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# *Pneumocystis carinii* pneumonia in heart transplant recipients

Rosa Cardenal[a], Francisco J. Medrano[b], Jose M. Varela[b], Antonio Ordoñez[c], Carmen Regordan[d], Manuel Rincon[b], Angel Martinez[a], Enrique J. Calderon[b,*]

[a]*Service of Cardiology, Virgen del Rocio University Hospital, Seville, Spain*
[b]*Service of Internal Medicine, Virgen del Rocio University Hospital, Seville, Spain*
[c]*Service of Cardiovascular Surgery, Virgen del Rocio University Hospital, Seville, Spain*
[d]*Service of Microbiology, Virgen del Rocio University Hospital, Seville, Spain*

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**Abstract**

**Objectives**: In spite of the high prevalence of *Pneumocystis carinii* (PC) pneumonia in immunocompromised patients, little is known about the epidemiological characteristics of this infection, and whether the cases of PC pneumonia in immunosuppressed patients are the result of a reactivation of a latent infection or a due to a recent infection is unknown. The aim of this study was to provide information about the epidemiological characteristics of PC pneumonia in a cohort of heart transplant (HT) recipients when compared with the epidemiology of PC infection in a cohort of chronic sputum producers (CSP) representative of the general population of the same geographical area. **Methods**: We identified all the cases of PC pneumonia in the cohort of 72 subjects who underwent cardiac transplantation at our institution between January 1991 and December 1996 and compared them with the cases of PC infection identified in a non-selected cohort of 34 CSP. This second group was included to obtain an approximation of the frequency of PC carriers in the general population. Identification of PC was accomplished through customary stain techniques and immunofluorescence with monoclonal antibodies. **Results**: Of the 72 HT recipients four (5.5%) developed PC pneumonia, but one had two episodes. Only one had received primary chemoprophylaxis, but developed PC pneumonia 2 months after discontinuing prophylactic therapy. PC pneumonia episodes were produced 53, 102, 230, 181 and 772 days after the moment of transplant, respectively. PC was identified in two (5.8%) of the 34 CSP. No significant differences were found when the accumulative incidences of PC pneumonia in HT patients and PC infection in CSP were compared ($P = 0.7$). **Conclusions**: The frequency of PC pneumonia among HT patients is the same as the frequency of PC infection in the general population. This observation and the long interval between transplantation and the development of PC pneumonia observed in the study support the hypothesis that the occurrence of PC pneumonia in immunocompromised patients might be from a new infection rather than from the reactivation of latent organisms. Therefore, continuous prophylaxis might be indicated in areas with a high prevalence of PC for patients at highest risk. 

*Keywords*: *Pneumocystis carinii*; Heart transplant; Prophylaxis; Epidemiology

## 1. Introduction

*Pneumocystis carinii* (PC) pneumonia is a major cause of mortality and morbidity in immunocompromised individuals, including AIDS patients [1] and recipients of solid organ allografts [2]. In heart transplant (HT) recipients, the reported incidence of PC pneumonia ranges from 2 to 10% [3–7]. This variability could be attributable, at least in part, to the differences in the spreading of PC infection observed among the general population of different geographical areas [8,9].

In spite of the high prevalence of PC pneumonia in immunocompromised patients, little is known about the epidemiological characteristics, transmission process and sources of this infection, and whether the cases of PC pneumonia in subjects with immunosuppressive therapy are the result of the reactivation of a latent infection or to a due to a recent infection is unknown.

The aim of this study was to provide information about the epidemiological characteristics of PC pneumonia in a cohort of HT recipients when compared with the epidemiology of PC infection in a cohort of chronic sputum producers (CSP) representative of the general population of the same geographical area.

## 2. Materials and methods

We identified all the cases of PC pneumonia in the cohort of subjects who underwent cardiac transplantation at our

* Corresponding author. Avda. Italia 41, 41710 Utrera, Sevilla, Spain. Tel.: +34-95-5860357.
*E-mail address:* sandube@cica.es (E.J. Calderon).

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institution between January 1991 and December 1996 (cohort 1, 72 individuals) and compared these with the cases of PC infection identified in a non-selected cohort of patients with chronic bronchial disease (CSP) attending our hospital (cohort 2, 34 individuals). This second group was included to obtain an approximation of the frequency of PC carriers in the general population because in CSP, it is easy to obtain sputum samples for analysis. Both cohorts were followed until January 1999. The protocol was designed and performed according to the Helsinki Declaration and was approved by the Research Ethics Committee, Virgen del Rocio University Hospital, Seville, Spain.

