

Late Onset of *Pneumocystis jirovecii* Pneumonia in Kidney Transplant: How Long is too Long in Opportunistic Infection Prophylaxis?

Círia Leandra Martins de Sousa¹ , Cátia Raquel Figueiredo² , Sofia Ventura³ , Manuela Almeida⁴ , La Salette Martins⁴ 

¹ Centro Hospitalar Trás-os-Montes e Alto Douro, Vila Real, Portugal.

² Centro Hospitalar do Médio Tejo, Torres Novas, Santarém, Portugal.

³ Hospital do Divino e Espírito Santo, Ponta Delgada, Açores, Portugal

⁴ Centro Hospitalar e Universitário do Porto, Porto, Portugal

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■ CS: Conceptualization, methodology, investigation, writing original draft – review and editing.

■ CF and SV: Conceptualization, methodology.

■ MA and LM: Supervision, review and editing.

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ABSTRACT

Pneumocystis jirovecii (PJ) opportunistic infections occur in immunocompromised patients impacting significantly hospitalizations and mortality. Trimethoprim-sulfamethoxazole (TMP-SMX) is universally used as prophylaxis of *Pneumocystis jirovecii* pneumonia (PJP) and therefore, this infection is rare condition in solid organ transplant (SOT) recipients.

We present a case of a 46-years-old male, who received an ABO-incompatible transplant with prior desensitization protocol with plasmapheresis, rituximab, and anti-CMV immunoglobulin. IgG anti-B title pre-desensitization was 1:128. The patient had 6 ABDR mismatches, without HLA antibodies, and the CDC crossmatch for T and B cells was negative. Both recipient and donor were CMV positive (D+/R+). The patient received induction immunosuppression with corticosteroids, basiliximab, calcineurin inhibitor, and mycophenolate mofetil. Immediate kidney function was verified, and three additional plasmapheresis sessions were performed. At discharge serum creatinine (sCr) was 1.38 mg/dL, but kidney function declined during the first 6 months (sCr 2.5 mg/dL). Urinalysis was unremarkable. A kidney biopsy was declined by the patient. Unit protocol maintained the prophylaxis for PJP and cytomegalovirus (CMV) infection with TMP-SMX and valganciclovir. The patient was admitted to the emergency department 20 months after the transplant with respiratory symptoms and was diagnosed with PJP. Bronchoalveolar lavage fluid was also positive for CMV. Intensive care unit (ICU) admission was necessary due to clinical deterioration, with subsequent good evolution without mechanical ventilation. At discharge, prophylaxis with TMP-SMX and valganciclovir was maintained for more than six months.

Here we discuss the late onset of PJP, and the main risk factors related to severe infection. Transplant subgroups in which longer PJP prophylaxis could be beneficial and the indication to re-start PJP prophylaxis is still under discussion.

Keywords: Antibiotic Prophylaxis; Kidney Transplantation/adverse effects; Pneumonia, *Pneumocystis*/drug therapy; Pneumonia, *Pneumocystis*/prevention & control

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INTRODUCTION

Pneumocystis jirovecii (PJ) is an environmental and opportunistic fungus with affinity to the lung tissue and, in particular, to type I pneumocytes. Immunocompromised are the most affected, and *Pneumocystis jirovecii* pneumonia (PJP) is still a significant cause of infection in these patients.¹ Among solid organ transplant (SOT) recipients, PJP was associated with high mortality rates.²

After universal institution of trimethoprim-sulfamethoxazole (TMP-SMX) for PJP prophylaxis in SOT recipients during the first-year post-transplantation the occurrence of PJP declined.^{3,4} Rates of PJP infection vary between 0%-2%, with 50% of mortality.⁵ A significant reduction in PJP incidence from 10% to 1% was documented in kidney transplant patients.⁶

Many factors have been proposed as a risk for PJP, like older age, immunosuppressant agents, cytomegalovirus (CMV) infections, graft

rejection episodes, and low lymphocyte count.^{4,7} Allograft rejection and CMV infection were frequently identified as major risk factors for PJP development.⁸

Current guidelines recommend prophylaxis for PJ in all kidney transplant recipient patients, however, the length of treatment, benefits of extending this period, and in which patients reintroduction of prophylaxis should be considered are still under discussion.⁹ Herein, we describe a case of a patient with late-onset PJP after several months of prophylaxis withdrawal.

■ CASE REPORT

We describe the case of a 45-year-old male with end-stage kidney disease (ESKD) secondary to glomerulonephritis who started peritoneal dialysis in 2015.

