Management of "Pneumocystis carinii" pneumonia in HIV-infected patients: empiric treatment versus microscopic confirmation

CARLOS VIEGAS[1], ROB ROY MACGREGOR[2], RONALD G. COLLMAN[1]

To determine the need for microscopic confirmation as compared to empiric treatment based on a clinical diagnosis in HIV-infected patients with suspected *Pneumocystis carinii* pneumonia (PCP), we reviewed the data of 82 patients admitted to our institution with respiratory infections during 1994. These patients formed a PCP group (n = 37) of whom 17 had a confirmed diagnosis and 20 were treated empirically, and a non-PCP group (n = 45) with respiratory infectious other than PCP. The PCP group differed significantly from non-PCP patients in having longer duration of symptoms, more frequent dyspnea at presentation, predominant bilateral chest X ray lesions, lower CD4 cells number and less frequent anti-PCP prophylaxis use. When empirically treated and confirmed were compared, there were no significant differences for any variable, except for a higher serum LDH in the confirmed patients. Patients treated empirically did not differ from those with confirmed diagnosis in any measures of outcome. Thus, microscopic confirmation may not be essential for HIV-infected patients with typical features of PCP, and empiric treatment based on clinical diagnosis is a reasonable alternative in this group of patients. *(J Pneumol 1997;23(2):61-65)*

Controle da pneumonia por "Pneumocystis carinii" em pacientes HIV-positivos: tratamento empírico "versus" confirmação microscópica

Com o objetivo de determinar a necessidade de confirmação microscópica do diagnóstico de pneumonia por Pneumocystis carinii *(PPC), comparando grupos de pacientes tratados empiricamente com aqueles com confirmação diagnóstica, foram revisados os dados clínicos e laboratoriais de 82 pacientes internados em nossa instituição com infecção respiratória durante o ano de 1994. Estes pacientes formaram um grupo PPC (n = 37), dos quais 17 tiveram diagnóstico confirmado e 20 foram tratados empiricamente; e um grupo não-PPC (n = 45), com infecção respiratória que não PPC. O grupo PPC diferiu significativamente dos pacientes não-PPC por apresentarem maior duração dos sintomas, dispnéia mais freqüente, predomínio de lesões radiológicas bilaterais, menor contagem de células CD4 e menor uso de profilaxia anti-PPC. Quando comparamos os pacientes tratados empiricamente para PPC com os que tiveram confirmação diagnóstica de PPC, não observamos diferença estatisticamente significativa em qualquer das variáveis estudadas, exceto por um maior nível sérico de DHL nos pacientes com diagnóstico confirmado. Portanto, concluímos que confirmação microscópica pode não ser essencial em pacientes infectados pelo HIV com achados típicos de PPC e que tratamento empírico baseado no diagnóstico clínico pode ser uma alternativa razoável neste grupo de pacientes.*

Key words – PCP management. Empiric treatment.
Descritores – Controle de PPC. Tratamento empírico.

1. Pulmonary & Critical Care Division, Department of Medicine, University of Pennsylvania.
2. Infectious Disease Division, Department of Medicine, University of Pennsylvania.
Corresponding author – Carlos Viegas, SQS 310, Bloco D, Apto. 303 – 70363-040 – Brasília, DF.

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INTRODUCTION

Pneumocystis carinii pneumonia (PCP) continues to be the most common serious opportunistic infection in HIV-infected patients despite the extensive use of prophylactic measures[1-5]. The ideal management of an HIV-infected patient suspected of having PCP is still controversial. Several authors argue that empirical therapy is inapropriate because pathogens other than *Pneumocystis carinii* are often responsible for pulmonary complications and anti-Pneumocystis therapy may be prolonged and potentially toxic[6-8]. On the other hand, others[6,9,10] have questioned the necessity of ob-

taining microscopical confirmation of the diagnosis when the criteria suggested by the Centers for Disease Control (CDC) have been met, which include a history of dyspnea on exertion or non-productive cough of recent onset, radiographic evidence of diffuse bilateral interstitial lung disease, arterial hypoxemia, and lack of evidence for bacterial pneumonia[11]. To address the role of clinical diagnosis and empiric treatment in our patient population, we compared clinical, laboratory and radiographic data from HIV-infected patients with confirmed PCP, presumed PCP treatment empirically, and lung infectious other than PCP, during a recent 1-year period at our institution.

