CLINICAL ARTICLES

Should Prophylaxis for *Pneumocystis carinii* Pneumonia in Solid Organ Transplant Recipients Ever Be Discontinued?

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Solid organ transplant recipients are at risk for *Pneumocystis carinii* pneumonia (PCP), but the risk of PCP beyond 1 year is poorly defined. We identified 25 cases of PCP in 1,299 patients undergoing solid organ transplantation between 1987 and 1996 at The Cleveland Clinic Foundation (4.8 cases per 1,000 person transplant–years [PTY]). Ten (36%) of 28 PCP cases (transplantation was performed before 1987 in three cases) occurred ⩾1 year after transplantation, and no patient developed PCP while receiving prophylaxis for PCP. The incidence of PCP during the first year following transplantation was eight times higher than that during subsequent years. The highest rate occurred among lung transplant recipients (22 cases per 1,000 PTY), for whom the incidence did not decline beyond the first year of transplantation. We conclude that the incidence of PCP is highest during the first year after transplantation and differs by type of solid organ transplant. Extending the duration of PCP prophylaxis beyond 1 year may be warranted for lung transplant recipients.

Solid organ transplant recipients are at increased risk for opportunistic infections including *Pneumocystis carinii* pneumonia (PCP) [1, 2]. Seventeen percent of 583 cases of PCP in five large series of patients without AIDS occurred in solid organ and bone marrow transplant recipients [3–7]. Trimethoprim-sulfamethoxazole (TMP-SMZ) is highly effective in preventing PCP and is the agent of choice for chemoprophylaxis [8, 9]. Primary prophylaxis is often discontinued within 12 months after transplantation because the risk of PCP is greatest in the first 6 months after transplantation [1, 10]. The occurrence of cases of PCP beyond 1 year after transplantation at our institution prompted a retrospective review of cases of PCP in solid organ transplant recipients to further define the appropriate duration of primary chemoprophylaxis.

See editorial response by Arend and van't Wout on pages 247–9.

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Materials and Methods

Patients

The Cleveland Clinic Foundation is a 934-bed tertiary care medical center and serves as one of the largest transplantation centers in the United States. A total of 1,299 patients underwent solid organ transplantations at The Cleveland Clinic Foundation between January 1987 and March 1996, including 534 renal transplantations (including 16 kidney-pancreas transplantations), 399 heart transplantations (including 5 heart-lung transplantations), 265 liver transplantations, and 101 lung transplantations.

Case Definition

We included all cases of PCP occurring in any solid organ transplant patient at The Cleveland Clinic Foundation between January 1987 and March 1996. A diagnosis of PCP was established by identification of compatible cysts in sputum, bronchoalveolar lavage (BAL) fluid, a transbronchial or open-lung biopsy specimen, or an autopsy specimen by using Grocott-Gomori methenamine–silver nitrate, toluidine blue, or modified Wright-Giemsa staining methods.

Case Ascertainment

Patients with PCP were identified retrospectively through a search of computerized discharge medical records, selecting the diagnostic related group code of ''pneumocystosis,'' and through the pathology and microbiology registration systems.

Clinical data abstracted from patient records included general demographic information, underlying immunosuppressing conditions, immunosuppressive drug regimens, methods of diagnosis, and the presence of additional pulmonary pathogens including bacteria, fungi, acid-fast organisms, or viruses.

Information was obtained regarding several aspects of the corticosteroid regimen utilized for immunosuppression. The dose of prednisone at time of diagnosis of PCP was noted. Previous dose-time relationships were classified by the methods used by Arend et al. [5]: continuous low dosage ($<$30 mg/d for $\geq$1 month), continuous high dosage ($\geq$30 mg/d for $\geq$1 month), and intermittent high dosage for rejection ($\geq$500 mg/d for $\geq$2 days). Cumulative dose and total duration of prednisone therapy were also recorded. Data were collected regarding the clinical characteristics seen at presentation, the use of primary PCP prophylaxis, antipneumocystis treatment instituted, direct cost of an episode of PCP, and attributable mortality. Cost data were obtained from computerized medical records for cases of PCP occurring after 1993 (1995 dollars).

