The Impact of Prophylaxis on Outcome and Resource Utilization in Pneumocystis carinii Pneumonia*

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Study objective: Pneumocystis carinii pneumonia (PCP) is a major late complication of HIV infection associated with morbidity and mortality. Because chemoprophylaxis is highly effective, cases of PCP can be viewed as failures in the management of HIV disease. Methods: We reviewed demographic, clinical, and cost data for all cases of confirmed HIV-related PCP at The Johns Hopkins Hospital in 1991 to determine consequences of missed prophylaxis. We also analyzed hospital discharge data for Maryland in 1991 to assess hospital charges, length of stay, and outcome for all patients with a principal diagnosis of HIV-related PCP. Results: Pneumocystis carinii pneumonia was diagnosed in 79 patients. Of the 79 patients, 61 (77%) did not receive prophylaxis, including 26 who were not previously known to have HIV infection, 17 who did not have prophylaxis prescribed, and 18 who had prophylaxis prescribed, but were not compliant with the regimen. Patients not taking prophylaxis accounted for all 12 deaths ascribed to PCP. This group also accounted for 85% of the hospital days, 100% of the ICU days, and 89% of the inpatient charges. The total hospital charges were $549,540. Extrapolation of these figures for the state of Maryland suggest that the failure to receive prophylaxis in 1991 resulted in 62 patient deaths and a cost of approximately $4.7 million. Conclusion: Patients who developed PCP despite prophylaxis had a better outcome and used fewer resources than patients not receiving preventive therapy. This study emphasizes the impact of PCP prophylaxis on the morbidity, mortality, and economics of HIV health care.

C hemoprophylaxis for Pneumocystis carinii pneumonia (PCP) markedly decreases the incidence of and mortality from PCP, and contributes to improved survival of patients with human immunodeficiency virus (HIV) infection.1-10 Nevertheless, PCP continues to be an important cause of illness and death among patients with AIDS. Because PCP is a preventable disease, cases should be viewed as failures in the management of HIV disease. Pneumocystis carinii pneumonia may result from failure of the medical system to provide adequate health care, failure of patients to seek medical care or HIV testing or to comply with therapy, failure of medical providers to test patients for HIV or to provide PCP prophylaxis when indicated, or failure of the prophylactic regimen itself.

To evaluate the impact of prophylaxis on the outcome of patients who develop PCP and on hospital costs and the use of medical resources, we conducted a retrospective review of all cases of histologically confirmed PCP among adult HIV-infected patients at The Johns Hopkins Hospital in 1991. We also evaluated the impact of PCP on the state of Maryland for the same year, assessing total hospital charges, hospital and ICU days, and mortality.

METHODS

A retrospective chart review was conducted on all HIV-infected patients found to have P carinii on sputum or bronchoalveolar lavage smears at The Johns Hopkins Hospital from January 1 to December 31, 1991. Diagnosis of PCP was made using both Giemsa (Diff-Quik) and direct immunofluorescence stains.11 Data collected included patients' knowledge of their HIV status at the time of diagnosis, prior prescription of PCP prophylaxis, number of days hospitalized, number of ICU days, and survival. Total hospital charges were obtained from computerized hospital billing records for all patients who required admission to the hospital. Outpatient charges were not included. The inpatient charges were complete, with the exception of professional fees. Hospital charges reflect cost in Maryland according to regulations established by the Maryland Cost Review Commission.

Key words: AIDS; cost; HIV; outcomes research; Pneumocystis carinii pneumonia; prophylaxis

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Compliance with aerosolized pentamidine was assessed by compliance with scheduled visits for these treatments in the outpatient clinics; patients were listed as noncompliant if there had been no treatments during the 6 weeks prior to the diagnosis of PCP. Compliance with oral medications was based on chart data for both outpatient and inpatient records; in cases where compliance was not discussed in the medical record, the patient was assumed to be compliant. Regimens meeting the criteria for PCP prophylaxis included aerosolized pentamidine (300 mg monthly by Respigrad II nebulizer), trimethoprim-sulfamethoxazole (TMP-SMX) (minimum dose, one double-strength tablet three times weekly or one single-strength tablet daily), and dapsone (minimum dose, 150 mg weekly).

