Decreasing Frequency But Worsening Mortality of Acute Respiratory Failure Secondary to AIDS-Related Pneumocystis carinii Pneumonia*

Philippa H. Hawley, MD; Juan J. Ronco, MD; Silvia A. Guillemi, MD; Jean Quieffin, MD; James A. Russell, MD; Lindsay M. Lawson, MD, FCCP; Martin T. Schechter, MD, MSc, PhD; and Julio S. G. Montaner, MD, FCCP

Objective: To describe changes in incidence and outcome of acute respiratory failure (ARF) due to AIDS-related Pneumocystis carinii pneumonia (PCP) at a tertiary care center over the 4-year period starting April 1, 1987 with reference to previously reported data from the preceding 6 years.

Methods: All patients admitted to St. Paul's hospital with a diagnosis of AIDS-related PCP during the study period were reviewed with regard to diagnostic, clinical, therapeutic, and outcome variables.

Results: A total of 456 episodes of PCP were diagnosed during the study period. These were compared against 127 cases diagnosed between 1981 and 1987. The frequency of hospitalization for PCP decreased to 78% in 1987 to 1991 from 100% in 1981 to 1987 (p=0.001). A similar decreasing trend was observed with regard to the incidence of PCP-related ARF that declined from 21% in 1981 to 1987 to 9% in 1987 to 1991 (p=0.009). Despite this, overall PCP-related mortality remained stable at 13% in 1981 to 1987 and 9% in 1987 to 1991 (p=0.26). The proportion of patients with PCP-related ARF who received mechanical ventilation decreased from 59% in 1981 to 1987 to 64% in 1987 to 1991 (p<0.001). Despite this, the case fatality rate among mechanically ventilated patients increased from 50% in 1981 to 1987 to 89% in 1987 to 1991 (p=0.003). These changes were associated with a significant change in the pattern of use of corticosteroids as adjunctive therapy for AIDS-related PCP. In 1985 to 1986, nearly 100% of patients admitted to the ICU received corticosteroids only after admission to the ICU, following the development of ARF. In contrast, in 1989 to 1990, 50% of patients were admitted to the ICU already receiving systemic corticosteroids. The rise in the proportion of patients receiving corticosteroids prior to ICU admission between these two intervals was statistically significant (p=0.017).

Conclusion: Our data show a decreasing frequency but a worsening mortality of ARF secondary to AIDS-related PCP. We conclude that ARF secondary to AIDS-related PCP developing despite maximal therapy, including adjunctive corticosteroids, carries a dismal prognosis.

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Key words: AIDS; corticosteroids; ICU; PCP; prognosis; respiratory failure; survival

The outcome of acute respiratory failure (ARF) among patients with AIDS-related Pneumocystis carinii pneumonia (PCP) has been extensively debated in the literature over the last decade. From 1981 to 1986, several series reported a uniformly poor prognosis for patients with AIDS-related PCP who required admission to intensive care units (ICU) for mechanical ventilation following the development of ARF.1-5 Hospital survival in these series was below 15%. Furthermore, only exceptional patients who were discharged from the hospital alive in these series survived for more than a few months thereafter, and therefore, clinicians and patients developed equally negative feelings toward ICU support in this situation.6,7

In late 1989, we reported a survival rate of 50% in patients who required mechanical ventilation for the support of ARF secondary to AIDS-related PCP.8 We
speculated at that time that the improved outcome was at least partially related to the use of adjunctive systemic corticosteroids. The beneficial effect of adjunctive corticosteroids in patients with ARF secondary to AIDS-related PCP was later confirmed in a placebo-controlled study. A similar benefit was shown in a larger, open-label study involving patients with varying degrees of respiratory involvement. However, this issue has not been reexamined in the context of recent therapeutic advances.

We undertook the present study to ascertain the mortality of ARF secondary to AIDS-related PCP in the 4-year period starting April 1, 1987, and to compare it with our previously reported experience.

METHODS

All cases of AIDS-related PCP in patients admitted to St. Paul’s Hospital (SPH) between April 1, 1987 and March 31, 1991 were identified from the hospital’s PCP registry. In addition, all patients with the hospital discharge diagnosis of PCP were identified through a computerized search of the Medical Records Department. Medical charts of patients who developed respiratory failure requiring mechanical ventilation were reviewed. Patients who died with a diagnosis of PCP prior to the institution of mechanical ventilation or who refused mechanical ventilation were also included in this review. All charts were reviewed using standardized case report forms with special emphasis on cause of admission to the ICU, use of mechanical ventilation, medications, and survival. The data collection was performed in the same fashion as in our previous report so that trends over time could be compared. Both cohorts are mutually exclusive. Additional drug use data were obtained from computerized pharmacy records.