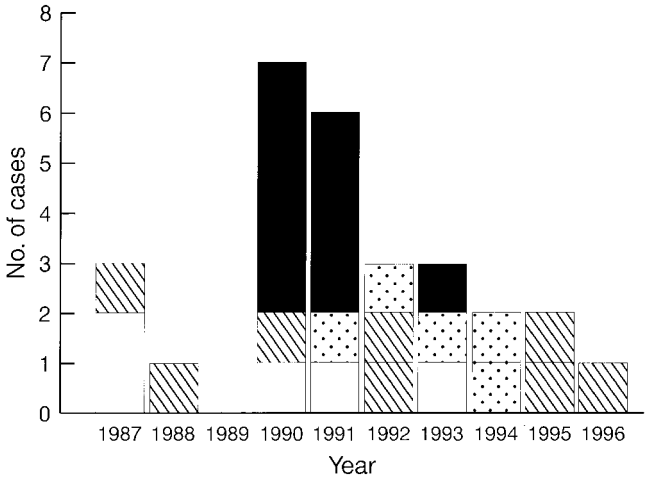

Figure 1. Distribution of 28 cases of *Pneumocystis carinii* pneumonia in solid organ transplant recipients of The Cleveland Clinic Foundation during 1987–1996. *White bar* = renal transplant recipients; *solid bar* = liver transplant recipients; *striped bar* = heart transplant recipients; and *dotted bars* = lung transplant recipients.

Primary PCP Prophylaxis for Solid Organ Transplant Recipients

Protocols for primary PCP prophylaxis for solid organ transplant recipients in the various transplant groups were not uniform during the study period: heart transplant recipients, one double-strength tablet of TMP-SMZ was given every other day for 6 months; lung transplant recipients, one double-strength tablet of TMP-SMZ was given daily for 1 year; and renal transplant recipients, one-half double-strength tablet of TMP-SMZ was given daily for 1 year. Notably, liver transplant recipients did not routinely receive primary PCP prophylaxis until 1992, following the occurrence of nine cases of PCP in 1990 and 1991 (figure 1). The current protocols for first-line PCP prophylaxis with TMP-SMZ at our institution are as follows: heart-lung and lung transplant recipients, one double-strength tablet thrice weekly indefinitely; liver transplant recipients, one double-strength tablet thrice weekly for 1 year; renal transplant recipients, one-half double-strength tablet daily for the life of the allograft; and heart transplant recipients, one double-strength tablet every other day for 1 year.

Calculation of Rates of PCP

The crude attack rates of PCP for each group of transplant patients were determined by calculating the number of cases occurring in the study period divided by the total number of patients undergoing solid organ transplantation during the study period. Three kidney transplant recipients who underwent transplantation before 1987 and for whom PCP was diagnosed during the study period were included in the study but excluded from calculation of the incidence and attack rates of PCP. The intervals from transplantation to PCP for these three patients were 182, 575, and 832 weeks, respectively. For this reason, the total number of cases was 28, of which 25 were used to calculate incidence and attack rates. The incidence rates of PCP were measured in units of the reciprocal of person transplant–years (PTY) calculated through March 1996. Incidence rates were subsequently stratified for the first year of transplantation and the remainder of the follow-up period.

Risk Factors for Survival

Survivors of PCP were those patients who recovered from the acute respiratory illness; nonsurvivors were those patients who died of acute respiratory failure. Nonsurvivors were compared with survivors to assess for any potential risk factors for mortality, including serum lactate dehydrogenase (LDH) levels measured within 3 days of the diagnosis of PCP, respiratory rate, serum albumin level, and resting arterial-alveolar oxygen gradient ($AaPO_2$) at presentation. The normal range for LDH levels at our laboratory is 100–220 U/L.

Statistical Methods

All data were entered into a computerized database for analysis (EPI-Info, Version 6.02 [11]). Student's *t* test and Fisher's two-tailed exact test were used for univariate analyses of the significance of associations. Multivariate logistic regression and Cox regression for association with mortality were done by using PC SAS/STAT (SAS Institute, Cary, NC). Differences were considered statistically significant at a P value of $\leq$.05.

