Acute Respiratory Failure Secondary to Pneumocystis carinii Pneumonia in the Acquired Immunodeficiency Syndrome*  
A Potential Role for Systemic Corticosteroids

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Pneumocystis carinii pneumonia (PCP) remains the most frequent life-threatening complication of HIV infection. A retrospective study was undertaken in an attempt to establish the incidence of acute respiratory failure (ARF) in AIDS-related PCP, its mortality, and the impact of adjunct systemic corticosteroids on its outcome. Of 127 AIDS-related PCP episodes diagnosed at St. Paul's Hospital between Jan 1, 1981, and March 31, 1987, 27 developed ARF (21 percent), and the 24 who consented to ICU admission for ventilatory support were reviewed. All were given IV pentamidine or trimethoprim-sulfamethoxazole or both sequentially. Overall mortality of ARF secondary to AIDS-related PCP was 50 percent. The use of adjunct systemic corticosteroids was associated with a decreased mortality. Of the 15 patients treated with IV hydrocortisone (400 to 1,000 mg/day in divided doses for the duration of ARF followed by a tapering regimen over 10 to 15 days), seven (39 percent) died, while five of six (84 percent) treated without corticosteroids died (p = 0.05). Survivors received ventilation for 5 ± 2 (mean ± SD) days and all were discharged from hospital after 20 ± 4 days. Survivors were also younger (34 ± 8 vs 43 ± 10 years, p = 0.034) and presented earlier (14 ± 3 vs 34 ± 7 days after onset of symptoms p = 0.017). Known AIDS, previous PCP episodes, and arterial blood gas values at the onset of ARF did not correlate with outcome. We conclude that ARF secondary to AIDS-related PCP merits aggressive management. In particular, younger patients presenting early after the onset of respiratory symptoms appear to have a better prognosis. The decreased mortality associated with the use of adjunct corticosteroids supports the need for prospective controlled evaluation of this therapeutic modality.

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Pneumocystis carinii pneumonia (PCP) remains the most frequent serious opportunistic infection in patients with infection by the human immunodeficiency virus (HIV). Either alone or in combination with other organisms, Pneumocystis carinii (Pc) causes 85 percent of their respiratory infections.1-3 Although the prognosis for PCP has been favorably altered by the use of specific antimicrobials, the mortality of this condition when acute respiratory failure (ARF) develops remains higher than 80 percent.4-5 In 1985, two cases were reported in which AIDS-related PCP had a favorable response to corticosteroid therapy.6,7 Since then an additional 40 cases have been reported in which corticosteroids were used as adjunctive therapy for severe AIDS-related PCP.8-13 Of a total of 42 reported cases, there were only four deaths (9.5), which is in contrast with a 40 percent mortality among 22 nontoxic steroid-treated historical control subjects in these series.8-9 These corticosteroid-treated patients were in moderate respiratory distress, as demonstrated by the fact that only seven of them received mechanical ventilation.9,10,12 More recently a 33 percent mortality was reported among six mechanically ventilated patients whose AIDS-related PCP was treated with adjunctive corticosteroid therapy.14

Despite these isolated encouraging reports, evidence from the literature suggests that corticosteroids may have a PCP-promoting effect,15,17 further supported by the use of corticosteroids in the commonly used animal model of PCP.18 Since 1985, and despite the above-mentioned controversy, corticosteroids were adopted in St. Paul's Hospital for the treatment of ARF secondary to AIDS-related PCP. The present review was undertaken to identify the impact of adjunctive corticosteroid therapy on this group of critically ill patients. We found that the use of corticosteroids was associated with a reduction of mortality.

Material and Methods

Records of all patients with AIDS who had bacteriologically proven PCP treated at St. Paul's Hospital from Jan 1, 1981, until March 31, 1987, were reviewed (n = 127). Twenty-seven patients who required intensive care (ICU) admission for ventilatory support due to the development of ARF were identified. ARF was defined as the inability to maintain arterial oxygen tension over 50 mm Hg despite maximal inspired fraction of oxygen by face mask necesi-
Table 1—Clinical, Laboratory, and Treatment Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr (± SD)</td>
<td>34 ± 8</td>
<td>43 ± 10*</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>12:0</td>
<td>10:2</td>
</tr>
<tr>
<td>First PCP episode</td>
<td>10 (83)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Homosexual</td>
<td>12 (100)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Transfusion-related HIV</td>
<td>0</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Prior diagnosis of AIDS</td>
<td>6 (50)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Pentamidine alone</td>
<td>6 (50)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>TMX-SMX alone</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pentamidine then TMX-SMX</td>
<td>2 (17)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>TMX-SMX then pentamidine</td>
<td>4 (33)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Symptoms prior to admission, days (± SD)</td>
<td>14 ± 11</td>
<td>34 ± 23±</td>
</tr>
<tr>
<td>pH, (± SD)</td>
<td>7.41 ± 10</td>
<td>7.37 ± 65</td>
</tr>
<tr>
<td>PaCO₂, mm Hg (± SD)</td>
<td>38 ± 11</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>P(A-a)O₂, mm Hg (± SD)</td>
<td>409 ± 154</td>
<td>419 ± 105</td>
</tr>
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*p = 0.034.

†p = 0.017.

The prevalence of ARF among patients with AIDS-related PCP was 21 percent. Three patients with ARF who refused ventilatory support and received regular antimicrobial therapy and no adjunctive corticosteroids died during the episode. These were not included in the present series. Among the 24 patients admitted to the ICU for ventilatory support, 22 were men. One man and two women had contracted HIV infection through transfusions. There were no IV drug abusers (Table 1).

