Risk of *Pneumocystis jiroveci* pneumonia in patients long after renal transplantation

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Abstract

**Background.** *Pneumocystis jiroveci* pneumonia (PCP) is an important cause of morbidity and mortality in renal transplant recipients (RTRs). Chemoprophylaxis with trimethoprim/sulphamethoxazole is recommended during the early post-transplantation period, but the optimal duration has not been determined and a main drawback of chemoprophylaxis is the development of resistance of the commensal faecal flora. A cluster outbreak of PCP occurred in our outpatient Renal Transplant Unit. We aimed to investigate risk factors for PCP in RTRs to determine who should receive long-term chemoprophylaxis.

**Methods.** In a case–control study, we investigated common demographic variables and immunological parameters. Nine PCP cases diagnosed between August 2006 and April 2007 were matched with 18 control patients, who did not develop PCP, received their transplant in the same time-period and had a similar follow-up period with a comparable immunsuppressive drug regimen.

**Results.** The median time from transplantation to PCP was 19 months. We observed no significant differences in gender, age, donor type or number of rejections. In PCP cases, the median lymphocyte count just before PCP diagnosis was 0.49 (0.26–0.68), which was significantly reduced compared to the control patients after a similar follow-up period (median 1.36, 0.59–3.04, P = 0.002). This lymphocytopenia was chronic and existed in most patients already for many months. CD4⁺ T-cell counts...
were also significantly reduced in the PCP cases. We found no difference in the Th1, Th2 and Th17 subsets between PCP cases and control patients.

Conclusion. Long-term prophylactic therapy for PCP may be indicated for RTR with persistent severe lymphocytopenia.

Keywords: chemoprophylaxis; lymphocytopenia; Pneumocystis jiroveci pneumonia; renal transplantation

Introduction

Pneumocystis jiroveci is an opportunistic fungal pathogen that causes life-threatening pneumonia in immunocompromised individuals. Among human immunodeficiency virus (HIV)-positive individuals in developed countries, the incidence of Pneumocystis jiroveci pneumonia (PCP) has decreased since the introduction of highly active antiretroviral therapy and PCP chemoprophylaxis [1]. Nowadays, most PCP infections occur in patients unaware of their HIV status or in otherwise immunocompromised patients. The incidence of PCP among solid organ transplant recipients ranges from 5 to 15%, depending on organ type, transplant centre and immunosuppressive drug regimen [1, 2].

The epidemiology and natural history of P. jiroveci infection in humans is not completely understood. The fungus is ubiquitous throughout the world. The reservoir for P. jiroveci has not been fully determined yet, but includes children, symptomatic and asymptomatic immunocompromised patients [3–5]. Airborne transmission via humans has been shown as the main route of infection [6–10]. Certain individuals may represent transient carrier states and as outbreaks tend to cluster, it could well be that some patients become asymptomatic reservoirs, which can infect other patients attending the outpatient clinic. Moreover, it has been described that non-immunocompromised health care workers caring for HIV-infected patients with PCP have colonization rates up to 24% [11].

In HIV-positive patients, P. jiroveci infection is associated with markedly reduced peripheral blood CD4+ T-cells [12]. Interestingly, a recent report in mice suggested a role for the IL-17/IL-23 axis in the defense against P. jiroveci [13]. CD4+IL-17+ T-cells are known to play a significant role in host mucosal immunity to several pulmonary pathogens, including fungi. However, in humans, nothing is known about the role of the Th17 response in the pathogenesis of PCP.

In HIV-negative immunocompromised patients, the onset of symptoms is generally more sudden, severe and associated with higher mortality compared to HIV-positive patients (30–60% versus 10–20%) [2, 14, 15]. In renal transplant recipients (RTRs), PCP usually presents itself during the early post-transplantation period. Risk factors for the development of PCP, identified in some studies but not always confirmed by others, include age, cytomegalovirus (CMV) infection, treatment of rejection episodes and use of anti-lymphocyte antibodies [16–21].

