Outbreak of *Pneumocystis carinii* Pneumonia in a Renal Transplant Unit

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The charts for seven renal transplant recipients who developed *Pneumocystis carinii* pneumonia were reviewed. They included six men and one woman transplanted a mean of 150 days before the diagnosis of this infection. Six presented at least one episode of acute graft rejection. Cytomegalovirus pneumonia was diagnosed in six of the patients. All patients were treated with cotrimoxazole. Global mortality was 43 %. In additional to the classic hypothesis of latent *Pneumocystis carinii* reactivation in immunocompromised hosts, this and previous reports of outbreaks strongly suggest either a person-to-person transmission or acquisition from the environment. Molecular typing of isolates could be of value in identifying the source of such outbreaks. Chemoprophylaxis should be more systematically administered to renal transplant patients, co-trimoxazole being the drug of choice.

The incidence of *Pneumocystis carinii* pneumonia (PCP) has dramatically increased during the past decade as a result of the AIDS epidemic. Before 1981, sporadic cases or small clusters were described in malnourished or immunocompromised hosts, often transplant recipients or patients with malignancy. Recently, some authors have reported an increase in the incidence of PCP in HIV-negative immunocompromised patients, postulating transmission from HIV-positive patients in the same hospital (1, 2). We report retrospectively a cluster of seven cases of PCP over a five-month period in renal transplant patients. Only two cases of PCP had been diagnosed in the transplant unit since 1984 (one in 1984 and one in 1987); without an increase in the number of renal transplantations performed in the unit, this group of patients was considered an outbreak. We reviewed the epidemiological, clinical and biological records to investigate the possible modes of acquisition of this infection and the possibility of preventing further infections.

Patients and Methods. From May to October 1991, seven cases of PCP were diagnosed in the Renal Transplantation Unit of the Necker-Enfants Malades Hospital. Since 1986, post-transplantation immunosuppression was administered as follows: from day zero to day ten, prednisone 1 mg/kg/d), azathioprine (3 mg/kg/d, then adapted to blood cell count) and monoclonal antibody anti-CD_{30} (OKT3) (5 mg/d intravenously until day 14); and from day 10, prednisone (progressively decreasing down to 15 mg/d), azathioprine (stop) and cyclosporine (6 mg/kg/d, then adapted according to the serum level). In case of tubulopathy, cyclosporine is not given, and OKT3 is continued until day 30. For acute graft rejection, patients are treated with three bolus each of 1 gram per day for five days of methyl prednisolone or high doses of prednisone, i.e. 4 mg/kg/d for four days then progressively decreasing in doses for one month.

Diagnosis of PCP was based on the demonstration of cysts or vegetative forms of *Pneumocystis carinii* in broncho-alveolar lavage (BAL) fluid after Giemsa and/or silver staining. Cytomegalovirus (CMV) pneumonitis diagnosis was based on the visualisation of large inclusion cells and/or detection of antigens in infected cells of the BAL fluid. Hypoxemia was defined as an arterial partial pressure of oxygen (P_aO_2) < 70 mmHg (9.33 KPa) in ambient air ventilation. Lymphopenia was defined as an absolute lymphocyte count $\leq 1{,}200/mm^3$. The lactate dehydrogenase (LDH) serum level was considered to be abnormally elevated when it reached 500 IU/l.

Results and Discussion. Seven renal transplant patients were diagnosed as having PCP. Six were males and one was female, with an age range from 35 to 63 years old (mean 49 years) (Table 1). Five patients were hospitalised for acute respiratory symptoms which led to the diagnosis of PCP (Figure 1). Two patients were hospitalised for other reasons, one for 22 days and the other for 42 days, when PCP was diagnosed. Before the diagnosis of PCP, six patients had been treated for acute graft rejection. The delay between transplantation and PCP diagnosis was between 41 to 578 days (mean 150 days). Simultaneous CMV pneumonitis was

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Table 1: *Clinical, epidemiological and biological characteristics of seven renal transplant recipients with Pneumocystis carinii pneumonia.*

