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Risk factors for *Pneumocystis jiroveci* pneumonia (PcP) in renal transplant recipients

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Abstract

Background. *Pneumocystis jiroveci* pneumonia (PcP) is a potentially life-threatening complication in renal transplant recipients with increased reports during the past few years. Individual risk factors for susceptibility to PcP are incompletely understood.

Methods. We retrospectively analysed 60 cases of confirmed PcP, diagnosed in six German transplant centres between 2004 and 2008, as well as 60 matched controls.

Results. Compared with controls, PcP cases revealed the following significant differences: PcP cases had a poorer renal function (eGFR 31 vs. 42 mL/min in controls), more biopsy-proven rejections (18 vs. 5 patients), more frequent treatment with mycophenolate mofetil (53 vs. 44 patients) and less frequent treatment with interleukin-2 receptor antagonist (20 vs. 32 patients). According to centre policy, in those years, none of the patients or controls had received PcP prophylaxis after transplantation. Of the 60 patients with PcP, 30% developed the disease after the currently recommended duration of prophylactic treatment, 27% died in the course of the disease and 45% required treatment in the ICU.

Conclusions. Our case–control study reveals a novel risk profile for PcP. Renal transplant recipients with more pronounced renal insufficiency following rejection episodes and treated with intensified immunosuppression are at particular risk for PcP.

Keywords: case–control study; glomerular filtration rate; immunosuppression; infectious complication; renal function

Introduction

Pneumocystis jiroveci is an opportunistic pathogen that can cause severe pulmonary infections (*P. jiroveci* pneumonia, PcP) in immunocompromised renal transplant recipients [1,2]. The European Renal Association and the American Society of Transplantation recommend PcP prophylaxis for the first 4 months following renal transplantation [1,3]. The recently published KDIGO guideline recommends PcP prophylaxis in all renal transplant recipients for 3–6 months after transplantation [4]. However, there is a wide variability in the local approach to PcP prophylaxis. A US survey published in 2002 found that 16% of renal transplant centres never prescribed PcP prophylaxis, whereas 18% prescribed PcP prophylaxis for more than 12 months following renal transplantation [5]. The European PcP prophylaxis policy is largely unknown. In Germany, several renal transplant centres discontinued their routine PcP prophylaxis, while a few centres had never prescribed any PcP prophylaxis during the past 40 years mainly because of very low local PcP rates. Starting about 6 years ago, several German renal transplant centres noted a dramatic increase in the number of PcP cases.

Individual risk factors for the occurrence of PcP in renal transplant recipients (i.e. the patient subgroups that might have the most benefit of PcP prophylaxis) are still poorly defined [2]. The overall load of immunosuppression is thought to increase the PcP risk. The data regarding the PcP risk of specific immunosuppressants are largely missing or controversial. The influence of donor age and comorbidity of renal transplant recipients on PcP risk is also incompletely understood.

Following reports of increased local PcP rates at national German conferences, we decided to perform a case–control-study by pooling all renal transplant recipients with documented PcP from six participating transplant centres and comparing these patients to a matched control cohort. Given the well-known influence of individual differences in common practice at local centres and the time since transplantation on the occurrence of PcP, we tried to reach a par-

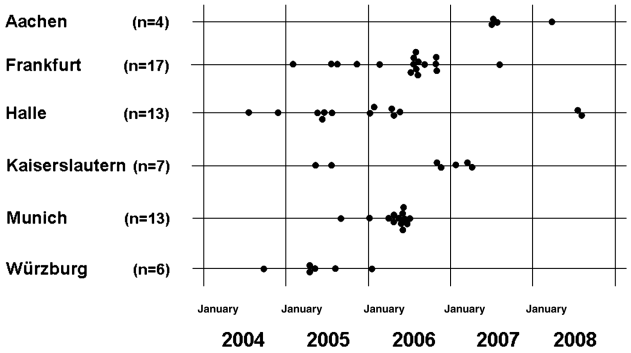

Fig. 1. PcP infections occurred in local outbreaks with a local peak typically within a few months. A total of 60 PcP cases were diagnosed in six transplant centres between 2004 and 2008. Each dot indicates an individual case of PcP infection at the time of microbiological PcP diagnosis.

ticularly close match for these parameters. Our central aim of this study was the identification of individual risk factors for the occurrence of PcP in renal transplant recipients.

