Determinants of Short- and Long-term Outcome in Patients With Respiratory Failure Caused by AIDS-Related Pneumocystis carinii Pneumonia

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**Objectives:** To determine (1) predictors of in-hospital mortality and long-term survival in patients with acute respiratory failure (ARF) caused by acquired immunodeficiency syndrome–related Pneumocystis carinii pneumonia (PCP) and (2) long-term survival for patients with ARF relative to those without ARF.

**Methods:** A retrospective medical chart review was conducted of all cases of PCP-related ARF for which the patient was admitted to the intensive care unit of a single tertiary care institution between 1991 and 1996. Data were extracted regarding physiologic scores, relevant laboratory values, and duration of previous maximal therapy with combined anti-PCP agents and corticosteroids at entry to the intensive care unit. Duration of survival was determined by Kaplan-Meier methods from date of first hospital admission and compared for patients with and without ARF.

**Results:** There were 41 admissions to the intensive care unit among 39 patients, with 56.4% in-hospital mortality. Higher physiologic scores (Acute Physiology and Chronic Health Evaluation II [APACHE II], Acute Lung Injury, and modified Multisystem Organ Failure scores) were predictive of in-hospital mortality. Duration of previous maximal therapy also predicted in-hospital mortality (45% for patients with <5 days of previous maximal therapy vs 88% for those with ≥5 days of previous maximal therapy; P = .03). Combining physiologic scores and duration of previous maximal therapy enhanced prediction of in-hospital mortality. There was no difference in long-term survival between patients with PCP with ARF and those without ARF (P = .80), and baseline characteristics did not predict long-term survival.

**Conclusions:** In-hospital mortality of patients with acquired immunodeficiency syndrome–related PCP and ARF is predicted by duration of previous maximal therapy and physiologic scores, and their combination enhances predictive accuracy. Long-term survival of patients with ARF caused by PCP is comparable to that of patients with PCP who do not develop ARF, and determinants of in-hospital mortality do not predict long-term survival.

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Despiste advances in antiretroviral therapy and improved prophylaxis, Pneumocystis carinii pneumonia (PCP) remains a frequent life-threatening opportunistic infection complicating human immunodeficiency virus infection and the acquired immunodeficiency syndrome (AIDS). Indeed, despite a recent decline in AIDS incidence, the rate of human immunodeficiency virus infection is increasing, and PCP remains the most common AIDS-defining illness. Acute respiratory failure (ARF) complicates PCP in 5% to 30% of cases, usually requiring admission to the intensive care unit (ICU). Because ARF in the setting of AIDS-related PCP has been reported frequently to have a poor prognosis and high in-hospital mortality, many have questioned the appropriateness of offering ICU care to these patients and have attempted to identify prognostic factors predictive of mortality. Although physiologic scores have been validated as predictive of in-hospital mortality, the clinical utility of such tools in assisting decision making is unclear.

Staikowsky and colleagues showed that mortality among patients who develop ARF after at least 5 days of maximal therapy with anti-PCP drugs and corticosteroids was significantly worse than that of patients with fewer than 5 days of previous maximal therapy. Duration of maximal therapy therefore may be a more clinically relevant variable in determining prognosis for AIDS-related ARF if this can be validated.

Decision making about critical care support for patients with PCP and ARF is also affected by the long-term prognosis of...
PATIENTS AND METHODS

All patients with AIDS-related PCP who were admitted to St Paul’s Hospital, Vancouver, British Columbia, between January 1, 1991, and September 30, 1996, were identified through a computerized search of hospital records. Patients were further identified who were admitted to the ICU for respiratory failure (whether or not mechanical ventilation was instituted) during the same period, and all such hospital charts were reviewed using a standardized case report form.

Data were recorded regarding the Acute Physiology and Chronic Health Evaluation II (APACHE II), Acute Lung Injury (ALI), AIDS, and modified Multisystem Organ Failure (MSOF) scoring instruments; CD4+ counts; and lactate, pH, albumin, and lactate dehydrogenase levels at entry to the ICU. Data were also recorded regarding the number of days of therapy with anti-PCP drugs and corticosteroids; use, timing, and duration of noninvasive ventilatory support (nasal continuous positive airway pressure or BiPAP [Respironics, Murraysville, PA]) and mechanical ventilation; and duration of ICU and hospital stay. Measurements were compared between (1) in-hospital survivors and nonsurvivors and (2) those receiving fewer than 5 days of combined anti-PCP and corticosteroid therapy and those receiving at least 5 days of such maximal treatment. Analyses were repeated including only patients with ARF who required mechanical ventilation. Predictability of duration of previous maximal therapy was further assessed in combination with other significant prognostic variables.

