Response of Renal Allograft Recipients to Pneumococcal Vaccine

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Antibody responses to pneumococcal polysaccharide vaccine were compared in a control group of 17 normal adults and in a group of 27 adult patients with stable renal function (serum creatinine 0.8–2.1 mg/dl) seven months to nine years following renal transplantation. Using the indirect hemagglutination technique, antibody titers to 13 of the 14 capsular antigens contained in the vaccine were determined for each patient just prior to and again three weeks following immunization. There was no significant difference between the two groups in the proportion of patients responding with a fourfold rise in titer to 12 of the 13 antigens tested. The response rate to antigen type 3 was reduced in the transplant group ($p < 0.05$). Mean fold increase in indirect hemagglutination titers was likewise determined for each antigen, and a reduced response in the transplant group was noted only to antigen type 23 ($p = 0.037$). Immunosuppressed renal allograft recipients appear capable of mounting a nearly normal antibody response to pneumococcal vaccine.

ALTHOUGH THE MORTALITY from pneumococcal infection has markedly declined with the advent of antimicrobial agents, the attack rate of such infections remains virtually unchanged. Moreover, bacteremic pneumococcal infection is associated with a high mortality rate which reaches 28% in patients who are over 50 years of age or who are chronically ill, despite the administration appropriate antibiotics.[1]

Because of these data and the increased susceptibility of renal transplant recipients to infection, the effects of a recently available polyvalent pneumococcal polysaccharide vaccine were studied in a group of renal transplant patients.

The objectives of this study were: 1) to compare the antibody responses of renal allograft recipients to those of a control group; 2) to determine the effects of the vaccine on engraftment and renal function; 3) to assess the influence of immunosuppressive agents in responders compared to nonresponders within the experimental group; and, 4) to determine the adverse effects of vaccination, if any.

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Methods

The study group consisted of 27 adult patients with stable renal function seven months to nine years after allografting. Five of the patients had received kidneys from living, related donors; the remainder received cadaveric organs. Serum creatinine levels ranged from 0.8–2.1 mg/dl (mean: 1.3 mg/dl). These patients were receiving the immunosuppressive agents prednisone, 0–25 mg/day (mean: 18.2 mg) and azathioprine, 25–200 mg/day (mean: 141 mg). Two of the patients had undergone splenectomy. The control group consisted of 17 normal physicians and nurses.

All persons in the study and control groups received 0.5 ml of a tetradecavalent pneumococcal polysaccharide vaccine containing 50 μg of each polysaccharide type (American types 1, 2, 3, 4, 6, 8, 9, 12, 14, 19, 23, 25, 51, and 56) dissolved in isotonic saline solution containing 0.25% phenol as preservative (Pneumovax, Merck Sharp and Dohme, lot number 178A). Immunizations were given subcutaneously in the deltoid area, and the patients were observed for local and systemic reactions including alterations in renal function.

Serum was collected from all patients and controls just prior to and again three weeks following immunization. All serum samples were stored at −20 C before evaluation. Subsequently, antibody titers against 13 of the 14 antigens contained in the vaccine were determined using an indirect hemagglutination technique modified after Ammann and Pelger.[2] Briefly, human type O positive red blood cells obtained from a single donor were coated with type-specific purified pneumococcal polysaccharide antigen using chromic chloride as a coupling agent. After preabsorption with 5% donor red blood cells, serially diluted serum samples were in-

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TABLE 1. *Antibody Response to Pneumococcal Vaccine**

	Responders (%)												
Antigen	1	2	3	4	6	8	9	12	14	19	23	51	56
Controls	58.3	58.8	94.1	54.2	62.5	58.3	33.3	54.2	41.7	33.3	29.2	76.5	41.7
Transplant patients	58.3	44.4	60.0	58.3	44.0	48.1	48.0	56.0	51.9	32.0	24.0	63.0	56.0
p value	NS	NS	<0.05	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