The general methodology of the transplant procedure was standard and has been described previously [10]. In summary, the immunosuppressive regimen consisted of induction with OKT3 and maintenance with cyclosporin A, azathioprine, and corticosteroids. Doses of cyclosporin were targeted to achieve a plasma level of 200–400 ng/ml during the first month posttransplantation. Thereafter, levels of 100–200 ng/ml were targeted. Rejection episodes were diagnosed by endomyocardial biopsy and treated with intravenous boluses of methylprednisolone. Prophylaxis against toxoplasmosis (6 weeks of pyrimethamine, 25 mg/day, plus folinic acid) was administered in all cases, but anti-PC prophylaxis (6 months of trimethoprim–sulfamethoxazole (TMP-SMX), 160–800 mg 3 days/week) was not introduced until 1993.

CSP were younger than 66 years on entry to the cohort because it is the limit for HT in our cardiac transplant program. All subjects in this group denied being at risk for HIV infection and no other reason could be found for immunosuppression. A commercial enzyme immunoassay (EIA; Abbot Laboratories, N. Chicago, IL) did not detect HIV-1 infection in either group.

Upon clinical and radiological findings of pulmonary infection, definitive PC pneumonia diagnosis in HT recipients was accepted only after demonstration of the microorganism's presence in respiratory secretions or lung tissue. The presence of PC in CSP was investigated in sputum samples following the protocol described previously [11]. Clinical specimens were simultaneously assayed by four different methods in order to improve the specificity of the test: toluidine blue O stain, modified Giemsa stain, methenamine silver stain and immunofluorescence with monoclonal antibodies (Pneumo-cell IF test; Cellabs, Brookvale, Australia). Identification was considered positive for PC when the parasite was detected by all four techniques.

The differences in the study variables were assessed using the Student's *t*-test and Pearson's Chi-square test for categorical variables. All analyses were done using the Statistical Package for Social Studies (SPSS) software, version 5.0 (SPSS, Inc., Chicago, IL).

## 3. Results

The causes leading to HT were: ischemic cardiopathy (65%), idiopathic dilated myocardiopathy (30%), and valvular disease (4%). Seventeen percent of patients had diabetes before transplantation. Sixty-four percent of patients had at least one episode of acute rejection and 12.5% had cytomegalovirus (CMV) infection.

During the study period, four (5.5%) of the 72 HT recipients developed PC pneumonia, but one had two episodes. In these subjects, the causes leading to HT were ischemic cardiopathy (two cases) and idiopathic dilated myocardiopathy (two cases). One patient had diabetes before transplantation. PC pneumonia was diagnosed at days 53, 102, 230 and 181 after HT. In the last patient, a second PC pneumonia episode occurred at day 772 after HT, i.e. 19 months after the first episode. Only one had received primary TMP-SMX prophylaxis, but developed PC pneumonia 2 months after discontinuing prophylactic therapy. None of the patients received secondary prophylaxis. All four patients who were diagnosed as having PC pneumonia were successfully treated with a standard dose of TMP-SMX (20 mg/kg per day for 21 days). Two of these four subjects had CMV infection and all of them had at least one episode of acute rejection. No patient developed PC pneumonia while receiving TMP-SMX prophylaxis.

Sputum analyses of 34 CSP identified two (5.8%) subjects as carriers of PC. No significant differences were found when the accumulative incidences of PC pneumonia in HT patients and PC infection in CSP were compared ($P = 0.7$). The mean age was significantly lower in the first group ($50 \pm 9$ vs. $57 \pm 9$, $P < 0.001$). Sex distribution was comparable in both groups. The general characteristics of HT patients with PC pneumonia and PC carrier subjects are shown in Table 1.

## 4. Discussion

The results from this study demonstrate that the frequency of PC pneumonia among HT recipients is the same as the frequency of PC infection in a cohort of CSP representative of the general population of the same geographical area. This observation, and the long interval between the transplanta-

Table 1
General characteristics of HT recipients with PC pneumonia and CSP with PC infection[a]

| Case | Age (years) | Sex | Lymphocytes/mm$^3$ at PC diagnosis |
|---|---|---|---|
| HT1 | 60 | Male | 600 |
| HT2 | 58 | Male | 300 |
| HT3 | 54 | Male | 2400 |
| HT4 | 50 | Female | 400 |
| HT1 (2nd episode) | 62 | Male | 1800 |
| CSP1 | 63 | Male | 1030 |
| CSP2 | 65 | Male | 2910 |

[a] PC, *Pneumocystis carinii*; HT, heart transplant recipient; CSP, chronic sputum producer.

tion and the development of PC pneumonia observed in the study strongly support the idea that PC pneumonia in HT recipients results from a new infection rather than from the reactivation of a latent infection. Other important conclusions of our study are that the incidence of PC pneumonia among HT recipients is highest during the first year following transplantation and that no patient developed PC pneumonia while receiving primary prophylaxis.