Current guidelines recommend that HIV-positive individuals receive chemoprophylaxis for PCP if they have CD4+ T-cell counts of <200/μL, a history of oropharyngeal candidiasis or PCP [12]. The first choice agent for chemoprophylaxis is trimethoprin/sulphamethoxazole (TMP/SMX). However, similar criteria guiding the use of chemoprophylaxis are not available for HIV-negative individuals. European Transplant guidelines and the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend PCP chemoprophylaxis for 3 to 6 months after transplantation and for another 6 weeks to 4 months after a rejection episode [22, 23], whereas other experts recommend the use of PCP chemoprophylaxis for a period of 6–12 months after transplantation [24]. However, in RTRs, PCP has been shown to occur after discontinuation of chemoprophylaxis [25–27]. Awareness of risk factors for the development of PCP may guide the use of chemoprophylaxis and would avoid unnecessary use and associated toxicity in RTRs. In addition, restricted use of chemoprophylaxis would limit the potential development of drug resistance.

In our centre, the incidence of PCP has been approximately 1–5% since start of our renal transplantation programme in the 1970s; hence no chemoprophylaxis with TMP/SMX was routinely administered. However, between August 2006 and April 2007, we encountered a cluster of nine PCP cases in RTRs. Following the occurrence of these nine consecutive cases of PCP, we performed a retrospective case–control study on risk factors for PCP development in RTRs. In view of our knowledge about risk factors for PCP in HIV-positive patients, it was of special interest to investigate the association between CD4+ T-cell numbers, in particular CD4+IL-17+ T-cell numbers and the occurrence of PCP.

Materials and methods

Study population

This study was performed in the Renal Transplant Unit of the Academic Medical Centre in Amsterdam, The Netherlands. From 1970, an average of 100 renal transplants is performed yearly. Between August 2006 and April 2007, a cluster of nine PCP cases in RTRs occurred in our centre. At that moment, PCP chemoprophylaxis was not routinely administered.

Cases and control definitions

All PCP cases diagnosed between August 2006 and April 2007 were included. PCP was diagnosed by P. jiroveci staining with Giemsa and methenamine silver in bronchoalveolar lavage (BAL) specimens. Each PCP case was matched with two control patients, who received their transplant in the same period; did not develop PCP; had a similar follow-up period following transplantation and comparable immunosuppressive drug regimen including use of anti-thymocyte globulin (ATG). All patients were HIV negative.

Data collection

The following data were retrospectively collected from medical records: sex, age, race, original renal disease, organ origin (living related or post-mortem), HLA mismatches, immunosuppressive regimen, data on rejection episodes, rejection treatment, use of corticosteroids, use of ATG or monoclonal antibodies, CMV infection, other infections and the presence of diabetes mellitus. Acute rejection episodes and infection episodes occurring between transplantation and PCP diagnosis or concomitant with PCP were considered for analysis. The control patients were followed for a period of time similar to the time between transplantation and PCP diagnosis of the matching PCP cases. Routinely measured peripheral blood lymphocyte counts were recorded from the hospital database.

Immunosuppressive regimen

Baseline immunosuppressive regimen in cases and control patients consisted of triple therapy containing cyclosporine or tacrolimus, corticosteroids...
and either mycophenolate mofetil or mycophenolate sodium. Some patients received induction with an IL-2 receptor antagonist. RTRs with stable renal function tapered their triple immunosuppressive therapy to double maintenance at average 1 year after transplantation. In the case of an acute cellular rejection episode, the RTRs received pulse therapy with methylprednisolone. Steroid-resistant acute cellular rejection episodes were treated with ATG or rituximab, in case the patient had received ATG previously. In case of a rejection episode, triple therapy was continued.