Methods

We retrospectively reviewed medical records including clinical history, laboratory data and radiographic reports of all HIV-infected patients suspected of pneumonia and admitted to the hospital during 1994. Patients were divided in groups according to the characterization of their lung infection as confirmed PCP, presumptive PCP treated empirically and non-*Pneumocystis carinii* infection. The presumptive diagnosis of PCP was determined independently by the individual physician during caring for each patient based on clinical setting, symptoms and chest radiographic appearances, while a confirmed diagnosis was based on the finding of organisms in sputum or material obtained by fiberoptic bronchoscopy. Chest X rays were classified as "normal", or showing "unilateral" or "bilateral" infiltrates. CD4 lymphocyte counts were recorded at the time of admission when available, and otherwise were considered for analysis only if they had been done within three months before the episodes. Microbiological cultures when performed were obtained by sputum or broncho-alveolar lavage. Data are expressed as mean ± SD; statistical analysis was performed using the Student's test and Chi square test; $p < 0.05$ was considered significant.

Results

In 1994 there were 82 HIV-infected patients admitted to the hospital for treatment of lung infections (table 1 & 2). Thirty seven of them (45%) were given a diagnosis of PCP either by microscopic confirmation (n = 17) or on a clinical basis (n = 20), and the other 45 (55%) were determined to have infections other than PCP (table 3). There were no significant differences between the PCP and non-PCP groups in age, gender, or ethnicity (table 1). A trend towards a greater proportion of individuals in the non-PCP group who acquired infection through injecting drug use was noted, but this did not reach statistical significance ($p = 0.07$). Table 1 shows the symptoms reported by patients at presentation. The PCP group had symptoms for a significantly longer duration prior to presentation, with a mean of 17.1 ± 10.9 days as compared to 5.6 ± 5.7 days in the non-PCP group ($p < 0.05$). In addition, dyspnea was noted less frequently among patients without PCP (49 vs 92%; $p < 0.05$). Of note, while there was a trend towards fewer patients with sputum production and chest pain in the PCP group, these differences were not statistically significant ($p = 0.23$ and $p = 0.11$, respectively). The PCP group had a higher proportion of patients with bilateral infiltrates on chest X ray (89 vs 22%; $p < 0.05$) and was less likely to be receiving anti-Pneumocystis prophylaxis at the time of presentation (32 vs 60%; $p < 0.05$). Laboratory data for the two groups are shown in table 2. As expected, there was evidence for more advanced immune deficiency among patients with PCP, as indicated by lower mean CD4 counts (31 ± 23 vs 122 ± 181 cells/mm^3) and CD4 percentages (3.8 ± 2.5 vs 12.6 ± 10.4%; $p < 0.05$). In contrast, there were no significant differences between the PCP and non-PCP groups in hematocrit, white blood cells count, neutrophils, lymphocytes, serum lactate dehydrogenase (LDH) or PaO_2 breathing room air.

TABLE 1
Demographics, clinical characteristics, and chest radiographs of 82 HIV-infected patients with respiratory infection