We also analyzed 1991 calendar year hospital discharge abstract data for all nonfederal, acute-care hospitals in Maryland. These data are maintained by the Health Services Cost Review Commission (HSCRC) of Maryland for all hospital admissions in order to regulate the rates charged by hospitals in the state.\(^\text{12}\) These anonymous data include principal and up to four secondary discharge diagnoses, length of hospital and ICU stays, and hospital charges for the admission. We selected all hospital admissions with a principal discharge diagnosis of PCP (ICD-9-CM 136.3) in which at least one secondary diagnosis also indicated infection with HIV (ICD-9-CM 0420.0-044.9, 795.8). We assessed the mean, median, and total hospital charges and length of stay for these patients.

Our analyses focused on patients who had been prescribed prophylaxis vs those who had not, and on patients taking prophylaxis vs those not. Statistical analyses comparing the association between dichotomous categorical variables were done using Fisher’s exact test. Statistical analyses comparing the association between length of hospital stay or hospital charges and dichotomous variables were done using the nonparametric Wilcoxon Rank-Sum Test.

\begin{table}[h]
\centering
\caption{Characteristics of Study Group}
\begin{tabular}{|l|c|}
\hline
Characteristic & No. (\%)
\hline
Sex & \\
Male & 62 (78)
Female & 17 (22)
\hline
Race & \\
White & 15 (19)
Black & 63 (80)
Hispanic & 1 (1)
\hline
HIV transmission group & \\
Homosexual & 29 (37)
Injecting drug use & 33 (42)
Heterosexual transmission & 11 (14)
Other & 2 (3)
Unknown & 4 (5)
\hline
HIV diagnosis at time of PCP & \\
Known & 53 (67)
Unknown & 26 (33)
\hline
PCP prophylaxis & \\
Never prescribed & 43 (54)
Prescribed & 36 (46)
Compliant & 18 (50)
Noncompliant & 18 (50)
\hline
Prophylaxis type & \\
Aerosol pentamidine & 26 (72)
Dapsone & 4 (11)
TMP/SMX & 6 (17)
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Prophylaxis Status Based on Demographic Characteristics}
\begin{tabular}{|l|c|c|c|}
\hline
Variable & Taking Prophylaxis, No. (\%) & Not Taking Prophylaxis, No. (\%) & p Value
\hline
Sex & \\
Male & 14 (23) & 48 (77) & >0.05
Female & 4 (24) & 13 (76) & \\
\hline
Race & \\
White & 7 (47) & 8 (53) & 0.014\(^\text{*}\)
Black & 11 (17) & 52 (83) & \\
Hispanic & 0 (0) & 1 (100) & \\
\hline
HIV transmission group & \\
Homosexual & 11 (38) & 18 (62) & 0.018\(^1\)
Injecting drug use & 4 (12) & 29 (88) & \\
Heterosexual & 3 (27) & 8 (73) & \\
Other & 0 (0) & 2 (100) & \\
Unknown & 0 (0) & 4 (100) & \\
\hline
\end{tabular}
\end{table}

*White vs nonwhite.
\(^1\)Homosexual vs injecting drug user.