**T-cell subset analysis**

T-cell subset analysis was performed on peripheral blood mononuclear cells (PBMCs) from blood samples available prior to the diagnosis of PCP and in control patients after a comparable follow-up period following transplantation. PBMC from RTRs, who participate in a longitudinal study concerning CMV infection after transplantation, are routinely obtained and stored. This study has been approved by our Hospital Institutional Review Board. When patients sign the informed consent form, they sign for future use of the PBMC for the CMV study and other studies. PBMC were isolated by standard Ficoll density-gradient centrifugation and cryopreserved until analysis. Intracellular cytokine staining was performed as previously described [28]. The following monoclonal antibodies were used: CD8-PE-Alexa Fluor 610 (Invitrogen Corporation, Carlsbad, CA), CD3-Pe-Cy7 (BD Biosciences, San Jose, CA), IFN-gamma-FITC (BD Biosciences), IL-4-APC (BD Pharmingen) and IL-17-PE (eBioscience Inc., San Diego, CA). Cells were washed and measured on FACS-CANTO flowcytometer (BD Biosciences) and analysed with FlowJo software (Treestar Inc., Ashland, OR).

**Statistical analysis**

Univariate analysis was performed to identify risk factors associated with PCP. Cases and control patients were stratified into nine groups of one case and its two matched control patients. Discrete variables were expressed as numbers (percentages) and compared by Cochran–Mantel–Haenszel Test. Associations of discrete variables were expressed in terms of exposure odds ratios with their 95% confidence interval. The continuous variables were analysed with a linear mixed model. This model was used to take into account the possible correlation, which was created by the matching procedure, between a case and its two control patients. Stratum number (1 to 9) was used as random factor and the case–control variable as fixed factor in the linear mixed model. To analyse the effect of time and to compare lymphocyte counts between cases and control patients, we used a linear mixed model to account for repeated observations in the same patients. Univariate correlations between different variables were assessed using Spearman rank correlation test. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistical software, version 16.0 (SPSS Inc., Chicago, IL).

**Results**

**Clinical characteristics of PCP cases**

Clinical characteristics of nine consecutive PCP cases between August 2006 and April 2007 are presented in Table 1. The median time between transplantation and PCP diagnosis was 19 (5–58) months. All patients presented with dyspnoea. In all cases, *P. jiroveci* was found in BAL specimens. Median lactate dehydrogenase levels were elevated compared to reference values in healthy individuals. Treatment in eight patients consisted of TMP/SMX. One patient was allergic to TMP/SMX and received atovaquone. All patients recovered from PCP. Five cases had one or two herpes virus coinfections during the PCP episode (2 × HSV, 3 × CMV, 1 × Epstein-Barr virus), one case had a coinfection with histoplasmosis and two cases had in addition to their viral coinfection a bacterial coinfection (enterococcal sepsis, *Klebsiella pneumoniae*). Two PCP cases had received additional immunosuppressive therapy with either ATG 36 months or rituximab 2.7 months prior to their PCP diagnosis. One case had received ATG and rituximab, respectively, 72 and 5.6 months before PCP diagnosis.

**Univariate analysis of risk factors for PCP**

Table 2 shows the results from the univariate analysis of risk factors for PCP in RTRs. No significant difference was found between cases and control patients with respect to gender, age, ethnicity, donor type, duration of dialysis, transplant number, number of rejection episodes, rejection treatment, CMV-infection or diabetes mellitus, although diabetes mellitus and donor type had substantial odds ratios (6.0 and 3.5, respectively, Table 2). There was no difference between PCP cases and control patients with regard to the cumulative amount of immunosuppressive drugs they had received before transplantation. PCP cases did have more infectious episodes between transplantation and PCP diagnosis, compared to their control patients who were followed for a similar time period [median number 4, (range 1–7) and 2 (range 0–8) respectively, Tables 2 and 3], but this difference was not significant (*P* = 0.068).

Figure 1 shows the results from the lymphocyte and neutrophil counts in peripheral blood. The median time between blood withdrawal and PCP diagnosis was 0 (range −17 to 2) days for cases and −1 (range −25 to 46) days for control patients, who were followed for a similar time period. None of the control patients had an infectious episode at the moment of blood withdrawal. In PCP cases, the median lymphocyte count just before PCP diagnosis was $0.49 \times 10^9/L$, range 0.26–0.68, which was significantly reduced compared to the control patients after a similar follow-up period (median $1.36 \times 10^9/L$, range 0.59–3.04 (*P* = 0.002, Figure 1a).