Results

Twenty-eight cases of PCP were identified in solid organ transplant recipients, accounting for 30% of 92 cases of histo-

Table 1. Comparative incidence rates of PCP among 1,299 solid organ transplant recipients at The Cleveland Clinic Foundation during 1987–1996.

Type of transplant	No. of transplants	All cases of PCP	No. of cases of PCP ⩾1 y after transplantation	Attack rate (%)	Overall incidence rate*	Incidence rate during first year	Incidence rate* after first year
All categories	1,299	25	8	1.9	4.8	14.5	1.9
Lung	101	5	3	5	22	26	19.6
Heart	399[†]	8	3	2	5	14	2.6
Liver	265	10	1	3.7	10	39	1.3
Kidney	534[‡]	2	1	0.4	0.8	2	0.5

NOTE. PCP = *Pneumocystis carinii* pneumonia.
* Per 1,000 person transplant–years.
[†] Includes five heart-lung transplant recipients.
[‡] Includes 16 kidney-pancreas transplant recipients.

logically proven PCP in patients without AIDS at our institution during the 9-year study period (figure 1). The mean interval from the date of transplantation to the diagnosis of PCP was 20 weeks (range, 6 weeks to 16 years). Fifty-four percent (15) of 28 solid organ transplant recipients developed PCP within 6 months of transplantation; 36%, ⩾1 year after transplantation; and 21%, ⩾2 years after transplantation.

No patient developed PCP while receiving prophylaxis. Eight solid organ transplant recipients (29%) had received primary PCP prophylaxis (all with TMP-SMZ) for a mean duration of 49 weeks (range, 6 to 312 months). The reasons for discontinuation of TMP-SMZ prophylaxis included elevated creatinine level (1 patient), protocol (5), and unknown (2). The mean interval from the discontinuation of primary prophylaxis to the development of PCP was 34 weeks (range, 8 to 168 weeks).

Incidence Rates of PCP During the First Year After Transplantation and Beyond

The overall incidence rate of PCP among 1,299 solid organ recipients was 4.8 cases per 1,000 PTY. The incidence rate of PCP during the first year following transplantation was approximately eight times higher than the rate in the subsequent years (14.5 cases per 1,000 PTY vs. 1.9 cases per 1,000 PTY, respectively) (table 1). Overall organ-specific incidence rates ranged from a high of 22 cases per 1,000 PTY for lung transplant recipients to 0.8 case per 1,000 PTY for kidney transplant recipients. Notably, the incidence rate of PCP beyond 1 year when compared with the first year following transplantation declined significantly for all groups except lung transplant recipients (table 1).

Patient Characteristics

Selected clinical features of the 28 solid organ transplant recipients are listed in table 2. Ninety-two percent of patients were admitted to the hospital with a presumed infectious process, and a pneumonic process was initially suspected in 60%. The mean duration of symptoms before the diagnosis of PCP was 14 days, and the mean interval from admission to the diagnosis was 5.1 days. The diagnosis was made by BAL for 86% (24) of the patients; transbronchial biopsies, 7% (2); and open-lung biopsies, 7% (2).

The most prevalent concomitant pulmonary infection was that due to cytomegalovirus (CMV), which was isolated from the BAL fluid from 36% (10) of 28 patients. Bacteria or fungi were isolated from BAL fluid from eight other patients, includ-

Table 2. Clinical features of 28 solid organ transplant recipients with *Pneumocystis carinii* pneumonia at The Cleveland Clinic Foundation during 1987–1996.

Feature	Value*
Male gender	57
Mean age (y) ± SD	46 ± 13.5
Dyspnea	68
Fever	64
Rales or rhonchi	39
Interstitial infiltrates	36
Normal chest radiograph	3.5
Mean arterial oxygen tension (mm/Hg) ± SD	65.6 ± 20.1
Mean arterial oxygen gradient (mm/Hg) ± SD	59.5 ± 49.5
Mean serum LDH level (U/L)	296
Mean total lymphocyte count (/mm^3) ± SD	758 ± 65
Mean CD4 lymphocyte count (/mm^3)[†]	281
Mean prednisone dose (mg/d)	19.9
Intensity of prednisone	
Continuous low dose	68
Continuous high dose	29
Acute graft rejection	36
Chronic graft rejection	28

NOTE. LDH = lactate dehydrogenase.
* Values are percentage of patients unless specified otherwise.
[†] Only measured for three patients (50/mm^3, 292 and 501).