Duration of survival after admission to the ICU was determined from hospital records (for those with in-hospital mortality) and from medical records and through linkage with Vital Statistics Canada (for those discharged alive from hospital). For the purposes of the survival analysis, long-term survival was calculated for each patient from the date of first admission to the hospital with a diagnosis of PCP so that readmissions were not counted. Analysis was truncated as of September 29, 1997.

Patients with microbiologically proven PCP by bronchoscopic or autopsy examination and those with presumptive PCP were included in the analysis. A presumptive diagnosis of PCP was made if human immunodeficiency virus-seropositive patients had a compatible clinical history and physical examination findings, a CD4+ lymphocyte count of less than 0.20 × 10^9/L (<200/mm^3), hypoxemia with an alveoloarterial oxygen gradient of 30 mm Hg or greater, a chest radiograph showing diffuse alveolointerstitial infiltrates, and no other diagnosis established. Patients subsequently readmitted to the hospital with a diagnosis of PCP were considered to have separate episodes if there were more than 30 days separating the previous discharge and subsequent readmission dates. Readmissions for PCP within 30 days of discharge for PCP were considered a single episode. Acute respiratory failure was defined as a ratio of alveolar partial pressure of oxygen to fraction of inspired oxygen of less than 150.

STATISTICAL ANALYSIS

Continuous variables were compared using Wilcoxon rank sum tests, and the chi^2 test 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. Long-term survival was assessed by Kaplan-Meier methods, and differences between patients with PCP with and without ARF were assessed by the log-rank test. A Cox proportional hazards model was used to assess predictors of long-term survival. All statistical tests were 2-sided, and P<.05 was considered statistically significant. Analyses were performed using statistical software (SAS version 6.11; SAS Institute, Cary, NC).

RESULTS

Of 3334 admissions of patients with AIDS to St Paul’s Hospital between January 1, 1991, and September 30, 1996, 777 (23.3%) had a discharge diagnosis of PCP and a median length of hospital stay of 8 days. There were 143 in-hospital deaths among this latter group (18.4%). Of the 777 episodes of in-hospital treatment for PCP, there were 41 admissions (5.3%) to the ICU with ARF in 39 patients; 2 patients were admitted to the ICU twice. Aggregate baseline characteristics are summarized in Table 1.

Among the 41 ICU admissions, 25 patients (61%) received mechanical ventilatory support. A total of 12 patients (29%) were treated with BiPAP or nasal continuous positive airway pressure, 4 of whom were subsequently mechanically ventilated. All patients received corticosteroids and anti-PCP treatment while in the ICU. Eight patients (20%) received at least 5 days of combined anti-PCP and corticosteroid therapy before ICU admission. Median length of ICU stay was 4 days (range, 1-17 days), and median length of hospital stay was 14 days (range, 2-105 days).

Overall in-hospital mortality among patients admitted to the ICU was 56% (95% confidence interval [CI], 38%-69%). Mortality among patient subgroups was distinguished by duration of maximal therapy with corticosteroids and anti-PCP medication: the in-
hospital mortality of those treated with fewer than 5 days of maximal therapy before ICU admission was 45% (95% CI, 28%-63%), whereas those who had been treated for at least 5 days had a mortality of 88% (95% CI, 47%-99%; \( P = .03 \)). Whether patients received mechanical ventilatory support during their ICU stay was not predictive of in-hospital mortality (53% [95% CI, 32%-73%] of survivors vs 68% [95% CI, 45%-85%] of those who died were ventilated; \( P = .31 \)). There were no significant differences at baseline regarding AIDS score or lactate dehydrogenase levels between survivors and nonsurvivors (Table 2). When stratified by CD4+ count according to Kumar and Krieger,\(^{29} \) (CD4+ counts 0-0.010, 0.011-0.050, 0.051-0.100, and >0.100 \times 10^9/L), there was no significant trend in mortality (varying from 44% to 20% across categories; \( P = .49 \)).