\section*{Results}
A confirmed diagnosis of PCP was made in 79 patients at Johns Hopkins Hospital during the 1-year study period. Demographic characteristics of the study group and information related to prior PCP prophylaxis are shown in Table 1. Forty-three patients (54\%) had never had prophylaxis prescribed. Of those, 26 (60\%) had not been diagnosed with HIV before the episode of PCP, and 17 had a diagnosis of HIV but had never received chemoprophylaxis. The latter group included one patient who failed to return to the clinic after his initial visit, and 16 for whom outpatient records were not available, either because they had received no primary care or had received outpatient care elsewhere prior to their diagnosis of PCP. In those patients, information on prophylaxis was obtained from the outpatient medication list recorded at the time of admission to the hospital. Of the 36 (46\%) who had been prescribed prophylaxis, 18 (50\%) were assessed to be noncompliant. This noncompliant group included 13 prescribed aerosol pentamidine and five prescribed TMP-SMX. Thus, 61 patients (77\%) were not receiving PCP prophylaxis. The 18 compliant patients who developed PCP included 13 receiving aerosol pentamidine, 4 receiving dapsone, and 1 receiving TMP-SMX. There were no significant differences by race, sex, or HIV transmission category between groups who were prescribed prophylaxis and those who were not, or between those who were compliant or noncompliant (p>0.05). However, when these two reasons for lack of prophylaxis were combined, white patients and homosexuals were more likely to be taking prophylaxis than nonwhites (p<0.05) and injection drug users (p<0.05), respectively (Table 2).
Sixty-five patients (82%) were hospitalized for treatment of PCP, for a total of 937 hospital days (median, 9 days; range, 3 to 76 days). Ten patients (13%) required admission to the ICU, for a total of 202 ICU days (median, 20 days; range, 2 to 73 days). Twelve of the 79 patients (15%) died during hospitalization. Associations between prescription and use of prophylaxis with outcome variables are shown in Table 3. Two types of analysis were performed for each variable: an “intention-to-treat” analysis, in which patients who had been prescribed prophylaxis were compared with those who had not, and a “compliance” analysis, in which patients who were actually receiving prophylaxis were compared with those not taking prophylaxis for any reason. Only one patient who had been prescribed prophylaxis (3%) required admission to the ICU, compared with nine (21%) of those not prescribed prophylaxis (p<0.05). No patient who took prophylaxis required ICU admission. Eleven of 18 (61%) patients who took prophylaxis were hospitalized, compared with 54 of 61 (89%) who did not take prophylaxis (p<0.05). Twelve (20%) of the latter group died during hospitalization, whereas all patients who took prophylaxis survived their episode of PCP (p<0.05). Eleven of the 12 deaths were a result of respiratory failure that was attributed to PCP. The 12th patient died as a result of a gastrointestinal hemorrhage that developed while receiving mechanical ventilation for PCP. Two patients who died were never admitted to the ICU because of advance directives leading to Do Not Resuscitate orders.

To assess the impact of prophylaxis on the use of medical resources by patients with PCP at our institution, we examined the total number of hospital and ICU days required by patients in the two groups. Patients who did not take prophylaxis accounted for 800 (85%) of the 937 total hospital days and for all 202 of the ICU days (Table 4). Data on hospital charges for hospitalized patients were available on 63 of the 65 patients who required admission. The total hospital charges for the 63 patients were $849,540. The median charge was $9,014 (range, $2,127 to $148,842). Although differences in charges and length of stay based on prophylaxis status were not significant, charges for patients who were not taking pro-

### Table 3—Prophylaxis Status and Outcome From PCP

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Prophylaxis Prescribed, No. (%) (n=36)</th>
<th>Prophylaxis Not Prescribed, No. (%) (n=43)</th>
<th>p Value</th>
<th>Compliance Analysis</th>
<th>Not Taking Prophylaxis, No. (%) (n=61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td>27 (75)</td>
<td>38 (88)</td>
<td>0.12</td>
<td>11 (61)</td>
<td>54 (89)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ICU stay</td>
<td>1 (3)</td>
<td>9 (21)</td>
<td>&lt;0.05</td>
<td>0</td>
<td>10 (16)</td>
<td>0.06</td>
</tr>
<tr>
<td>Died</td>
<td>3 (8)</td>
<td>9 (21)</td>
<td>0.15</td>
<td>0</td>
<td>12 (20)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Table 4—Hospital Resources and Charges for Patients Admitted With PCP

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Prophylaxis Prescribed (n=27)</th>
<th>Prophylaxis Not Prescribed (n=38)</th>
<th>Compliance Analysis</th>
<th>Not Taking Prophylaxis (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hospital days</td>
<td>284</td>
<td>653</td>
<td>137</td>
<td>800</td>
</tr>
<tr>
<td>Median length of stay*</td>
<td>7</td>
<td>12</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>ICU days</td>
<td>14</td>
<td>188</td>
<td>0</td>
<td>202</td>
</tr>
<tr>
<td>Total charges</td>
<td>$225,437</td>
<td>$624,103</td>
<td>$95,932</td>
<td>$753,608</td>
</tr>
<tr>
<td>Median charge*</td>
<td>$8,097</td>
<td>$10,325</td>
<td>$5,524</td>
<td>$9,337</td>
</tr>
</tbody>
</table>

* Differences in length of stay and hospital charges were not significant by Wilcoxon-Rank Sum Test.

