients with clinical and radiological data suggesting PCP were treated presumptively. Bronchoscopy was usually performed during the first week in hospital. Antibiotic therapy included intravenous or oral trimethoprim-sulphamethoxazole (20-100 mg/kg/day respectively) or intravenous pentamidine (4 mg/kg/day) according to the decision of the attending physician. Corticosteroids were not routinely used before 1990 and were only given to some patients with severe acute respiratory failure who were admitted to the respiratory intensive care unit (RICU). Patients enrolled in the present study did not receive primary prophylaxis for PCP which was initiated in our institution from October 1989.[17]

For the purpose of this study only the mortality related to the PCP episode during the period in hospital (inhospital mortality) has been considered.

STATISTICAL ANALYSIS

In the univariate analysis the χ^2 test and Fisher exact test were used when appropriate. The odds ratio, the 95% confidence intervals and their level of significance were calculated as previously described.[18] A relative risk of death of 1 was arbitrarily assigned to the lowest risk category within each variable studied. The multivariate analysis was performed using a stepwise logistic regression analysis as described by Cox[19] and Lee.[20] The logistic equation obtained allowed the calculation of probability for survival or mortality. The unconditional logistic regression was also applied in order to adjust to confounding factors in the case-control study as described by Breslow and Day[21] and by Schlesselman.[18] A stepforward approach was used with 0·10 as a limit for entering or removing terms. All variables were entered in the logistic regression as categoric variables with two categories: −1 = absent or normal, 1 = present or abnormal.

Results

CHARACTERISTICS OF THE POPULATION STUDIED

Of the 102 patients studied there were 95 men; the mean age of the group was 34 years (range 18–70). Risk factors for HIV were drug abuse in 51 patients (51%), homosexuality in 45 (45%) and other in six (6%). *Pneumocystis carinii* pneumonia was the AIDS defining event in 64 cases, Kaposi's sarcoma in seven, and other opportunistic infections in the remaining 31.

Cough and fever were the most frequent symptoms (90% of patients). Dyspnoea and weight loss were present in almost 50% of cases (table 1). In 36 patients physical examination did not reveal abnormalities while crackles or rales were heard in the remaining patients.

Chest radiography on admission showed bilateral infiltrates in 63 cases, localised infiltrates in 28, and a normal radiograph in nine. Mean Pa_{O_2} breathing room air at admission was 8·9 kPa (range 5·5–16). Almost 40% of the patients had values of Pa_{O_2} lower than 8 kPa. Nineteen patients required mechanical ventilation. The haematological and biochemical

Table 2 Laboratory characteristics of patients on admission to ICU

	Mean (SD)	*Reference values*
Arterial P_{O_2} (kPa)		
Mean	8·9	
Range	5·5–16	
<8	40 (39%)	
Haemoglobin (g/l)	107 (24)	120–160
Leucocyte count (10^9/l)	5·657 (2·832)	4–10
Lymphocyte count (10^9/l)	0·659 (0·449)	1·5–3
CD4 lymphocyte count (10^9/l)	0·11 (0·09)	0·8–1·2
<0·2 × 10^9/l	80%	
Serum albumin (g/l)	31 (7·5)	35–50
Serum cholesterol (mmol/l)	3·54 (1·06)	<6·20
Serum LDH (μkat/l)	15·7 (10·9)	<7.5

LDH = lactate dehydrogenase.

Table 3 Prognostic factors of Pneumocystis carinii pneumonia in patients with AIDS: univariate analysis

Variable	*No. died/total (%)*	*Odds ratio (95% CI)*	*p value*
Sex			
Female	0/7 (0%)		
Male	29/95 (30%)	6·65 (0·37 to 1·17)	NS
Age			
<35 years	16/71 (22%)		
>35 years	13/31 (42%)	2·48 (0·91 to 6·77)	NS
Risk group			
Drug abuser	7/51 (14%)		
Non-drug abuser	22/51 (43%)	4·77 (1·65 to 14·21)	<0·001
AIDS diagnosis			
1988–9	12/62 (19%)		
1985–7	17/40 (43%)	3·08 (1·16 to 8·26)	<0·05
Symptoms before admission			
<28 days	18/73 (25%)		
>28 days	11/29 (38%)	1·87 (0·67 to 5·16)	NS
Pa_{O_2} on admission			
>8 kPa	11/62 (18%)		
<8 kPa	18/40 (45%)	3·79 (1·41 to 10·35)	<0·01
ARF			
Absent	22/95 (23%)		
Present	7/7 (100%)	49·00 (6·98 to 343)	<0·001
Mechanical ventilation			
Absent	14/83 (17%)		
Present	15/19 (79%)	18·50 (4·76 to 84·67)	<0·001
Therapy			
TMT/SMX	10/72 (14%)		
No TMT/SMX	19/30 (63%)	10·71 (3·56 to 33·30)	<0·001
AIDS indicator event			
Kaposi's sarcoma and other	8/38 (21%)		
PCP	21/64 (33%)	1·83 (0·66 to 5·22)	NS
Chest radiography			
Severe abnormal	15/63 (24%)		
Normal/mildly abnormal	12/37 (32%)	1·54 (0·57 to 4·15)	NS
Multiple microbial infections			
Absent	19/86 (22%)		
Present	10/16 (62%)	5·88 (1·68 to 21·29)	<0·005
LDH			
<22·5 μkat/l	15/75 (20%)		
>22·5 μkat/l	11/17 (65%)	7·33 (2·06 to 27·12)	<0·001
Albumin			
>30 g/l	7/54 (13%)		
<30 g/l	21/43 (49%)	6·41 (2·16 to 19·68)	<0·001
Leucocytes			
$<4·5 \times 10^9$/l	8/42 (19%)		
$>4·5 \times 10^9$/l	21/60 (35%)	2·29 (0·82 to 6·59)	NS
CD4 + lymphocytes			
$>0·1 \times 10^9$/l	4/23 (17%)		
$<0·1 \times 10^9$/l	7/26 (27%)	1·75 (0·37 to 8·70)	NS
Haemoglobin			
<100 g/l	8/38 (21%)		
>100 g/l	20/64 (31%)	1·70 (0·61 to 4·88)	NS
Cholesterol			
>3·1 mmol/l	14/62 (23%)		
<3·1 mmol/l	13/33 (39%)	2·23 (0·81 to 6·17)	NS