The median MSOF, APACHE II, and ALI scores were significantly different between those patients who survived hospitalization and those who did not (\( P = .02 \) for MSOF, \( P = .009 \) for APACHE II, and \( P = .02 \) for ALI) (Table 2). In each case, a higher score corresponded to a worse outcome. For example, those with MSOF scores of 1 to 2 had a mortality of 46% (95% CI, 29%-63%), whereas those with an MSOF score of 3 or greater had a mortality of 100% (95% CI, 61%-100%; \( P = .01 \)). None of the scores was different between those who had shorter vs more prolonged maximal therapy (\( P = .59 \) for MSOF, \( P = .82 \) for APACHE II, and \( P = .10 \) for ALI) (Table 3). Median pH was higher in those who had received at least 5 days of maximal therapy with anti-PCP drugs and corticosteroids compared with those who had received fewer than 5 days of such treatment (7.46 vs 7.43; \( P = .03 \)) (Table 3), but there was no difference in median pH on admission between those who survived and those who died (Table 2). Albumin concentration was higher among those who survived vs those who did not (24.5 vs 22.5; \( P = .04 \)) (Table 2).

The analysis was repeated for those 25 patients who received mechanical ventilatory support. Mortality in this subset of patients was 60% (95% CI, 39%-78%). The APACHE II and MSOF physiologic scores remained significant predictors of outcome, but the ALI score and category of CD4+ count did not (data not shown). Although mortality tended to be higher among those who had received at least 5 days of maximal therapy (75% [95% CI, 22%-99%] vs 57% [95% CI, 34%-77%] among those who had received <5 days of maximal therapy), this difference was not statistically significant (\( P = .50 \)).

The effect of physiologic scores and duration of maximal therapy in predicting in-hospital mortality among the entire cohort of patients with ARF was studied by logistic regression analysis, adjusting for age. Only duration of maximal therapy (<5 vs \( \geq 5 \) days) before development of ARF and the APACHE II score were predictive of outcome in this model. The odds ratio for duration of maximal therapy was 12.43 (95% CI, 1.23-125.13; \( P = .03 \)). The odds ratio for the APACHE II score was 1.36 (95% CI, 1.06-1.75; \( P = .02 \)) for each additional point in the scoring scheme. The variables were independent predictors of mortality, and there was no significant inter-

<table>
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<th>Characteristic</th>
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<td>Age, y</td>
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<td>Men, %</td>
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<td>First episode, %</td>
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<td>PCP confirmed, %</td>
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<td>Duration of hospital to ICU admission, d</td>
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<td>ALI score</td>
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<td>pH</td>
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<td>LDH level, U/L</td>
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<td>Mortality, %</td>
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* Values are expressed as median (range) except where indicated as proportion (percent). ICU indicates intensive care unit; AIDS, acquired immunodeficiency syndrome; PCP, Pneumocystis carinii pneumonia; APACHE II, Acute Physiology and Chronic Health Evaluation II; ALI, Acute Lung Injury; MSOF, modified Multisystem Organ Failure; and LDH, lactate dehydrogenase.

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* Values are expressed as median (range) except as indicated otherwise. ICU indicates intensive care unit; AIDS, acquired immunodeficiency syndrome; PCP, Pneumocystis carinii pneumonia; APACHE II, Acute Physiology and Chronic Health Evaluation II; ALI, Acute Lung Injury; MSOF, Multisystem Organ Failure; A-a DO2, alveoloarterial oxygen difference; LDH, lactate dehydrogenase; and Tx+CS, anti-PCP and corticosteroid therapy.

† Wilcoxon rank sum test.
‡ Mantel-Haenszel \( x^2 \) test.
§ \( x^2 \) Test.

Table 1. Baseline Characteristics of Patients Admitted to the ICU With AIDS-Related PCP and Respiratory Failure Between January 1, 1991, and September 30, 1996*

Table 2. Characteristics and Outcomes by In-Hospital Mortality Among Patients Admitted to the ICU With AIDS-Related PCP and Respiratory Failure Between January 1, 1991, and September 30, 1996*
Those who had a low APACHE II score (95% CI, 45%-85%) and 73% (95% CI, 45%-91%), therapy had intermediate in-hospital mortality (68% score and prolonged duration of previous maximal therapy or a low APACHE II or MSOF score and short duration of previous maximal therapy. Thus, the in-hospital mortality of 4 patients in this series who had a combination of a high APACHE II score (>18) or a high MSOF score (>1) and prolonged duration of previous maximal therapy (>5 days) was 100% (95% CI, 47%-100%). Patients who had combinations of a high APACHE II or MSOF score and short duration of previous maximal therapy or a low APACHE II or MSOF score and prolonged duration of previous maximal therapy had intermediate in-hospital mortality (68% [95% CI, 45%-85%] and 73% [95% CI, 45%-91%, respectively). Those who had a low APACHE II score (≥18) or a low MSOF score (≤1) and a short duration of previous maximal therapy (<5 days) had lower in-hospital mortality (20% [95% CI, 5%-49%] and 35% [95% CI, 17%-57%, respectively).