Table 3. Results of a Cox regression model for association with death due to PCP in solid organ transplant patients at The Cleveland Clinic Foundation during 1987–1996.

Variable	*P* value	Parameter estimate	SE	RR (95% CI)
LDH level	.06	0.0058	0.0031	1.006
Resting $AaPO_2$	.14	0.0129	0.0088	1.013
Absolute lymphocyte counts	.31	−0.0013	0.0013	0.999
Cell count in BAL fluid	.10	−0.0190	0.0114	0.981
For every increase of 100 U/L in serum LDH level	.06	0.5841	0.313	1.8 (1.3–2.4)
For every increase of 200 U/L in serum LDH level	.06	1.1682	0.626	3.2 (1.7–6.0)

NOTE. $AaPO_2$ = arterial-alveolar oxygen gradient; BAL = bronchoalveolar lavage; LDH = lactate dehydrogenase; PCP = *Pneumocystis carinii* pneumonia.

ing *Staphylococcus* species (2 patients), viridans streptococci (2), *Candida* species (3), and *Aspergillus* species (1).

Patients with PCP >1 Year After Transplantation

The 11 patients developing PCP beyond 12 months after transplantation included 4 kidney transplant recipients, 3 lung transplant recipients, 3 heart transplant recipients, and 1 liver transplant recipient. The median interval from the time of transplantation to PCP was 157 weeks (range, 64 weeks to 16 years). The clinical and laboratory findings for these patients were similar to those for the 17 patients with PCP during the first year following solid organ transplantation. All 11 patients were receiving prednisone therapy at the time of PCP (mean dosage, 18 mg/d); three (27%) were receiving tapering doses, and one (9%) was receiving increasing doses. Sixty-four percent of patients had histological evidence of acute rejection (two patients) or chronic rejection (five patients) at the time of PCP. CMV was isolated from 27% of the BAL fluid cultures. None of these patients had histological evidence of CMV pneumonia.

Treatment, Outcome, and Risk Factors for Death

High doses of TMP-SMZ were given to 89% (25) of 28 patients as initial treatment for PCP. The remaining three patients were allergic to TMP-SMZ and were treated with pentamidine parenterally. A change in therapy was made for 10 patients because of drug allergy, drug toxicity, or therapeutic failure, including 32% (eight) of 25 patients receiving TMP-SMZ therapy. Corticosteroid therapy was given to 85% of patients during antipneumocystis treatment. Support with mechanical ventilation was required for 21% of patients because of acute respiratory failure; two of these patients died.

Eight patients (29%) died within 30 days of the episode of PCP, of whom five died of PCP or related complications (including three of the 11 patients who had PCP after the first year of transplantation). Comparing survivors and patients who died of other causes with those who died of PCP, we found that one risk factor was significantly associated with death: a higher mean serum LDH level at presentation (392 U/L vs. 277 U/L, respectively). A Cox regression model was used to assess the relationship of four continuous variables (serum LDH level, resting $AaPO_2$, absolute lymphocyte counts, and cell count in BAL fluid) with survival. The model suggested that increasing serum LDH levels were associated with an increased risk of mortality ($P = .06$) (table 3). There was no relationship between survival and resting $AaPO_2$, absolute lymphocyte counts, or cell count in BAL fluid. Those patients with high serum LDH levels were at greater risk of death. For every increase of 100 U/L of serum LDH, the relative risk of death nearly doubled (table 3).

Cost-Benefit Analysis of PCP Prophylaxis Beyond the First Year of Transplantation

The mean cost of hospitalization for the 28 cases of PCP was $25,000 per case (1995 dollars) or $200,000 for the eight cases in organ transplant recipients between 1987 and 1996 that occurred >1 year after transplantation. The costs of PCP prophylaxis beyond the first year of transplantation for the duration of the 9-year study period for the entire cohort of patients was estimated to be $121,560 by using the following assumptions: $30 per year for TMP-SMZ therapy (thrice weekly) [9] and a total of 4,052 cumulative PTY for the 1,171 organ transplant recipients who survived the first year of transplantation. Therefore, TMP-SMZ prophylaxis would be cost-effective from an economic perspective if it prevents all cases of PCP.