The proposed transplant was ABO-incompatible (donor B+, recipient A+) from his wife in July 2018. The patient was submitted to desensitization protocol with plasmapheresis (4 sessions), rituximab (375 mg/kg/1.72 m²), and anti-CMV immunoglobulin (0.1 g/kg after each plasmapheresis) before the scheduled transplant. IgG anti-B titer pre-desensitization was 1:128. The patient had 6 ABDR mismatches, without HLA antibodies, and the CDC cross-match for T and B cells was negative. Both recipient and donor were CMV positive (D+/R+). Induction immunosuppression was performed with corticosteroids, basiliximab, a calcineurin inhibitor (tacrolimus), and mycophenolate mofetil. Immediate kidney function was controlled, and the patient was submitted to more 3 plasmapheresis sessions. At discharge serum creatinine (sCr) was 1.38 mg/dL.

Declining of kidney function with sCr increase (1.38 to 2.5 mg/dL) was documented during the first 6 months. Urinalysis was unremarkable, and isoagglutinin titles were persistently low without de novo DSAs. At this time, a kidney biopsy was proposed but declined by the patient. Prophylaxis for PJP and CMV infection with TMP-SMX and Valganciclovir was maintained as per unit protocol.

The patient was admitted to the emergency department 20 months after the transplant with cough, fever and severe asthenia. On admission, the patient was hypotensive, and had analytical parameters compatible with systemic inflammation but without worsening kidney function. Chest X-ray showed a reticular infiltrate in both lung bases (Fig. 1). Empirical treatment with ceftriaxone, azithromycin, and ganciclovir was started since the patient had a recent CMV viremia (1236 UI/mL copies). Computed tomography has found a diffuse ground-glass opacities (Fig. 2). Intravenous prednisolone (1 mg/kg/day), and empirical cotrimoxazole were immediately started (day 1 of admission) in the context of a possible PJP. PJ were positive in bronchoalveolar lavage fluid. On day 7 the patient was admitted to the intensive care unit (ICU) due to severe hypoxemia. Antibiotic treatment was changed to piperacillin-tazobactam, and tacrolimus was stopped. After 6 days in ICU, the patient returned to the nephrology department and tacrolimus was re-started. During admission CMV viremia decreased, but at discharge, the bronchoalveolar lavage fluid was positive for CMV.

The patient remained under prophylaxis with TMP-SMX and valganciclovir. No other opportunistic infections were documented during the follow-up, and sCr was stable at 2.8 mg/dL.

■ DISCUSSION

PJP is a severe opportunistic infection in immunocompromised patients. In SOT recipients, PJP is associated with graft dysfunction, severe respiratory failure, and increased mortality. Before prophylaxis use, approximately 5%-15% of patients would develop PJP, but now it is uncommon.¹⁰ Previous studies reported an incidence rate between 3.0 to 3.7 per 1000 persons in cohorts where PJP prophylaxis was used routinely.⁴

In a retrospective case-control study with 16 years of follow-up, PJP was diagnosed on average after six years post-transplant. The morbidity and mortality were high, 40% of the patients required ICU admission and mechanical ventilation, and one-half died. Lower post-transplant lymphocyte was strongly associated with PJP, with absolute lymphocyte count (ALC) $\leq 500 \times 10^6$ cells/uL connoting a 19-fold higher disease risk in multivariate analysis. The authors proposed that in presence of severe lymphopenia prophylaxis for PJP should continue or re-started.¹¹

The real incidence of late-onset PJP in kidney transplant recipients is not known, but some studies report rates between 1.4%-4.5%.^{4,5} The risk is higher in the first 6 months, however, has also been reported one-year post-transplant,¹⁰ and occasionally first 6 months after stopping prophylaxis.⁵ Our case shows that similarly to what was previously described in the literature, late PJP can occur several months after prophylaxis discontinuation. Despite the need for ICU admission, the evolution was quite good, and could be related to younger age, and no other significant comorbidities in this patient. The American Society for Transplantation proposed to continue prophylaxis at least 6-12 months post-transplant, or even longer, due to increased morbidity and mortality associated with PJP.⁹

The efficacy of TMP-SMX was first demonstrated in heart transplant patients and after that, most kidney transplant programs instituted this antibiotic as PJP prophylaxis in the first 6 to 12 months.¹² TMP-SMX has proved highly effective with a PJP risk reduction near 90%.³ However the main issue remains the duration of maintenance therapy, which is reflected in the heterogeneity of protocols in many centers.³ At our institution, all patients receive primary prophylaxis for PJP with TMP-SMX during the first 3-6 months after transplantation, in an individualized decision. Our patient received 6 months of treatment because of previous immunosuppression with rituximab. Some authors proposed that despite lower incidence, in the second-year post-transplant the risk of PJP is still increased, and because of that this period should be considered a new critical period.⁴

