Acute respiratory failure due to Pneumocystis pneumonia: outcome and prognostic factors

Viboon Boonsarnsuk*, Supinda Sirilak, Sumalee Kiatboonsri

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand

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Introduction

Pneumocystis pneumonia (PCP), the disease caused by Pneumocystis jirovecii, emerged as an important cause of morbidity and mortality in HIV-infected patients from early in the AIDS epidemic.1,2 Currently, with the use of highly active
antiretroviral therapy (HAART), the prescription of prophylactic agents to persons at high clinical risk, and the availability of more sensitive immunofluorescence methods of *P. jirovecii* detection, the overall incidence of PCP cases and survival following PCP in AIDS patients has generally improved. In spite of this, the high mortality of patients requiring mechanical ventilation (MV) has remained unchanged, ranging from 50% to 60%.

In contrast to AIDS-related cases, cases of PCP in patients with other predisposing immunodeficiency states, such as organ transplant recipients, patients with hematologic and solid tumors receiving chemotherapeutic agents, and persons with chronic inflammatory diseases requiring prolonged use of corticosteroids, may be increasing, and the associated mortality may be >50%. However, the previous literature on both HIV- and non-HIV-related PCP has indicated that the mortality of patients with acute respiratory failure (ARF) requiring MV does not differ widely and ranges between 40% and 60%, despite the use of new aggressive supportive interventions and monitoring.

In order to examine the outcome and prognostic factors of in-hospital mortality in patients with ARF requiring MV caused by PCP at our institution, we retrospectively collected data for PCP patients requiring MV and admitted to a medical intensive care unit (ICU) between 2000 and 2006. Clinical, laboratory, and radiologic features, as well as mechanical ventilation parameters were examined as prognostic factors of patient outcome.

**Materials and methods**

**Subjects**

We performed a retrospective analysis on all consecutive patients ≥15 years of age with a microbiologically confirmed diagnosis of PCP, who were admitted to the medical ICU of Ramathibodi Hospital, a tertiary university referral hospital in Bangkok, Thailand, and required treatment for ARF with MV between January 1, 2000 and November 30, 2006. All cases of PCP included in the study had cytologic documentation of the organisms by immunofluorescence or Giemsa staining in specimens of bronchoalveolar lavage (BAL) fluid or transbronchial biopsy (TBBX) specimens. Cases of presumptive diagnosis of PCP were not included. The study protocol was approved by the Ethics Committee on Human Experimentation of Ramathibodi Hospital, Faculty of Medicine, Mahidol University.

**Data collection**

Clinical data abstracted included the following: general demographic information, HIV status, underlying immunosuppressive condition, including medications and PCP prophylaxis, laboratory analysis, radiology, microbiology, APACHE (acute physiology and chronic health evaluation) II score on the day of ARF, mechanical ventilation parameters, antibiotic and steroid therapy, and hospital and ICU length of stay (LOS), as well as overall hospital mortality.

In our ICU, to ventilate any patient who developed acute respiratory failure with diffuse bilateral lung diseases, we routinely used a tidal volume of 8–10 ml per kilogram of predicted body weight and optimal positive end-expiratory pressure (PEEP) by lung mechanics as described by Suter et al. With this technique, the PEEP was increased sequentially with a consistent tidal volume, and the static compliance was measured at each interval. Optimal PEEP, defined as the level of PEEP corresponding to maximal compliance, was chosen. The level of optimal PEEP was titrated once daily and recorded for three consecutive days. A plateau pressure of ≤30–35 cmH2O was allowed.

**Statistical analysis**

All values were expressed as the mean ± standard deviation (SD) for continuous variables and percent for categorical variables. To determine the association of independent variables with hospital mortality, continuous variables were compared using the Student’s two-tailed t-test or nonparametric Mann–Whitney U-test, in case of distribution not being normal. The Chi-square test or the Fisher’s exact test, in case of low expected frequencies, was used for comparisons of categorical variables. Variables identified as significant in the univariate analysis were assessed as predictors of mortality using logistic regression analysis. Then, subgroup analysis in both the HIV group and non-HIV-related PCP group was performed to find the prognostic factors associated with hospital mortality in the same manner. In-hospital survival was assessed by Kaplan–Meier methods, and differences between the HIV group and the non-HIV-related PCP group were assessed by the log-rank test. All statistical tests were two-sided, and *p* < 0.05 was considered statistically significant. All data were analyzed with a statistical software package (SPSS, version 11.5 for Windows; SPSS Inc., Chicago, IL, USA).

