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Pneumococcal Vaccine Immunization of Patients with Renal Impairment[1] (42367)

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Abstract. The immunogenicity of the polyvalent pneumococcal vaccine was studied in renal allograft recipients and dialysis patients. There was no significant overall difference in the antibody response of the allograft recipients compared to control subjects at 1 month following immunization. Chronic hemodialysis patients had significantly lower postvaccination antibody levels for 6 of 12 serotypes. Better graft function in the allograft recipients correlated positively with higher antibody levels. Azathioprine and prednisone in dosages employed had no consistent effect on antibody response. No deterioration of renal function ascribable to the vaccine was observed. Patients were sampled at 1, 2, and $3\frac{1}{2}$ years following immunization. Geometric mean titers (GMT) were calculated for all the serotypes per group for each time of sampling. There was a significant decrease with time in antibody GMTs for all the groups ($P < 0.01$). Chronic hemodialysis patients had significantly lower GMTs than control subjects and allograft recipients at 1, 2, and $3\frac{1}{2}$ years postimmunization ($P < 0.05$). The $3\frac{1}{2}$ years postimmunization antibody levels were very low in dialysis patients, suggesting that reimmunization of these patients may be required.

Infections due to *Streptococcus pneumoniae* are more common in asplenic renal allograft recipients than has been originally recognized (1–3). Chronic hemodialysis patients may also be at an increased risk for pneumococcal infections due to the impairment of their renal function (4). Thus, we felt it of interest to determine the immunogenicity of pneumococcal vaccine in these two groups of patients. We also wished to assess the effect of certain variables, particularly renal function and immunosuppression, on antibody response. Finally, we wanted to determine whether persistence of antibodies in these patients is comparable to normal controls.

Materials and Methods. *Study population Phase I.* Study subjects were divided into three groups: Group A included 9 healthy adults and 10 nonimmunosuppressed patients with chronic diseases for whom the vaccine had been recommended. No control subjects had been splenectomized. There were 9 males and 10 females (mean age ± 1 SD: 48 ± 19 years). Group B consisted of 61 renal allograft recipients, who were at least 6 months post-transplantation and were free of any acute complications at the time of vaccination. Fifty-seven of the allograft recipients had undergone splenectomy. Anti-thymocyte globulin was not used in any of them. There were 32 males and 29 females (mean age ± 1 SD: 40 ± 14 years). Group C comprised 23 patients on chronic hemodialysis. Four of these had undergone splenectomy. There were 12 males and 11 females (mean age ± 1 SD: 39 ± 16 years). The differences in age and sex among the groups were not significant.

All subjects received the 14-valent vaccine preparation containing the purified pneumococcal capsular polysaccharides of the Danish types 1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23F, and 25 (Pneumovax, Lot 724-5/C-F138-5; Merck, Sharp & Dohme, West Point, Pa.). Each 0.5-ml vaccine dose contained 50 μg of capsular polysaccharide from each pneumococcal serotype and was administered subcutaneously in the upper extremities. Serum specimens were obtained prior to and 3 to 5 weeks following vaccination.

Study population Phase II. One year later, when follow-up samples were obtained, the control group (Group A) was comprised of 7 healthy adults. The 10 nonimmunosuppressed

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patients with chronic diseases, who were included in assessment of the initial response, were not included because they were no longer available for study. Group B consisted of 55 renal allograft recipients. Group C comprised 13 patients on chronic hemodialysis. There was a progressive decrease in the number of participants with time of sampling, at 2 and $3\frac{1}{2}$ years, respectively: Group A, 4 and 2; Group B, 34 and 24; and Group C, 8 and 2. The attrition was due to departure from the area for Group A subjects, departure and death for Group B subjects, and transplantation for Group C subjects.

All serum samples were stored at −70°C prior to testing.

Antibody determinations. Serum antibodies to 12 polysaccharide types were measured by an RIA method previously described (5), and reported in terms of nanograms of antibody nitrogen per milliliter. Testing was done separately for Phase I and II specimens. Specimens were tested concurrently, however, for each phase of the study.

Assessment of renal function. The endogenous creatinine clearance was calculated using lean body weight, measured serum creatinine, and an estimation of 20 mg/kg/24 hr of creatinine production divided by the serum creatinine.

Statistical analysis. In Phase I, results for the two control groups comprising Group A (normal subjects and nonimmunocompromised patients) were pooled after *t* tests for each serotype showed no significant differences. A one-way analysis of variance was used to compare the pre- and postimmunization geometric mean titers (GMTs), and the mean fold increases for the control group versus the dialysis and the transplant groups. Multiple regression analysis was used to assess the effect of creatinine clearance, splenectomy status, weight-standardized azathioprine dose and weight-standardized prednisone dose on antibody titers, and fold increases in the transplant group.

