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## Prophylaxis and Treatment of *Pneumocystis jirovecii* Pneumonia after Renal Transplantation

With the introduction of new immunosuppressants *Pneumocystis pneumonia* (PCP) remains to be a threat to kidney transplant recipients. Based on the results from our kidney transplantation center an overview concerning incidence, prophylaxis, therapy and outcome is provided.

The incidence of PCP at our center was 0.75 cases per 100 patients and year (period May 2002 to December 2007), the frequency with reference to the 316 kidney transplantations performed was 4.1%. 13 cases of PCP occurred during the observation period and 3 of these patients (23%) died from the pneumonia. In only 4 patients (31%) a complete restitution of the transplant function was achieved.

The letality of PCP among kidney graft recipients is up to 50% - thus a prophylactic treatment in the early post-transplantation period is recommended for at least 4 months and should be lengthened depending on the course of immunosuppression. Administration of 80/400 mg TMP/SMZ is highly effective in preventing PCP and adverse effects from TMP/SMZ seem to be rare using this regimen.

### Key words:

pneumocystis, PCP, pneumonia, infection, immunosuppression, kidney transplantation

### *Prophylaxe und Behandlung der Pneumocystis Jiroveccii-Pneumonie nach Nierentransplantation*

*Mit der Einführung neuer Immunsuppressiva stellt die Pneumocystis-Pneumonie nach wie vor eine Bedrohung für Nierentransplantat-Empfänger dar. Vor dem Hintergrund der Ergebnisse aus unserem Nierentransplantationszentrum geben wir in diesem Beitrag einen Überblick über Häufigkeit, Prophylaxe, Behandlung und Ergebnis.*

*Die Inzidenz der PCP betrug in unserem Zentrum 0,75 Fälle pro 100 Patienten und Jahr (von Mai 2002 bis Dezember 2007), die Häufigkeit in Bezug auf die 316 durchgeführten Nierentransplantationen lag bei 4,1%. 13 PCP-Fälle traten während der Beobachtungsdauer auf und drei dieser Patienten (23%) verstarben infolge der Pneumonie. Bei lediglich vier Patienten (31%) konnte die Transplantatfunktion vollständig wiederhergestellt werden.*

*Die Letalität infolge PCP bei Nierentransplantat-Empfängern erreicht bis zu 50% - eine prophylaktische Behandlung wird daher*

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*in der frühen Phase nach Transplantation über mindestens 4 Monate hinweg empfohlen und sollte je nach Verlauf der Immunsuppression verlängert werden. Die Gabe von 80/400 mg TMP/SMZ ist zum Schutz vor PCP sehr effektiv, Nebenwirkungen durch TMP/SMZ scheinen bei diesem Behandlungsregime selten zu sein.*

**Schlüsselwörter:**

*Pneumocystis, PCP, Pneumonie, Infektion, Immunsuppression, Nierentransplantation*

**Introduction**

The development of new and increasingly potent immunosuppressants has led to a lower rate of acute rejection reactions but favours the occurrence of opportunistic infections in this group of patients (1). *Pneumocystis pneumonia* (PCP) is a severe and potentially life-threatening complication in patients following renal transplantation. Interest has again focussed on this problem particularly since the clinical introduction of the mTOR inhibitors (2).

It was long assumed that “classical“ PCP is caused by the fungus *Pneumocystis carinii*, which occurs in rodents. However, the actual cause of this pneumonia in humans is *Pneumocystis jirovecii*, which must be distinguished from the former, so that PCP today no longer means “*Pneumocystis Carinii* Pneumonia“, but “*PneumoCystis (jirovecii) Pneumonia*“ (3).

Most cases of PCP occur within the first six months after renal transplantation. The risk of PCP does not depend primarily on the time since transplantation but on the intensity of the immunosuppressant therapy, previous rejection therapy, CMV and hepatitis C infection (1). An increased incidence of PCP with tacrolimus-based therapy was described by a few authors, which appears plausible in view of the stronger immunosuppressant effect of this drug compared with cyclosporin A (4). Similar observations were made in previous decades after azathioprine was superseded by cyclosporin A (5). The incidence of PCP is centre-specific, and the customary immunosuppression regimes employed there contribute to this, along with the human-to-human route of transmission by droplet infection, which time and again causes minor epidemics among immunosuppressed patients (6 -9). Reactivation of pathogens

persisting in lung tissue probably plays a subordinate role; in the general population up to >75% of healthy 4-year olds have had contact with the pathogen and are seropositive (10, 11).