All blood analysis were performed on admission.
ARF = severe acute respiratory failure; TMT/SMX = trimethoprim-sulphamethoxazole; LDH = lactate dehydrogenase.

determinations are summarised in table 2. The mean serum LDH concentration was 15·7 (10·9) μkat/l and the mean serum albumin concentration was 31 (7·5) g/l.

MORTALITY AND PROGNOSTIC FACTORS

Twenty nine patients died, giving a mortality from PCP of 28%. This increased threefold to 79% (15/19) in patients requiring mechanical ventilation for severe respiratory failure. Prognostic factors associated with mortality, their odds ratios and statistical significance levels are summarised in table 3. The univariate analysis for prognosis showed the following 10 factors to be related to a poor outcome: age >35 years; risk factor for HIV infection other than drug abuse; diagnosis of AIDS made before 1987; Pa_{O_2} <8 kPa at admission; severe acute respiratory failure on admission; the need for mechanical ventilation; antibiotic treatment for PCP other than trimethoprim-sulphamethoxazole; multiple pulmonary microbial infection; serum LDH >22·5 μkat/l; and serum albumin <30 g/l. The following variables were not associated with a poor prognosis: indicator event of AIDS; duration of the symptoms before admission; chest radiographic characteristics; leucocyte count, CD4 lymphocyte count; and haemoglobin and cholesterol levels.

The multivariate analysis demonstrated that only one significant variable from the univariate analysis was independently associated with a worse prognosis – namely, mechanical ventilation requirement ($p<0·0002$). The serum level of LDH >22·5 μkat/l ($p=0·07$) and antibiotic treatment for PCP other than trimethoprim-sulphamethoxazole ($p=0·056$) almost reached statistical significance. Table 4 shows the results of this multivariate analysis.

Table 4 Prognostic factors of Pneumocystis carinii pneumonia in patients with AIDS: multivariate analysis

Variable	*High risk*	*Odds ratio (95% CI)*	*p value*
Mechanical ventilation	Present	68·96 (7·70 to 621·54)	<0·0002
PCP therapy	No TMT/SMX	4·08 (0·98 to 16·39)	NS
Serum LDH	>22·5 μkat/l	3·39 (0·80 to 14·28)	NS

The variables used for the multivariate analysis were age, HIV risk factor, year of AIDS diagnosis, Pa_{O_2} on admission, mechanical ventilation, type of PCP therapy, presence of a pulmonary polymicrobial infection, serum LDH level, and serum albumin level.
TMT/SMX = trimethoprim-sulphamethoxazole; LDH = lactate dehydrogenase.

Discussion

The main finding of the present study was that mechanical ventilation requirement was the only factor independently related to a poor outcome in a multivariate analysis in patients with AIDS presenting with a first episode of PCP before 1990.

The crude mortality of our patients was 28%, which is similar to other publications[1 4 6 13 22] for PCP in patients with AIDS, although in these studies the percentage mortality depended on whether it was the first or second episode of PCP.[6 23] In patients presenting with severe acute respiratory failure mortality was higher than the overall mortality and is consistent with previous reports.[7–11] However, the mortality ratio of PCP is falling over time to less than 5% for mild episodes and to about 20% for severe episodes.[26] In fact, the mortality ratio in our earlier patients (1985–7) was 43%, but in the most recent cases (1988–9) it was only 19%, probably due to improved experience and the introduction of corticosteroids.[26 27]

Four studies have investigated prognostic factors of PCP in patients with AIDS using univariate techniques. Overall these studies showed that clinical severity at admission (measured by APACHE II score), severe respiratory failure, serious radiographic abnormalities, extent of malnutrition and the level of serum LDH were the main factors related to poor prognosis.[3 4 6 7] In addition, the severity of interstitial pulmonary oedema seen on transbronchial biopsy and more than 5% neutrophils in bronchoalveolar fluid samples were also associated with a poor prognosis.[12]

Few studies for assessing the prognosis of PCP have used a statistical multivariate approach. The APACHE II score and the serum LDH level on admission were the only variables

related to prognosis in one study.[3] Another found that severe chest radiographic abnormalities and an A–a Po_2 of >4 kPa on admission were indicators of poor prognosis during treatment for acute episodes of PCP.[6] In our study the requirement for mechanical ventilation was the only variable independently related to a poor outcome.

Serum LDH levels are increased in PCP[4] and may be a good marker of interstitial pulmonary inflammation. We found that a high level of lung inflammation was related to a poor prognosis, and a progressive decrease of LDH during treatment indicated response to treatment.[4]

Patients treated with pentamidine or pentamidine plus trimethoprim-sulphamethoxazole had a higher rate of mortality. This reflects a possible selection bias as initial treatment in most cases was trimethoprim-sulphamethoxazole. Treatment was changed to pentamidine in patients not doing well or if allergic reactions occurred.

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