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Pneumocystis jiroveci pneumonia in renal transplantation: time to review our practice?

Jennifer A. McCaughan and Aisling E. Courtney

Regional Nephrology Unit, Belfast City Hospital, Belfast, UK

Correspondence and offprint requests to: Jennifer A. McCaughan; E-mail: jamccaughan@doctors.org.uk

Pneumocystis jiroveci pneumonia (PJP) is a feared opportunistic infection in the renal transplant population. The unicellular fungus is ubiquitous in the environment but has an untreated mortality of 90–100% in immunocompromised HIV-negative patients [1]. This falls to 35% with treatment [2]. Many, but not all, transplant centres routinely prescribe PJP prophylaxis. Current European Best Practice Guidelines recommend at least 4 months of PJP prophylaxis post-renal transplantation [3], while KDIGO guidelines suggest 3–6 months [4]. Both guidelines advocate additional prophylaxis during and following the treatment of acute rejection [3, 4].

Recent outbreaks

The World Health Organization classifies a disease outbreak as the occurrence of cases of disease in excess of what would normally be expected in a defined community. By this definition, there are six recent reports of outbreaks of PJP in renal transplant recipients.

In Tokyo, there were 27 confirmed cases of PJP in 12 months followed by 6 in the next 36 months in a centre that had seen only three cases in 28 years. Twenty-two affected recipients were >12 months post-transplantation and 6 were more than a decade from the date of their transplant [5]. Over a similar 12-month period, 22 cases of PJP were identified in renal transplant patients in Leiden, with 11 affected individuals >1 year post-transplant [6], and recently the Royal Liverpool University Hospital reported 18 cases of PJP in their renal transplant population [7]. There had been a solitary confirmed case of PJP in the Liverpool population in the last 10 years [7]. A Swiss centre had a cluster of 19 PJP cases in recipients of donor kidneys [8] and there was a second Japanese outbreak involving 10 renal transplant patients [9]. In both these groups, the majority of patients developed PJP beyond the suggested period for prophylaxis [8, 9].

The first reported outbreak in a paediatric renal transplant population involved three children contracting PJP within 5 months; there had been no cases in the unit for >20 years. The infections occurred 4, 9 and 24 months after transplantation [10]. None of these centres had altered their immunosuppressive practices and none routinely used PJP prophylaxis after renal transplantation.

Our own renal unit performs ~50 transplants annually and PJP prophylaxis is not routinely given. In 40 years of kidney transplantation in this centre, there have been three recipients with PJP and none in the last decade. In the past 9 months, however, we have had four further confirmed cases of PJP. All these occurred >6 months after transplantation. There has been no regional increase in PJP incidence and no alteration to our immunosuppressive practice. Direct transmission between these patients did not occur as none had concurrent hospital admissions or clinic attendances. One patient had received anti-thymocyte globulin and plasma exchange for early acute rejection. The others had standard immunosuppression with prednisolone, tacrolimus and mycophenolate mofetil at the time of transplantation with no antibody treatment. Three of the patients had also been treated for cytomegalovirus (CMV) disease.

In the reported outbreaks of PJP, the existence of a prevalent genotype has been noted. In Tokyo, all cases had an identical genotype; in Leiden, 12 of 16 were of the same strain; in Liverpool, 12 of 14 genotypes tested were identical and all seven patients tested in Zurich had the same genotype as did the three paediatric patients [5–7, 8, 10]. This raises the question of whether these outbreaks are caused by inter-human transmission, and in three groups, there was direct contact between the PJP-infected patients [5]. In our own cluster, none of our patients had contact with another patient who developed PJP and two of the four were being reviewed at other renal units at the time of their diagnosis.

Discussion

Defects in T-cell immunity predispose to PJP, and the risk is greatest in those with HIV, lung transplantation and after stem cell transplant [11–13]. The current guidelines for renal transplant recipients have largely been extrapolated from evidence in these groups [14] and advocate a minimum of 3 months PJP prophylaxis post-transplantation. There is, however, a scarcity of evidence in the renal transplant literature to guide management. There are two reported randomized controlled trials, which assess trimethoprim–sulfamethoxazole prophylaxis against bacterial infections in renal transplant recipients but neither includes PJP infection as a primary outcome [15, 16]. In HIV-negative immunocompromised patients in general, trimethoprim–sulfamethoxazole prophylaxis reduced the incidence of PJP by 91% and reduced PJP-related mortality but not all-cause mortality [17].