Case no.	Sex/age in years	Immunosuppressive therapy[a]	Episode(s) of acute rejection before PCP	Days between RT and PCP diagnosis	Concurrent CMV pneumonitis	Lymphocyte count (/mm^3)	P_aO_2[b] (mmHg)	LDH serum level[b] (IU/l)	Assisted ventilation[b]	Outcome	Associated infection
1	F/50	OKT3, then cyclosporine	1	81	yes	117	40	924	CPAP + MV	death (day 12)	*S. epidermidis* septicemia
2	M/63	OKT3, then cyclosporine	1	82	yes	180	43	916	CPAP + MV	death (day 11)	multiple organ failure
3	M/47	OKT3 alone	0	41	yes	1120	70	408	none	favourable	*P. aeruginosa* parotitidis
4	M/46	OKT3, then cyclosporine	2	82	yes	1179	45	1347	CPAP + MV	death (day 7)	*E. coli* bacteriemia
5	M/35	OKT3 alone	1	70	yes	612	86	411	none	favourable	none
6	M/49	OKT3, then cyclosporine	2	578	yes	420	76	712	CPAP	favourable	tuberculosis
7	M/52	OKT3, then cyclosporine	2	131	no	250	60	420	CPAP	favourable	none

[a] Post-transplantation immunosuppressive therapy: prednisone + azathioprine + OKT3 for 10 days, followed by cyclosporine or OKT3 alone for one month.
[b] Identified as negative predictive factors: an increase in LDH serum level ($p = 0.03$, Wallis-Kruskall's test) and decrease in P_aO_2 and the need of mechanical ventilation ($p = 0.03$, Fisher's test). Statistical analysis performed using EPI Info v. 5.01b program (Centers for Disease Control and Prevention, Atlanta, USA).
RT: renal transplantation; PCP: *Pneumocystis carinii* pneumonia; P_aO_2: artenal partial pressure of oxygen; LDH: lactate dehydrogenase. CPAP: continuous positive airway pressure; MV: mechanical ventilation.

diagnosed in six cases. On the day of PCP diagnosis, the seven patients showed lymphopenia, four were hypoxemic and four patients had an increase in LDH serum level.

The seven patients were treated with trimethoprim-sulfamethoxazole (TMP-SMX) (15–20 mg/kg and 75–100 mg/kg per day, respectively) orally or intravenously for at least 15 days. Assisted ventilation was used for 5 patients.

Three patients died (global mortality 42.9 %); in one case, PCP was the only cause evident. The delay between the diagnosis of PCP and death was seven, 11 and 12 days. No post-mortem examinations were performed. For the remaining patients maintenance therapy was not instituted. No relapse was noted. All patients were and remained seronegative for HIV.

Following this outbreak, chemoprophylaxis with TMP-SMX (160 mg–800 mg/d) was administered to all patients during the first three months following a transplantation. One new case of PCP was diagnosed in March 1992, in a patient who was treated with high doses of corticosteroid for inflammatory colitis seven months after his transplantation.

Reactivation of latent organisms is the classic hypothesis for PCP in immunocompromised patients (3). This conclusion was drawn from several studies that demonstrated high prevalence of seropositivity to *Pneumocystis carinii* (up to 100 %) in adult blood donors and thus a high frequency of past asymptomatic infection (4). CMV may be involved as a local immunosuppressive co-factor in renal transplant patients who developed PCP (5). Six out of our seven patients developed CMV pneumonitis at the same time as PCP. However, because there is no serological test available to distinguish between past and recently acquired infection, reactivation of latent *Pneumocystis carinii* is difficult to prove.

Recent studies have shown that PCR and immunohistological analyses were not able to find *Pneumocystis carinii* in BAL fluid or lung tissue in immunocompetent adults (6, 7). The number of PCP outbreaks reported for several decades favoured person-to-person transmission or acquisition from environmental foci (8, 9). DNA sequences identical to *Pneumocystis carinii* have been recently detected in samples of ambient air (A.E. Wakefield and M.S. Bartlett, Meeting of the Society of Protozoologists, 1994, USA). Recent works indicate that numerous strains may infect humans (10). Molecular typing based on the internal transcribed spacers of rRNA sequences

