Prognostic Indicators in the Initial Presentation of *Pneumocystis carinii* Pneumonia*

Stuart M. Garay, M.D., F.C.C.P.; and Jeffrey Greene, M.D.

We prospectively evaluated 150 consecutive patients with *Pneumocystis carinii* pneumonia (PCP) as their sole initial manifestation of AIDS (group 1). Admission laboratory and radiographic criteria were analyzed for diagnostic and prognostic indicators and compared with those of patients presenting with non-PCP pulmonary manifestations of AIDS (group 2). Mean admission serum LDH level was 465 ± 67 IU/L in PCP patients (group 1) and 211 ± 25 IU/L in group 2 (p<0.01). Seventy-eight percent of PCP patients (117 of 150) survived. Comparing survivors with nonsurvivors, the mean admission LDH level was 394 ± 45 vs 717 ± 51 IU/L (p<0.01), and the mean P(A-a)O₂ gradient was 42 ± 6 vs 55 ± 6 mm Hg (p<0.05). Serum LDH levels and P(A-a)O₂ gradients have diagnostic and prognostic implications in patients with AIDS-related PCP.

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*Pneumocystis carinii* pneumonia (PCP) is the most frequently diagnosed pulmonary opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS).² Between 50 and 80 percent of patients with *P. carinii* survive their initial episode.³,⁴ Early clinical experience at New York University Medical Center suggested that certain routine laboratory data were highly indicative of the diagnosis of Pneumocystis pneumonia and had prognostic implications.⁵ The elevation of serum lactic dehydrogenase levels usually accompanied the diagnosis of PCP and distinguished it from other pulmonary opportunistic processes in AIDS patients. Further, the degree of its elevation as well as the increase in admission, room air P(A-a)O₂ gradient appeared to have prognostic implications. The present study analyzes the diagnostic and prognostic implications of serum LDH elevation in patients with AIDS or patients thought to have AIDS who presented with *P. carinii* pneumonia.

**Material and Methods**

**Patient Population**

We evaluated 185 consecutive patients with *P. carinii* pneumonia during their initial presentation with AIDS. Thirty-five were eliminated because: (1) 25 patients had concurrent pulmonary infections (cytomegalovirus, Legionella, Cryptococcus, and *Mycobacterium tuberculosis* or *M avium-intracellulare*); and (2) ten patients had diffuse liver function abnormalities (elevations in serum SGOT, SCPT, LDH, and alkaline phosphatase levels). Thus, 150 patients presenting with Pneumocystis as their initial manifestation of AIDS composed group 1. Sixty-seven newly diagnosed AIDS patients with pulmonary processes other than *P. carinii* pneumonia (and no previous history of pneumonia) composed group 2. These patients had pulmonary disease due to: Kaposi's sarcoma (30 patients), cryptococcal pneumonia (five), tuberculous infections (11), bacterial pneumonia (four, all with *S pneumoniae*), coccidiodomycosis (one), cytomegalovirus (five), nonspecific interstitial inflammation (12), lymphocytic interstitial pneumonia (two), and pulmonary lymphoma (one). A third group of 15 AIDS patients with no pulmonary manifestation composed group 3.

The patient population in group 1 (PCP patients) consisted of 140 men and ten women. There were 125 homosexual men, 17 IV drug abusers, five patients with transfusion-related disease, and three women who were sexual partners of known AIDS patients. The mean age was 33 ± 5 years. Group 2 consisted of 62 homosexual men and five women, who were IV drug abusers. The mean age was 35 ± 3 years. Group 3 consisted of 15 homosexual men whose mean age was 31 ± 4 years.

**Diagnostic Approach**

The diagnosis of *P. carinii* pneumonia was based on the demonstration of organisms in alveolar lavage fluid or by transbronchial biopsy specimens obtained by fiberoptic bronchoscopy. Lung biopsy specimens were fixed and stained by hematoxylin and eosin, methenamine silver, Giemsa, and Ziehl-Neelsen stains. Lavage fluid was stained with methenamine silver, PAS, Ziehl-Neelsen, and mucicarmine stains. The diagnosis of pulmonary Kaposi's sarcoma was confirmed by open lung biopsy (nine patients), bronchoscopy (11 patients) and autopsy (ten patients). Open lung biopsy results confirmed the diagnoses of lymphocytic interstitial pneumonia as well as pulmonary lymphoma. All 12 patients with nonspecific interstitial pneumonitis underwent lavage and transbronchial biopsy, which proved negative for organisms. None had follow-up open lung biopsy, and all were discharged from the hospital.