**Results**

**Demographic features**

A total of 44 confirmed cases of PCP in adult patients who developed ARF and required treatment with MV were identified during the period between January 1, 2000 and November 30, 2006. PCP was diagnosed by BAL in 41 out of 44 patients, while 13 cases were diagnosed by TBBX. Fourteen cases were HIV-seropositive and 30 cases had other conditions associated with immunosuppression. Of these 44 patients, 27 were female. The mean age of the patients was 46.3 years. The mean APACHE II score on day 1 was 22.3 (Table 1). The mean ICU and hospital LOS were 18 days and 25 days, respectively.

**Immunosuppressive conditions**

In the HIV group, seven (50%) were female and the mean age was 35.2 years. Of the 14 patients, 10 had been tested for CD4 count and the mean result was 53.1 cells/μL. Only one case had received trimethoprim/sulfamethoxazole (TMP/SMZ) prophylaxis.

In the non-HIV group, 20 (66.7%) were female and the mean age was 51.5 years. The underlying diseases of the conditions associated with immunosuppression are presented in Table 1. Eight patients had received systemic corticosteroids only. Two patients were treated with cytotoxic che-
motherapy not containing corticosteroids, and the remainder had received a combination of both corticosteroids and chemotherapy. The mean prednisolone-equivalent dose (PED) and duration of corticosteroid use prior to diagnosis of PCP was 41.5 mg and 4.1 months, respectively. No one was given prophylactic medications for PCP prior to onset of pneumonia.

### Clinical symptoms

The mean duration of symptoms prior to ARF was about 9.7 days and was found to be significantly longer in the HIV group (13.1 ± 5.7 vs. 8.1 ± 6.1 days for the HIV group and the non-HIV group, respectively; \( p = 0.015 \)). Twenty-nine patients had received anti-PCP medication prior to ARF with a mean