Discussion

The most important conclusions of our study are that the incidence of PCP among solid organ transplant recipients is highest during the first year following transplantation and that no patient developed PCP while receiving primary prophylaxis. Rates of PCP differed between types of transplant recipients.

Table 4. Review of cases of PCP in solid organ transplant recipients at risk for this infection.

Transplant type, location [reference]	Study period	No. of PCP cases/total no. of patients at risk* (%)	No. of deaths due to PCP/total no. of cases (%)	Mean time from transplantation to onset of PCP in w (range)
Heart-lung				
Pittsburgh [12]	1983–1986	14/16 (88)	3/14 (2)	25 (10–72)
Pittsburgh [13]	1981–1986	6/18 (33)	NS	12–76
Stanford [14]	1981–1990	13/49 (26)	NS	17
Cambridge [15]	1984–1987	2/23 (9)	1/2 (50)	20 and 48
Subtotal		35/106 (33)	4/16 (25)	
Heart				
Philadelphia [16]	1989	9/140 (6)	2/9 (22)	16
Stanford [17]	1982–1984	2/77 (3)	NS	20 and 102
Utah [8]	1988–1989	7/17 (41)	0/7	NS
Italy [18]	1985–1991	7/241 (3)	NS	14 (8–48)
Pittsburgh [13]	1981–1986	5/92 (5)	NS	NS
Spain [19]	1988–1994	5/138 (3.6)	1/5 (20)	9–17
South Africa [20]	1970–1981	1/40 (2.5)	0/1	204
Germany [21]	1983–1986	2/150 (1.3)	0/2	6 and 10
Subtotal		38/895 (4.2)	3/24 (12.5)	
Liver				
Nebraska [22]	1985–1989	14/109 (13)	3/14 (21)	24 (2–82)
Mayo Clinic [23]	1985–1987	6/69 (9)	1/6 (17)	8–12
Pittsburgh [24]	1984–1985	11/101 (11)	3/11 (27)	13 (3–20)
Subtotal		31/279 (11)	7/31 (23)	
Kidney				
Pittsburgh [25]	1977–1982	20/335 (6)	NS	NS
Puerto Rico [26]	1985–1987	13/245 (5)	5/11 (45)	NS
Oslo [27]	1985–1986	14/305 (5)	7/14 (50)	12
France [28]	1989–1990	10/42 (24)	NS	12
Japan [29]	1970–1990	23/567 (41)	12/23 (52)	64 (4–192)
United Kingdom [30]	1985–1986	4/39 (10)	NS	NS
Houston [31]	1985–1987	9/227 (4)	NS	14 (8–19)
Houston [32]	1981–1985	8/401 (2)	NS	100
Wisconsin [33]	1984–1985	1/66 (1.5)	0/1	6
Sweden [34]	1985–1989	8/214 (4)	4/8 (50)	12
The Netherlands† [35]	1980–1995	15/860‡ (2)	NS	16 (9–59)
Subtotal		125/3,301 (3.8)	28/57 (49)	
Total		229/4,581 (4.9)	42/144 (29)	

NOTE. NS = not stated; PCP = *Pneumocystis carinii* pneumonia.
* Not receiving prophylaxis.
† Includes kidney-pancreas transplants.
‡ Specifics of prophylaxis not stated.

The highest incidence occurred among lung transplant recipients (22 cases per 1,000 PTY), for whom there was no decline in rates beyond 1 year of transplantation (in contrast to the other groups of solid organ transplant recipients) (table 1).