All patients in groups 1 and 2 were evaluated similarly. The duration of the three most common symptoms (fever, cough, and dyspnea), as well as the presence of physical findings (temperature, respiratory rate, and inspiratory crackles) were noted. Admission leukocyte and lymphocyte counts, room air arterial blood gas values (with calculation of the P(A-a)O₂ gradient), serum chemistry values including LDH, and chest roentgenograms were obtained (Table 1). The pulmonary diagnoses were confirmed by techniques described above. Patients in group 3 did not undergo bronchoscopy or open lung biopsy.

Choice of therapy was determined by the individual physicians caring for the patient. Seventy-eight percent (117 patients) of those

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Table 1—Admission Assessment*

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<thead>
<tr>
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<th>PCP</th>
<th>Non-PCP</th>
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<tbody>
<tr>
<td>Temperature (°C)</td>
<td>39 ± 1</td>
<td>39 ± 1</td>
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<tr>
<td>Respiratory rate (breaths/min)</td>
<td>23 ± 5</td>
<td>22 ± 4</td>
</tr>
<tr>
<td>Inspiratory crackles</td>
<td>25/150</td>
<td>30/41</td>
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<tr>
<td>Arterial P_{O_2} (mm Hg)</td>
<td>73 ± 7</td>
<td>78 ± 5</td>
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<tr>
<td>(A-a) O_2 gradient (mm Hg)</td>
<td>44 ± 8</td>
<td>36 ± 6</td>
</tr>
<tr>
<td>Leukocyte (/mm³)</td>
<td>5500 ± 1230</td>
<td>4750 ± 960</td>
</tr>
<tr>
<td>Lymphocyte (/mm³)</td>
<td>591 ± 10</td>
<td>501 ± 365</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>465 ± 67</td>
<td>211 ± 28</td>
</tr>
<tr>
<td>Diffuse interstitial infiltrates</td>
<td>60/150</td>
<td>26/41</td>
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*All data represent mean values except the categories "inspiratory crackles" and "diffuse interstitial infiltrates" which represent number/total.

with PCP survived their initial episode. Among survivors 40 of the 117 patients successfully completed a three-week course of trimethoprim-sulfamethoxazole (TMP-SXT). The remaining successfully treated 77 patients initially received TMP-SXT but were switched to pentamidine therapy because of toxic reactions (30 patients) or failure to improve within five days of initiation of TMP-SXT therapy (47 patients). Among the 33 nonsurvivors, 27 initially received TMP-SXT but were switched to pentamidine because of clinical deterioration, while seven patients received only pentamidine. Serial serum LDH and P(A-a)O_2 gradients were obtained in 50 patients who survived their initial episode. Samples were obtained on days 1, 10, and 17 of therapy.

All data are presented as their mean ± SD. To evaluate whether two independent groups of values were statistically equivalent, the Student’s t test was used, and one-sided p values were obtained. The sensitivity and specificity were calculated utilizing the following formulas:

\[
\text{Sensitivity} = \frac{\text{true positive results}}{\text{total patients with disease}}
\]

and

\[
\text{Specificity} = \frac{\text{true negative results}}{\text{total patients without disease}}
\]

RESULTS

Fever, cough, and dyspnea occurred in 97 percent, 86 percent, and 76 percent of group 1 patients vs 90 percent, 90 percent, and 72 percent of group 2 patients (p = NS). Table 1 lists the admission physical and laboratory findings of both groups. The only significant differences were the presence of inspiratory crackles (greater in pulmonary processes other than Pneumocystis), the presence of diffuse interstitial infiltrates (greater in non-PCP patients), the increased P(A-a)O_2 gradient, as well as the elevation in serum LDH (greater in PCP patients). The mean serum LDH (normal ≤220 IU/L) was 465 ± 67 IU/L in group 1 patients with PCP vs 211 ± 28 IU/L in group 2 patients with non-PCP pulmonary processes (p<0.01) (Fig 1).