The diagnosis of PCP was obtained bronchoscopically in 22 cases and by open lung biopsy in two cases in whom the diagnosis of PCP was unsuspected. Sputum examination for PC was not routinely done at St. Paul's Hospital. ARF developed within eight days of the bacteriologic confirmation of PCP in all cases. Patients were treated with conventional antimicrobial regimens consisting of either trimethoprim-sulfamethoxazole (TMX-SMX, 20-100mg/kg) or pentamidine isethionate (4 mg/kg) given IV for not less than 14 days. Survival was defined as recovery sufficient to permit discharge from hospital. Variables measured included age, sex, risk factors for HIV disease, duration of respiratory symptoms prior to hospitalization, prior diagnosis of AIDS, prior episodes of PCP, antimicrobial therapy, arterial blood gas values, alveolar-arterial oxygen tension difference, or P(A-a)O₂, after admission to the ICU, and use of adjunctive systemic corticosteroid therapy. Systemic corticosteroids were administered at the onset of ARF according to the preference of the treating physician in an unselected fashion. Patients so treated received 400 to 1,000 mg/day of IV hydrocortisone in divided doses for the duration of ARF, followed by a tapering regimen over ten to 15 days. Continuous variables of survivors and nonsurvivors were compared using a t test. Survival among the corticosteroid-treated patients was compared with that of noncorticosteroid-treated patients using a χ² analysis.

**Results**

Overall mortality for treated ARF secondary to AIDS-related PCP was 50 percent. Figure 1 demonstrates that adjunctive systemic corticosteroid therapy was largely responsible for this reduction in mortality. Among the 18 corticosteroid-treated patients there was a 39 percent mortality, while 84 percent (five of six) of the noncorticosteroid-treated patients died (p = 0.05). Survivors required ventilatory support for 5 ± 2 days, and eventually all were discharged back to the community after 20 ± 4 days. Nonsurvivors received ventilation for 11 ± 6 days and were hospitalized for 20 ± 6 days prior to their demise. As shown in Table 1, survivors were also younger (34 ± 8 vs 43 ± 10 years p = 0.034) and presented earlier (14 ± 11 vs 34 ± 23 days after onset of symptoms p = 0.017) than nonsurvivors. Prior diagnosis of AIDS, prior PCP episodes, arterial pH, PCO₂, and P(A-a)O₂ after admission to ICU of survivors and nonsurvivors did not differ. All three patients with transfusion-related AIDS died during their first episode of PCP. Antimicrobial therapy was not different between survivors and nonsurvivors.

**Discussion**

The present study suggests that the addition of systemic corticosteroids to the usual antimicrobial regimens can reduce mortality of patients with ARF secondary to AIDS-related PCP (Fig 1). The 30 percent mortality among the corticosteroid-treated patients in this series compares favorably with an 84 percent mortality among the noncorticosteroid treated group (p = 0.05). Although our noncorticosteroid group is small, its mortality is similar to that of larger series. Physicians' attitudes based on such reports have been biased towards advising against ventilatory support of these patients. Further, patients themselves have often been reluctant to undergo mechanical ventilation for the same reasons, perpetuating the impression that ARF secondary to AIDS-related PCP carries a dismal prognosis. Although previous series drew attention to a potential benefit of using corticosteroids in PCP, our report is the first to show such a benefit in critically ill patients with respiratory failure. This is of particular importance in view of recent reports show-
ing no benefit of corticosteroids in other forms of ARF.\textsuperscript{10-22} The mechanism by which corticosteroids could alter the course of PCP in AIDS remains unclear. HIV-infected patients have a profound deficit in their cellular immunity.\textsuperscript{23} When confronted with a critical mass of PC organisms, they generate an inflammatory exudate rich in immunoglobulins, as demonstrated by bronchoalveolar lavage studies.\textsuperscript{24-27} We speculate that this inflammatory response is unable to deal with the organisms in the absence of an intact cellular immunity and eventually floods the alveolar spaces, leading to ARF. Corticosteroids could control this inordinate response, allowing for the antimicrobials to reduce the organism load below a critical threshold and therefore controlling the disease process.

All survivors in our series were successfully weaned from ventilatory support within a week. This supports our hypothesis, since previous reports have documented that the response to antimicrobials in this condition tends to be slow, requiring between five and nine days before a significant symptomatic improvement is achieved.\textsuperscript{28} Corticosteroids therefore could act in this early phase, suppressing symptoms and reversing respiratory failure, allowing for the antimicrobial effect to take place. Survivors in our series were also younger and presented earlier than non-survivors (Table 1). This supports the concept that early recognition and treatment has critical importance in terms of prognosis, as already suggested in the literature.\textsuperscript{2,23} Other variables (ie, nutritional support, mechanical ventilation, and antimicrobial therapy) did not differ between survivors and nonsurvivors.

Given the retrospective nature of our study, it is important to recognize its limitations. However, with Luce et al\textsuperscript{21} we concur that our results, together with those recently reported by Amundson et al\textsuperscript{24} and El-Sadr and Simberkoff,\textsuperscript{29} should stimulate further research aimed to prospectively evaluate potential prognostic factors and therapeutic modalities in these critically ill patients.

In summary, we reviewed our experience in the management of patients with ARF secondary to AIDS-related PCP, which suggests that earlier recognition and use of adjunctive corticosteroid therapy could improve survival in these patients. Prospective studies, some already underway,\textsuperscript{32} are needed to confirm these observations.

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