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### Table 1 Clinical characteristics of 44 patients with Pneumocystis pneumonia-related acute respiratory failure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (N = 44)</th>
<th>Patients who survived (N = 16)</th>
<th>Patients who died (N = 28)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46.3 (14.6)</td>
<td>47.4 (13.4)</td>
<td>45.7 (15.4)</td>
<td>0.717</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>27 (61.4)</td>
<td>7 (25.9)</td>
<td>20 (74.1)</td>
<td>0.017</td>
</tr>
<tr>
<td>Underlying immune defect, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>14 (31.8)</td>
<td>6 (42.9)</td>
<td>8 (57.1)</td>
<td>0.541</td>
</tr>
<tr>
<td>Non-HIV</td>
<td>30 (68.2)</td>
<td>10 (22.7)</td>
<td>20 (77.3)</td>
<td></td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>10 (22.7)</td>
<td>4 (40.0)</td>
<td>6 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>16 (36.4)</td>
<td>4 (25.0)</td>
<td>12 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4 (9.1)</td>
<td>2 (50.0)</td>
<td>2 (50.0)</td>
<td>0.459</td>
</tr>
<tr>
<td>Immunosuppressive drug, n (%) (N = 30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids alone</td>
<td>8 (26.7)</td>
<td>3 (37.5)</td>
<td>5 (62.5)</td>
<td>0.204</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>2 (6.7)</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>0.197</td>
</tr>
<tr>
<td>Combined steroids + chemotherapy</td>
<td>20 (66.7)</td>
<td>6 (30.0)</td>
<td>14 (70.0)</td>
<td>0.814</td>
</tr>
<tr>
<td>CD4, cells/µl (n = 10)</td>
<td>53.1 (47.2)</td>
<td>54.6 (56.3)</td>
<td>50.7 (37.3)</td>
<td>0.907</td>
</tr>
<tr>
<td>PED before ARF, mg (n = 24)</td>
<td>41.5 (16.5)</td>
<td>34.1 (20.1)</td>
<td>44.0 (15.0)</td>
<td>0.014</td>
</tr>
<tr>
<td>Duration PED before ARF, months (n = 24)</td>
<td>4.1 (3.0)</td>
<td>5.6 (4.9)</td>
<td>3.6 (2.0)</td>
<td>0.361</td>
</tr>
<tr>
<td>Duration before treatment, days</td>
<td>6.9 (5.3)</td>
<td>5.8 (4.1)</td>
<td>7.5 (5.9)</td>
<td>0.329</td>
</tr>
<tr>
<td>Duration before ARF, days</td>
<td>9.7 (6.4)</td>
<td>9.3 (5.9)</td>
<td>10.0 (6.7)</td>
<td>0.737</td>
</tr>
<tr>
<td>Duration from treatment to ARF, days (n = 29)</td>
<td>5.0 (4.1)</td>
<td>3.8 (3.6)</td>
<td>5.8 (4.4)</td>
<td>0.197</td>
</tr>
<tr>
<td>LDH, U/l</td>
<td>632.7 (239.2)</td>
<td>606.9 (247.6)</td>
<td>646.3 (240.4)</td>
<td>0.681</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>22.3 (4.9)</td>
<td>19.8 (4.8)</td>
<td>23.6 (4.4)</td>
<td>0.016</td>
</tr>
<tr>
<td>Anti-PCP drug, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMP/SMZ</td>
<td>36 (81.8)</td>
<td>13 (36.1)</td>
<td>23 (63.9)</td>
<td></td>
</tr>
<tr>
<td>Clindamycin + primaquine</td>
<td>4 (9.1)</td>
<td>1 (25.0)</td>
<td>3 (75.0)</td>
<td></td>
</tr>
<tr>
<td>TMP/SMZ → clindamycin + primaquine</td>
<td>4 (9.1)</td>
<td>2 (50.0)</td>
<td>2 (50.0)</td>
<td>0.761</td>
</tr>
<tr>
<td>PED treatment, mg</td>
<td>66.8 (31.5)</td>
<td>60.6 (31.7)</td>
<td>70.3 (31.4)</td>
<td>0.331</td>
</tr>
<tr>
<td>Lung mechanics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance, ml/cmH2O</td>
<td>24.7 (6.6)</td>
<td>27.3 (7.5)</td>
<td>23.5 (6.3)</td>
<td>0.372</td>
</tr>
<tr>
<td>PaO2:FiO2, mmHg</td>
<td>173.4 (91.5)</td>
<td>187.0 (72.5)</td>
<td>166.9 (100.0)</td>
<td>0.523</td>
</tr>
<tr>
<td>PEEP day 1, cmH2O</td>
<td>5.9 (1.8)</td>
<td>4.9 (1.4)</td>
<td>6.5 (1.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>PEEP day 2, cmH2O</td>
<td>6.1 (1.8)</td>
<td>5.3 (0.8)</td>
<td>6.6 (2.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>PEEP day 3, cmH2O</td>
<td>6.3 (1.8)</td>
<td>5.3 (1.0)</td>
<td>6.9 (1.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Respiratory co-pathogen, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>21 (47.7)</td>
<td>8 (38.1)</td>
<td>13 (61.9)</td>
<td>0.820</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>7 (15.9)</td>
<td>2 (28.6)</td>
<td>5 (71.4)</td>
<td>0.640</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>15 (34.1)</td>
<td>4 (26.7)</td>
<td>11 (73.3)</td>
<td>0.336</td>
</tr>
<tr>
<td>Fungus</td>
<td>4 (9.1)</td>
<td>0 (0.0)</td>
<td>4 (100.0)</td>
<td>0.113</td>
</tr>
<tr>
<td>Strongyloides</td>
<td>3 (6.8)</td>
<td>0 (0.0)</td>
<td>3 (100.0)</td>
<td>0.175</td>
</tr>
<tr>
<td>Other</td>
<td>8 (18.2)</td>
<td>4 (50.0)</td>
<td>4 (50.0)</td>
<td>0.375</td>
</tr>
<tr>
<td>Pneumothorax, n (%)</td>
<td>16 (36.4)</td>
<td>4 (25.0)</td>
<td>12 (75.0)</td>
<td>0.236</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or n (%).

