Clindamycin/Primaquine as Prophylaxis for *Pneumocystis carinii* Pneumonia

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The records of 206 patients with advanced infection due to human immunodeficiency virus type 1 who were receiving prophylaxis with clindamycin/primaquine (C/P), trimethoprim-sulfamethoxazole (TMP-SMZ), or dapsone to prevent *Pneumocystis carinii* pneumonia (PCP) were retrospectively examined. Two hundred sixty-two patient-years of prophylaxis were accrued (176.2 of TMP-SMZ, 63.4 of dapsone, and 22.8 of C/P). The rates of PCP in the TMP-SMZ, dapsone, and C/P groups were 3.4, 11.0, and 30.7 per 100 patient-years, respectively. Pairwise comparisons showed C/P to be less effective than TMP-SMZ (relative risk [RR], 9.02; 95% confidence interval [CI], 3.03–26.83).

A similar trend was apparent for C/P vs. dapsone (RR, 2.78; 95% CI, 0.98–7.93). When only those receiving primary prophylaxis were analyzed, C/P recipients remained at greater risk than TMP-SMZ recipients (RR, 13.19; 95% CI, 3.54–49.12) and dapsone recipients (RR, 3.85; 95% CI, 1.12–13.31). Failure of C/P prophylaxis could be due, at least in part, to underdosing (clindamycin, 300 mg/d; primaquine, 15 mg/d). C/P recipients had more nonspecific diarrhea than did TMP-SMZ recipients (RR, 2.99; 95% CI, 1.61–5.55).

**Methods**

The inpatient and outpatient medical records of patients infected with HIV who were being actively observed by the Infectious Diseases Section of Bowman Gray School of Medicine were reviewed. These patients received essentially all of their care at our institution and, thus, records were believed to be complete. In the rare instances when subjects had been evaluated at other health care facilities, all appropriate medical records were obtained if possible.

Patients were evaluated if at least one of their absolute CD4 cell counts was <200/µL and if they were taking TMP-SMZ, dapsone, or C/P as prophylaxis for PCP. The dosage was considered high if a patient was taking at least 160/800 mg of TMP-SMZ daily, 100 mg of dapsone daily, or 300 mg and 15 mg, respectively, of C/P; dosages less than these (e.g., three-times-a-week regimens) were considered low. No measure of compliance was available for any of the prophylactic regimens.

PCP prophylaxis was classified into two categories, according to patients’ CD4 cell counts. Prophylaxis occurring when a subject’s CD4 cell count was 101–200/µL was categorized as CD4 > 100, whereas CD4 ≤ 100 denoted prophylaxis administered after the first measured CD4 cell count of ≥100/µL. Prophylaxis was further characterized as primary (for patients never having had PCP) or secondary (following an episode of PCP).

Efficacy was evaluated only for regimens that lasted at least 60 days. This minimized the possibility that an episode of PCP was due to subclinical disease present before initiation of the patient’s indicated prophylactic regimen. Failure rates were calculated per 100 patient-years. Diagnostic evaluation of ill subjects was dependent upon the practices of individual clinicians but typically included routine blood cell counts, serum chemistries, determinations of arterial oxygenation, expectorated sputum stains and cultures, and blood cultures; occasion-
ally, bronchoalveolar lavage and stains of the fluid were performed.

PCP was defined as probable if all five of the following criteria were met: (1) a clinically compatible syndrome including fever, cough, and dyspnea; (2) a chest radiograph showing a diffuse interstitial infiltrate; (3) evidence of abnormal oxygenation or a lactate dehydrogenase level of >300 IU/mL (normal, 90–250 IU/L); (4) a clinical response to standard PCP therapy or death; and (5) no etiology, other than PCP, identified to account for these abnormalities.

No autopsies were performed on the three subjects whose death was a qualifying criterion for probable PCP. PCP was defined as definite when the above criteria were met and evidence of *P. carinii* was revealed by direct fluorescence antibody testing of bronchoalveolar lavage fluid or expectorated sputum. PCP prophylaxis was considered to have failed if probable or definite PCP developed.

