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Effectiveness of low-dose cotrimoxazole prophylaxis against *Pneumocystis carinii* pneumonia after renal and/or pancreas transplantation

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Abstract. We retrospectively examined the effectiveness of prophylaxis with cotrimoxazole in preventing *Pneumocystis carnii* pneumonia in recipients of kidney and combined kidney-pancreas transplants between 1985 and 1989. Cotrimoxazole prophylaxis (480 mg daily or 300 mg/m^2), when used, was started within 2 months after transplantation and usually continued until 6 months after surgery. Eight (3.7%) of the 214 patients who were not given prophylaxis were infected with *Pneumocystis carinii,* and there were 4 fatalities (50% mortality). There were no cases among the 161 patients given prophylaxis ($P \leq 0.03$). No serious adverse effects were noted in the prophylaxis group. It is concluded that prophylaxis against *Pneumocystis carinii* infection is well tolerated and should be given as soon as possible to all organ transplant recipients for at least 6 months.

Key words: *Pneumocystis carinii* prophylaxis – Prophylaxis, *Pneumocystis carinii* – Cotrimoxazole prophylaxis – Kidney transplantation, *Pneumocystis carinii* prophylaxis – Pancreas transplantation, *Pneumocystis carinii* prophylaxis

Pneumocystis carinii pneumonia is a serious infection that may affect patients given immunosuppressive therapy for various reasons. In 1977, Hughes et al. [6] reported a cumulative incidence of *Pneumocystis carinii* pneumonia exceeding 15% among leukemic children treated with immunosuppressive drugs. The fatality rate was 30%–40%. Fortunately, prophylaxis with cotrimoxazole (trimethoprim and sulfamethoxazole in a proportion of 1:5) was shown to be highly effective [4, 6]. In the beginning, relatively high doses of cotrimoxazole were administered – 900 mg/m^2 of body surface area daily – something which for an adult (1.7 m^2) corresponds to three tablets of 480 mg cotrimoxazole (Bactrim) daily. In a subsequent study 10 years later, the same dose of cotrimoxazole, given only on 3 consecutive days each week, was found to be equally effective in preventing *Pneumocystis carinii* pneumonia [7].

Pneumocystis carinii pneumonia also occurs after transplantation. The cumulative incidence during the 1st year following renal transplantation has been on the order of 3%–5% [3, 5, 13]. At the beginning of the 1980s, it was reported that prophylaxis with cotrimoxazole was also effective in preventing infections with *Pneumocystis carinii* after renal transplantation [3, 10]. In spite of these reports, prophylaxis with cotrimoxazole has not been universally adopted, probably due to concerns about possible side effects, particularly effects on renal function.

Prophylaxis with cotrimoxazole was implemented at the Department of Transplantation Surgery at Huddinge Hospital relatively recently (1987) and was initially given only to some of the transplanted patients. In this communication we present data on confirmed cases of *Pneumocystis carinii* pneumonia occurring in transplant recipients, some of whom did and some of whom did not receive cotrimoxazole prophylaxis.

Patients and methods

We examined the records of all kidney and/or pancreas transplant recipients during the time period 1985–1989. All patients who had a functioning transplanted organ for more than 6 weeks after transplantation were included in the study. A total of 375 patients were identified – 225 males and 150 females – with a mean age of 44.7 years (range 1–74 years) and 41.1 years (range 2–70 years), respectively. Each patient's use of cotrimoxazole prophylaxis during the 1st year after transplantation was noted, as were confirmed cases of *Pneumocystis carinii* infection. The immunosuppression given to the transplanted patients during this time period was based on a triple drug regimen including cyclosporin (initially 8 mg/kg orally, later at a lower dose aiming at a whole blood concentration of 100 ng/l after 3 months), azathioprine (2 mg/kg tapered to 1 mg/kg after 1 month), and a low dose of prednisolone (100 mg daily tapered to 20 mg over 1 week and to 10 mg over 3 months). In addition, patients who received combined renal and pancreatic transplants received a 1-week course of rabbit-antithymocyte globulin (RATG). Rejection episodes were treated with bolus doses of methylprednisolone (usually a total dose of 1.25–2.0 mg) and, in the event of steroid-resistant rejection, with RATG or OKT3.