Only eight of 150 PCP (group 1) patients (5 percent) had normal LDH levels (four had normal chest roentgenograms), while 12 (8 percent) had mildly elevated levels, ranging from 220 to 300 IU/L. In the 67 non-PCP pulmonary AIDS patients (group 2), 55 patients had LDH levels in the normal range (less than 220 IU/L); eight patients had mildly elevated LDH levels ranging from 220 to 300 IU/L (all had biopsies revealing nonspecific interstitial inflammation); four patients (7 percent) had LDH>300 IU/L (two patients with lymphocytic interstitial pneumonia, one patient with pulmonary lymphoma, and one patient with Legionella). Two of 15 nonpulmonary AIDS patients (group 3) had LDH>300 IU/L; both had extrapulmonary lymphoma.

Isoenzyme studies were performed in 50 patients whose mean LDH = 436 ± 29 IU/L. The distribution among the patients was: increased LDH −3/4 = 19; increased LDH −1 = 1; increased LDH −2 = 13; increased LDH −5 = 4; and “normal” or isomorphic isoenzyme distribution = 13.

Seventy-eight percent (117 of 150) of PCP patients in group 1 survived their initial episode of pneumonia. When survivors were compared with nonsurvivors, the mean LDH level was 394 ± 45 vs 717 ± 51 IU/L (p<0.01), the mean P(A-a)O_2 gradient was 42 ± 6 vs 55 ± 6 mm Hg (p<0.05) and the mean respiratory rate was 18 ± 3 vs 27 ± 4 breaths/min (p<0.05) (Fig 2). There was no significant difference between survivors and nonsurvivors with respect to duration of symptoms, presence of physical findings (other than respiratory rate), and admission leukocyte or lymphocyte counts. Radiographic presentation had limited prog-

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21592/)

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21592/)

Prognostic Indicators in PCP (Garay, Greene)

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nantic value; all patients with normal findings (ten, among whom six had elevated serum LDH; mean = 345 ± 10 IU/L) survived.

Serial LDH levels and calculated P(A-a)O₂ gradients were obtained in 50 survivors (mean initial LDH = 373 ± 32 IU/L and mean initial P(A-a)O₂ gradient = 40 ± 4 mm Hg) (Fig 3 and 4). LDH levels returned to normal (±220 IU/L) in 26 patients (65 percent) by completion of therapy (mean duration of therapy, 17 ± 3 days). In the remaining 14 patients (35 percent), LDH levels fell to less than 300 IU/L by completion of therapy (mean duration of 18 ± 3 days). Twenty-four of the 40 survivors demonstrated a decline in P(A-a)O₂ gradients to less than 15 mm Hg. The mean P(A-a)O₂ gradient for the entire 50 patients on completion of therapy was 19 ± 4 mm Hg.

**DISCUSSION**

*Pneumocystis carinii* pneumonia continues to be the most frequent pulmonary manifestations of AIDS. Its subtle, subacute presentation has been well documented; a high index of suspicion must be maintained, because there are few clinical or laboratory clues to the diagnosis. The rate of recovery from a first bout of *Pneumocystis* has ranged from 50 to 80 percent.⁴ The duration of symptoms does not correlate with prognosis. Rather, the degree of respiratory distress on presentation as measured by respiratory rate, room air PaO₂ as well as P(A-a)O₂ gradient have prognostic value.⁴

Early in the AIDS epidemic, we presented preliminary data suggesting the diagnostic and prognostic value of elevations in serum LDH in patients with *Pneumocystis*. Subsequently, Silverman and Rubinstein⁵ found an elevation in serum LDH in 12 patients with *Pneumocystis* and suggested that it might be a laboratory indicator of *P carinii* pneumonia. Extremely high levels of LDH appeared to reflect more extensive interstitial inflammation and declined with successful therapy. Increased LDH values were also seen in five pediatric cases of LIP and one adult with pulmonary Kaposi sarcoma. Zaman and White⁶ recently found an increase in serum LDH in patients with *Pneumocystis* (mean, 361 IU); however, they noted an overlap in HIV-infected patients with PCP and other causes of pulmonary disease.