Episodes of disseminated infection due to *Mycobacterium avium* complex and cerebral toxoplasmosis were recorded if they occurred during administration of one of the PCP prophylactic regimens under investigation.

Side effects attributed to the PCP prophylaxis and resulting in the discontinuation of a particular regimen were recorded, regardless of the duration of the regimen. Hypersensitivity reactions included urticaria, pruritis, dermatitis, fever, and malaise. Hematologic side effects included cytopenia and methemoglobinemia. Gastrointestinal side effects included nausea, vomiting, diarrhea, and pancreatitis. Only side effects that resulted in discontinuation of the regimen (i.e., were treatment-limiting) were recorded, with the exception of diarrhea.

Diarrhea was recorded whenever a clinically diagnosed episode was noted in the patient’s chart. The episode of diarrhea was considered nonspecific if no diagnostic tests were ordered or if tests did not identify an etiology. *Clostridium difficile* colitis was diagnosed if stool toxin assays and/or cultures were positive and the clinical setting was appropriate. Other causes of diarrhea such as *Cryptosporidium parvum* and *Giardia lamblia* were occasionally sought, but no cases were identified in our review.

Data were transcribed on a data collection sheet and entered into an Epi-Info database (version 6.02; Centers for Disease Control and Prevention, Atlanta). All data entries were verified by an independent operator. Statistical analyses were performed with Epi-Info and SAS software (SAS Institute, Cary, NC). The rates of PCP and nonspecific diarrhea per each drug regimen were expressed as incidence density (the total number of events, divided by the number of patient-years of a given treatment × 100). Course-limiting side-effect rates were calculated by number of events per episode of exposure.

Categorical variables were statistically evaluated with Fisher’s exact test. Bonferroni adjustments were employed in the pairwise analyses of each hypothesis to allow for multiple comparisons. The multivariate analysis used stepwise model building in a multiple regression model utilizing the following variables: drug regimen (TMP-SMZ vs. dapsone vs. C/P), CD4 cell count (>100/µL vs. ≤100/µL), primary vs. secondary prophylaxis, and dose (low vs. high).

## Results

A total of 527 patients were reviewed, of which 206 patients met the eligibility criteria for PCP prophylaxis (as outlined in Methods). A total of 262.4 patient-years of prophylaxis were accrued (22.8 of C/P, 176.2 of TMP-SMZ, and 63.4 of dapsone). Two hundred eighty-nine separate prophylactic courses were given; there were 32 exposures to C/P, 182 exposures to TMP-SMZ, and 75 exposures to dapsone. No significant difference existed between the prophylactic regimens with regard to gender, race, or age.

There was a higher percentage of patient-years of secondary prophylaxis in the C/P group (40%) than in the TMP-SMZ group (19%) and dapsone group (17%), but this did not reach statistical significance (*P* = .06). A significantly higher percentage of patient-years was accrued by subjects whose CD4 cell counts were ≤100/µL in both the C/P group (90%) and the dapsone group (87%), in comparison with the TMP-SMZ group (69%) (*P* = .002). The percentage of patient-years of prophylaxis with low-dose regimens (table 1) was not significantly different between C/P (68%), TMP-SMZ (55%), and dapsone (44%) recipients (*P* = .10).

There were 20 cases of probable or definite PCP in which prophylaxis failed. There were 7 failures of C/P (3 definite cases), 6 of TMP-SMZ (1 definite), and 7 of dapsone (2 definite), resulting in failure rates of 30.7, 3.4, and 11.0 events per 100 patient-years, respectively. Pairwise comparisons (with use of a Bonferroni adjusted level for α of 0.05/3 = 0.017) revealed a significantly higher failure rate for C/P than for TMP-SMZ (*P* = .002; RR, 9.02; CI, 3.03–26.83). Higher failure rates of borderline significance were also noted for dapsone vs.