Differences in attack rates of PCP between categories of solid organ transplant recipients have been suggested by previous studies of solid organ transplant recipients not receiving PCP prophylaxis (table 4). The crude attack rate of primary PCP among 4,581 at-risk (no prophylaxis) solid organ transplant recipients was 4.9% (229 cases); most of these 229 cases occurred within 6 months of transplantation, although some cases occurred after the first year of transplantation [12, 13, 17, 20, 22, 29, 32, 35]. The organ-specific attack rates of PCP ranged from a low of ~4% among heart transplant recipients [8, 13, 16–21] and renal transplant recipients [25–35] to 11% among liver transplant recipients [22–24] and 33% among heart-lung transplant recipients [15–17, 35]. None of these studies measured incidence rates as was done in our study, but there were two randomized prospective studies of primary prophylaxis with TMP-SMZ vs. no prophylaxis for 58 heart transplant recipients [8] and 132 renal transplant recipients [33]. It is interesting that the study of heart transplant recipients

was prematurely terminated because of the high attack rate of PCP among the control group (41% vs. 0 among patients receiving prophylaxis), whereas only one case of PCP occurred in the renal transplant patients (1.5% vs. 0 among patients receiving TMP-SMZ prophylaxis).

The attributable mortality rate of 18% that we observed is slightly lower than the rate of 29% that was reported in prior studies (table 4). The association we observed between serum LDH level and prognosis of PCP in solid organ transplant recipients has been previously described in studies of PCP in patients with AIDS [36].

There were limitations to our study that should be highlighted. Our case definition for PCP was very restrictive, and it is possible that additional cases of PCP occurred that were not histologically proven. Although incidence rates of PCP for each transplant category could be measured, we could not measure incidence rates by PTY without prophylaxis because the protocols for primary prophylaxis for PCP were not standardized during the entire study period. The small number of patients with PCP >1 year after transplantation also limited the power to identify specific risk factors associated with late-onset PCP.

Although reactivation of latent infection has been considered the primary explanation for PCP in immunosuppressed patients, studies have demonstrated genetic variation in PCR-amplified *P. carinii* DNA from lung tissue specimens from patients with multiple episodes of PCP [37]. Unlike HIV-infected patients with CD4 cell counts of $<200/\mu$L or those with <14% CD4 cells who define individuals at risk [9], the risk of PCP in immunocompromised patients without AIDS, including solid organ transplant recipients, cannot be accurately quantified at present. Primary prophylaxis for PCP is strongly recommended as the standard of care for all solid organ transplant recipients, at least for 6 months after transplantation [10, 38]. Notably, most cases of PCP in our study occurred within 6 months of transplantation in patients who did not receive prophylaxis and would be considered errors of omission by current standards. TMP-SMZ is ideal prophylaxis for nonallergic organ transplant recipients because of the following: its activity against opportunistic pathogens such as *P. carinii, Nocardia* species, *Toxoplasma gondii,* and *Listeria monocytogenes;* its activity against the common bacteria causing infections in these patients [33]; its minimal toxicity; and its low cost (the wholesale cost of 160 mg of TMP and 800 mg of SMZ orally three times per week is $30 per year) [39].

Extending PCP prophylaxis beyond 1 year after transplantation for all solid organ transplant recipients has not been recommended [38]. The cost-benefit analysis of long-term prophylaxis with TMP-SMZ for solid organ transplant patients should not only take into account economic issues but should also include the effect of prophylaxis on colonization and infection by antibiotic-resistant bacteria and fungi [40–42]; the toxicity of TMP-SMZ on hematologic, hepatic, and renal function; and interactions between TMP-SMZ and cyclosporine or tacrolimus (FK-506) [43, 44].

A preemptive strategy of targeting indefinite PCP prophylaxis to the 5%–10% of transplant recipients with recurrent or chronic rejection has been suggested [38]. The primary risk for PCP (and other opportunistic infections) in solid organ transplant recipients is the ''net state of immunosuppression,'' to which a number of factors contribute, including the total amount of previous and current immunosuppressive treatments, the presence of acute and chronic graft rejection, and the presence of concomitant infections (especially those due to CMV) [10, 35, 45, 46]. Notably, 67% of our patients with PCP after the first year of transplantation had acute or chronic rejection at the time of PCP. We advocate targeting PCP prophylaxis beyond 1 year of transplantation to those patients with recurrent or chronic rejection, and we favor indefinite prophylaxis for lung transplant recipients.

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