Variable	Non-PCP (n = 45) Nº pts. (%)	PCP (n = 37) Nº pts. (%)	Confirmed** (n = 17) Nº pts. (%)	Probable** (n = 20) Nº pts. (%)
Age (y)	35.8 ± 6.6	36.5 ± 6.8	35.6 ± 5.4	37.3 ± 7.9
Sex				
Male	30 (67%)	30 (81%)	13 (76%)	17 (85%)
Female	15 (33%)	7 (19%)	4 (24%)	3 (15%)
Ethnic				
Black	32 (71%)	26 (70%)	12 (71%)	14 (70%)
White	11 (24%)	10 (27%)	5 (29%)	5 (25%)
Hispanic	2 (4%)	1 (3%)	0 (0%)	1 (5%)
Risk factors				
Homosexual	11 (24%)	14 (38%)	7 (41%)	7 (35%)
Heterosexual	8 (18%)	11 (30%)	4 (24%)	7 (35%)
Drug users	15 (41%)	6 (16%)	4 (24%)	2 (10%)
Transfusion	3 (7%)	1 (3%)	0 (0%)	1 (5%)
Undetermined	8 (18%)	5 (14%)	2 (12%)	3 (15%)
Symptoms				
Duration (days)	5.6 ± 5.7	17.1 ± 10.9*	19.5 ± 10.2*	16.0 ± 11.3*
Cough	42 (93%)	35 (95%)	16 (94%)	19 (95%)
Dyspnea	22 (49%)	34 (92%)*	16 (94%)*	18 (90%)*
Fever	38 (84%)*	26 (70%)	14 (82%)	12 (60%)
Sputum	24 (53%)	14 (16%)	9 (53%)	5 (25%)
Chest pain	14 (31%)	6 (16%)	4 (24%)	2 (10%)
Hemoptysis	1 (2%)	1 (3%)	0 (0%)	1 (5%)
Chest X ray				
Normal	0 (0%)	2 (5%)	0 (0%)	2 (10%)
Unilateral	35 (76%)	2 (5%)*	2 (12%)*	0 (0%)*
Bilateral	10 (22%)	33 (89%)*	15 (88%)*	18 (90%)*
Prophylaxis	27 (60%)	12 (32%)*	3 (18%)*	9 (45%)

* $p < 0.05$ by Chi square test, as compared with non-PCP patients.
** There were no statistically significant differences between probable and confirmed PCP groups in any variable.

TABLE 2
Laboratory findings among 82 HIV-infected patients with respiratory infection

Variable	Non-PCP (n = 45) Mean ± SD	PCP (n = 37) Mean ± SD	Confirmed (n = 17) Mean ± SD	Probable (n = 20) Mean ± SD
Hematocrit (%)	31.2 ± 7.4	31.5 ± 6.8	33.2 ± 6.9	30.1 ± 6.5
WBC (cells. 10 /L)	7.7 ± 6.3	5.9 ± 2.8	5.7 ± 2.9	6.0 ± 2.7
Neutrophils (cells/mm^3)	5788 ± 6332	4467 ± 2367	4525 ± 2437	4421 ± 2377
Lymphocytes (cells/mm^3)	925 ± 629	865 ± 552	867 ± 648	863 ± 481
CD4 (cells/mm^3)	122 ± 181	31 ± 23*	30 ± 21*	32 ± 25*
CD4%	12.6 ± 10.4	3.8 ± 2.5*	4.7 ± 3.0*	2.8 ± 1.3*
CD8 (cells/mm^3)	679 ± 184	554 ± 190	480 ± 231	603 ± 161
PaO_2 room air (mmHg)	68 ± 13	64 ± 10	63 ± 10	66 ± 9
Albumin (g/dL)	2.7 ± 0.8	3.0 ± 0.8	3.1 ± 0.7	2.8 ± 1.1
LDH (U/L)	401 ± 217	521 ± 335	696 ± 410*	375 ± 159**

WBC – white blood cells; LDH – lactate dehydrogenase.
* $p < 0.05$ by Student's test, as compared with non-PCP patients.
** $p < 0.05$ by Student's test, between confirmed and empirically treated as PCP.