* Defined as fourfold rise in antibody titer three weeks after immunization.

cubated with the antigen-coated red blood cells for two hours at room temperature, and then readings were taken. Titers were expressed as the highest dilution that resulted in agglutination. The proportion of responders among the allograft recipients was determined and compared to that of the control group. Response to a given antigen was defined as a fourfold rise in antibody titer. In addition, the mean fold increase in indirect hemagglutination titer after three weeks was calculated for each antigen for control and study groups from the expression $\Sigma[\log_2(\text{postimmunization titer} \div \text{preimmunization titer})]/n$.

Results

There was no significant difference in the proportion of responders (defined as a patient with a four-fold rise in antibody titer three weeks postimmunization) in the transplant and control groups to 12 of the 13 antigens tested (Table 1). However, antibody response to antigen type 3 was reduced in the transplant group ($p < 0.05$). There was no significant difference in the dosage of prednisone or azathioprine or in the level of serum creatinine between responders and nonresponders within the study group.

The mean fold increase in antibody titer against antigen 23 was greater in the control group than in the transplant group ($p = 0.037$). However, there was no significant difference in mean fold titer increase for any of the remaining 12 antigens tested (Table 2).

One of the two patients who had undergone splenectomy evidently had an impaired antibody response to 12 of the 13 antigens since the titers to these antigens fell below the 95% confidence limits for both the remainder of the transplant group and the control group. Response to antigen type 2 was within the 95% confidence limits. The second asplenic patient had a normal response to antigens 4, 19, 23, 51, and 56 but had titers below the 95% confidence limits for the transplant and control groups for the remaining eight antigens.

No episodes of acute renal allograft rejection occurred following vaccination nor were any significant changes in serum creatinine levels noted. No adverse reactions associated with immunization were experienced by 18 of the 27 allograft recipients in the study group. The remaining nine patients had minor reactions including pain at the injection site for one to three days (seven patients), fever to 37.7 C (three patients), local swelling (three patients), local erythema (two patients), and ecchymosis at the injection site (one patient). Five patients reported systemic signs or symptoms in temporal relation to the vaccination but not clearly causually related: fever of 38.9 C and diarrhea (one patient), abdominal pain (one patient), nausea (one patient), and rhinitis (two patients).

Discussion

Polyvalent pneumococcal polysaccharide vaccines have been proved effective in preventing pneumococcal infection in several highly susceptible groups of patients. Recent controlled trials in South African gold miners have shown polyvalent vaccines to be 78.5% effective in preventing pneumococcal pneumonia and 82.3% effective in preventing pneumococcal bacteremia due to types in the vaccine.[3] Ammann and associates[4] found that patients with sickle-cell disease and those with anatomic or functional asplenia responded to immunization with pneumococcal polysaccharide in a manner similar to that of normal control groups.

In the present series, the asplenic patients had an impaired response to immunization. However, since only two such patients were available for study no general

TABLE 2. *Mean Fold Increase in Indirect Hemagglutination Titer at Three Weeks**

Antigen	1	2	3	4	6	8	9	12	14	19	23	51	56
Controls	1.94	2.41	3.41	2.59	1.29	1.88	1.53	2.29	1.38	1.12	1.59	2.71	1.71
Transplant patients	2.33	2.00	2.44	2.17	1.92	1.35	1.48	2.08	1.74	0.64	0.68	3.30	1.40
p value	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.037	NS	NS

* Calculated as $\Sigma[\log_2(\text{postimmunization titer} \div \text{preimmunization titer})]/n$.

conclusions can be reached concerning the ability of splenectomized transplant patients to respond to vaccination.