There were 777 hospital admissions of patients with AIDS and a diagnosis of PCP; there were 63 readmissions for PCP. Of the 714 patients, 586 patients (75% of 777 admissions) were evaluable for survival analysis; 128 patients were not evaluable because they could not be identified from medical records or through linkage with Vital Statistics Canada. The last point at which overall mortality data were available in all groups was at 862 days. In-hospital mortality for 38 patients with PCP who developed ARF evaluable by this means was 53.7%; for those who did not develop ARF, mortality was 16.4%. Despite this, there was no difference in the overall survival curves between the 2 patient groups by the log-rank test (P = .80). Median survival for patients admitted to the ICU was 249 days (95% CI, 37-847 days). Median survival for evaluable patients in the period reviewed who were admitted to the hospital with PCP and who did not develop ARF was 386 days (95% CI, 345-463 days).

Comparing patients with ARF who received mechanical ventilation with those who did not develop ARF, there was also no difference in long-term survival assessed by Kaplan-Meier methods (data not shown; P = .86). Mortality among patients with ARF who required mechanical ventilation at 862 days was 72%, whereas mortality at that point for patients who did not develop ARF was 73%. Finally, none of the prognostic variables examined was a significant predictor of long-term survival.

In this 5-year, single-institution study of PCP-related ARF, in-hospital mortality was predicted by physiologic scores (especially APACHE II and MSOF scores) on admission to the ICU and by duration of maximal therapy before ICU admission. The combination of physiologic scores and duration of previous maximal therapy enhanced predictive accuracy. Although in-hospital survival was lower for patients with PCP who developed ARF, the long-term survival of patients with ARF was no different from that of patients with PCP who did not develop ARF. Finally, no prognostic feature predictive of in-hospital mortality was predictive of duration of long-term survival.
Since 1989, survival to hospital discharge for patients with PCP and ARF has been reported consistently to be 25% or less. In contrast, we found an improved survival to hospital discharge since 1991 of 44% for patients with AIDS-related PCP and ARF. However, it cannot be concluded with certainty that survival is improved in the modern era because of small numbers of patients in our present study with resulting wide CIs for this result (95% CI, 31%-62%).

Poor in-hospital mortality may reflect a selection of patients destined to do poorly irrespective of treatment. Although many investigators have attempted to define a variety of prognostic variables, our findings support the use of physiologic scores as important predictors of in-hospital mortality, even among the subgroup of patients with ARF requiring mechanical ventilation. Hence, in-hospital mortality for patients with PCP and ARF seems dependent primarily on the degree of organ system dysfunction at the time of development of ARF. This supports previous findings of the predictability of physiologic scores in other critically ill populations and in patients with AIDS-related PCP and ARF.

Our findings also refute the conclusions of Kumar and Krieger, who found CD4+ count to be a predictor of in-hospital mortality in ventilated patients. Median albumin level on admission to the ICU was significantly different between patients who survived and those who did not (Table 2), but the difference is not clinically relevant.

Duration of maximal therapy with anti-PCP medications and corticosteroids was also predictive of in-hospital mortality (43% for those with <5 days of maximal combined therapy vs 88% for those with ≥5 days of maximal therapy; P = .03). This confirms the findings of a 5-year study (1987-1992) of 33 patients by Stai-kowsky et al., who identified a mortality rate of 95% among 19 patients who had received at least 5 days of combined therapy compared with 50% among patients who had received fewer than 5 days of maximal therapy. It also supports the validity of this variable as predictive of outcome in the modern era (since 1989).

It is not clear why duration of maximal therapy is an important predictor of in-hospital mortality, but it may be related to the pathophysiological mechanisms of pneumocystosis. Invasion of lung tissue by the organism and the resulting inflammatory response may induce acute damage and destruction of lung tissue. Initiation of anti-PCP therapy may exacerbate the inflammatory response by antimicrobial killing of Pneumocystis organisms, resulting in deterioration of oxygenation during the first 3 to 5 days of treatment. In patients with precarious oxygenation at the start of therapy, such a deterioration in gas exchange may precipitate ARF. Use of anti-inflammatory corticosteroids can mitigate against this deterioration and has been shown to improve significantly the outcome of PCP-related ARF, but adjunctive therapy with corticosteroids may not be sufficient to prevent development of ARF within the first 5 days of therapy. Nevertheless, ARF in the early stages of therapy seems to be a reversible process that is amenable to supportive management. In contrast, development of ARF despite 5 or more days of maximal therapy may represent the consequence of virtually irreversible lung destruction that cannot be remediated even with aggressive supportive antimicrobial and anti-inflammatory therapy.