### Table 1. Summary of data concerning subjects who received indicated prophylaxis for PCP.

<table>
<thead>
<tr>
<th>Variable</th>
<th>C/P</th>
<th>TMP-SMZ</th>
<th>Dapsone</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (% of n)</td>
<td>83</td>
<td>83</td>
<td>86</td>
<td>. . .</td>
</tr>
<tr>
<td>Caucasians (% of n)</td>
<td>53</td>
<td>47</td>
<td>54</td>
<td>. . .</td>
</tr>
<tr>
<td>No. of patient-years of prophylaxis</td>
<td>22.8</td>
<td>176.2</td>
<td>63.4</td>
<td>. . .</td>
</tr>
<tr>
<td>Percentage accrued as indicated type*</td>
<td>68</td>
<td>55</td>
<td>44</td>
<td>.10</td>
</tr>
<tr>
<td>Low-dose</td>
<td>68</td>
<td>55</td>
<td>44</td>
<td>.10</td>
</tr>
<tr>
<td>Secondary</td>
<td>40</td>
<td>19</td>
<td>17</td>
<td>.06</td>
</tr>
<tr>
<td>CD4 ≤ 100</td>
<td>90</td>
<td>69</td>
<td>87</td>
<td>.002</td>
</tr>
</tbody>
</table>

NOTE. C/P = clindamycin and primaquine; PCP = *P. carinii* pneumonia; TMP-SMZ = trimethoprim-sulfamethoxazole.

* See Methods for definitions of types of prophylaxis.
Similar findings were apparent when only data for patients with definitively diagnosed PCP were analyzed, but the confidence intervals became wider because of the small number of subjects. Pairwise comparisons demonstrated a higher failure rate for C/P vs. TMP-SMZ \((P = .005; \text{RR} = 23.2; \text{CI}, 2.41 - 222.9)\) and borderline higher rates for C/P vs. dapsone \(P = .12; \text{RR}, 4.17; \text{CI}, 0.70 - 24.96)\).

A total of 4 patients received treatment for PCP but did not meet the criteria for probable or definite PCP (2 in the C/P group and 1 each in the TMP-SMZ and dapsone groups). Inclusion of these subjects with possible PCP did not substantially alter the results.

Only one failure involved a subject whose absolute CD4 cell count was \(>100/\mu\text{L}\). Restricting the analysis to patient-years of prophylaxis accrued when the patients' CD4 cell counts were \(\leq 100/\mu\text{L}\) resulted in the following failure rates: 34.1, 4.1, and 12.8 events per 100 patient-years for C/P, TMP-SMZ, and dapsone, respectively. Pairwise comparisons, again with Bonferroni adjustment, demonstrated a persistently greater failure rate for C/P vs. TMP-SMZ \((P = .0005; \text{RR}, 8.27; \text{CI}, 2.62 - 26.06)\) and a similar trend with regard to C/P vs. dapsone \((P = .07; \text{RR}, 2.68; \text{CI}, 0.94 - 7.64)\) and dapsone vs. TMP-SMZ \((P = .06; \text{RR}, 3.09; \text{CI}, 0.98 - 9.73)\).

Because the percentage of total patient-years accrued as secondary prophylaxis for PCP was significantly greater in the C/P group than in the other two groups, efficacy rates were further evaluated in all three treatment groups after stratification by this variable. Rates of failure for subjects receiving primary prophylaxis were 36.8, 2.8, and 9.5 events per 100 patient-years for C/P, TMP-SMZ, and dapsone regimens, respectively. Pairwise comparisons revealed significantly greater failure rates for primary prophylaxis with C/P than for TMP-SMZ \((P = .0005; \text{RR}, 13.19; \text{CI}, 3.54 - 49.12)\) and, again, greater failure rates of borderline significance for C/P than for dapsone \((P = .04; \text{RR}, 3.85; \text{CI}, 1.12 - 13.31)\).

**Table 2.** Incidence of probable or definite PCP per 100 patient-years of prophylaxis among subjects receiving clindamycin/primaquine (C/P), trimethoprim-sulfamethoxazole (TMP-SMZ), or dapsone.