PCP, Pneumocystis pneumonia; PED, prednisolone-equivalent dose; ARF, acute respiratory failure; LDH, lactate dehydrogenase; TMP/SMZ, trimethoprim/sulfamethoxazole; PEEP, positive end-expiratory pressure.

a All 30 patients who received immunosuppressive drugs were in the non-HIV group.

b Ten out of 14 in the HIV group had CD4 cell count results.

To all 24 patients who had received prednisolone prior to the diagnosis of PCP were in the non-HIV group.

d The 29 patients who had received anti-PCP medication prior to acute respiratory failure.
duration of 5 days. Despite no statistical significance, the
duration from anti-PCP treatment to ARF in those who sur-
vived was less than in those who died (3.8 ± 3.6 vs. 5.8 ± 4.4
days; \( p = 0.197 \)). All patients in the HIV group had received
anti-PCP medication prior to ARF, while only 15 of the 30
patients in the non-HIV group had received it.

**Laboratory and radiographic features**

The mean lactate dehydrogenase (LDH) was 632.7 U/l. No
one had an LDH value within the normal range. No significant
difference was detected in the value of LDH between the HIV
and non-HIV groups.

As expected, chest radiographic examinations generally
revealed diffuse interstitial and ground-glass appearance on
the day of ARF. However, perihilar and basal interstitial
infiltration were present in 9.1% of all cases when they
developed ARF, and all of them were in the non-HIV group.
Subsequent chest radiographs in all patients identified 16
patients with pneumothorax over the course of their ICU stay.

**Co-pathogens**

Co-pathogens identified from BAL or TBBX are presented in
Table 1. Cytomegalovirus (CMV) infection was diagnosed
in 15 patients, nine by demonstration of cytomegalic
intranuclear inclusions in TBBX specimens and six by posi-
tive PCR results for CMV-DNA (the AMPLICOR CMV test;
Roche Diagnostics, Branchburg, NJ, USA) in BAL fluid
obtained at the time of the diagnosis of PCP. Tuberculosis
was found as co-pathogen in seven patients. Furthermore,
Strongyloides infection was found in three patients and all
of them died.

Fungus was present in BAL fluid in four patients: *Candida
albicans* in two patients (one in the HIV group and the other in
the non-HIV group), *Aspergillus spp* in one in the non-HIV
group, and *Cryptococcus neoformans* in one in the HIV group.
Positive respiratory specimen results of *Candida* were
deemed to be secondary to colonization rather than active
disease.

**Treatment and lung mechanics**

Forty of the 44 patients were treated with TMP/SMZ.
Because the physician suspected TMP/SMZ-resistant PCP
infection, four of these 40 patients had their initial anti-
microbial therapy changed to clindamycin—primaquine. As
there was no pentamidine available at our hospital during
this period, four patients who had a history of suspected
allergy to TMP/SMZ received clindamycin—primaquine
instead. All patients were additionally treated with adjunc-
tive corticosteroids. The mean PED of corticosteroids used in
the treatment for ARF related to PCP in these patients was
66.8 mg.

The mean duration of MV requirement was 14.9 days. The
levels of PEEP applied on the first three days of ARF are shown
in Table 1. Although it did not reach statistical significanc,
the level of PEEP applied on day 3 was higher in non-HIV
patients (6.6 ± 2.0 vs. 5.7 ± 1.0 cmH2O; \( p = 0.087 \)). The
mean lung compliance was 24.7 ml/cmH2O. The mean ratio
of PaO2 to fraction of inspired oxygen was 173.4, with 12
(27.3%) patients having a ratio >200.

**Outcomes**

The overall in-hospital mortality rate for the 44 identified
cases was 63.6% (Figure 1). In the first 7 days after ARF, the
mortality rate was significantly higher in the HIV group
(mortality 14.3% vs. 0%; log rank \( p = 0.025 \)) (Figure 2). How-
ever, the in-hospital mortality rate was higher in the non-HIV
group, although without statistical significance (66.7% vs.
57.1%; log rank \( p = 0.606 \)).

**Logistic regression analysis**

Statistical analyses were performed to identify clinical
features associated with mortality. Using univariate ana-
lyses, clinical features associated with mortality are pre-
sented in Table 1. Three parameters were proved to be
significantly associated with death from PCP: female gen-
der (\( p = 0.017 \)), APACHE II score on day 1 (\( p = 0.016 \)), and
level of PEEP on all of the first three days of ARF (\( p = 0.004, \)

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**Figure 1** Kaplan–Meier estimate of overall survival for patients with acute respiratory failure caused by Pneumocystis pneumonia.