To determine whether patients treated empirically for presumed PCP ("probable PCP") differed from those with a microscopic diagnosis ("confirmed PCP"), we then compared the clinical and laboratory data for these two groups (tables 1 & 2). There were no significant differences between them in demographics, symptoms, or chest X ray appearance. A slightly lower proportion of individuals with probable than confirmed disease reported sputum production, and a somewhat higher proportion had received prophylactic anti-Pneumocystis therapy, but these differences were no significant. Importantly, for all clinical characteristics in which patients with confirmed PCP differed from non-PCP patients, the probable group also differed, except for use of prophylactic therapy. Similarly, laboratory values in the probable and confirmed groups were highly concordant, including both measures of underlying immunosuppression (CD4 count and percentage) and respiratory compromise (PaO_2). The one exception to this finding was a lower serum LDH level in individuals with probable PCP as compared to those with confirmed disease (375 ± 159 vs 696 ± 410 U/L; $p < 0.05$).

Finally, to determine whether a presumptive diagnosis followed by empiric treatment for PCP resulted in poorer outcomes than for those in whom the diagnosis was confirmed, we compared the results for individuals in these group (table 4). One patient out of 17 in the confirmed group died, for a mortality rate of 6% and there were no deaths in the probable PCP group. In contrast, there were five deaths among 45 patients in the non-PCP group, for a mortality rate of 11%. No differences were found in the duration of hospitalization among any of the groups.

TABLE 3
Respiratory infections other than PCP in HIV-infected patients

Diagnosis	Nº pts.	% of total
Bacterial pneumonia		
Pathogen identified*	11	24.4
Presumptive	22	48.9
M. tuberculosis	5	11.1
M. avium complex	1	2.2
M. kansasii	1	2.2
Toxoplasma gandii	1	2.2
Viral infection		
Herpes simples	1	2.2
Varicella-zoster	1	2.2
Fugal infection		
Aspergillus sp	1	2.2
Cryptococcus neoformans	1	2.2
Total	45	

Nº pts. – number of patients; * – 3 cases of *Streptococcus pneumoniae*, 3 *Hemophilus influenzae*, 2 *Streptococcus pyogens*, 1 *Staphylococcus aureus*, 1 *Pseudomonas aeruginosa*, and 1 *Klebsiella sp.*

TABLE 4
Outcome in patients with AIDS and respiratory infection

	Number of patients	Mortality Nº pts. (%)	Hospital stay (days) Mean (range)
PCP			
Confirmed	17	1 (6%)	8.2 (5-17)
Probable	20	0 (0%)	8.0 (3-19)
Non-PCP	45	5 (11%)	9.4 (2-30)
Total	82	6 (7%)	8.5 (2-30)

Discussion

The role of empiric treatment in the management of pulmonary infection in HIV-positive patients remains controver-

sial. In 1987 the Centers for Disease Control (CDC) suggested guidelines for presumptive diagnosis of PCP that included a history of dyspnea on exertion or non productive cough within the past three months; diffuse bilateral interstitial infiltrates on chest X ray; arterial PaO_2 of < 70 mmHg or elevated alveolar-arterial oxygen tension gradient or low diffusing capacity; and no evidence of a bacterial pneumonia[11]. Although useful for suiveillance purposes, however, the CDC emphasized that these criteria should not substitute for specific microbiological diagnosis. Nevertheless, two thirds of the responders in a recent survey of respiratory physicians said that for an HIV-positive patient with a compatible clinical history and chest radiographic, they would treat empirically for PCP as opposed to immediate bronchoscopy[9]. Such empiric treatment of patients with typical clinical and radiological features of PCP was predicted by one analysis to result in correct management in over 95% of cases, and reduce by more than 63% the number of bronchoscopies carried out on HIV-positive patients[12]. Another decision analysis model that compared early bronchoscopy versus empirical PCP treatment followed by delayed bronchoscopy at five days in non-responders suggested that early bronchoscopy offered no survival benefits, and that empirical treatment appeared to be the superior management strategy[10]. In contrast, a different group reported that of 77 patients who met CDC's criteria for the "presumptive diagnosis" of PCP, only 57% (44 patients) had PCP documented by bronchoalveolar lavage and/or transbronchial biopsy. Those authors concluded that empiric treatment would have subjected 43% of patients to prolonged, inappropriate or toxic therapy, and that except for very unusual circumstances, presumptive diagnosis and empiric treatment should be avoided[6]. They stressed that the empiric approach might be detrimental if it either missed a proper diagnosis, failed to provide adequate therapy, or subjected individuals to unecessarily toxic therapy. Our data, however, suggest that the group treated presumptively did not have a worse outcome despite similar severity of hypoxemia at presentation, and argue that empiric therapy in a selected group may be appropriate. In fact, in our analysis this was a very substantial group which represented more than half of our total PCP cases.