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Table 1. Characteristics of patients acquiring *Pneumocystis carinii* pneumonia (PCP). CyA, Cyclosporin; Aza, azathioprine; Pred, prednisolone; MP, methylprednisolone; RATG, rabbit antithymocyte globulin

Patient	Age	Sex	Tx date	Organ	Basal immunosuppression	Antirejection treatment	Date of PCP diagnosis	Outcome
1	6	Female	Jan 1985	Kidney	CyA + Pred	None	June 1985[a]	Died
2	27	Male	Mar 1985	Kidney + pancreas	CyA + Pred + Aza + RATG	MP (3.5 g)	July 1985[a]	Died
3	61	Male	Jan 1987	Kidney	CyA + Pred	MP (1.25 g)	May 1987[a]	Died
4	5	Male	Jan 1988	Kidney	CyA + Aza + Pred	MP (2.75 g)	May 1988	Alive
5	54	Male	Feb 1988	Kidney	CyA + Aza + Pred	MP (1.25 g)	May 1988[a]	Alive
6	37	Male	May 1988	Kidney	CyA + Aza + Pred	MP (1.25 g)	Sept 1988	Died
7	62	Male	Nov 1988	Kidney	CyA + Aza + Pred	MP (1.375 g)	Jan 1989	Alive
8	59	Male	Jan 1989	Kidney	CyA + Aza + Pred	MP (1.375 g)	Feb 1989	Alive

[a] CMV was concomitantly isolated in bronchoalveolar lavage fluid and in buffy coat sample

Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis, when given, was usually started within 1–2 months after transplantation (for 18 patients within 2.5 months) and continued until at least 6 months after surgery. Due to the impaired renal function of transplant recipients, lower doses of cotrimoxazole were used than for patients with leukemia [6]. The standard dose prescribed was 480 mg (one tablet of Bactrim) or, for children, 300 mg/m^2 every night. If serum creatinine exceeded 200 µmol/l, the dose was reduced to one tablet every other day.

Cotrimoxazole prophylaxis was only given to 4.8% of the transplanted recipients during 1985. In 1986, prophylaxis was given to 18.9% and in 1987 to 29.1% of the recipients. Prophylaxis was, in the beginning, mainly prescribed to patients who had received both pancreas and kidney transplants and to those who had been given extensive immunosuppression, such as RATG or OKT3, because of severe and/or repeated rejection episodes and who were thus considered to have an increased risk of becoming infected with *Pneumocystis carinii*. Later, a greater proportion of the transplanted patients were given prophylaxis, depending mainly on which doctor came to see the patient at discharge. In 1988, 75% were given prophylaxis, and since 1989 all recipients are given it.

Diagnosis and monitoring of Pneumocystis carinii

All patients were routinely monitored by ELISA serology at 3, 6, and 12 months before transplantation for significant differences in antibody titers against *Pneumocystis carinii* [9]. In suspected cases of *Pneumocystis carinii* pneumonia the diagnosis was confirmed by bronchoalveolar lavage obtained by fiberoptic bronchoscopy and the subsequent detection of *Pneumocystis carinii* antigen and histological investigation of the fluid [1].

Diagnosis of cytomegalovirus (CMV)

Bronchoalveolar lavage fluid was investigated for the presence of CMV-infected cells using CMV-specific mononuclear antibodies and an indirect immunofluorescence technique, as well as by virus isolation in tissue culture. Virus isolation was also performed from buffy coat when there was clinical suspicion of pneumonia.

Diagnosis of bacterial infection

Bronchoalveolar lavage was used for cultures of bacteria inculding *Legionella, Mycobacterium, Nocardia,* and fungal species.

Results

Eight cases (3.7%) of *Pneumocystis carinii* pneumonia occurred (in one female and in seven males) in the 214 patients who were not given any prophylaxis. There were no cases of *Pneumocystis carinii* pneumonia among the 161 patients given prophylaxis no later than 2 months after transplantation and for at least 6 months ($P \leq 0.03$ Fischer's exact test). The infections developed between 5 and 24 weeks after transplantation and had a high fatality rate (4/8, or 50%), despite appropriate treatment with high doses of cotrimoxazole. Forty-five of all 375 patients had received combined kidney and pancreas transplants. Out of 31 patients given cotrimoxazole prophylaxis, none was infected, whereas 1 of 14 not given cotrimoxazole got *Pneumocystis carinii* pneumonia.

Table 1 presents the characteristics of the eight patients with *Pneumocystis carinii* pneumonia. Four of these patients concomitantly had CMV pneumonia diagnosed by antigen detection in bronchoalveolar lavage as well as by virus isolation from buffy coat. Three of the four patients with combined infection succumbed.

No cases of *Listeria* or *Nocardia* infections were verified in any of the patients, whether or not they had been given prophylaxis.

No severe adverse effects, such as interstitial nephritis or Stevens-Johnson syndrome, were seen in any of the 161 patients prescribed cotrimoxazole. A slight increase in serum creatinine was observed in a few patients (< 10%). The drug did not have to be withdrawn from any of the 161 patients who were followed.