Only patients in whom the diagnosis of PCP was microbiologically proved were included. Patients who were not actively treated for PCP, either as a result of the patient’s wishes or because the diagnosis was not suspected prior to the patient’s death, were excluded. Patients who required hospital readmission with an episode of PCP were considered as separate episodes if the hospital discharge date from the initial episode and the subsequent readmission date were more than 30 days apart; readmissions within a 30-day period were considered as a single PCP episode. Acute respiratory failure was defined as a PaO₂ <5 mm Hg while FiO₂ >0.6.

Proportions were compared using χ² test and Fisher’s exact test where appropriate. The Mantel trend test was used to analyze changes in proportions over time. All p values are two sided.

RESULTS

A total of 456 episodes of PCP were diagnosed between April 1, 1987 and March 31, 1991 (1987 to 91) at SPH. Of these, 78% were admitted to hospital for medical management. Ambulatory patients continued to be followed up through the hospital’s outpatient services. A total of 42 patients developed ARF, representing 9% of all PCP cases diagnosed during the study period. A total of 27 patients were mechanically ventilated, representing 64% of patients who developed ARF. Of these, 24 died as a result of progressive respiratory failure. This represents a mortality of 89% for ventilated PCP episodes. The three patients who survived mechanical ventilation died within 6 months of the ARF episode. One of them died during the same hospitalization, 19 days after ICU discharge from another AIDS-related condition. Of the two patients who survived to hospital discharge, one died 168 days later, 46 of which were spent in the hospital and the other died 32 days later, 23 of which were spent in the hospital.

Table 1 shows the incidence and selected associated outcomes of AIDS-related PCP at SPH from April 1, 1987 to March 31, 1991. A steady increase in the number of episodes of AIDS-related PCP occurred between 1987 and 1990 with a decrease after 1990, consistent with the implementation of PCP prophylaxis. The proportion of patients with hospitalization, the rate of ARF, the overall mortality, and the PCP-specific mortality remained relatively constant during the study. The annual number of ventilated patients with PCP-related ARF during the study period was 4, 12, 7, and 4 with a mortality of 75%, 83%, 100%, and 100%, respectively.

This contrasts with our experience during the years 1981 to 1987 as shown in Table 2 and Figure 1. During this period, 127 episodes of PCP were diagnosed with a hospital admission rate of 100%; ARF developed in 27 episodes (21%) and most of those (24 patients) were ventilated with a ventilatory mortality of 50%. Thus, between these two periods, there was a striking difference in the case-fatality rate among ventilated patients, which increased from 50% to 89% (p=0.003). A decrease in the rate of ARF per hospitalization (21% vs 9%; p=0.009) and a decrease in the frequency of ventilation per ARF episode (89% vs 64%; p<0.001) were observed during the study period. Severity of illness at the time of admission to ICU was estimated using the multisystem organ failure (MSOF) score, as previously described. The MSOF was 1.59 in 1981 to 1987
Table 2—Incidence, Complications, Ventilation, and Outcome of AIDS-Related PCP From Jan 1, 1981 to March 31, 1987 and the Subsequent 4 Years

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<tr>
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<tbody>
<tr>
<td>Episodes of PCP</td>
<td>127</td>
<td>456</td>
<td></td>
<td></td>
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<tr>
<td>Hospitalized episodes (% of episodes)</td>
<td>127 (100)</td>
<td>556 (78)</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>ARF (% of episodes)</td>
<td>27 (21)</td>
<td>42 (9)</td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>Deaths (% of episodes)</td>
<td>15 (12)</td>
<td>45 (10)</td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>Ventilated episodes (% of ARF)</td>
<td>12 (15)</td>
<td>39 (9)</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Case fatality rate of ventilated episodes (% of episodes)</td>
<td>12 (50)</td>
<td>24 (89)</td>
<td></td>
<td>0.003</td>
</tr>
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*See reference 8.

1.51 in 1987 to 1991 (p=0.99). Of note, all of the patients with nonventilated ARF episodes during the study period died during hospitalization with "do-not-resuscitate" orders.

Corticosteroid use in our patient population evolved rapidly over the last decade. Adjunctive corticosteroid therapy was not used until late in 1985. At that time, corticosteroids were generally reserved for patients with established respiratory failure. After 1987, based on the results of contemporary studies, there was a trend to the earlier use of corticosteroids, prior to the development of respiratory failure.8-10,15-17 Adjunctive corticosteroid therapy was used in 25% of patients hospitalized with a diagnosis of PCP in 1986 and 1987, against 75% of patients admitted to the hospital with the same diagnosis in 1991 (data not shown). In 1985/1986, nearly 100% of ICU admitted patients received corticosteroids only after admission to the ICU, following the development of ARF. In contrast, between 1989/1990, 50% of patients were admitted to ICU due to ARF that was refractory to systemic corticosteroid therapy. The rise in the proportion of patients treated with corticosteroids prior to ICU admission in these intervals was statistically significant (trend test p=0.017).