In our study, several clinical, radiographic and laboratory features were significantly different between HIV-infected patients with PCP and those with other etiologies of lung infection. The duration of symptoms prior to presentation was longer for those with PCP, consistent with previous reports[13-15]. Among the major presenting symptoms, the only significant difference was the more frequent occurrence of dyspnea in the PCP group. Interestingly, sputum production was not significantly less frequent in patients with PCP, being reported in 53% of the confirmed group and 38% of the PCP group overall, as compared to 53% of the non-PCP group. Similar results have been reported previously[16], although this observation has not received much attention. Bilateral disease on chest X ray was strongly associated with PCP while unilateral disease correlated with infections other than PCP. As expected, laboratory features showed that PCP was strongly associated with more advanced immune deficiency, based on CD4 counts and percentages[17], whereas the increased susceptibility to bacterial pneumonias begins at a higher CD4 cell count.

When the features of individuals in whom a clinical diagnosis of PCP was made were compared with those who had a confirmed diagnosis, we found that they were very similar. Furthermore, for nearly all those characteristics in which the confirmed PCP group differed from non-PCP patients, the presumed PCP group differed as well. This concordance is not unexpected, since it is likely that the presence of "typical" PCP features contributed to the clinicians presumptive diagnosis of *Pneumocystis carinii* infection. Nevertheless, the similarity of these groups, combined with outcome data, underscores the fact that clinical assessment can accurately identify a group highly likely to respond to empiric anti-PCP therapy.

The only feature that differed between the probable and definite PCP groups was a significantly lower serum LDH in patients treated empirically. Elevated serum LDH is reported to occur more frequently in PCP than in pulmonary tuberculosis and bacterial pneumonia[18], although there is significantly overlap and even normal values may be seen in PCP[19,20]. The lower mean LDH values in our presumed versus confirmed PCP patients raises the possibility that the presumed group included individuals with less severe disease. Consistent with this, two patients in this group had a normal chest X ray, which is well-described in PCP in AIDS[21]. In addition, a slightly higher (but not statistically different) proportion of presumed than confirmed cases were reported to have been receiving prophylactic anti-PCP treatment, which can also result in less severe disease[22]. On the other hand, the similar PaO_2 levels in the two groups suggests similar levels of respiratory compromise. Alternatively, the lower LDH levels may indicate that there might have been some individuals included who did not in fact have PCP. Nevertheless, the good overall outcome among these patients indicates that if so, it did not fail to treat other clinically important infections, and that LDH levels fail to distinguish those who will respond to anti-PCP treatment from those who will not. Thus, while the knowledge of a confirmed diagnosis is often reassuring to physicians caring for individual patients, we believe that the critical question is whether empiric treatment based on a presumptive clinical diagnosis results in a poorer outcome due to the failure to treat other process actually present, or to potentially toxic effects of inappropriate therapy[6]. Our results suggest that this is not the case since none of the patients in the empiric group died and their hospital stay did not differ from those with a confirmed diagnosis.

In conclusion, our data show that HIV-infected individuals in whom a clinical diagnosis of PCP is made are similar to those who had microscopic confirmation, and that empiric treatment for PCP in this group results in similar outcomes. Thus, an approach involving empiric treatment based on a clinical diagnosis is a reasonable alternative in the group of patients with HIV infection and typical features of *Pneumocystis carinii* infection. These results support the argument that an empiric treatment approach can reduce the need for extensive screening or invasive diagnosis without having a negative impact on outcome[23], and that invasive procedures for definitive diagnosis may be reserved for those with atypical features who fail to respond to empiric therapy[24].

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