In six cases and eight control patients, PBMC had been stored for T-cell subset analysis. The median time between blood withdrawal and PCP diagnosis was −100 days (range −238 to 0) for cases and −78 (range −331 to 614) days for control patients, who were followed for a similar time period. The median CD4+ T-cell count was significantly reduced in PCP cases as compared to their control patients (0.18 × 10^9/L, range 0.06–0.63 and 0.73 × 10^9/L, range 0.16–1.52, respectively, *P* = 0.040, Figure 1b). In this small group of patients, no difference was found in the Th1, Th2 and Th17 subsets between PCP cases and control patients (Figure 2). The number of B cells in peripheral blood in PCP cases and control patients was very low compared to reference values in healthy individuals. However, there was no difference in B-cell numbers between PCP cases and control patients (data not shown). The median number of neutrophils in PCP cases just before PCP diagnosis was $9.29 \times 10^9/L$, range 0.56–14.66, which was significantly higher compared to the control patients after a similar follow-up period (6.19 × 10^9/L, range 3.12–8.89, *P* = 0.043, Figure 1c).

The lymphocyte count on the day the patients received their renal transplant was lower in RTRs with PCP compared to RTRs without PCP, although this difference was not significant (*P* = 0.171, Figure 3a). Figure 3b shows longitudinal measurements of lymphocyte counts of PCP cases during the follow-up period (6.19 × 10^9/L, range 3.12–8.89, *P* = 0.043, Figure 1c)
### Table 1. Characteristics of nine cases of PCP among RTRs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 9)</th>
<th>Control patients (n = 18)</th>
<th>Odds ratio (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>56 (42–67)</td>
<td>55 (26–65)</td>
<td>1.0 (0.01–4.32)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>6</td>
<td>12 (67)</td>
<td>2.0 (0.7–5.8)</td>
<td>0.007</td>
</tr>
<tr>
<td>Postmortal donor n (%)</td>
<td>8</td>
<td>11 (61)</td>
<td>0.5 (0.01–1.9)</td>
<td>0.66</td>
</tr>
<tr>
<td>Duration dialysis (months), median (range)</td>
<td>16 (15–72)</td>
<td>30 (0–96)</td>
<td>1.0 (0.01–10.03)</td>
<td>0.90</td>
</tr>
<tr>
<td>Transplant number &gt;1 n (%)</td>
<td>1 (11)</td>
<td>3 (17)</td>
<td>0.5 (0.03–9.46)</td>
<td>0.64</td>
</tr>
<tr>
<td>Rejection treatment/monoclonal antibody n (%)</td>
<td>4 (44)</td>
<td>10 (56)</td>
<td>1.00 (0.14–7.10)</td>
<td>1.00</td>
</tr>
<tr>
<td>Steroids</td>
<td>5 (56)</td>
<td>12 (67)</td>
<td>0.5 (0.01–4.32)</td>
<td>0.04</td>
</tr>
<tr>
<td>ATG</td>
<td>2 (22)</td>
<td>3 (17)</td>
<td>2.0 (0.13–31.99)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rejection number &gt;1 n (%)</td>
<td>4 (44)</td>
<td>10 (56)</td>
<td>1.00 (0.25–4.00)</td>
<td>1.00</td>
</tr>
<tr>
<td>Lymphocyte count, median (range)</td>
<td>0.49 (0.26–0.68)</td>
<td>1.36 (0.59–3.04)</td>
<td>6.0 (0.56–64.71)</td>
<td>0.04</td>
</tr>
<tr>
<td>CD4⁺ T-cell count, median (range)</td>
<td>0.18 (0.06–0.63)</td>
<td>0.73 (0.16–1.52)</td>
<td>0.002</td>
<td>0.040</td>
</tr>
</tbody>
</table>

*Tx, transplantation; LDH, lactate dehydrogenase.