Materials and methods

Identification of PcP patients and uninfected controls

Renal transplant recipients with PcP between 2004 and 2008 were identified and documented in six geographically separate German renal transplant centres in a retrospective multicentre case–control approach. PcP was defined as a microbiologically confirmed *P. jiroveci* detection (by cytology, histology or PCR). For each PcP case, we identified a single control renal transplant recipient following a standardized procedure. First, each centre identified all patients who had received a renal transplant between 3 months prior to and 3 months after the transplantation of each PcP case. Second, all cases with documented PcP were excluded from this list. Third, controls were matched for the transplant status of the PcP case (living/deceased donor). Fourth, controls were matched for the sex of the PcP case. Fifth, controls were selected who presented within ±3 months of the PcP case in the outpatient transplant clinic. Employing such a strategy, we were typically able to identify one to three controls for each PcP case. In the event of more than one possible control, we chose the patient who was transplanted closest to the PcP case. Each control patient could only be used for one PcP case. If the best fitting control had already been matched to another PcP case, then the next best fitting control was selected. In the event that this strategy did not produce an appropriate precisely corresponding control patient, we chose controls with a different transplant status, sex, or time frame of transplantation or follow-up visit.

Investigators from the six transplant centres completed anonymous surveys for each PcP case and control patient. Surveys included baseline clinical characteristics, outcome data of PcP cases, as well as renal functional data, comorbidities and immunosuppressive medications. The glomerular filtration rate (eGFR) was estimated using the MDRD formula on the basis of serum creatinine, sex and age. Information was retrieved from the clinical source data, i.e. patient's charts. The data were collected in a combined database in Aachen.

Statistics

Means and standard deviations (notation: mean ± SD) as well as frequencies and percentage were given to describe the data. According to the matched-pairs study design, we used paired *t*-tests to identify mean differences between cases and controls, e.g. for eGFR and serum creatinine. Furthermore, the McNemar test, stratified by pairs, was used to compare proportions between cases and controls, e.g. use of steroids. We compiled combinations of medications and studied their association to the occurrence of PcP. Statistical significance was assessed if the P-value of the corresponding test fell below the significance level of 0.05. The simultaneous effect of the univariate risk factors was studied by a corresponding logistic regression model stratified by pairs. We included only factors that showed a univariate P-value of 0.25 or less. Further possible effect modifiers (interaction terms) were studied. We used SAS® V9 under Windows XP for computations.

Results

PcP occurred in local outbreaks with a local peak typically within a few months

We identified a total of 60 individual PcP cases in the six participating centres between 2004 and 2008. PcP was microbiologically diagnosed in all 60 patients by staining (n = 25), PCR (n = 25) or both (n = 10). Two additional patients who were clinically suspected of suffering from PcP and treated accordingly were excluded from further analysis because of missing microbiological PcP confirmation (one each in Wuerzburg and Kaiserslautern). No controls were selected for these two cases.

A striking feature of PcP was the local accumulation that was typically limited to a narrow time frame, i.e. appearing as local outbreaks often with a cluster of newly diagnosed PcP patients within a few days (Figure 1) The cases in Munich all showed identical PcP genotypes [6]. No routine PcP genotyping was performed in the five other centres of

Table 1. Clinical characteristics of PcP cases and controls

	PcP cases	Controls	P-value
n =	60	60	
Sex (male:female)	40:20	41:19	
Deceased-donor kidneys	46 (77%)	50 (83%)	
Living-donor kidneys	14 (23%)	10 (17%)	
Age at transplantation (years)			
Mean ± SD	53.9 ± 13.9	51.7 ± 13.5	0.2503
Min–max	14–75	19–74	
Renal function at PcP onset/follow-up			
Serum creatinine (mg/dL)			
mean ± SD	2.4 ± 1.1	1.9 ± 1.0	0.0015*
eGFR (mL/min)			
mean ± SD	31 ± 11	42 ± 16	<0.0001*
eGFR <30 mL/min	24 (40%)	15 (25%)	
eGFR <60 mL/min	58 (98%)	52 (87%)	
Renal function prior to PcP onset (median 15 days prior to PcP diagnosis)			
Serum creatinine (mg/dL)			
Mean ± SD	2.2 ± 0.9		
eGFR (mL/min)			
Mean ± SD	32 ± 11		
eGFR <30 mL/min	26 (43%)		
eGFR <60 mL/min	58 (98%)		
PcP infection onset after transplantation (days)			
Median	142		
Mean ± SD	403 ± 930		
<90 days	8 (13%)		
<180 days	42 (70%)		
<365 days	52 (87%)		

eGFR, estimated glomerular filtration rate.
*P < 0.05.