It has been suggested that PJP prophylaxis should be considered when the risk of disease is judged to be >3% [13, 18]. The incidence of PJP in moderately immunosuppressed renal transplant recipients is as low as 0.6% but increases exponentially with additional immunosuppressive factors such as extra corticosteroids, anti-thymocyte globulin and CMV disease [19]. The rationale for routine PJP prophylaxis in renal transplant recipients who receive moderate immunosuppression and have no other risk factors is unclear and the evidence to support this is not robust. It is therefore argued by some that the very low incidence of PJP in this group does not justify the potential exposure of this entire population to iatrogenic morbidity. There are multiple reported complications of trimethoprim–sulfamethoxazole therapy including bone marrow suppression, deranged hepatic function and hyperkalaemia although a review of trimethoprim–sulfamethoxazole as PJP prophylaxis did not demonstrate a significant increase in adverse events in this treatment group compared to those receiving other antibiotics or no treatment [17, 20, 21, 22, 23]. Some centres, with historically low rates of PJP infection, consider the risk of harm, in conjunction with increased pill burden and economic cost, to outweigh the benefit of routine prophylaxis therapy.

It is notable, however, that all six centres that have reported recent outbreaks had adopted this stance. Prophylaxis therapy for PJP was not routinely prescribed in any of these units. Is it possible that routine prophylaxis for the whole transplant population reduces PJP carriage and thereby minimizes the incidence of infection? Certainly in some reported outbreaks, genotyping results support the suggestion of transmission of the organism between patients or of the emergence of a particularly virulent PJP strain. Enhanced virulence seems a less plausible explanation given that these outbreaks have not been associated with an increased incidence of PJP infection in other susceptible groups. This may represent a difference in epidemiology to that observed in HIV-associated PJP infection where there has not been robust evidence of inter-human spread. PJP is prevalent in the environment and routine prophylaxis in transplant recipients would not reduce general population carriage that is estimated to be 20% [24]. In the recently

reported outbreaks, the majority of patients presented beyond the acute transplant period when most of their contacts were not transplant recipients or medical staff. Reducing PJP carriage in the transplant population would be ineffective in lowering the incidence of PJP in this group but would certainly reduce the potential for spread between transplant recipients. It would also be prudent to ensure the highest level of hand hygiene and to encourage recipients to wear face masks at clinic if they have respiratory symptoms. Units should make arrangements to review unwell individuals separately thus minimizing the risk to other patients.

The guidance to continue prophylaxis for 3–6 months after transplantation is intuitively sensible: the risk of PJP is greatest in those most heavily immunosuppressed and the immunosuppressive load is highest in the early post-transplant period. The recent outbreaks challenge this presumption. In these six geographically and ethnically diverse populations, the majority of PJP occurred >6 months post-transplantation and 60% of the reported cases developed >1 year after transplant [5, 6, 8, 9].

Patients who receive enhanced immunosuppression are clearly at higher risk of PJP. In susceptible individuals, the duration of prophylaxis should not be limited to 6 months but continued until such a time that the immunosuppressive burden can be reduced [5, 25]. In the current era of rapidly developing biological therapies, it is important to remember that these can cause prolonged immunosuppression and extended prophylaxis should be provided in these circumstances [25–28]. An increase in herd immunity by routine prophylaxis of all recipients in the early period should provide some protection for the more heavily immunosuppressed group but given the potentially fatal outcome of PJP infection, prophylaxis in this subpopulation would be prudent.

In light of recent outbreaks of PJP, the mortality risk associated with infection and the increasing use of biological therapies in renal transplant recipients, the current practice in regard to prophylaxis may need to be reviewed. High-quality randomized controlled trials should be conducted to assess the optimum duration of routine PJP prophylaxis in this population. Until then, it may be prudent to extend the period of prophylactic therapy for individual patients. As a minimum, each recipient's risk should be assessed and those at high risk of infection offered prophylaxis, regardless of the time after transplantation.

Conflict of interest statement. None declared.

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