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Pneumocystis jirovecii pneumonia is rare in renal transplant recipients receiving only one month of prophylaxis

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Abstract: Prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) is recommended for at least 4–12 months after solid organ transplant. In our center, renal transplant recipients receive only 1 month of post-transplant trimethoprim–sulfamethoxazole, which also may provide limited protection against *Nocardia*. We identified only 4 PCP cases and 4 *Nocardia* cases in 1352 patients receiving renal and renal-pancreas transplant from 2003 to 2009 at the University of Michigan Health System. Two PCP cases were identified <1 year after transplant, and 2 PCP cases were identified >1 year after transplant (gross attack rate 4/1352, 0.3%). Two *Nocardia* cases were identified <1 year after transplant, and 2 cases were identified >1 year after transplant. All identified cases received induction therapy (7 of 8 with anti-thymocyte globulin), whereas about one-half of all renal transplant patients received induction therapy at our institution. No patient was treated for rejection within 6 months of PCP; 2 of 4 patients with PCP had recent cytomegalovirus infection. All patients with PCP and 3 of 4 patients with *Nocardia* survived. The benefits of prolonged PCP prophylaxis should be weighed against the adverse events associated with prolonged use of antimicrobials.

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As *Pneumocystis jirovecii* pneumonia (PCP) occurs in immunocompromised hosts, including solid organ transplant recipients (1), the current American and European guidelines recommend PCP prophylaxis for at least 4–12 months after renal transplant (2, 3). Trimethoprim–sulfamethoxazole (TMP-SMX) is recommended as the first-line agent for PCP prophylaxis, and this agent may provide some protection against other opportunistic pathogens including *Nocardia* species (4). PCP is very rare in renal transplant recipients receiving TMP-SMX prophylaxis; in one series, no cases were observed among 534 patients while on prophylaxis (5).

PCP rates from <1% to 41% have been observed in renal transplant recipients before the routine use of PCP prophylaxis (5). As most centers currently use some form of prophylaxis to prevent PCP pneumonia, recent data are limited regarding the rates of PCP and *Nocardia* after renal transplant with modern immunosuppressive regimens but without prophylaxis. A large observational study of PCP infection in renal transplant recipients from 2000 to 2004 revealed a cumulative incidence of 0.4%; the use of prophylaxis in those patients was not reported (6). A recent single-center study of *Nocardia* infection in organ transplant patients from 1995 to 2005 determined a rate of 0.2% in renal transplant patients (7).

In our institution, renal transplant recipients receive only 1 month of post-transplant TMP-SMX (1 single-strength tablet daily) after renal transplantation, partially for prophylaxis against urinary tract infection. Because this brief duration of prophylaxis is uncommon in transplant centers in the United States (8), we sought to determine the rate of PCP in renal transplant patients receiving very short courses of TMP-SMX. As TMP-SMX also has activity

against *Nocardia*, we also assessed rates of *Nocardia* infection.

Methods

The University of Michigan Health System is a 930-bed tertiary care medical center performing >400 solid organ transplants annually. Cases of PCP and nocardiosis in renal and renal-pancreas transplants performed from 2003 to 2009 were identified by querying the electronic medical record of renal transplant recipients with the search terms "*Pneumocystis* pneumonia," "PCP pneumonia," "*pneumocystis*," "pneumocytosis," "*Pneumocystis jirovecii*," "*Pneumocystis carinii*," "*Nocardia*," and "nocardiosis."

As per long-standing institutional practice, a diagnosis of PCP was established with a positive PCP polymerase chain reaction assay from a bronchoalveolar lavage (BAL) or sputum specimen. A diagnosis of nocardiosis was established with a positive culture from sputum, BAL, or brain biopsy. The gross attack rates for PCP and nocardiosis were calculated by dividing the number of PCP or *Nocardia* cases by the total number of renal and renal-pancreas transplant recipients in the study period. In infected patients, demographic data, immunosuppressive medications, the receipt of induction or rejection therapy, receipt of PCP prophylaxis including type and duration, history of cytomegalovirus (CMV) infection, and survival were recorded.

Standard maintenance immunosuppression consisted of tacrolimus (goal trough tapered to 4–8 ng/mL by month 3) or cyclosporine (goal trough tapered to 150–200 ng/mL by month 3), mycophenolate mofetil (MMF) 1 g twice daily, and prednisone (tapered to 10 mg daily by month 2). Rabbit anti-thymocyte globulin (ATG) (Thymoglobulin; Genzyme, Cambridge, Massachusetts, USA) induction was given to patients at high risk for rejection. Patients not receiving ATG with delayed graft function were treated with basiliximab.