The classic pathogenic hypothesis that PC remains latent in the lung after primary infection is supported by the high prevalence of PC antibodies detectable at an early age and persisting for life in normal persons [12], and by the occurrence of PC pneumonia with the advent of immunosuppression [13]. However, PC appeared to be cleared from the lungs of 75% of animals within 1 year after an episode of PC pneumonia [14], implying that persistence of latent organisms is limited. Moreover, depletion of CD4+ cells in reconstituted severed combined immunodeficiency mice that had resolved PC pneumonia failed to reactivate the infection [15]. On the other hand, despite effective prophylaxis, recurrent episodes of PC pneumonia are relatively common in HIV-infected patients, and molecular studies have shown that genetically distinct isolates were associated with each episode of PC pneumonia [16]. Furthermore, recurrent PC colonization in lung and heart–lung transplant recipients on long-term TMP-SMX prophylaxis has been reported [17,18]. These cumulative data support the concept that the occurrence of PC pneumonia in immunocompromised patients might be from a new infection resulting from exposure to exogenous sources of PC through contact with environmental sources or infected persons.

In HT recipients, the knowledge of the exact moment at which the immunosuppression is started and the possibility of controlling the intensity and duration of the immunosuppressive therapy provided an appropriate situation to appraise whether PC pneumonia represents a reactivation of a latent infection or whether it is a primary PC infection taking advantage of the immunosuppression. If the hypothesis of reactivation was true, the period of highest risk for PC pneumonia would be the first 2 months posttransplantation, when the immunosuppressive therapy is most intense. However, most of our patients developed PC pneumonia after this period, and in one case, a second PC pneumonia episode occurred 2 years after HT. Moreover, in our study, the frequency of PC pneumonia in HT recipients and PC infection in CSP is the same, suggesting that a similar rate of exposition to the parasite in both groups might lead to the development of an opportunistic disease (HT recipients) or a subclinical infection (CSP), depending on the status of the immune system. These results, together with those of others [14–18], reinforce the notion that PC pneumonia that occurs in immunocompromised patients is probably the result of infection by exogenous PC.

Knowledge on the natural history of PC infection is important to design the strategies of prophylaxis in patients who receive maintenance immunosuppressive treatment. TMP-SMX prophylaxis in HT reduces the incidence of PC pneumonia to nearly zero [19], but it is effective only as long as it is administered [20]. Currently, most authors recommend universal prophylaxis during the first 2–4 months posttransplantation, while others select only high-risk patients [19]. Unlike HIV-infected patients with CD4+ lymphocyte counts of $<200/\mu l$ or those with $<14\%$ CD4+ lymphocytes who define subjects at risk, the risk of PC pneumonia in immunocompromised patients without AIDS, including solid organ transplant recipients, cannot be accurately quantified at present, and clinically useful biological markers that guide the initiation of chemoprophylaxis are not available [21,22]. However, the primary risk for PC and other opportunistic infections in solid organ transplant recipients is the 'net state of immunosuppression', to which a number of factors contribute, including the total amount of previous and current immunosuppressive treatments, the presence of acute and chronic graft rejection, and the presence of concomitant infections, especially those due to CMV [23].

In our study, the occurrence of PC pneumonia lasting more than 4 months in posttransplantation patients was common, and the frequency of PC carriers in the general population was relatively high. Although the role of these PC carriers in the transmission of PC to immunocompromised patients is yet to be deduced, our results argue for the convenience of continuous anti-PC chemoprophylaxis, at least in areas where the prevalence of PC infection is high. Further investigation is needed to ascertain the relative risk of PC infection and the optimal duration of anti-PC prophylaxis in each area.

In conclusion, the results of this and other studies [14–18] strongly support the hypothesis that the occurrence of PC pneumonia in immunocompromised patients might be from a new infection resulting from exposure to exogenous sources of PC through contact with infected persons or other environmental sources rather than through reactivation of a latent organism. Therefore, chemoprophylaxis against PC in areas where the prevalence of PC infection is high could be continuous, at least to patients at the highest risk, such as those with recurrent or chronic rejection and following onset of CMV infection.