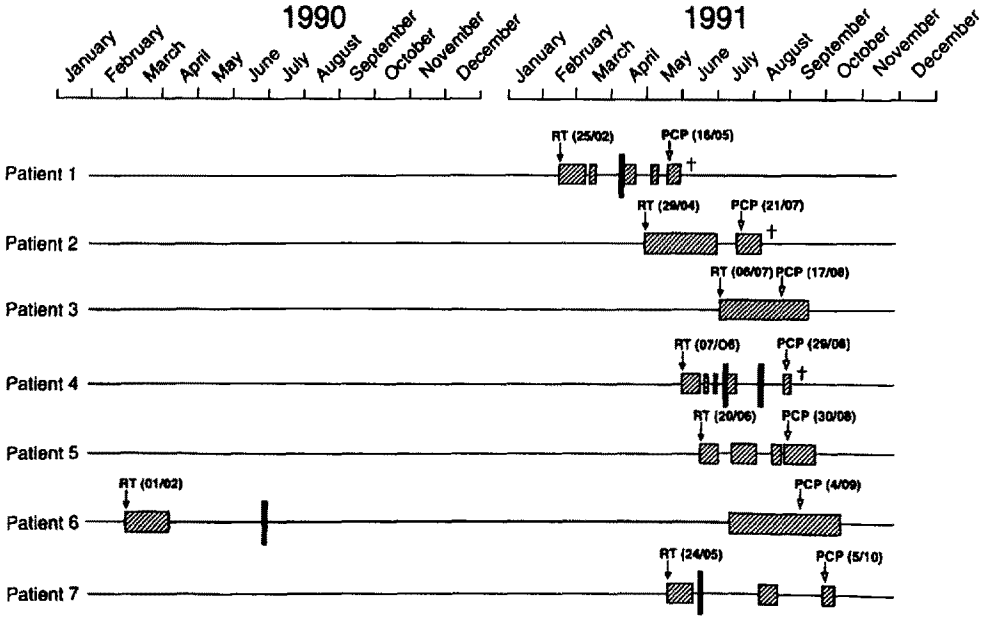

Figure 1: Admissions to hospital of the seven renal-transplant patients with *Pneumocystis carinii* pneumonia from February 1990 to October 1991. Shaded blocks: hospitalization; solid blocks: treatment of acute rejection in the out-patient clinic. †: death; RT: renal transplantation; PCP: *Pneumocystis carinii* pneumonia.

of clinical strains may provide information about the possibility of horizontal transmission (J.J. Lu et al., Meeting of the Society of Protozoologists, 1994, USA).

In our study, transmission of *Pneumocystis carinii* from HIV-positive patients to transplant recipients was possible because, since 1987, both groups of patients are cared for in the same building and share waiting rooms. Moreover, in the case of acute graft rejection, corticosteroid therapy was administered to four patients in the out-patient clinic, which was used for aerosol pentamidine prophylaxis of HIV-positive patients against PCP. Some authors believe a connection exists between the incidence of PCP in HIV-negative immunocompromised patients and the number of AIDS patients cared for in the same hospital (1, 2). A case control study strongly suggested transmission from AIDS patients to renal-transplant recipients (1). However, this cannot be confirmed without molecular typing of the strains isolated. Without assay testing the viability of the organisms, the contagious period for PCP under treatment remains uncertain. Clusters of patients with PCP have been reported which were not associated to the AIDS epidemic (8, 9). In our centre, despite the absence of chemoprophylaxis for PCP in our transplant recipients, prevalence of PCP had not increased during the previous years. The heightened awareness of PCP as a result of the AIDS epidemic, the more routine use of bronchoscopy and the use of more sensitive diagnostic procedures, such as indirect immunofluorescence, may have led to the diagnosis of PCP in HIV-negative-immunocompromised patients, which would previously have been undetected.

Transmission between transplant patients could also occur (11, 12). Analysis of previous reports of outbreaks lead to estimates for an incubation time of four to eight weeks and for a contagiousness period of one week preceding and following the diagnosis of PCP (3, 13). From this, transmission between transplant recipients was possible for four of our patients (no. 2, 3, 5, and 7).

Transmission from one of the medical or nursing staff was also a possibility (8). *Pneumocystis carinii* de-hydro-folate-reductase amplification in serum could be used to detect asymptomatic infections in the staff in the event of an outbreak (14).

However, the possibility of person-to-person transmission should not to be overestimated. Parasitological loading in sputum of infected individuals is always low, even in HIV-positive patients, as it needs induction with hypersaline solution for the recovery of cysts or trophozoites of *Pneumocystis carinii.*

Contamination from an environmental source is another possibility. In spite of the number of cases of PCP reported since the beginning of the AIDS

epidemic, epidemiological knowledge is incomplete for *Pneumocystis carinii* (3). Its life cycle outside humans or infected animals is not known. The existence of undescribed stages of the parasite (spores) has been suggested (13) but has not been confirmed which would provide evidence of an environmental reservoir (15). Water and food have been excluded as possible sources of the infection but soil could be involved. All of our patients but one (no. 6) had been hospitalised during a period of one to two months prior the diagnosis of PCP, suggesting hospital acquisition of the infection.

In the view of the current level of knowledge, it is not possible to identify a single mode of transmission for *Pneumocystis carinii* in HIV-negative-immunocompromised patients. The different hypotheses are not mutually exclusive, and thus advice for prevention could not be univocal.

