

# Early and Late *Pneumocystis Jirovecii* Pneumonia Rates in Kidney Transplant Patients are Compared

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## Editorial

In the era of widespread prophylaxis following kidney donation, late *Pneumocystis Jirovecii* Pneumonia (PJP) is not uncommon. We used information from the Korean Organ Transplantation Registry (KOTRY), a national transplant cohort, to assess the prevalence of PJP prevention in Korea and evaluate the incidence, risk factors, and outcomes of early and late PJP. With the exception of patients who underwent multi-organ transplantation or were younger than 18 years old, we performed a retrospective analysis using data from 4,839 kidney transplant patients from KOTRY between 2014 and 2018. To identify risk factors for early and late PJP, Cox regression analysis was used. 50 patients in all experienced PJP [1]. The proportion of patients who acquired PJP was the same whether it appeared before or after the 6-month mark. The incidence, duration, or dose of PJP prophylaxis did not change between early and late PJP. Early PJP was linked to desensitization, a greater tacrolimus dose upon discharge, and acute rejection. Age and acute rejection were important risk factors for late PJP. As a result, late PJP must be treated with individual risk-based prophylaxis, such as prolonged prophylaxis for elderly patients with a history of rejection. Late PJP is just as common and dangerous as early PJP.

*Pneumocystis Jirovecii* Pneumonia (PJP) is a fatal opportunistic illness linked to higher mortality in recipients of kidney transplants. Prior to the development of prophylaxis, patients who underwent kidney transplantation had a PJP rate of 0.6% to 14% and those who underwent lung transplantation had the greatest incidence (6.5% to 43%). In spite of the widespread use of prophylaxis, the prevalence of PJP remains high in kidney transplant recipients, ranging from 0.4% to 2.2%. Tacrolimus and pre-transplant desensitization for HLA or ABO-incompatible kidney transplantation, as well as induction treatments such Anti-Thymocyte Globulin (ATG), may have contributed to the continuously high occurrence of PJP in transplant patients despite PJP prophylaxis<sup>5</sup>. Within the first six months following a kidney donation, a very immunocompromised time frame, PJP usually develops. Risk factors for PJP have been identified as cumulative dosages of tacrolimus, mycophenolate mofetil, corticosteroids, ATG use, history of acute rejection, number of anti-rejection therapies, infection with Cytomegalovirus (CMV), bacterial pneumonia, tuberculosis, and hepatitis C virus [2]. Based on these epidemiological findings, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines advise universal PJP prophylaxis with daily Trimethoprim-Sulfamethoxazole (TMP-SMX) for the first three to six months following a kidney transplant, the American Society of Transplantation advises prophylaxis for six months to twelve months, and the European Renal Association advises twelve months of prophylaxis.

However, no standardized recommendations for the length of prophylaxis have yet been established, and the dosage was not chosen based on a randomized control study. Kidney transplantation is a treatment option for end-stage kidney disease that is superior to dialysis in terms of the quality and length of life it offers as well as its affordability. Anything that is both better and cheaper but is not the predominant therapy must have additional drawbacks that prevent transplantation from completely replacing all dialysis procedures. The budgetary constraints that, in certain countries, place transplantation, properly, at a lesser priority than public health fundamentals like clean water, sanitation, and vaccination are among the obstacles to universal transplantation as the cure for end-stage renal disease [3]. Recently, patients with kidney transplants have experienced late-onset PJP six months after the procedure. However, based on nationwide data, it has not been possible to examine the risk factors and clinical outcomes of late-onset PJP in comparison to early-onset PJP. We used data from the Korean Organ Transplantation Registry (KOTRY), a national transplant cohort<sup>16</sup>, to establish the prevalence of PJP prevention in Korea and to compare the incidence, risk factors, and outcomes of early and late PJP in kidney transplant patients. Since 2014, 32 centers of the 66 centers in the KOTRY have voluntarily participated in the kidney transplant cohort, enrolling 82.8% of kidney transplant cases in Korea. This study showed that in the period of short-term universal prophylaxis, late PJP occurring more than 6 months after kidney transplantation happened at a rate equivalent to early PJP occurring during the first 6 months after transplantation. When risk factors for early and late PJP were examined independently, desensitization, a greater tacrolimus dose per body weight at discharge, and acute rejection were linked to early PJP, whereas old age and acute rejection were significant risk factors in late PJP [4]. There was no change in mortality rates between early and late PJP, despite the fact that PJP increased mortality.