Table 2. Comorbidities of PcP cases (n = 60) and controls (n = 60)

	PcP cases	Controls	P-value
Biopsy-proven acute rejections after Tx	18 (32%)	5 (8%)	0.0029*
CMV infections after Tx	25 (42%)	17 (28%)	0.1025
Diabetes at PcP onset/follow-up	10 (17%)	8 (13%)	0.5930

CMV, cytomegalovirus.
*P < 0.05.

this study. The majority of PcP occurred within the first 6 months following renal transplantation. However, 30% of PcP affected patients beyond 6 months (Table 1).

Following our pre-specified algorithm, we were able to match a single control patient for each PcP case. There was a complete match for the transplant centres. Ninety percent of the controls were transplanted within 2.4 months of the respective case (deviation of transplant time between case and control: mean ± SD 1.1 ± 1.0 months; median 1.0 months, maximum 4.9 months). Ninety percent of the controls had their respective follow-up outpatient visit within 2 months of the PcP onset of the case (deviation of follow-up time between case and control: mean ± SD 1.0 ± 1.9 months; median 0.4 months, maximum 12.4 months). Our matching procedure resulted in 59/60 sex matches and 56/60 transplant status matches; four controls with deceased donor kidneys were matched to four PcP cases with living-donor kidneys (Table 1).

Baseline clinical characteristics and comorbidity of PcP cases and controls

PcP cases had a mean age of 54 years at transplantation. We did not detect significant age differences between cases and controls at the time of transplantation or at the time of PcP onset/follow-up (Table 1). Significant renal functional differences were identified by univariate analysis. PcP cases had significantly higher serum creatinine values and significantly lower eGFR values at PcP onset than their matched controls (Table 1). Fifty-eight of the 60 PcP cases had an eGFR <60 mL/min. To rule out acute kidney injury at the time of PcP onset, serum creatinine and eGFR were additionally analysed prior to PcP. These measurements were performed at a median of 15 days prior to the PcP onset and might therefore reflect better the baseline renal function of these patients than the measurements at the time of PcP diagnosis. Serum creatinine and eGFR measurements did not differ significantly between the two time points analysed (Table 1).

PcP cases had significantly more biopsy-proven acute rejection (BPAR) episodes prior to the onset of PcP (Table 2). PcP infections occurred at a median of 75 days after BPAR (minimum 5 days and maximum 223 days). Treatment of these rejection episodes was prescribed following individual centre practice and was mostly based on corticosteroid pulses. There were no significant differences in the frequency of CMV infections or diabetes prior to the onset of PcP (Table 2).

PcP cases were more frequently treated with mycophenolate and less frequently with IL-2 receptor antagonists

Comparing the medication of cases and controls in a univariate manner, we identified two groups of immunosuppressants that differed significantly between cases and controls (Table 3). Mycophenolate mofetil (MMF) [as single substance, grouped together with mycophenolic acid (MPA) and in combination with steroids] was more frequently part of the immunosuppression of PcP cases. Interleukin-2 receptor antagonists (IL2-RA) were less frequently part of the immunosuppression of PcP cases. No significant differences in the use of calcineurin inhibitors, azathioprine, anti-lymphocyte globulin (ALG) or rituximab were seen. There was a non-significant trend towards more frequent use of sirolimus in the PcP cases.

By multivariate analysis, we failed to detect a significant interaction between biopsy-proven acute rejections and eGFR, the use of MMF or IL2-RA, nor between the use of MMF and eGFR or between the use of IL2-RA. Using a logistic regression model including all parameters with a P <0.25 by univariate analysis, the only significant parameter that differed between cases and controls was eGFR (odds ratio 1.23, confidence interval 1.06–1.44).