### Table 2. Univariate analysis of risk factors for PCP among RTRs

<table>
<thead>
<tr>
<th>Odds ratio (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 (0.10–11.03)</td>
<td>1.00</td>
</tr>
<tr>
<td>2.0 (0.27–15.09)</td>
<td>0.50</td>
</tr>
<tr>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>0.07</td>
<td></td>
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<tr>
<td>1.00 (0.14–7.10)</td>
<td>1.00</td>
</tr>
<tr>
<td>1.00 (0.03–9.46)</td>
<td>0.64</td>
</tr>
<tr>
<td>1.00 (0.01–4.32)</td>
<td>0.04</td>
</tr>
<tr>
<td>2.0 (0.13–31.99)</td>
<td>0.01</td>
</tr>
<tr>
<td>1.00 (0.25–4.00)</td>
<td>1.00</td>
</tr>
<tr>
<td>6.0 (0.56–64.71)</td>
<td>0.14</td>
</tr>
<tr>
<td>1.36 (0.59–3.04)</td>
<td>0.040</td>
</tr>
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</table>

*Associations of discrete variables with PCP are expressed in terms of exact odds ratios with their 95% confidence interval (CI) and analysed with a Cochran–Mantel–Haenszel test. Associations of continuous variables are analysed with a linear mixed model, taking into account the different strata.
cases and control patients during the 24 months preceding PCP diagnosis. For cases and control patients, there was no significant change in the lymphocyte counts in this time period ($P = 0.136$). However, the lymphocyte counts of the cases were significantly lower compared to their control patients during these 24 months ($P = 0.001$).

**Discussion**

Here, we show that PCP in RTRs is associated with significantly lower lymphocyte counts compared to RTRs without PCP. Furthermore, CD4$^+$ T-cell counts in PCP cases, from whom PBMC were available, were significantly reduced compared to their control patients. In the time period preceding PCP diagnosis, the cases had more other infectious episodes compared to control patients. No significant difference was found between PCP cases and control patients with respect to gender, age, ethnicity, donor type, dialysis duration, transplant number, number of rejection episodes, rejection treatment, cumulative amount of immunosuppressivedrugs, CMV-infection or diabetes mellitus.

These results confirm an important role for lymphocytes in host defense against *P. jiroveci* in HIV-negative patients, which is in agreement with observations from animal models [29] and limited reports in humans [14, 27, 30, 31]. However, not all PCP cases had a low lymphocyte count, which is in line with data from HIV-positive PCP patients, where 10–15% of PCP cases had a CD4$^+$ T-cell count above the threshold of 200/μL [32].

Factors other than T-cell mediated immunity may play a role in the defense against *P. jiroveci*, such as the capacity of lung epithelial cells to secrete cytokine IL-6 and chemokines IL-8 and monocyte chemoattractant protein-1 in response to *P. jiroveci* [33, 34] or alveolar macrophages. The latter play a role in degradation and clearance of *P. jiroveci* in the lung and previous reports have shown an inverse correlation between macrophage numbers and the severity of PCP [35, 36].
Our PCP cases had significantly higher neutrophil counts compared to the control patients. This is in agreement with data from Sadaghdar et al. [37] who showed a correlation between elevated neutrophil counts and inflammation and decreased pulmonary function during *P. jiroveci* infection in HIV-positive individuals.

The Th17 lineage with its IL-23/IL-17 axis is known to play a significant role in host mucosal immunity to a number of pulmonary pathogens, including fungi. *In vitro* studies have shown that *P. jiroveci* stimulates IL-23 expression by alveolar macrophages. IL-23- or IL-17-deficient mice and mice treated with anti-IL-23 antibodies had significant heavier fungal burdens than wild-type mice at 1, 2, 3 and 4 weeks after inoculation [13]. This was associated with a decrease in CD4⁺ T-cells and with diminished levels of cytokine and chemokine production in the lungs. Therefore, we hypothesized that RTR who acquired a PCP infection might have an impaired Th17 response as compared to RTR without PCP infection. However, we did not find a difference in circulating Th1, Th2 and Th17 subsets between PCP cases and control patients, although future studies should include more detailed functional analysis of peripheral blood lymphocytes in PCP cases compared to control patients. We tried unsuccessfully to locate a possible source of infection. Analysis of our PCP cases revealed that they did not come in contact with each other at the outpatient clinic and had not been hospitalized before PCP was diagnosed. Indeed, they were all treated by the same healthcare professionals. Based on these observations, we have no reason to presume an unequal level of *P. jiroveci* exposure. Because several studies have shown that human transmission is the main route of infection [8, 10], it could well be that a RTRs or health care worker at the outpatient clinic functioned as an asymptomatic reservoir, infecting our PCP cases attending the outpatient clinic. We therefore hypothesize that it is the...
combination of relatively low lymphocyte counts and the degree of exposition, though not confirmed, which caused the sudden clustered occurrence of PCP infection in our outpatient clinic.