Results

We reviewed 1352 patients receiving renal and renal-pancreas transplants. Four cases of PCP (gross attack rate 4/1352, 0.3%) and 4 cases of *Nocardia* (gross attack rate 4/1352, 0.3%) were identified. Two cases of PCP occurred <1 year after transplant and 2 PCP cases occurred >1 year after transplant (Table 1). Two *Nocardia* cases occurred <1 year after transplant and 2 cases occurred >1 year after transplant (Table 2). Two of 4 PCP cases received TMP-SMX 1 single-strength tablet daily for 30 days after transplant, 1 PCP case received TMP-SMX for 1 year as required by a study protocol, and 1 PCP case received 1 dose of inhaled pentamidine because of sulfa allergy. Three of 4 *Nocardia* cases received TMP-SMX for 30 days after transplant, and 1 *Nocardia* case received 1 dose of inhaled pentamidine.

Immunosuppressive regimens for all cases included MMF, prednisone, and either cyclosporine or tacrolimus. All identified PCP and *Nocardia* cases received induction immunosuppression, with 7 of 8 cases receiving ATG, whereas approximately one-half of all renal transplant patients received induction immunosuppression at our institution. No patient was treated for rejection within 6 months before diagnosis of PCP or *Nocardia* infection. Two of 4 patients with PCP

***Pneumocystis jirovecii* pneumonia (PCP) cases among 1352 renal and renal-pancreas transplant recipients from 2003 to 2009**

Year of transplant	PCP months after transplant	Survival	Rejection	Induction	Maintenance immunosuppression	Prophylaxis (comment)
2007	10 months	Yes	None	ATG	MMF, PRED, TACRO	TMP-SMX × 30 days (CMV 2 months before PCP)
2006	10.5 months	Yes	None	ATG	MMF, PRED, CYP	TMP-SMX × 30 days (CMV 4 months before PCP)
2004	15 months	Yes	None	Anti-IL2Rα	MMF, PRED, TACRO	TMP-SMX × 1 year (study protocol)
2006	15 months	Yes	Steriod pulse × 2	ATG	MPA, PRED, TACRO	IP × 1 dose pulse 8 months before PCP

ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil; PRED, prednisone; TACRO, tacrolimus; TMP-SMX, trimethoprim-sulfamethoxazole; CMV, cytomegalovirus; CYP, cyclosporine; IL2Rα, interleukin 2 receptor alpha; MPA, mycophenolic acid; IP, inhaled pentamidine.

Table 1

***Nocardia* cases among 1352 renal and renal-pancreas transplant recipients from 2003 to 2009**

Year of transplant	*Nocardia* months after transplant	Survival	Rejection	Induction	Maintenance immunosuppression	Site; *Nocardia* species
2009	3 months	No	None	ATG	MMF, PRED, CYP	CNS; *N. asteroides*
2003	4.5 months	Yes	None	ATG	MMF, PRED, TACRO	Pulmonary; *N. asteroides*
2005	18.5 months	Yes	None	ATG	MMF, PRED, TACRO	CNS; *N. asteroides*
2006	30 months	Yes	None	ATG	MPA, PRED, TACRO	Pulmonary; *N. farcinica*

ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil; PRED, prednisone; CYP, cyclosporine; CNS, central nervous system; TACRO, tacrolimus; MPA, mycophenolic acid.

Table 2

infection had recent CMV infection. All patients with PCP and 3 of 4 patients with *Nocardia* survived.

Two of the 4 PCP cases presented with hypoxia. Treatment of PCP was variable; 1 patient received TMP-SMX, 1 patient received clindamycin and primaquine owing to sulfa allergy, and 2 patients started TMP-SMX but completed therapy with atovaquone owing to TMP-SMX intolerance. Secondary prophylaxis was also variable; 1 patient received TMP-SMX 3 times per week for >4 years, 1 patient received atovaquone daily for about 1 year, 1 patient received dapsone 3 times per week for about 2.5 years until immunosuppression was tapered for graft failure, and 1 patient received no secondary prophylaxis. In all cases, MMF or mycophenolic acid was held during treatment of infection, and in 1 case, a lower dose of MMF was resumed after completion of PCP treatment.