Outcome of PcP

The clinical course of PcP was severe in the majority of cases: 27/60 (45%) were admitted to the intensive care unit, 23/60 (38%) required mechanical ventilation and 16/60 (27%) died as a direct consequence of PcP.

Discussion

In a case–control study (matching for centre, time, donor status and sex), we identified specific differences between PcP-infected and PcP-uninfected renal transplant recipients. The major novel finding of this study is the identification of a risk profile for PcP in these patients. Renal transplant recipients with a poorer GFR and with a history of biopsy-proven acute rejection episodes were at higher risk for PcP. Analysis of the immunosuppressive medication revealed that the use of MMF did not confer any protection but was rather associated with an increased incidence of PcP, while the use of IL2-RA was associated with a decreased incidence of PcP.

Local PcP outbreaks have been reported increasingly over the last few years in centres from the Netherlands, Germany and Japan [6–9]. Most of the research focused on modes of infection and indicated airborne transmission. Thorough microbiological analyses revealed locally identical strains in most of the PcP cases [6,8]. These reports provide further evidence for both interhuman transmission of the pathogens (including via asymptomatic carriers) and environmental contamination (detection of PcP DNA in swabs from inpatient and outpatient rooms) [6–8]. These reports did not identify specific risk factors for PcP. A group from Argentina matched 17 PcP cases in renal transplant recipients with 34 uninfected controls [10]. An increased risk for PcP was related to the number and types

Table 3. Immunosuppression of PcP cases ($n = 60$) and controls ($n = 60$)

	PcP cases	Controls	P-value
Use of individual immunosuppressants (at PcP onset/follow-up)			
Corticosteroids	58 (97%)	58 (97%)	
Cyclosporine A (CyA)	25 (42%)	24 (40%)	0.8415
Tacrolimus (Tac)	27 (45%)	33 (55%)	0.2568
Mycophenolate mofetil (MMF)	53 (88%)	44 (73%)	0.0290*
Mycophenolic acid (MPA)	2 (3%)	3 (5%)	0.6547
Azathioprine	2 (3%)	1 (2%)	0.5637
Sirolimus (Sir)	6 (10%)	1 (2%)	0.0588
Combinations of immunosuppressants (at PcP onset/follow-up)			
MMF or MPA	55 (92%)	47 (78%)	0.0209*
CyA or Tac	52 (87%)	57 (95%)	0.0588
CyA + (MMF or MPA)	24 (40%)	18 (30%)	0.2393
Tac + (MMF or MPA)	24 (40%)	26 (43%)	0.7150
Sir + (MMF or MPA)	5 (8%)	1 (2%)	0.1025
Corticosteroids+ CyA	24 (40%)	22 (37%)	0.6831
Corticosteroids+ Tac	26 (43%)	33 (55%)	0.1779
Corticosteroids+ (MMF or MPA)	54 (90%)	46 (77%)	0.0209*
Corticosteroids+ Sir	6 (10%)	1 (2%)	0.0588
Corticosteroids+ CyA + (MMF or MPA)	24 (40%)	17 (28%)	0.1615
Corticosteroids+ Tac + (MMF or MPA)	23 (38%)	26 (43%)	0.5775
Corticosteroids+ (CyA or Tac) + (MMF or MPA)	47 (78%)	43 (72%)	0.3458
Use of antibodies (at any time after Tx)			
IL-2 receptor antagonists (IL-2RA)	20 (34%)	32 (53%)	0.0186*
Anti-lymphocyte globulin (ALG)	17 (29%)	15 (25%)	0.5271
Rituximab (Ritux)	2 (3%)	2 (3%)	0.1624
IL-2RA or ALG or Ritux	34 (59%)	39 (67%)	0.3173

*$P < 0.05$.

of rejection episodes and CMV infections [10]. A retrospective analysis of the USRDS database identified 142 PcP cases in a cohort of 32 757 renal transplant recipients between 2000 and 2004 [11]. The authors report that expanded criteria donor, donation after cardiac death and a prior history of cancer were associated with the development of PcP [11]. Interestingly, acute rejections were not associated with risk for PcP in this analysis.