There is no evidence to support the decision on which kidney transplant patients should prophylaxis be extended after the first year post-transplant and for how long.^{4,7} SOT recipients need the same precise thresholds, for instance as HIV patients, in order to define which patients might benefit from longer exposure to prophylaxis and in which unnecessary toxicity could be avoided.¹³ Predictors of

late-onset PJP in kidney transplants have been studied, mainly to help decide which patients the prophylaxis should be extended. The most relevant risk factors for late-onset PJP were CMV infection and the type of treatment used in rejection episodes. Exposure to lymphocyte-depleting agents (such as anti-thymocyte-ATG, alemtuzumab, or rituximab), chronic use of steroids and calcineurin inhibitors, lower lymphocyte and low CD4+ T-cell count, and older age has also been associated with late-onset PJP.^{4, 8,9,11}

CD4+ T-cells play a central role in PJP. In patients treated with ATG regimen, slower CD4-cell reconstitution is expected.¹⁴ In a cohort of allogeneic hematopoietic cell transplant recipients, the authors proposed that ATG-based graft versus host disease prophylaxis, CD4 T-cell at 6 months should be measured, and if less than 200 CD4 T-cells/mL, PJP prophylaxis should be extended to 24 months.¹⁵ In a systematic review with human immunodeficiency virus-negative immunocompromised population, including 47 SOT patients, the authors proposed that CD4 cells counts <200/ μ L is a sensitive biomarker to identify patients at risk of PJP. This could guide clinicians to decide which patients need to extend prophylaxis beyond the protocol period.¹⁶

CMV infection is a common viral infection after a kidney transplant, even during antiviral prophylaxis period. It was associated with allograft rejection and failure, chronic scarring of allograft, with important morbidity and mortality.¹⁷ It is unclear until now that previous CMV infection increased the risk of PJP by inducing impairment of cell-mediated immunity or if it is just a mark of severe immunosuppression.¹⁸

Some authors advocate that TMP-SMX should be extended on patients after a history of CMV infection, in the early or late post-transplant period.⁷ The presence of CMV viremia could be an opportunity to re-institute prophylaxis. Recognizing CMV as a significant risk factor and re-starting prophylaxis when viremia is detected, might guide the re-start of TMP-SMX. However, further studies are needed.

A previous study with a large cohort showed that a total of 67 (1.7%, range 0%-3.8%) PJP episodes occurred after stopping TMP-SMX prophylaxis. The median (interquartile range) time to PJP after transplantation was 12 (9-18) months. Late-onset disease was found in 23 (48.9%) of patients and occurred 2 years after kidney transplant. Allograft rejection or CMV infection were observed in approximately 70% of patients who develop PJP and the association was also confirmed by multiple regression models. These authors also found that an additional 6 and 9 months of prophylaxis after rejection and CMV infection, respectively, prevent PJP in 52.9% of patients.¹⁹

In patients submitted to more intense immunosuppression, with lymphocyte-depleting agents, the need of extended prophylaxis should be considered. Kim *et al*, also described that kidney transplant patients treated with rituximab, for desensitization or during acute rejection, had a superior incidence of PJP, and 90% of infections occurred during the first 6 months after stopping prophylaxis. They proposed that prophylaxis for 12 months would be beneficial in patients whose this treatment was performed.²⁰

Severe lymphopenia, even many years after transplant, and previous corticosteroid bolus were independently associated with late-PJP,

and Kaminski *et al* proposed these variables as criteria for long-term PJP prophylaxis.¹¹ Lymphocyte counts could be an indication to continue or to re-start prophylaxis in the SOT recipients. Additionally, lower total gamma globulin can also alter humoral immunity, with particular importance against PJP,⁴ and our patient also had this risk factor.

The late onset of PJP in kidney transplants has a significant impact on the morbidity and mortality of these patients, and these reports open an opportunity for the transplant community to rethink strategies and develop novel studies to improve clinical practice. Most of the centers re-start PJP prophylaxis after an episode of rejection, however other risk factors, like CMV infection, and lymphocyte count are less explored but might play a role in guiding who benefits from TMP-SMX maintenance or reinstitution.

In the era of modern immunosuppression, an individualized approach based on risk criteria could potentially define kidney transplant patients for whom extended time or reinstitution of prophylaxis is needed. We suggest that for patients submitted to more intensive immunosuppression, like ATG or Rituximab, prophylaxis should be continued until immunological reconstitution occurs. CD4 cell count could help as a biomarker to guide time of PJP prophylaxis.

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Corresponding Author:

Círia Sousa 

Centro Hospitalar Trás-os-Montes e Alto Douro, Avenida da Noruega
5000-508 Vila Real, Portugal

E-mail: ciriasousa@msn.com