Patients developing ARF at fewer than 5 days of maximal therapy were indistinguishable from those developing ARF at a later point, implying that patients were admitted to the ICU with similar derangement of physiologic condition and burden of illness. It is not clear, therefore, whether earlier institution of critical care support could have altered our results. Furthermore, doing so would entail exposing many patients needlessly to the potential complications of critical care intervention and would mandate significant resource use that would be unnecessary in many cases.

Even when shown to have good predictive value, no physiologic score seems sufficiently reliable to direct clinical decision making. For instance, it is not clear that failure of individual organ systems can be weighted equally, and the aggregate performance of physiologic scores may not be applicable to individuals. Although duration of maximal therapy at the time of development of ARF is an easily identifiable and clinically relevant prognostic marker, it too may not be sufficiently predictive to direct decision making.

Our findings show that the predictive accuracy of physiologic scores and duration of maximal therapy is enhanced by their combination. Thus, the combination of a poor physiologic score (a modified MSOF score of >1 or an APACHE II score of >18) and prolonged duration of maximal therapy (≥5 days) predicts high in-hospital mortality. On the other hand, a low APACHE II or MSOF score and shorter duration of maximal therapy (<5 days) is associated with a better outcome, and other combinations predict an intermediate prognosis. This suggests that these prognostic variables indeed may be useful in identifying subgroups of patients likely to have a poor, moderate, or reasonably good chance of survival. However, given the small numbers of patients in our study, with wide CIs, this observation requires confirmation with a larger sample of patients.

The second important finding of our study is that the long-term survival of patients with PCP who develop respiratory failure requiring admission to the ICU is not different from the long-term survival of the entire cohort of patients admitted to the hospital with PCP during the same period. Although there is an obvious difference in median survival of patients with and without ARF (249 vs 386 days, respectively), this difference is caused by the higher in-hospital mortality of patients in whom PCP is complicated by ARF and does not alter the significance of the finding that there is no difference in overall long-term survival. Furthermore, no prognostic variable was predictive of time to death, which supports the findings of Nielsen et al. Our results emphasize the importance of offering maximal care to patients with AIDS-related PCP who develop ARF.

There are several limitations of this study. First, the number of patients studied is relatively small, with re-
sulting wide CIs. Nevertheless, the main differences identified in this study are statistically significant, correlate with findings of previous investigations, and are clinically plausible. Second, there is insufficient power to conclude that there are truly no differences in the other variables assessed. However, this does not detract from the difference in mortality and strength of predictability identified related to duration of maximal therapy and physiologic scores. Third, duration of therapy may be a surrogate for some other more important variable not identified. Fourth, the incremental effect on mortality of each additional day of previous maximal therapy could not be assessed because of the small number of patients. Nevertheless, comparing patients in 2 groups according to their having received fewer than vs at least 5 days of previous maximal therapy allows testing of the original observation of Staikowsky et al.\textsuperscript{15}

Finally, the short- and long-term survival of patients with respiratory failure related to PCP has changed throughout the AIDS epidemic,\textsuperscript{3} with corresponding changes in patterns of use of the ICU for such patients,\textsuperscript{18,20,31,52} and differing patient selection for critical care support.\textsuperscript{1,13} Thus, attitudinal changes may have enhanced observed differences if physicians had a low threshold for withdrawal of treatment in those believed to have a poor prognosis. Although there have been few advances in therapy for ARF secondary to AIDS-related PCP since the advent of corticosteroids for adjunctive treatment, it is premature to surmise that the observations in this and other recent studies will be unchanged, especially in the modern era of antiretroviral therapy. Increasing use of corticosteroids with less severe forms of PCP may affect substantially the outcome of patients with PCP-related respiratory failure.\textsuperscript{57

In summary, in a 5-year retrospective analysis of PCP-related respiratory failure, we demonstrated that inhospital mortality of patients with AIDS-related PCP and ARF is predicted by physiologic scores (especially the APACHE II and modified MSOF scores) and duration of previous maximal therapy with combined anti-PCP and corticosteroid treatment, and their combination enhances predictive accuracy. Furthermore, our results show that the long-term survival of patients with ARF caused by PCP is comparable to that of patients with PCP who do not develop ARF and that variables predictive of in-hospital mortality do not predict long-term survival.

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REFERENCES