According to risk profiles of kidney transplant populations, the incidence of PJP appears to vary. The incidence of PJP varies from 0.3% in a single-center research conducted in the US to 1.58% in a single-center study conducted in France. ABO-incompatible cases with desensitization had a 3% PJP incidence, compared to ABO-compatible cases without desensitization, according to a German single-center study. In US multi-center studies, the percentages of HLA-incompatible and ABO-incompatible kidney transplantation were 7.4% and 1.3%, respectively. 20% to 30% of kidney transplants in Japan are ABO-incompatible with desensitization, which is comparable to the rate in Korea [5]. However, other nations do not have a high rate of desensitization. As a result, a substantial percentage of the high-risk group with desensitization in this study sample would be indicated by the PJP incidence (1.033%) (22.3%). This study proved that severe immunosuppression, such as desensitization and a greater dose of tacrolimus per body weight at discharge, were important risk factors for PJP, supporting earlier reports in this regard. In line with a prior study that shown that expanded-criteria donors, including old donors, are a risk factor for PJP, old donor age was also linked to PJP. However, given that the group with acute rejection had older donors than the group without acute rejection (48.99 12.49 vs. 46.75 13.03, P 0.001) [6], acute rejection may actually be a more significant risk factor for PJP than old donor age alone. Additionally, compared to non-PJP, PJP was linked to greater rates of graft failure and mortality. The survey in this study revealed that 85% and 9% of Korean transplantation facilities adopted universal and recommended prophylaxis for high-risk populations, respectively, in light of the prevalence and considerable influence of PJP on clinical outcomes. In this investigation, TMP-SMX prophylaxis was given to the vast majority of patients (n=4,676, 96.7%). The later time of PJP was shifted by universal PJP prophylaxis for 3 months to 6 months. In this study, late PJP may have been caused by six months of PJP prophylaxis (6.0 1.0). This study shown that late PJP had negative effects on patient survival in a manner comparable to that of early PJP [7].

The high rate of PJP (96%) during PJP prophylaxis in the early PJP group is another problem. It is unclear if this alleged breakthrough infection was caused by TMP-SMX resistance, inadequate exposure, or noncompliance. We made an effort to clarify the differences between the risk factors for early and late PJP. A substantial risk factor for both early and late PJP is a previous episode of acute rejection coupled with severe immunosuppression in the management of acute rejection. Desensitization and tacrolimus dose per body weight at discharge, which reflect initial severe immunosuppression, were linked to an increased risk for early PJP but not late PJP. Age, on the other hand, was only a significant risk factor for late PJP, indicating that a patient's overall health and the level of immunosuppression are linked to PJP risk in later stages [8]. A higher incidence of late PJP was linked to CMV infection before PJP, according to a study; however, there was only one CMV infection case among 50 instances of PJP, making it impossible to do a meaningful analysis. Although lymphopenia was proposed as a risk factor for late PJP in other studies, the absence of lymphocyte count data in the KOTRY database prevented us from investigating this problem.

Recent investigations have shown that outbreaks frequently result in late PJPs, and it has been suggested that sites where outbreaks have occurred continue PJP prophylaxis for more than 12 months. Prophylaxis for a minimum of a year is advised in Australia due to cost-effectiveness and high mortality costs, however this cost-saving must be weighed against TMP-SMX side effects such as elevated creatinine levels and the development of resistance. A case of outbreak occurred 10 years after transplantation despite the administration of PJP prophylaxis for 1 year, according to Jung et al., indicating that a prolonged term of prophylaxis may not be the only treatment for late PJP. A better strategy might be to determine the appropriate prophylaxis duration based on an individual's risk assessment. For instance, older kidney transplant recipients with a history of recurrent anti-rejection therapy who have a high risk of developing late PJP might require a longer prophylaxis duration [9].

The nationwide analysis of post-kidney transplant PJP based on a national Korean transplant cohort and a survey of 32 participating hospitals regarding their PJP prevention policies are the study's strong points. Additionally, we contrasted early and late PJP's risk variables and clinical effects. However, this study has a number of drawbacks. The findings from this study, where desensitization was highly prevalent, could not be applicable to other nations with lower levels of desensitization. As a registry-based trial, we were unable to collect as much specific data as single center-based studies, such as lymphocyte counts and problems. Additionally, we were unable to determine the precise reason for the apparent breakthrough PJP in the early PJP group [10]. Another bias in this registry-based study could be a difference between drug prescriptions and actual drug use.

To support our conclusions, additional research containing more specific data is required. In conclusion, late PJP requires personalized risk-based prophylaxis, such as longer prophylaxis for elderly patients with a history of rejection, and is just as common and dangerous as early PJP.

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