Patients who have completed therapy for Hodgkin's disease have decreased levels of antibody to pneumococcal polysaccharides and fail to respond normally to immunization with pneumococcal vaccine. It appears that the impaired response in these patients is primarily related to the treatment received, chemotherapy, radiotherapy, or both, since untreated patients with Hodgkin's disease appear to have a normal antibody response to immunization with various antigens.[5]

Although transplantation patients are inordinately susceptible to infection, it is not clear whether they represent a very high risk group for pneumococcal infection. Briggs and associates[6] reported that three of eight life-threatening pneumonias occurring in seven nonsplenectomized patients within six months after transplantation were due to pneumococcus. However, other reports[7–9] indicating high rates of fulminant pneumococcal infection come from transplant centers in which most of the patients undergo splenectomy in association with transplantation. The enhanced risk in these patients may be related to splenectomy rather than to immunosuppression, or to both.

During a 12-month period during which 65 transplant patients were observed at the Los Angeles County-University of Southern California Medical Center, 35 cultures of pneumococcus were obtained from 26 patients including 18 from sputum, 13 from the throat, three from bronchoscopic washings, and one from a tongue ulcer. However, significant disease to which this organism may have contributed occurred in only seven of the patients, none of whom had undergone splenectomy. Each of these seven were hospitalized with pneumonitis, and multiple organisms were cultured in each case.

In patients able to respond, the tetradecavalent vaccine should reduce the incidence of serious pneumococcal infection by about 65% since the 14 antigenic types contained in the vaccine account for about 80% of bacteremic infections, and the vaccine appears to be about 80% effective.[1,10]

The present study indicates that renal allograft recipients receiving maintenance doses of prednisone and azathioprine can be immunized without serious side effects and are capable of responding with a normal increase in antibody titer to 11 of the 13 antigenic strains assayed. Confirmation of protective efficacy requires further observation. Antigenic types 3 and 23 to which transplant patients evidently have a reduced response account for about 7% and 4% of bacteremic pneumococcal infections, respectively.[3]

These results taken together with the data reviewed suggest that renal allograft recipients should receive the presently available tetradecavalent pneumococcal vaccine, but the timing of immunization is problematic. It would seem desirable to vaccinate patients prior to transplantation and before immunosuppressive drugs are begun. However, the ability of such dialysis patients to respond to the vaccine is uncertain. At present, patients in this clinic are immunized three to four weeks following transplantation.

References

1. Austrian R. Pneumococcal infection and pneumococcal vaccine. N Engl J Med 1977; 297:938–939.
2. Ammann AJ, Pelger RJ. Determination of antibody to pneumococcal polysaccharides with chromic chloride-treated human red blood cells and indirect hemagglutination. Appl Microbiol 1972; 21: 679–683.
3. Austrian R, Douglas RM, Schiffman G, et al. Prevention of pneumococcal pneumonia by vaccination. Trans Assoc Am Physicians 1976; 89:184–194.
4. Ammann AJ, Adiego J, Wara DW, et al. Polyvalent pneumococcal-polysaccharide immunization of patients with sickle-cell anemia and patients with splenectomy. N Engl J Med 1977; 197:897–900.
5. Siber GR, Weitzman SA, Aisenberg AC, et al. Impaired antibody response to pneumococcal vaccine after treatment for Hodgkin's disease. N Engl J Med 1978; 299:442–448.
6. Briggs WA, Merrill JP, O'Brien TF, et al. Severe pneumonia in renal transplant patients. Ann Intern Med 1971; 75:887–894.
7. Bourgault A, Van Scoy RE, Wilkowske CJ, et al. Severe infection due to Streptococcus pneumoniae in asplenic renal transplant patients. Mayo Clin Proc 1979; 54:123–126.
8. Linnemann CC Jr., First MR. Risk of pneumococcal infections in renal transplant patients. JAMA 1979; 241:2619–2621.
9. Munda R, Alexander JW, First MR, et al. Pulmonary infection in renal transplant recipients. Ann Surg 1978; 187:126–133.
10. Austrian R. Random gleanings from a life with the pneumococcus. J Infec Dis 1975; 131:474–484.