**Results**

In the period from May 2002 to December 2007 315 renal transplants were performed in our institution. About 500 renal transplant patients attend our follow-up outpatient clinic. Since the publication of the European Best Practice Guidelines in 2002, trimethoprim/sulphamethoxazole in a dose of 80/400 mg per day has been given as standard prophylaxis for a period of at least 4 months after transplantation.

In this period, 69 pneumonias occurred in renal or cardiac transplant patients. In 14 of these patients (13 renal transplants, 1 cardiac transplant), *Pneumocystis jirovecii* was found to be the cause. This was confirmed in all cases

by PCR of the bronchial lavage. Only one of these 13 renal transplant patients was still receiving TMP/SMZ prophylaxis at the time of the infection. 80% of the cases of PCP occurred within the first year after renal transplantation (Table 1).

Of these 13 patients, 10 (77%) were cured and 3 patients (23%) died of the pneumonia. 5 (38%) required one or more haemodialysis treatments and in one of these patients, transplant function was not restored. Complete normalisation of transplant function to the baseline values was achieved in only 4 patients (31%), and the other patients demonstrated more or less marked permanent impairment of renal function.

**Diagnosis and Treatment**

We test for the pathogen exclusively by PCR of the bronchial lavage. Before PCR became available, which has a sensitivity of 80 to 95% for detection in the bronchial lavage, diagnosis was microscopic (8,12).

Treatment is with TMP/SMZ; pentamidine (4 mg/kg) and atovaquone (750 mg tid) are an alternative possibility. The combination of primaquine 30 mg once daily and clindamycin 600 mg tid is also used. Because of the high mortality of this disease, i.v. TMP/SMZ is used in our centre initially, deviating from the European Guidelines, which suggest this only when the PaO2 is below 70 mmHg (13). Discontinuation of treatment because of the side effects of

Tab. 1: Patient characteristics and outcome

n = 13 patients (9 males, 4 females)	Mean	Range
Age (years)	58	44 - 72
Years after RTX	2.4	0.3 - 16 (80% < 1 year)
Serum creatinine before / after PCP	153.8 / 171.4	103 - 195 / 138 - 190 (3 patients died, 1 patient on permanent haemodialysis, 4 patients temporarily on dialysis)
GFR before / after PCP	42 / 33.5	32 - 68 / 20 - 62
CMV positive	8 of 13	
History of ATG or basiliximab	6 of 13	
Immunosuppressive regimen: CNI + mycophenolate mofetil + methylprednisolone	8 of 13	

this medication (incl. leukopenia) occurs in up to 5% of cases (5), but was not necessary in our patients.

TMP/SMZ (80/400 mg) is also the agent of first choice for prophylaxis. The same or double the dose taken three times per week appears to have the same protective effect. In the case of intolerance, pentamidine (once a month by inhalation), dapsone (50 mg bd or 100 mg once daily) or the known anti-malarial atovaquone 1500 mg once daily or 750 mg bd can be used (9, 13).

## Discussion

The incidence of PCP or PJP after renal transplantation was 0.75 cases per 100 patients and year in our centre; the frequency – with reference to the renal transplants performed – was 4.1% and thus corresponds essentially to the internationally accepted figures of ~5% (14). Despite its relative rarity, this disease is of great relevance for the transplant physician because of the mortality of 23% (up to 50% in the literature (15)).

The duration of at least three to four months recommended in the European guidelines for TMP/SMZ prophylaxis (13) should in fact be regarded only as an absolute minimum when the patient's course is uncomplicated and it should be reviewed and if necessary extended in each individual case. In patients with a combination of immunological risk factors, the gradual dose reduction of the immunosuppressants is usually handled cautiously. These risks include a poor HLA match, high historical or current titre of anti-HLA antibodies, repeated renal transplantation and previous rejection episodes. By

prolonging the TMP/SMZ prophylaxis, the occurrence of PCP can be prevented with great certainty in this group of patients (16, 17). Only a few transplant centres continue prophylaxis for all renal transplant patients for longer than a year (18). At the dosage of 80/400 mg TMP/SMZ daily no significant side effects are to be expected. A few centres give this dose only three times weekly with the same protective efficacy (17). The standard treatment in our centre currently consists of continuing the chemoprophylaxis as long as the Cell-Cept dose exceeds 1g per day and the dose of the steroid component of the triple drug therapy at the same time is above 8 mg methylprednisolone per day. In patients given rapamycin, TMP/SMZ prophylaxis is continued indefinitely as obligatory concomitant therapy, regardless of whether this is initial therapy after transplantation or whether this preparation is used subsequently in the long-term course.

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