In Phase II, a one-way analysis of variance was used to compare the postimmunization GMTs, and the mean fold increases for the control group versus the allograft recipient group versus the chronic dialysis patient group.

Results. *Antibody response Phase I.* The antibody responses in all three groups are depicted in Table I. Results are expressed as a GMT in nanograms of antibody nitrogen per milliliter of both the pre- and postimmunization sera for each of the 12 serotypes tested.

TABLE I. ANTIBODY RESPONSE TO EACH OF 12 CAPSULAR POLYSACCHARIDE ANTIGENS OF *Streptococcus pneumoniae*

Group[a]	Capsular type	Preimmunization	Postimmunization
A	1	268 (222–323)	553 (405–756)
B	1	168 (106–266)	280 (167–470)
C	1	114 (50–258)	268 (206–349)
A	3	36 (14–94)	625 (350–1120)
B	3	30 (18–51)	258 (165–402)
C	3	9 (3–26)[b]	89 (39–203)[c]
A	4	34 (15–74)	262 (109–626)
B	4	114 (77–168)[c]	567 (377–853)
C	4	43 (20–94)	88 (29–267)[c]
A	6A	96 (72–134)	250 (169–371)
B	6A	66 (47–91)	219 (152–315)
C	6A	69 (52–92)	178 (111–284)
A	7F	92 (65–130)	124 (88–175)
B	7F	50 (36–70)	152 (118–196)
C	7F	40 (23–70)	111 (77–160)
A	8	72 (49–105)	271 (182–405)
B	8	47 (34–63)	215 (151–305)
C	8	42 (30–60)	136 (71–259)
A	9N	14 (4–42)	202 (76–532)
B	9N	26 (15–43)	179 (97–331)
C	9N	7 (3–18)	52 (16–168)
A	12F	49 (29–82)	163 (105–236)
B	12F	44 (29–65)	118 (88–157)
C	12F	24 (13–43)	54 (26–112)[b]
A	14	13 (5–35)	100 (42–241)
B	14	8 (5–14)	58 (35–96)
C	14	7 (3–16)	40 (15–106)
A	18C	278 (165–470)	989 (555–1763)
B	18C	199 (129–308)	713 (503–1000)
C	18C	87 (40–192)[b]	278 (116–668)[c]
A	19F	50 (35–70)	86 (67–110)
B	19F	26 (21–33)[b]	75 (59–95)
C	19F	25 (18–33)[b]	43 (29–64)[b]
A	23F	390 (218–696)	1993 (1130–3484)
B	23F	135 (77–237)	1039 (658–1641)
C	23F	90 (40–205)	303 (105–871)[c]

Note. GMT (ng N/ml; 95% confidence levels). Controls compared to other groups for each serotype.

[a] Group A, control subjects; Group B, renal allograft recipients; Group C, chronic dialysis patients.

[b] $P < 0.05$.

[c] $P < 0.01$.

Normal subjects and patients with chronic diseases, comprising the controls, were virtually identical in response and were thus included in one group.

Results in allograft recipients whose kidney had been present less than 1 year, 1 to 3 years, and greater than 3 years were analyzed separately. No differences were observed in either antibody levels or graft function (data not shown). These data were, therefore, pooled.

Three weeks postimmunization, there was no difference in the response of allograft recipients (Group B) when compared to control subjects (Group A), although the trend was for allograft recipients to have slightly lower antibody levels. Dialysis patients (Group C), however, had the lowest antibody levels for 10 of 12 serotypes in preimmunization sera; three of the GMTs (types 3, 18C, 19F) were significantly lower ($P < 0.05$). In the postimmunization sera, the dialysis patients had the lowest GMTs for 12 of 12 serotypes. Six of these were significantly lower, including four (types 3, 4, 18C, 23F), where the difference was statistically highly significant ($P < 0.01$).

The response to the vaccine, as measured by the fold increase in GMT, was comparable in all three groups (data not shown). However, regression analysis showed an inverse relationship between initial antibody level and the fold increase in the control and transplant groups, but not in the dialysis group. This was significant ($P < 0.01$) for six serotypes in the control group and for seven serotypes in the transplant group. Five of these serotypes were the same in both groups: 3, 7F, 12F, 14, and 19F. The response was also analyzed as the percentage of postimmunization sera with an antibody level greater than 300 ng N/ml. The control and allograft groups were similar. In the dialysis group, there was a significant diminished response by this parameter, only for type 3.

Antibody response Phase II. Unlike Phase I, where results for the immediate postimmunization response were analyzed separately for each serotype, the results in the follow-up study were expressed in terms of GMTs for all the serotypes per group for each time of sampling. Moreover, these results could not be compared directly to the pre- and immediate postimmunization antibody levels due to differences in standardization.