**Figure 2** Kaplan–Meier plot of survival for HIV patients and non-HIV patients with acute respiratory failure caused by Pneumocystis pneumonia.
0.008, and 0.001, respectively). In the multivariate approach, only APACHE II score on day 1 and level of PEEP on day 3 remained independently associated with lethal outcome (Table 2).

Although age was significantly higher in the non-HIV group \( (p < 0.001) \), it was not an influence on mortality \( (p = 0.131) \). In the HIV group, using a univariate logistic regression model, sex, APACHE II score on day 1, level of PEEP on day 3, and CMV co-infection were independent predictors of survival, whereas history of prior use of corticosteroid, duration of symptoms before treatment, level of PEEP on day 3, and the subsequent development of pneumothorax were found to be independent predictors of survival in the non-HIV group (Table 3). Although it did not attain statistical significance, the non-survivors had higher APACHE II scores on day 1 than survivors in the non-HIV group \( (24.0 \pm 5.1 \text{ vs. } 21.4 \pm 5.2; p = 0.228) \). In a multivariate logistic regression model, in the non-HIV group, the results indicated only two clinical parameters that were independently associated with hospital mortality. They were history of prior use of corticosteroid and level of PEEP on day 3 (Table 4). Because of small numbers in the HIV group, multivariate analysis was not performed.

Table 2 Odors ratios for variables independently associated with an increased risk of death; multivariate analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II scores</td>
<td>1.247 (1.012—1.537)</td>
<td>0.039</td>
</tr>
<tr>
<td>PEEP day 3, cmH(_2)O</td>
<td>2.741 (1.136—6.613)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; PEEP, positive end-expiratory pressure.

Table 3 Univariate analysis for independent factors associated with hospital mortality; subgroup analysis for HIV and non-HIV patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients who survived</th>
<th>Patients who died</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV group ( (n = 14) )</td>
<td>6 (42.9)</td>
<td>8 (57.1)</td>
<td>0.031</td>
</tr>
<tr>
<td>Sex, female, ( n ) (%)</td>
<td>1 (14.3)</td>
<td>6 (85.7)</td>
<td>0.031</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>17.0 (2.4)</td>
<td>22.8 (2.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Level of PEEP day 3, cmH(_2)O</td>
<td>5.1 (0.4)</td>
<td>6.2 (1.1)</td>
<td>0.037</td>
</tr>
<tr>
<td>CMV co-pathogen, ( n ) (%)</td>
<td>0 (0.0)</td>
<td>4 (100)</td>
<td>0.040</td>
</tr>
<tr>
<td>Non-HIV group ( (n = 30) )</td>
<td>10 (33.3)</td>
<td>20 (66.6)</td>
<td>0.037</td>
</tr>
<tr>
<td>Prior used corticosteroid, ( n ) (%)</td>
<td>6 (25.0)</td>
<td>18 (75.0)</td>
<td>0.020</td>
</tr>
<tr>
<td>Duration before treatment, days</td>
<td>4.2 (3.0)</td>
<td>8.4 (6.6)</td>
<td>0.026</td>
</tr>
<tr>
<td>Level of PEEP day 3, cmH(_2)O</td>
<td>5.4 (1.2)</td>
<td>7.2 (2.0)</td>
<td>0.019</td>
</tr>
<tr>
<td>Pneumothorax, ( n ) (%)</td>
<td>1 (10)</td>
<td>9 (90)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or \( n \) (\%).

PEEP, positive end-expiratory pressure; CMV, cytomegalovirus.

Table 4 Multivariate analysis of independent factors associated with hospital mortality in non-HIV patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior use of corticosteroid</td>
<td>15.487 (1.018—235.488)</td>
<td>0.048</td>
</tr>
<tr>
<td>Level of PEEP day 3, cmH(_2)O</td>
<td>2.667 (0.999—7.119)</td>
<td>0.050</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>14.219 (0.769—263.034)</td>
<td>0.075</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; PEEP, positive end-expiratory pressure.