### Table 5—Hospital Days, Charges, and Outcome for Patients Hospitalized With PCP at Johns Hopkins and Maryland Hospitals in 1991

<table>
<thead>
<tr>
<th></th>
<th>Johns Hopkins</th>
<th>Maryland</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>65</td>
<td>424</td>
</tr>
<tr>
<td>Total charges</td>
<td>$849,540*</td>
<td>$5,315,991</td>
</tr>
<tr>
<td>Mean charge</td>
<td>$13,485*</td>
<td>$12,558</td>
</tr>
<tr>
<td>Median charge</td>
<td>$9,014*</td>
<td>$8,513</td>
</tr>
<tr>
<td>Hospital days</td>
<td>937</td>
<td>6,099</td>
</tr>
<tr>
<td>Mean length of stay, d</td>
<td>14.4</td>
<td>13.4</td>
</tr>
<tr>
<td>Median length of stay, d</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>ICU days</td>
<td>202</td>
<td>576</td>
</tr>
<tr>
<td>Mortality, No. (%)</td>
<td>12 (18)</td>
<td>62 (15)</td>
</tr>
</tbody>
</table>

* Based on data from 63 patients.
prophylaxis were $753,608, or 89% of the total charges.

Our analysis of the Maryland HSCRC data revealed that hospital charges for the 424 patients admitted to the hospital with a primary diagnosis of HIV-related PCP in 1991 were $5,315,991, with a median charge of $8,513 and a mean charge of $12,538 per admission (Table 5). This represents 19% of the total charges ($27,429,604) for the 2,561 patients admitted to the hospital with AIDS in 1991. Patients with PCP accounted for a total of 6,099 hospital days (median length of stay, 11 days) and 576 ICU days. Approximately half of the patients (210/424) were funded from federal resources, primarily Medicaid, and 15% (62/424) were uninsured. Sixty-two patients (15%) died during hospitalization.

DISCUSSION

The benefit of primary and secondary prophylaxis of PCP has been well documented. As a result of prophylaxis and improved care for patients with HIV disease, the incidence of PCP has declined, and PCP has become an uncommon cause of death among patients with AIDS who receive adequate medical care. In our study, 77% of the patients diagnosed as having PCP in 1991 had either never been prescribed prophylaxis or were noncompliant, and 27% had not been diagnosed as having HIV infection. These data underscore the importance of early detection of HIV infection and institution of prophylaxis in patients at risk for PCP.

We found that patients who developed PCP despite receiving prophylaxis were less likely to require hospitalization or ICU admission for treatment of their pneumonia. None of those patients died during their illness, compared with 12 (20%) of those who were not taking prophylaxis before the onset of PCP, all of whom died as a result of PCP or of complications related to its therapy. Patients not taking prophylaxis accounted for 83% of the 937 hospital days and all of the 202 ICU days of admissions for PCP to The Johns Hopkins Hospital in 1991.

Because the patients in this study did not have uniform outpatient care at a single clinic or institution, the cost of outpatient treatment and prophylaxis could not be determined. However, the cost-effectiveness of outpatient vs inpatient therapy and of all forms of Pneumocystis prophylaxis have been amply demonstrated. The total hospital charges for patients admitted to The Johns Hopkins for PCP were $850,000, 89% of which were incurred by patients who had not been taking prophylaxis prior to their illness. While hospital charges do not necessarily reflect the true costs of care, our findings are reflective of a trend toward disproportionate utilization of inpatient resources by HIV-infected patients who are noncompliant or not receiving adequate primary care.