However, when the GMTs for all of the 12 specific antibody types for each group were compared in the immediate (3- to 5-week) postimmunization sera, the results in nanograms of antibody nitrogen per milliliter were as follows: Group A (9 normal subjects only), 226; Group B (transplant recipients), 230; and Group C (dialysis patients), 109. Though the trend was clearly the same as when results were analyzed for each serotype individually, these results were *not* significantly different from each other.

All groups showed a significant decrease in antibody levels (GMTs) with time ($P < 0.01$) (Fig. 1). Renal allograft recipients had antibody levels which were intermediate to those of the normal control subjects and the dialysis patients. They were, however, not significantly lower than the controls. The chronic hemodialysis patients had significantly lower antibody levels than both other groups—the allograft recipients and the control subjects, at each follow-up time period of sampling ($P < 0.05$). The GMT in the dialysis patients at $3\frac{1}{2}$ years postimmunization was 22 ng antibody N/ml or 10% of the level in the controls (233 ng). The GMT curves also tended to be more separated with time.

The results in terms of mean fold antibody increases paralleled those of GMTs (data not shown). There was a significant decrease in antibody fold increases (reported in geometric

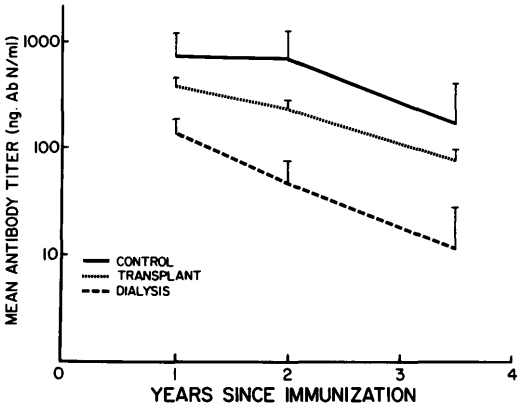

FIG. 1. Geometric mean titers of pneumococcal antibodies in nanograms antibody nitrogen per milliliter (±1SD) in control subjects, renal allograft recipients, and chronic hemodialysis patients at 1, 2, and $3\frac{1}{2}$ years following immunization with pneumococcal vaccine.

means) with time ($P < 0.01$), and a significant difference between the results in control subjects and dialysis patients ($P < 0.05$). Results in allograft recipients were intermediate and not different from those in control subjects.

Analysis of the effect of different variables in pneumococcal antibody response in allograft recipients. The results of multiple regression analysis of the effects of graft function, prednisone and azathioprine dose, and splenectomy on pneumococcal antibody levels are presented in Table II. Graft function was significantly and positively correlated with antibody levels both prior to and after immunization. In the preimmunization sera, antibody levels for 10 of 12 serotypes were significantly correlated with clearance ($P < 0.05$). In the postimmunization sera, there were also 10 significant correlations, including 6 with $P < 0.01$. There was a slight suppressive effect of prednisone and azathioprine on antibody levels in the dosages employed. The presence of the spleen did correlate with higher postimmunization antibody levels for 5 serotypes ($P < 0.05$).

Vaccine safety. Six months postimmunization an independent member of the Nephrology Section reviewed three cases whose graft function was deteriorating at the time of, or subsequent to, immunization. In two of these cases, the deterioration was felt to be chronic rejection, underway prior to immunization. The third case had a self-limited deterioration 4 months postimmunization, and this was felt to be due to other causes. During the $3\frac{1}{2}$ year follow-up, no adverse effects attributable to the vaccine had been noted in the vaccinated allograft recipients.

Discussion. Our data indicate that the immediate postimmunization response to the polyvalent pneumococcal vaccine in renal allograft recipients with normal graft function was similar to that of normal control subjects. Moreover, the vaccine had no adverse effect on graft function. The major factor influencing antibody levels, other than the initial antibody titer, appeared to be the degree of renal function impairment. There was a significant correlation between allograft function and antibody levels in allograft recipients. The dialysis group, comprising patients with the most severe renal impairment, had the lowest antibody levels. Regression analysis data indicated that the fold increases in dialysis patients should have actually been higher than in the other two groups, since dialysis patients started with the lowest antibody levels. A correlation between renal function and antibody response had been noted in a previous study of the influenza vaccine in graft recipients (6).