An impact of different immunosuppressive regimens on the PcP occurrence in renal transplant recipients was first reported by Lufft *et al*. [12]. It is now widely accepted that the quantity of overall immunosuppression increases the risk for PcP; however, there is still uncertainty regarding the individual contributions of different immunosuppressants [2]. First reports indicated an anti-*Pneumocystis* effect of MMF *in vitro* and in animal models [13]. The USRDS data are consistent in showing that MMF was more frequently used in uninfected controls [11]. Given the possible PcP-protective effect of MMF, some authors even raise the question of the necessity of PcP prophylaxis in patients on MMF [14]. Our study does not support this view and in fact shows quite the opposite, namely an increased number of PcP in MMF-treated patients. The use of ALG is thought to result in a high risk for PcP [1]. Our own data cannot confirm this concern, showing no difference in the use of ALG between cases and controls. One striking novel finding is the lower PcP rate in patients treated with an IL2-RA. It is currently not known whether IL-2RA might have any direct anti-*Pneumocystis* effects. This finding might also relate to an indirect IL-2RA effect via reduction of rejection episodes and thereby reduction of overall immunosuppression that is used for the treatment of rejections. However, our multivariate analysis did not detect any interaction between the use of IL2-RA and BPAR. Regarding the use of sirolimus, there was a trend towards more frequent use of sirolimus in PcP cases. However, our study was underpowered to assess this further, given the low total numbers of patients treated with sirolimus.

Episodes of allograft rejection have been linked to a higher risk for PcP [15]. Our data confirm this finding by demonstrating significantly more BPAR in PcP cases than in controls. We did not detect other potential clinical factors (e.g. CMV infection and diabetes) as PcP risk factors. A novel finding is the identification of a low eGFR as a risk factor for PcP in renal transplant recipients. Why might patients with a low eGFR be at a particular risk for PcP? It is possible that the low eGFR is a secondary result of BPAR episodes and a non-specific indicator for higher overall immunosuppression. However, our multivariate analysis did not detect any interaction between eGFR and BPAR. It might be that the relative uraemic milieu itself contributes to a further state of immunosuppression. Alternatively, a lower eGFR might result in a prolonged renal clearance of immunosuppressants, in particular MMF and corticosteroids, and their metabolites [16–18]. Based on the identification of both low eGFR and MMF as PcP risk factors, we hypothesize that MMF metabolites might accumulate in renal insufficiency and might cause over-immunosuppression. This hypothesis is supported by findings in Chinese patients where severe pneumonia, including several confirmed PcP cases, was reported in patients with IgA nephropathy, particularly in those treated with MMF and with impaired renal function [19].

A case–control study is always limited by its study design, i.e. the way controls are matched to the cases. Given our match design for sex, time and donor status, we were obviously unable to detect risk factors for PcP infections within these parameters. We cannot rule out that sex, donor status or time after renal transplantation might influence the risk for PcP. However, given the high likelihood of inter-patient PcP transmission, we tried to match the timing of outpatient visits in order to identify uninfected controls who had indeed been at risk for PcP. Finally, a recall bias with more visits being scheduled for patients developing complications cannot be ruled out by our case–control study design.

What were the reasons for not routinely prescribing PcP prophylaxis in these transplant centres? First, the potential side effects of the prophylaxis medication were regarded as significant. The drug most widely used for PcP prophylaxis, trimethoprim–sulphamethoxazole, can lead to an (albeit reversible) increase in serum creatinine, allergic reactions, including acute interstitial nephritis, myelosuppression and hyperkalaemia. Second, PcP almost completely vanished in many German transplant centres in the 1990s. Third, PcP can occur after withdrawal of the prophylaxis. Many centres therefore felt that the relatively high number of patients who would need to be treated in order to prevent a single case of PcP did not justify the potential side effects of the prophylaxis.

In conclusion, renal transplant recipients with poor renal function and with rejection episodes have an increased risk for PcP. Our analysis of the immunosuppressive medication suggests that induction with IL2-RA is PcP-protective, while treatment with mycophenolate mofetil increases the risk for PcP. Future research based on these risk factors needs to define optimal individualized PcP prophylaxis regimens in renal transplant recipients, which might implicate even prolongation of PcP prophylaxis in high-risk candidates, i.e. after acute rejection therapy, or in transplant recipients with poor renal function.

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(See related article by Woywodt *et al.* Friendly Fire. *NDT Plus* 2011; 4: 205–207.)

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