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## References

[1] Galtt AE, Chirgwin K. *Pneumocystis carinii* pneumonia in human

immunodeficiency virus-infected patients. Arch Intern Med 1990;150:271–279.
[2] Arend SM, Kroon FP, Wont JW. Pneumocystis carinii pneumonia in patients without AIDS, 1980 through 1993. Arch Intern Med 1995;155:2436–2441.
[3] Hofflin JM, Potasman I, Baldwin JC, Oyer PE, Stinson EB, Remington JS. Infectious complications in heart transplant recipients receiving cyclosporine and corticosteroids. Ann Intern Med 1987;106:209–216.
[4] Austin JHM, Schulman LL, Mastrobattista JD. Pulmonary infection after cardiac transplantation: clinical and radiological correlations. Radiology 1989;172:259–265.
[5] Dummer JS. Infectious complications of transplantation. Cardiovasc Clin 1990;20:163–178.
[6] Grossi P, Ippoliti GB, Goggi C, Cremaschi P, Scaglia M, Minoli L. *Pneumocystis carinii* in heart transplant recipients. Infection 1993;21:75–79.
[7] Muñoz P, Muñoz RM, Palomo J, Rodriguez-Creixems M, Muñoz R, Bouza E. *Pneumocystis carinii* infection in heart transplant recipients. Efficacy of a twice-a-week prophylaxis schedule. Medicine 1997;76:415–422.
[8] Calderón E, Regordán C, Medrano FJ, Ollero M, Varela M. *Pneumocystis carinii* infection in patients with chronic bronchial disease. Lancet 1996;347:977.
[9] Armbruster C, Hassl A, Kriwanek S. *Pneumocystis carinii* colonization in the absence of immunosuppression. Scand J Infect Dis 1997;29:591–593.
[10] Spanish Transplantation Infection Study Group, Cisneros JM, Muñoz P, Torre-Cisneros J, Gurgui M, Rodriguez-Hernandez MJ, Aguado JM, Echaniz A. Pneumonia after heart transplantation: a multiinstitutional study. Clin Infect Dis 1998;27:324–331.
[11] Calderón EJ, Wichmann I, Varela JM, Respaldiza N, Regordan C, Fernández-Alonso J, Medrano FJ, Cano S, Cuello JA, Nuñez-Roldan A. Presence of glomerular basement membrane antibodies in HIV-negative patients with *Pneumocystis carinii* pneumonia. Clin Exp Immunol 1997;107:448–450.
[12] Smulian AG, Sullivan DW, Linke MJ, Halsey NA, Quinn TC, MacPhail AP, Hernandez-Avila MA, Hong ST, Walzer PD. Geographic variation in the humoral response to *Pneumocystis carinii*. J Infect Dis 1993;167:1243–1247.
[13] Frenkel JK, Good JT, Schultz JA. Latent pneumocystic infection in rats, relapse and chemotherapy. Lab Invest 1966;15:1559–1577.
[14] Vargas SL, Hughes WT, Wakefield AE, Oz HS. Limited persistence in and subsequent elimination of *Pneumocystis carinii* from the lung after *P. carinii* pneumonia. J Infect Dis 1995;172:506–510.
[15] Chen W, Gigliotti F, Harmsen AG. Latency is not an inevitable outcome of infection with *Pneumocystis carinii*. Infect Immun 1993;61:406–409.
[16] Keely SP, Stringer JR, Baughman RP, Linke MJ, Walzer PD, Smulian AG. Genetic variation among *Pneumocystis carinii hominis* isolates in recurrent pneumocystosis. J Infect Dis 1995;172:595–598.
[17] Halme M, Lautenschlager I, Mattila S, Tukiainen P. Breakthrough *Pneumocystis carinii* infections in lung and heart–lung transplant patients with chemoprophylaxis. Transplant Proc 1999;31:197.
[18] Faul JL, Akindipe OA, Berry GJ, Doyle RL, Theodore J. Recurrent *Pneumocystis carinii* colonization in a heart–lung transplant recipient on long-term trimethoprim–sulfamethoxazole prophylaxis. J Heart Lung Transplant 1999;18:384–387.
[19] Olsen SL, Renlund DG, O'Connell JB, Taylor DO, Lassetter JE, Eastburn TE, Hammond EH, Bristow MR. Prevention of *Pneumocystis carinii* pneumonia in cardiac transplant recipients by trimethoprim sulfamethoxazole. Transplantation 1993;56:359–362.
[20] Hughes WT. Limited effect of TMP-SMX prophylaxis on *Pneumocystis carinii* pneumonitis. Antimicrob Agents Chemother 1979;16:333–335.
[21] Gordon SM, LaRosa SP, Kalmadi S, Arroliga AC, Avery RK, Truesdell-LaRosa L, Longworth DL. Should prophylaxis for *Pneumocystis carinii* pneumonia in solid organ transplant recipients ever be discontinued? Clin Infect Dis 1999;28:240–246.
[22] Mansharamani NG, Balachandran D, Vernovsky I, Garland R, Koziel H. Peripheral blood CD4 + T-lymphocyte counts during *Pneumocystis carinii* pneumonia in immunocompromised patients without HIV infection. Chest 2000;118:712–720.
[23] Arend SM, Westendorp RGJ, Kroon FP, van't Wout JW, Vandenbroucke JP, van Es LA, van der Woude FJ. Rejection treatment and cytomegalovirus infection as risk factors for *Pneumocystis carinii* pneumonia in renal transplant recipients. Clin Infect Dis 1996;22:920–925.