The reported results with pneumococcal vaccine in patients with renal disease have been mixed. Simberkoff *et al.* also found diminished response to the vaccine in adult

TABLE II. THE EFFECT OF DIFFERENT VARIABLES ON PNEUMOCOCCAL ANTIBODY RESPONSE IN THE ALLOGRAFT RECIPIENTS (MULTIPLE REGRESSION ANALYSIS)

	Preimmunization titer				Postimmunization titer			
Capsular type	Clearance (ml/sec)	Prednisone (mg/kg)	Azathioprine (mg/kg)	Spleen	Clearance (ml/sec)	Prednisone (mg/kg)	Azathioprine (mg/kg)	Spleen
1	<0.05	NS	NS	NS	<0.05	NS	NS	NS
3	NS	NS	NS	NS	NS	NS	NS	NS
4	<0.05	<0.05[a]	NS	NS	<0.01	NS	NS	<0.05
6A	<0.05	NS	NS	NS	<0.01	NS	NS	NS
7F	<0.05	NS	NS	NS	<0.05	<0.05[a]	NS	<0.05
8	<0.05	NS	NS	NS	<0.05	NS	NS	<0.05
9N	<0.05	NS	NS	NS	NS	<0.05[a]	NS	NS
12F	NS	<0.05[a]	NS	NS	<0.01	NS	<0.05[a]	<0.05
14	<0.05	NS	NS	NS	<0.05	<0.05[a]	NS	NS
18C	<0.05	NS	NS	NS	<0.01	NS	NS	NS
19F	<0.05	NS	NS	NS	<0.01	NS	<0.05[a]	<0.05
23F	<0.05	NS	NS	NS	<0.01	NS	NS	NS

Note. NS, not significant.
[a] Indicates an inverse correlation.

chronic hemodialysis patients at 3 weeks, but not at 6 months (7). Friedmen *et al.* found no difference in antibody GMTs between chronic dialysis patients and control subjects; however, the number of subjects in both groups was small and the individual variation was great (8). In another study where indirect hemagglutination was utilized for antibody assay, a comparable response to the pneumococcal vaccine was found in allograft recipients and control subjects (9). The frequency of splenectomy was not noted, however, and the effect of graft function on antibody response was not analyzed in that study.

The differences in GMTs between chronic hemodialysis patients and control subjects became more significant at 1, 2, and $3\frac{1}{2}$ years postimmunization; at $3\frac{1}{2}$ years the GMT in dialysis patients was only 10% of that in the controls. Antibody levels in renal allograft recipients, though lower, did not differ significantly from those in control subjects.

Marrie *et al.* reported that at 1 year following immunization of renal allograft recipients who had various underlying renal diseases, the GMTs had declined by 13.8, 37.1, and 32.7% from the 1-month levels for patients with glomerulonephritis, pyelonephritis, and miscellaneous renal disease, respectively (10).

More recently, Nikoskelainen *et al.* reported on persistence of pneumococcal antibodies following immunization of patients with chronic renal failure and of renal allograft recipients (11). Employing enzyme immunoassay (EIA) and separating antibody response into immunoglobulin classes, they found that control subjects had the best response in the IgG and IgA antibody classes and renal allograft in the IgM class. Control subjects and renal allograft recipients had better antibody responses than chronic hemodialysis patients. Furthermore, the antibody titers in the dialysis patients declined more rapidly (11).

The current recommendations from the Centers for Disease Control (CDC) (Atlanta, Ga.) call for only one dose of the pneumococcal vaccine (12). This is due to studies showing persistence of antibodies in healthy subjects for at least 5 years following immunization (13, 14). Indeed if such patients are reimmunized in 2 to 3 years, while their antibody levels remain high, they experience a high incidence of reactions most likely due to the Arthus phenomenon (15).

The antibody persistence in other immunocompromised groups may also be shorter than in normal subjects. It has been shown that antibody levels fall significantly at 6 months post immunization in patients with Hodgkin's disease (16). These patients do not respond optimally even 1 month after immunization if this is done postsplenectomy and while they are on chemotherapy (16). Similarly, antibody titers were reported to be suboptimal and to fall at a faster than the expected rate in splenectomized children (17).

What are the implications of our findings for vaccine recommendations in patients undergoing chronic hemodialysis and in renal allograft recipients? It has been suggested that the immunization of patients undergoing hemodialysis may avoid the potential problem of immunizing an immunocompromised host following transplantation (3). Our results and those of previous studies with influenza vaccine (6) would seem to indicate that azathioprine and corticosteroids in the dosages employed have little effect on antibody levels in transplant recipients. Thus, other than the recommendation that immunizations be done while the patient still has the spleen (16), it would appear from our data that immunization should actually be given following transplantation when the renal function is improved. Our data further suggest that patients undergoing chronic hemodialysis be reimmunized with the newer 23-valent pneumococcal vaccine at approximately 3 years following initial immunization. The response of such patients to revaccination has not, however, been determined to date. Finally, other immunocompromised groups may also require revaccination (18).

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