<table>
<thead>
<tr>
<th>Type of prophylaxis (total no. of patient-years)</th>
<th>No. of events of PCP per 100 patient-years, per prophylaxis group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (262.4)</td>
<td>C/P</td>
</tr>
<tr>
<td>CD4 (\leq 100) (196.5)</td>
<td>30.7*</td>
</tr>
<tr>
<td>Primary (209.5)</td>
<td>36.8*</td>
</tr>
<tr>
<td>Secondary (42.9)</td>
<td>21.7</td>
</tr>
</tbody>
</table>

**NOTE.** See Methods for definitions of types of prophylaxis. PCP = *P. carinii* pneumonia.

\* \(P < .01\) vs. TMP-SMZ.

\[ P < .001 \] vs. TMP-SMZ.

\[ P < .05 \] vs. dapsone.

Failure rates were not significantly different between groups in this study, which had limited power (table 2). Multivariate analysis of the entire study cohort revealed that the most important risk factor for acquiring PCP during the study was treatment with C/P \((P = .0001, \text{with use of the TMP-SMZ group as a reference})\), followed by a CD4 cell count of \(\leq 100/\mu\text{L}\) \((P = .03)\). No other variables reached significance in this analysis.

Seventy cases of diarrhea, 68 cases of nonspecific diarrhea, and 2 cases of *C. difficile* colitis were identified: 14 cases occurred in the C/P group, 36 in the TMP-SMZ group, and 20 in the dapsone group, resulting in 60, 20, and 31 episodes of diarrhea per 100 patient-years of prophylaxis, respectively. The diarrhea rate was significantly greater in association with C/P than with TMP-SMZ \((P = .001; \text{RR}, 2.99; \text{CI}, 1.61 - 5.55)\) at an adjusted level of \(\alpha = 0.017\), and a similar trend was noted for C/P vs. dapsone \((P = .08; \text{RR}, 1.93; \text{CI}, 0.98 - 3.82)\).

Course-limiting side effects totalled 83 (58 hypersensitivity, 14 hematologic, and 11 gastrointestinal effects). There were no significant differences between prophylactic regimens with regard to the overall number of treatment-limiting side effects or any specific side-effect category (table 3).

Only three cases of cerebral toxoplasmosis and nine cases of disseminated MAC infection were documented among the study patients, and the relative risk for these illnesses was not different between treatment groups.

**Discussion**

The percentage of patients infected with HIV who acquire PCP has significantly declined since the introduction of prophylaxis; however, PCP still occurs in up to 28% of such patients during the course of their illness \([8]\). Identified factors associated with the failure of prophylaxis include a CD4 cell count of \(\leq 100/\mu\text{L}\), use of aerosolized pentamidine, and use of low-dose \((\leq 50 \text{mg/d})\) dapsone \([1, 2]\). The efficacy of TMP-SMZ has been demonstrated to be superior to that of dapsone or aerosolized pentamidine in several studies \([9, 10]\), but rates of discontinuation of TMP-SMZ regimens due to side effects range from 13% to 27% \([2, 11, 12]\). In addition to having low efficacy, aerosolized pentamidine has been associated with the development of pneumothoraces \([13]\), does not provide protection against extrapulmonary disease, and is relatively expensive (\(~$300/month), including the cost of administration, at our institution). Thus, there is a clear need for additional, low-cost options for PCP prophylaxis.

The combination of clindamycin and primaquine has demonstrated activity against *P. carinii*, both in vitro and in vivo \([3]\). This activity led to its current role as an alternative treatment for moderately severe PCP and as salvage therapy when other regimens have failed \([4, 5]\). A randomized, double-blinded study showed that the efficacy of C/P as treatment for PCP was comparable to that of TMP-SMZ \([6]\). In a series of seven patients using C/P as secondary prophylaxis for 60–285 days, there were no reported failures \([7]\).
The results of our retrospective analysis of the use of C/P as a prophylactic regimen against PCP suggest that C/P may not provide efficacy equal to that of the better-established regimens of TMP-SMZ or dapsone. Our a priori hypothesis was that C/P would be an effective alternative to other oral prophylaxis regimens.

However, our results show a significantly higher failure rate for C/P than for TMP-SMZ with regard to the occurrence of probable or definite PCP, as well as a trend toward a higher failure rate for C/P when compared with dapsone. This is true even after stratification for CD4 cell count and secondary prophylaxis. The significantly higher rate of diarrhea was not unexpected, as clindamycin has frequently been shown to be a cause of antibiotic-associated diarrhea [14, 15].