Isolation of patient with PCP is either a reasonable or an absolutely necessary action, according to different authors (1, 13), but has not been proven to prevent transmission. Moreover, this solution obviously cannot be applied to patients before the diagnosis and thus before the treatment of the PCP, which may be a highly contagious period. However, it may be advisable to isolate renal transplant recipients during high-immunosuppression periods, in months following the transplantation and when bolus or high doses of corticosteroid are administered.

Primary prophylaxis is undoubtedly necessary during these periods. Sulfadoxine plus pyrimethamine have shown insufficient efficacy for renal transplant patients (2). TMP-SMX prophylaxis has been shown to be effective for various types of immunosuppression and is now the drug of choice for PCP prophylaxis in HIV-infected patients (16, 17). To our knowledge, there has been no comparative study conducted with renal transplant patients. However, in a prospective study TMP-SMX prophylaxis (80 mg–400 mg tid) led to only one case of PCP among more than 300 renal transplant patients (18). The optimal daily dose, which avoids hematological and dermatological side effects (uncommon among renal transplant patients), has yet to be determined.

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Yersinia enterocolitica Endocarditis: Case Report and Literature Review

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Endocarditis is a rare manifestation of *Yersinia enterocolitica* infection. The case of a 45-year-old man who presented with high fever and in whom prosthetic valve *Yersinia enterocolitica* endocarditis was diagnosed is described. The patient was successfully treated with ceftriaxone plus tobramycin, as proved by negative cultures of the prosthesis removed at the end of therapy. Including the patient reported, only 12 cases of *Yersinia enterocolitica* endocarditis have been published to date, two of which describe prosthetic cardiac valve endocarditis. The clinical characteristics do not distinguish septicemia from involvement limited to the cardiac valves. Diagnosis, however, has been improved by progress in echocardiography. Prognosis is grave but can be ameliorated if appropriate antimicrobial agents are administered, i.e. the combination of a third-generation cephalosporin plus an aminoglycoside. Fluoroquinolones may also constitute an attractive therapeutic alternative.

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Yersinia enterocolitica is an enteric pathogen encountered worldwide and associated with a wide spectrum of clinical and immunologic manifestations which, to some degree, depend on the host's predisposing underlying conditions (1). *Yersinia enterocolitica* bacteremia and septicemia are reported most often in patients with a predisposing underlying disease, such as an iron-overloading state (hemochromatosis, acute iron poisoning, deferoxamine therapy), transfusion-dependent blood dyscrasias, immunosuppressive therapy, diabetes mellitus, alcoholism, cirrhosis or malnutrition (1). Contrary to non-bacteremic syndromes, *Yersinia enterocolitica* bacteremia is associated with a fatality rate of 25 to 50 % (2). The bacteremic spread of organisms results in a wide spectrum of complications such as liver, splenic, renal and lung abscesses; infection of vascular prostheses and intravenous catheters; meningitis; septic arthritis; bone infection; and cutaneous involvement presenting with pustules and bullous lesions (1, 2), while endocarditis remains a rare manifestation (2). Eleven cases have been reported previously, one of which describes prosthetic valve endocarditis (2–11). We report the twelfth case of *Yersinia enterocolitica* endocarditis in the literature and the second involving a prosthetic valve (9). The literature on endocarditis caused by *Yersinia enterocolitica* is also reviewed (Medline since 1980).

Case Report. A 45-year-old man was admitted to our hospital because of high fever with rigors, headache, nausea and vomiting. Five years earlier, because of previous rheumatic heart disease, his mitral valve was replaced by a Starr-Edwards prosthetic valve, and aortic valve insufficiency was corrected by valvuloplasty. Three months earlier the patient had been operated on for febrile appendicitis; his course was uncomplicated. On clinical examination his temperature was 39.5°C, blood pressure 120/70 mmHg and pulse 90/min. No signs of heart failure were found, while the prosthetic valve was considered to be functioning normally, with no audible abnormal auscultatory findings. The hematocrit was 45 %, the leukocyte count 10,500/mm^3 with 80 % neutrophils and the platelet count 150,000 mm^3. The ESR was 45 mm/h and urinalysis was normal. Bilirubin was 15.39 µmol/l, aspartate aminotransferase 95 IU/l, alanine aminotransferase 105 IU/l and γ-glutamyl-transpeptidase 15 IU/l. C-reactive protein was 13.9 mg/dl (normal < 5 mg/dl). The chest x-ray and an electrocardiogram were normal. Ultrasound examination of the upper abdomen revealed multiple gallbladder stones. Three