Discussion

In our institution, PCP is rare in renal and renal-pancreas transplant recipients, despite common use of cell-depleting induction immunosuppression and only a 1-month duration of PCP prophylaxis. *Nocardia* cases are equally rare. Both PCP and *Nocardia* cases were evenly distributed <12 months and >12 months after transplant. No case occurred during the first 4–6 months after transplant, the time period generally considered of highest risk (2). Three of 4 PCP cases and all *Nocardia* cases received induction with ATG. No cases were treated for rejection, although 2 PCP cases had been treated for CMV within 6 months, which is a recognized risk factor for PCP (9, 10).

Historically, rates of PCP pneumonia after renal transplantation have varied from <1% to 41% (but generally around 5%) (5). As about 90% of transplant centers employ highly effective PCP prophylaxis for at least 3 months after transplantation (8), the expected incidence of PCP in patients using modern immunosuppressive regimens, but not receiving prophylaxis, is unclear. A number of reports do, however, describe a very low rate of PCP with no or incomplete prophylaxis, similar to the low rate noted in our study (11–15). These low rates of PCP were followed by outbreaks of PCP leading to the use of prophylaxis (11–15).

Two placebo-controlled trials of TMP-SMX prophylaxis after renal transplantation were published in the 1990s. Among 138 renal transplant recipients at the University of Wisconsin receiving anti-lymphocyte globulin induction randomized to TMP-SMX or placebo for 1 year, only 1 case of PCP occurred in the placebo group (16). Conversely, a study conducted at Massachusetts General Hospital comparing 6 months of ciprofloxacin with TMP-SMX for prevention of urinary tract infection demonstrated a 14% (7/51) rate of PCP in the ciprofloxacin arm (17).

We identified a number of factors that might account for the low rate of PCP observed over an extended period of time at our center. MMF has been demonstrated to have a protective effect against PCP in virus-free rats given dexamethasone (18). Furthermore, 3 registration trials conducted in the 1990s of MMF demonstrated no cases of PCP in the MMF group and 1.2–2.4% in the comparator group (19–21). Some patients did receive induction with ATG; receipt of PCP prophylaxis was not uniform or well described. The degree of protection against PCP provided by MMF is clearly limited, as many reported cases (particularly in outbreaks) as well as the cases in this report occurred in patients receiving MMF (6, 12). This suggests that any protective effect of MMF is far inferior (and may not be clinically relevant) to that provided by TMP-SMX or other commonly used preventative agents.

Recent data suggest that PCP colonization, even in healthy adults, may be more common than previously thought (22), leading to speculation that clinical disease in some circumstances may be related to reactivation of latent disease in the setting of immunosuppression (23). Theoretically, a brief course of TMP-SMX prophylaxis might eradicate colonization, resulting in a lower incidence of PCP even after withdrawal of prophylaxis.

A number of centers have reported outbreaks of between 10 and 27 cases of PCP among renal transplant recipients after a long period of few observed cases, despite incomplete or absent prophylaxis (11–15). No environmental source of PCP has been identified, and PCP is not a zoonosis. Thus, interhuman transmission is the most likely cause of these outbreaks (23).

Local or geographic factors (low rates of PCP colonization, clinic or hospital arrangement decreasing risk of person-to-person transmission) may have accounted for the low rate seen in our populations, as well as varying rates seen in other studies of patients not receiving prophylaxis.

In addition to decreasing the risk of PCP-associated morbidity and mortality, TMP-SMX prophylaxis may provide additional protection against opportunistic infections like *Nocardia* and toxoplasmosis. Our *Nocardia* rate was similar to the rate reported in a recent single-center study of *Nocardia* infection, suggesting that limiting prophylaxis to 1 month does not increase the risk of this infection (7). We did not specifically investigate for the occurrence of toxoplasmosis in our institution, but this infection is rare in recipients of renal transplants, and universal prophylaxis is not recommended (24).

Conclusions

Renal transplant recipients treated with only 1 month of TMP-SMX prophylaxis had a very low rate of PCP, with only 4 cases occurring in 1352 patients. This low rate was observed despite significant use of ATG for induction of immunosuppression. The benefits of PCP prophylaxis should be weighed against the adverse events associated with prolonged use of antimicrobials. Reports of outbreaks of PCP indicate that centers not using prophylaxis should monitor rates of PCP and be prepared to introduce prophylaxis. Furthermore, PCP prophylaxis is likely to be needed in patients who develop other PCP risk factors (e.g., CMV infection, treatment for organ rejection).

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