As cases and control patients were matched for immunosuppressive regimen including the use of ATG, the effect of these different drugs and/or acute rejection episodes on PCP development could not be assessed. However, it is remarkable that two of nine PCP cases had received rituximab. Due to the small number of patients in this case–control study, we hesitate to perform a multivariate analysis to analyse if the univariate risk factors are both independent risk factors.

European transplant guidelines and the 2009 KDIGO clinical practice guidelines recommend PCP chemoprophylaxis for at least 4 months after transplantation and for another 3 to 4 months after treatment for a rejection episode [22, 23]. In our cluster of nine patients, eight cases developed PCP >6 months after transplantation and none of them had a rejection episode within 3 months of PCP diagnosis, making them not eligible for chemoprophylaxis according current guidelines.

Our data suggest that lymphocyte counts may help to guide the indication for chemoprophylaxis from 4 months after transplantation. That in PCP cases, the lymphocyte count was low many months before PCP, suggests that lymphocytopenia may be causally related to the occurrence of PCP. Interestingly, the number of lymphocytes in PCP cases, compared to their control patients, was already lower on the day they received their transplant. This suggests that RTRs with persistent severe lymphocytopenia should continue using chemoprophylaxis after the recommended period of 4 months. Due to the stability of lymphocyte counts many months before PCP, we assume CD4+ T-cell counts would also show no big fluctuations during this time period.

The fact that PCP cases had more infectious episodes than control patients may reflect their state of severe immunosuppression. Interestingly, six PCP cases suffered from herpes virus coinfection like HSV and CMV. Some argue that CMV- or HHV-6 infection itself is a causal risk factor for PCP through the intrinsic immunosuppressive effects of the virus [16]. Another explanation for the high incidence of reactivation of CMV during PCP may be tumour necrosis factor-alpha induced viral replication of latent CMV [38].

That some PCP cases developed herpes zoster and mucocutaneous candidiasis, but not other opportunistic infections like Toxoplasma gondii infection may be related to the level of CD4+ T-cells. In HIV-positive patients, herpes zoster and mucocutaneous candidiasis can occur at any CD4+ T-cell count but are most often observed in patients with CD4+ T-cell counts <200 cells/µL [12]. However, cases of cerebral T. gondii among HIV-positive patients with CD4+ T-cell counts >200 cells/µL are rare. Here, the greatest risk occurs among patients with a CD4+ T-cell count of <100 cells/µL.

Limitations of our study were the retrospective design and the small number of patients. Thus, we acknowledge the need for further studies to assess risk of PCP at later time points after renal transplantation, which is beyond the first 6 months. However, we found a significant association between lymphocyte counts and the development of PCP, which may have important consequences concerning recommendations about chemoprophylaxis with TMP/SMX. Since the PCP outbreak in our centre, we routinely prescribe TMP/SMX for the first 6 months after transplantation. After this time period, only RTRs with persistent severe lymphocytopenia continue to use chemoprophylaxis.

In summary, our data suggest that long-term prophylactic therapy for PCP may be indicated for RTRs who are in a state of severe immunosuppression as appears from persistent severe lymphocytopenia, irrespective of the time interval after transplantation. We propose to prescribe PCP chemoprophylaxis not only in the initial time period following transplantation but to continue its use in RTRs with persistent lymphocytopenia.

Conflict of interest. None declared.

References


Received for publication: 5.10.10; Accepted in revised form: 11.1.11