Since C/P is considered a third-line regimen for PCP prophylaxis, it would be helpful to have a direct comparison group receiving the most widely used third-line regimen, aerosolized pentamidine. Too few patients in our review received aerosolized pentamidine to allow direct comparisons; however, several published studies have examined the efficacy of this regimen.

Aerosolized pentamidine is associated with a reported failure rate of 6.5–8.6 per 100 patient-years as primary prophylaxis [2, 9] and 23.1 per 100 patient-years as secondary prophylaxis [10]. Our study revealed C/P failure rates of 36.8 and 21.7 per 100 patient-years for primary and secondary PCP prophylaxis, respectively. Thus, aerosolized pentamidine may be a better choice than C/P for patients who cannot receive either TMP-SMZ or dapsone.

The rates of failure and significant side effects associated with TMP-SMZ and dapsone in this analysis are comparable to those reported in other series, a circumstance suggesting reasonable external validity. Several factors may explain the apparent lack of efficacy of C/P as prophylaxis for PCP. The retrospective nature of the study presents unavoidable limitations. Compliance was not explicitly measured and may have been inferior in the C/P group, as this regimen requires additional pills and possibly is associated with an increased incidence of gastrointestinal disturbances.

Furthermore, the patients in the C/P group tended to accrue a greater percentage of patient-years with secondary prophylaxis or with CD4 cell counts of ≤100/μL. This was invariably due to the fact that C/P was utilized after failure of or intolerance to the other oral PCP prophylactic regimens. However, analysis after stratification for these variables did not demonstrate either one to be a major contributor to the increased rate of failure of C/P.

Another factor may involve the dosage of clindamycin and primaquine. Queener et al. [3] demonstrated that primaquine (at concentrations of 10 μg/mL) reduced the total number of organisms in treated cultures to 7% of that in control (untreated) cultures, while clindamycin (at concentrations of 5 μg/mL) was ineffective. In a rat model of PCP prophylaxis, primaquine (0.5 mg/kg) was moderately effective alone, while clindamycin (5 mg/kg) was ineffective alone. The combination of primaquine (0.5 mg/kg) and clindamycin (5 mg/kg) was more effective than primaquine alone. However, primaquine (0.2 mg/kg) was ineffective as prophylaxis, as was the combination of clindamycin (5 mg/kg) and primaquine (0.2 mg/kg). Although the precise mechanism(s) of C/P activity against PCP are unknown, these findings suggest that primaquine may be the more active agent in the combination and that its efficacy is lost beneath a certain threshold.

Pharmacokinetic studies have demonstrated mean serum clindamycin levels of 3.6 μg/mL at 1 hour after a 300-mg dose of clindamycin given orally to adult humans [16]. Primaquine has a mean peak serum level of 57.7 ng/mL 2.2 hours after administration of 15 mg of base in adult males [17]. Direct extrapolation of serum concentrations to PCP prophylactic efficacy is complicated by the fact that both clindamycin and primaquine are concentrated in lung tissue [4] and that effective PCP prophylaxis is achieved with administration of very low doses of other agents (e.g., thrice weekly 80/400-mg doses of TMP-SMZ) [12].

The previously published series of cases of secondary PCP prophylaxis with C/P in which no failures occurred involved 150-mg doses of clindamycin four times a day and a 15-mg dose of primaquine once a day [7]. It is plausible that the “standard” doses administered to our patients (300 mg of clindamycin and 15 mg of primaquine base per day) were subtherapeutic. This possibility suggests that any future investigation of clindamycin and primaquine as prophylaxis for PCP should use at least 600-mg doses of clindamycin and 15-mg to 30-mg doses of primaquine base per day.

The costs of clindamycin (300 mg/d) and primaquine base (15 mg/d) are $54.75 and $20.26, respectively, for 1 month’s supply (wholesale price, Drug Topics Red Book, 1995). This is less expensive than aerosolized pentamidine, even when the dose is doubled. Thus, the combination of C/P continues to warrant clinical investigation, but probably at higher doses than those employed in this study. Until data from such studies are available, we recommend that physicians who use C/P as prophylaxis for PCP reconsider this practice.

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References