Discussion

PCP is an opportunistic infection that is associated with substantial morbidity and mortality even when it is properly treated.\(^6,9\) Recently, the frequency of ARF due to PCP has been reported to be decreasing. This may be as a result of early diagnosis and treatment, including the early use of adjunctive corticosteroids prior to ICU admission.\(^14\) Unfortunately, the case—fatality rate for mechanically ventilated patients has increased, suggesting that the development of respiratory failure despite maximal therapy, including corticosteroids, carries an extremely poor prognosis. In our series, the mortality rate in patients with ARF caused by PCP was 63.6%, which is comparable to previous studies.\(^6,15,16\) Although early mortality was higher in the HIV group, hospital mortality between the HIV and non-HIV groups was not statistically different. This finding is consistent with the previous reports of Mansharamani et al.\(^6\) and Ewig et al.\(^17\)

PCP was diagnosed by BAL alone in 93% of our patients. Broaddus et al.\(^18\) found BAL alone had high diagnostic yields. Because of this, some authors recommend it be done without biopsy in HIV patients with a high suspicion for PCP.\(^19\) The yield of BAL in patients on prophylaxis with aerosolized pentamidine has been reported to be decreased,\(^20\) in these cases, BAL or TBBX, or both, performed in areas of radiographic findings should be considered. In our series, only one case had had anti-PCP prophylaxis with TMP/SMZ and BAL was able to diagnose PCP. None received aerosolized pentamidine.

In our study, we found that elevated APACHE II score on day 1 and level of PEEP on day 3 were independently associated with lethal outcome in patients with ARF caused by
PCP. In agreement with our series, Forrest et al.\textsuperscript{11,16} and Benson et al.\textsuperscript{21} also found that APACHE II could predict the mortality in patients with HIV-related PCP and respiratory failure. In contrast, in our patients, APACHE II score on day 1 was not found to be a significant variable associated with hospital outcome in non-HIV PCP. To the best of our knowledge, there has been no report demonstrating APACHE II score to predict the mortality in non-HIV PCP. In a study by Torres et al.\textsuperscript{22} by using univariate analysis, high APACHE II score was found to be one of the predictors of death. However, using multivariate analysis, it could not be identified as an independent predictor of death. The updated APACHE III was designed to estimate the probability of in-hospital mortality for adult ICU patients,\textsuperscript{23} and the findings of Festic et al.\textsuperscript{15} showed that APACHE III scores were predictive of mortality among non-HIV patients with PCP.

The level of PEEP applied as a predictor of hospital outcome has been reported by others.\textsuperscript{24–26} Furthermore, Peruzzi et al.\textsuperscript{25} found that the level of PEEP required begins to decrease after approximately 72 hours of ICU care in the survivor group, whereas the non-survivor group demonstrated the need for continued escalation of support. In the earliest stage of disease course, the histology in the lung shows only intra-alveolar exudates and minimal inflammation. Progression to the chronic, organizing phase of diffuse alveolar damage is common, and evidence of interstitial and intraluminal fibrosis are present. In the late stage, extensive septal thickening with fibrosis is found with much less alveolar exudates.\textsuperscript{19,27} This results in recruitable and non-recruitable units under PEEP application. With the technique to determine the optimal PEEP as described by Suter,\textsuperscript{13} the higher the level of PEEP achieved, the more the alveolar process is represented and, on the other hand, the lower the level of PEEP achieved, the more the restrictive process is represented. So, in our patients, the higher level of PEEP applied on day 3 may represent the ongoing disease process despite standard treatment, which resulted in fatal outcome, whereas the lower level of PEEP applied on day 3 may represent change to a chronic process.