Discussion

The present observations of effective prophylaxis with low-dose cotrimoxazole is in accordance with recent reports from other transplantation units (Table 2). In Norway, Talseth et al. [15] have seen no cases of *Pneumocystis carinii* pneumonia since the introduction of cotrimoxazole prophylaxis at the same dose (1 × 1), whereas the incidence before the routine use of prophylaxis was about 4%. Likewise, Higgins et al. [5] in the United Kingdom

Table 2. Prevalence of *Pneumocystis carinii* pneumonia (PCP) in transplanted patients with and without cotrimoxazole prophylaxis

Country and author(s)	No. of patients with PCP/total no. of patients given:		
	No prophylaxis	Prophylaxis	Dose
USA, Hardy et al. (1984) [3]	20/335	0/?	(2×2)
Norway, Talseth et al. (1988) [15]	14/305	0/65	(1×1)
UK, Higgins et al. (1989) [5]	4/39	0/156	(1×1)
Sweden, this report	8/214	0/161	(1×1)

saw four cases of *Pneumocystis carinii* pneumonia among 39 patients without prophylaxis as compared to no cases among 156 patients given prophylaxis.

An increased incidence of *Pneumocystis carinii* pneumonia, as well as of other opportunistic infections, such as those caused by CMV, EBV, and adenovirus, have been shown to occur particularly in transplant recipients given intense immunosuppression, e.g., with polyclonal or monoclonal antibodies directed against T-cell receptor epitopes, such as RATG and OKT3 [11]. For this reason, prophylaxis with cotrimoxazole was initially only given to patients considered to have an increased risk of contracting *Pneumocystis carinii* infection. However, it is evident from Table 1 that fatal infections with *Pneumocystis carinii* also occur in young patients without any obvious predisposing risk factors. We were alerted to this risk in 1988 by the tragic death of a 37-year-old nondiabetic man who was generally in excellent physical condition before he became infected and who had been given only one rejection treatment with methylprednisolone.

In this study it was not possible to make a thorough evaluation of the side effects of cotrimoxazole prophylaxis, but it was evident from the records that no severe side effects, such as granulocytopenia or severe skin lesions, occurred. In some patients, a slight increase in serum creatinine was seen shortly after the prescription, but this was not considered to have any clinical importance and may well have been caused by other factors. In the United Kingdom, Higgins et al. [5] studied the renal function of 100 transplanted patients given cotrimoxazole prophylaxis and found no evidence of drug-mediated impairment of the transplanted kidney's function. In fact, there may even be beneficial effects, as Higgins et al. [5] saw fewer urinary tract infections in patients given cotrimoxazole prophylaxis.

As our criteria and treatment of urinary tract infections changed somewhat during the study period 1985 to 1989, we did not make any attempt to examine the incidence of urinary tract infections in patients with and without cotrimoxazole prophylaxis. A retrospective analysis may easily become severely flawed if the criteria for diagnosis change with time, particularly if the analysis is based on a nonrandomized group of patients, as in the present report. In a properly blinded and randomized study, Fox et al. [2] observed significantly fewer (3.3%) bacterial infections in patients given prophylaxis with cotrimoxazole following renal transplantation than in those not given any prophylaxis (7.7%). The frequency of urinary infections, in particular, decreased. Similarly, few side effects were recorded. The dose of cotrimoxazole prescribed by Fox et al. [2] was, however, twice the dose that we used.

The present report should be regarded as a clinical observation on the beneficial use of cotrimoxazole prophylaxis in preventing *Pneumocystis carinii* infections in transplanted patients and not as a proper randomized clinical study. Considering the severity of *Pneumocystis carinii* infections, it would seem unethical to conduct a study today in which transplanted patients are not given cotrimoxazole prophylaxis.

Nonetheless, our observations, together with previous work of other investigators, emphasize the value of low-dose cotrimoxazole prophylaxis. Without such prophylaxis, the cumulative incidence of *Pneumocystis carinii* pneumonia after kidney transplantation is about 3%–5% with a fatality of about 50% giving an overall mortality of 1%–2%. With an easy and practical prescription of one tablet (480 mg cotrimoxazole) per day, or every second day, the occurrence of *Pneumocystis carinii* pneumonia among transplanted patients decreases quite markedly. In the case of allergic side effects, prophylaxis with pentamidine [14] or 'treating through' hypersensitivity [8] should be considered. Recently, Ruskin and La Riviere [12] reported on the use of low-dose cotrimoxazole (two tablets of 480 mg given three times a week) in preventing *Pneumocystis carinii* pneumonia among patients with AIDS and AIDS-related complex. None of the patients given cotrimoxazole became infected with *Pneumocystis carinii,* a finding in accordance with ours.

It seems appropriate to start the prophylaxis as soon as possible after transplantation. We do not yet know how long the prophylaxis should be continued. The risk of infections with *Pneumocystis carinii* is likely to decrease with time elapsed since the transplantation. We have, however, seen one case of *Pneumocystis carinii* pneumonia that occurred in a nondiabetic 58-year-old female more than a year after transplantation and 5 months after the withdrawal of a 7-month prophylaxis with cotrimoxazole.

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