The isolated elevation of serum LDH levels in AIDS patients with *Pneumocystis* pneumonia appears to distinguish the *Pneumocystis* from other pulmonary processes in these patients with sensitivity = 0.94 and specificity = 0.82. Only 5 percent of patients with proved PCP had normal LDH levels. Zaman and White⁷ found normal serum LDH in 7 percent of proved PCP patients. Biopsy or lavage confirmation of *P carinii* pneumonia is still necessary for the diagnosis. Mild elevations in serum LDH were observed in patients with nonspecific interstitial pneumonitis, lymphoma, LIP, and Legionella, but in no patient with pulmonary Kaposi sarcoma. The finding of a normal serum LDH level in a symptomatic patient with an abnormal chest roentgenogram should suggest a non-PCP pulmonary process.

Admission clinical and laboratory data were analyzed as prognostic indicators, ie, for their ability to predict survival in patients with *P carinii* pneumonia. Mean duration of symptoms (fever, dyspnea, cough), physical findings (temperature and crackles), and initial mean leukocyte and lymphocyte counts on admission showed no significant statistical difference between those who survived and those who died. Similar findings were reported by Kales et al.,⁹ although crackles were found more frequently in nonsurvivors in that study. Kovacs et al.¹⁰ although crackles were found more frequently in nonsurvivors in that study. Kovacs et al.¹⁰ although crackles were found more frequently in nonsurvivors in that study.
published results by Brenner et al., who found that survivors had a lower initial P(A-a)O2 gradient. Both Kovacs et al. and Kales et al. reported an improved prognosis with a higher initial PaO2. The P(A-a)O2 gradients were not calculated in the former study. In the latter study normal PaO2 and P(A-a)O2 gradients were obtained in 21/109 patients: these patients did not have increased survival.

The lower admission serum LDH and P(A-a)O2 gradient findings in survivors may be due to less initial parenchymal damage secondary to Pneumocystis. With appropriate therapy for Pneumocystis, serum LDH levels and P(A-a)O2 gradient measurements returned close to baseline. This usually occurred following 17 to 21 days of therapy. In some patients, however, elevation of these values persisted, probably due to irreversible lung damage. Zaman and White have also found lower mean serum LDH levels in survivors than nonsurvivors (340 IU vs 441 IU, compared with the present study in which serum LDH values were 394 IU vs 719 IU, respectively).

Elevation of serum LDH levels has been reported in diseases that cause alveolar damage such as alveolar proteinosis. An increased LDH level has occasionally been reported in pneumococcal as well as Legionella pneumonia. Hemolysis may be responsible in the former, while liver dysfunction may contribute to its elevation in the latter. When normal pulmonary tissue is homogenized and assayed for LDH, the isoenzyme pattern found is characteristically isoenzymes 3, 4, and 5. This specific “pulmonary” isoenzyme pattern is found in the serum of patients with pulmonary infarction. Increased LDH-3 and LDH-4 (which predominate in lung tissue) found in some AIDS patients with P carinii pneumonia may reflect alveolar damage. However, this pattern was only seen in one third of the patients in the present series and infrequently in the series of Silverman and Rubinstein. Recently, Smith et al. explained this discrepancy between serum and lavage LDH isoenzymes in AIDS patients with Pneumocystis.

An elevated serum LDH level may be due to a backflow of BAL-LDH through a more permeable alveolar-capillary. Cationic isoenzymes LDH 3, 4, and 5 are preferentially retained in the air spaces. In particular, selective backflow of BAL-LDH isozyme 2 may be responsible for the isomorphic pattern seen in the serum of patients with PCP.

Elevations of P(A-a)O2 gradient and serum LDH have diagnostic and prognostic value in AIDS patients with P carinii pneumonia. Serum LDH is elevated in most AIDS patients with Pneumocystis in contrast to other pulmonary processes in AIDS patients. Serum LDH and P(A-a)O2 gradients return to the normal range with therapy.