In HIV-related PCP with ARF, the identifiable different variables between the survivors and non-survivors other than APACHE II score on day 1 and level of PEEP applied on day 3 were sex and CMV co-infection. Various studies have confirmed that patients with concomitant CMV infections have a higher mortality rate as compared with patients with PCP alone;\textsuperscript{28–30} however, these studies were conducted after the introduction of adjunctive corticosteroid treatment in patients with severe PCP. Jensen et al.\textsuperscript{30} showed that CMV-positive patients treated with adjunctive corticosteroids have a worse vital prognosis than CMV-positive patients without corticosteroid treatment. Corticosteroid therapy may result in a more rapid development of CMV disease in HIV-infected patients and thus the clinical importance of concomitant CMV infection in PCP has changed.\textsuperscript{31}

For those who developed ARF in the non-HIV-related PCP group, the level of PEEP on day 3 as well as history of prior use of corticosteroid were associated with hospital mortality. Previous studies have demonstrated prior use of corticosteroids as a risk of death in these patients.\textsuperscript{32,33} and a resultant high mortality rate.\textsuperscript{6,14,17} Several mechanisms have been postulated to explain the role of steroids in promoting the development of \textit{P. jirovecii} including CD4+ lymphocyte depletion and immune dysfunction.\textsuperscript{9}

The subsequent development of pneumothorax was associated with mortality in univariate analysis; however, it was not found to be a significant factor when using multivariate analysis. Development of pneumothorax complicating PCP is thought to represent a poor prognosis.\textsuperscript{15,24,34} In a study by Festic et al.,\textsuperscript{15} all of their non-HIV-related PCP and ARF patients who developed pneumothorax died, compared to a 90% mortality rate in our patients.

Because of the high mortality in patients with ARF requiring MV caused by PCP and the fact that it is not possible to distinguish which of these patients will or will not survive to hospital discharge based on information routinely available before ICU admission, we agree with the use of anti-PCP prophylaxis in both the HIV- and non-HIV patients who are at high risk of developing PCP. Although the clinical significance of prophylaxis for PCP remains controversial in non-HIV patients, some authors have suggested that immunosuppression induced by chemotherapy or radiotherapy, or patients with inflammatory diseases receiving glucocorticosteroids 20 mg/day or more for 4 weeks or more should receive prophylaxis.\textsuperscript{32,35,36} Furthermore, strongyloidiasis and CMV disease should be considered as co-infections in these patients, and aggressive work-up may be required in cases who are not improving despite maximal therapy. Protective lung ventilation strategies in mechanical ventilated patients should be used to prevent pneumothorax and other ventilator-associated lung injury.\textsuperscript{37}

There are several limitations to this study. The number of patients studied is relatively small. Presently, with the use of HAART, the prescription of prophylactic agents to persons at high clinical risk, and empirical treatment for patients with clinically suspected PCP, the overall incidence of PCP cases with ARF is reduced, especially in AIDS patients. Furthermore, only microbiologically confirmed cases were eligible. Although, in our study, we evaluated the role of many prognostic variables, only three prognostic factors were proved to be significantly associated with death in univariate analysis and included in the logistic model. Nevertheless, the main prognostic factors identified in this study are statistically significant, correlate with findings of previous investigations,\textsuperscript{11,16,21,24–26} and are clinically plausible. Pooling of data from several centers could add statistical power to an analysis of prognostic markers of poor outcome.

Another limitation is related to the retrospective nature of this review. It remains possible that some important variables may not have been recorded. However, we believe this to be unlikely, since the data set analyzed for each significant prognostic factor was nearly complete (100% data availability for gender, level of PEEP, history of prior use of corticosteroid, duration of symptoms before treatment, and the subsequent development of pneumothorax and 91% data availability for APACHE II scores).

Finally, our ventilator management was perhaps not the best and was open to debate. Even though optimal PEEP was applied, the low tidal volume strategy was not used. The Acute Respiratory Distress Syndrome Network demonstrated that mechanical ventilation with a lower tidal volume (6 ml per kilogram of predicted body weight) than is traditionally used (12 ml per kilogram of predicted body weight) results in decreased mortality.\textsuperscript{38} However, when plateau pressure was
not high, a tidal volume of 7 ml/kg was found not to be associated with lower mortality compared with a tidal volume of 10 ml/kg. Nevertheless, the widespread belief that tidal volume reduction is without benefit when plateau pressure is already lower than 30–35 cmH₂O has not been substantiated. Further research is necessary to demonstrate the difference in benefit for these patients.

In conclusion, we found various risk factors associated with hospital mortality in patients with ARF requiring MV caused by PCP include APACHE II score on day 1, level of PEEP with hospital mortality in patients with ARF requiring MV with respiratory failure caused by AIDS-related Pneumocystis carinii pneumonia. Arch Intern Med 1999;159:741–7.


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