**DISCUSSION**

In contrast to previous reports,8-10,12,20 our data suggest that the prognosis of respiratory failure in the context of AIDS-related PCP is extremely poor, if this develops despite maximal therapy, namely antimicrobials and adjunctive corticosteroids.17 It must be emphasized that this may not apply to patients who present late, with established respiratory failure, as this would have developed prior to receiving maximal therapy.

We have been able to account for all diagnosed cases at SPH and we have failed to identify other potential sources for the rise in the case-specific mortality described above. The overall mortality of AIDS-related PCP during the study period remained relatively constant, between 6% and 11% per year. No pattern emerged after careful review of individual ventilated cases with regards to complications of their disease or of the ventilation itself that could account for the worsening in outcome. In particular, the MSOF score did not change significantly during the study. Therefore, the observed changes in mortality cannot be attributed to a selective admission to ICU of more severe cases in latter years.19

The decrease in hospitalizations between the two study periods could be attributed to earlier diagnosis and increased use of oral antimicrobials for the treatment of mild to moderate PCP.18 This would have acted as a conservative bias in the context of our study, as these patients remained under care of our outpatients services and were accounted for with regards to the study outcomes. Against this, we noticed a significant decrease in the frequency of respiratory failure that we can confidently attribute to the increased use of adjunctive corticosteroids on the basis of the available literature.8-18

As noted above, the overall mortality of AIDS-related PCP remained unchanged between the study periods; however, resource utilization changed dramatically as proportionally fewer patients required ventilatory support. The relative decrease in the proportion of patients with respiratory failure who were ventilated between the two study periods can be attributed to an increase in the number of patients presenting with PCP in addition to a multiple other medical problems during the terminal phase of the illness.19 Previous reports, including our own, suggest that survival of patients requiring ICU support in the context of advanced HIV disease decreases rapidly with the number of organs involved.19,21 Again, this would have acted as a conservative bias by discouraging ICU admission of patients perceived as having

**FIGURE 1.** Pattern of corticosteroid use among ICU-admitted patients with PCP between 1985 and 1990. The proportion of corticosteroid-treated patients receiving corticosteroids before (white bars) and after (black bars) ICU admission is shown.
the worse prognosis in the later phase of our study. Our results show a decreasing frequency but a worsening mortality of ventilated respiratory failure in the context of AIDS-related PCP (Tables 1 and 2). Earlier use of corticosteroids was documented during the study period (Figure 1). Although our data involve only an ecologic correlation, we believe that adjunctive corticosteroid use is responsible, at least in part, for the observed changes in outcome. A number of prospective studies have now confirmed the beneficial effect of corticosteroids in decreasing the mortality of respiratory failure due to AIDS-related PCP.9,10 Similarly, the effect of oral corticosteroids in preventing the development of respiratory failure among patients with moderately severe AIDS-related PCP has also been documented.13 Our data suggest that increased use of adjunctive corticosteroids led to a decrease in mortality from ARF due to AIDS-related PCP in our series during the years 1981 to 1987. Subsequently, with earlier and more liberal use of corticosteroids, before the development of respiratory failure, we have seen a decrease in the frequency of ARF in this disease. Unfortunately, the small number of patients who were admitted to the ICU for ventilator support, having failed adjunctive corticosteroid therapy, had a very dismal prognosis as shown by a mortality of 100% for the last 2 years of the study.

It must be emphasized that our data show a significant overall decrease in the frequency of ARF secondary to AIDS-related PCP that is attributable to improved management strategies. Despite these encouraging results, we found that the relatively small proportion of individuals who develop ARF despite maximal therapy have a very high mortality. We conclude, therefore, that the frequency of respiratory failure developing in the context of AIDS-related PCP has decreased significantly as a result of improved management strategies. However, patients who develop respiratory failure despite maximal medical therapy, including systemic corticosteroids, have a dismal prognosis.

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REFERENCES

3 Schein RMH, Fischl MA, Pitchenik AE, Sprung CL. ICU survival of patients with the acquired immunodeficiency syndrome: Crit Care Med 1986; 142:1026-27
13 Wachter RM, Luce JM, Hopewell PC. Critical care of patients with AIDS. JAMA 1992; 267:541-47