To place our findings in a larger context, we analyzed the 1991 calendar year hospital discharge data for all nonfederal, acute-care hospitals in Maryland. We found that hospital charges for patients admitted with a primary diagnosis of HIV-related PCP in 1991 were over $5.3 million, with a median charge of $8,500 per admission, representing 19% of the total charges for patients hospitalized with AIDS. These patients accounted for over 6,000 hospital days and almost 600 ICU days. Fifteen percent died during hospitalization. Although data on Pneumocystis prophylaxis is not available for those patients, if the experience at our hospital is representative and we extrapolate our findings to the state of Maryland, effective implementation of prophylaxis could presumably have averted 62 deaths and approximately $4.7 million in hospital costs. Clearly, hospitals vary widely in the populations they serve and in their criteria for hospital admission and discharge. Furthermore, variation in hospital experience with PCP has been shown to be associated with differences in mortality. Nevertheless, the estimate based on the experience at The Johns Hopkins Hospital serves to highlight the potential costs and consequences of the underdiagnosis of HIV, poor access to health care, and noncompliance with medical therapy.

There are a number of limitations to a retrospective study such as this one. Outcome measures such as hospital stay and death are only indirect measures of the severity of PCP. Patients receiving prophylaxis may have better access to medical care than patients not receiving prophylaxis, and may be more aware of or attentive to symptoms of PCP. They are also more likely to be taking antiretroviral therapy and therapy directed at other HIV-related conditions. Patients not receiving primary care may have concurrent untreated illnesses that could contribute to mortality or prolonged hospital stay. The need for hospitalization is not necessarily a good indicator of severity of disease, since a patient with access to primary medical care may be less likely to be admitted to the hospital than a patient with no medical care or no prior HIV diagnosis. Social factors may also have contributed to need for or length of hospitalization. Furthermore, such patients may be more likely to delay seeking medical attention for pneumonia until the condition has become more severe, or may be more likely to have PCP misdiagnosed because of lack of knowledge of their underlying HIV infection or degree of immunosuppression. Finally, to collect data on both inpatients and outpatients with PCP, we analyzed only microbiologically confirmed cases. Although empiric therapy for PCP is discouraged at our institution, it is likely that many cases of PCP were diag-
nosed and treated presumptively, and that our selection criteria would tend to identify a disproportionate number of sicker patients requiring hospitalization. Nevertheless, the striking differences in outcome, and especially in ICU admission and mortality due to PCP, support a benefit from prophylaxis even when it fails to prevent PCP.

Compliance could be measured objectively in patients receiving aerosolized pentamidine, who represented 72% of the patients taking prophylaxis. For the remaining patients, we relied on the statements by the treating physician recorded in the medical record to assess compliance. Because of the obvious relevance of compliance with prophylaxis to the development of PCP, this was usually addressed in the hospital admission note or clinic note, but in a prospective study, compliance could be assessed more directly. By assuming that the patient was compliant when compliance was not mentioned in the medical record, we minimized the likelihood of a type I error. In light of existing data, it is unlikely that compliance with prophylaxis would be associated with a poorer outcome. Therefore, if our assumption were incorrect and noncompliant patients were misclassified as being compliant, the effect would be only to decrease the difference between groups.

In the second decade of the AIDS epidemic, individuals who develop PCP, and especially those who are hospitalized or die as a result, will be very different from those who developed PCP before the widespread use of chemoprophyaxis. Most of the estimated 1 million HIV-infected men and women in the United States are unaware of their HIV infection16-20 and do not benefit from early intervention. The demographics of the AIDS epidemic have shifted, so that racial and ethnic minorities are now overrepresented among those with HIV infection, and intravenous drug use and heterosexual contact make up increasingly important routes of transmission.21-25 A growing proportion of HIV-infected individuals are uninsured and have problems with access to health care.26-29 This results in difficulties in obtaining primary medical care, which can lead to increased morbidity and mortality from preventable illness. For example, in Baltimore, blacks were found to be significantly less likely than whites to have received appropriate antiretroviral therapy or PCP prophylaxis before their referral to an HIV clinic,30 and in the present study, blacks and intravenous drug users were less likely to have been taking Pneumocystis prophylaxis before the development of PCP.

Our findings are consistent with other studies showing the negative consequences of inadequate therapy for advanced HIV disease31,32 and illustrate the disproportionate use of medical resources by patients without appropriate primary care. Our findings emphasize the importance of early diagnosis of HIV infection and of institution of prophylaxis in patients at risk for PCP. Although the choice of prophylactic regimens is an important consideration, access to primary health care, early detection of HIV infection, and compliance with appropriate preventive therapy are ultimately as important or more important in decreasing morbidity, mortality, and cost associated with PCP and AIDS.

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