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Persistence of antibodies to pneumococcal vaccine in patients with chronic renal failure

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Persistence of antibodies to pneumococcal vaccine in patients with chronic renal failure and renal allograft recipients. Antibody response to the 14-valent pneumococcal capsular polysaccharide vaccine was measured by the enzyme-linked immunosorbent assay (EIA) in 17 renal allograft recipients, 29 azotemic, 11 hemodialysis, and 33 control patients. The IgG, IgM, and IgA antibodies were measured against six pneumococcal antigen types 1, 3, 4, 6A, 8, and 19F. The control patients had the best antibody responses in the IgG and IgA antibody classes and the renal allograft recipients in the IgM class. The renal allograft recipients had significantly stronger antibody responses than the azotemic and hemodialysis patients. The hemodialysis patients had significantly weaker antibody responses than the control patients and the renal allograft recipients, and they also lost their antibodies most rapidly. Thus, the hemodialysis patients and probably some azotemic patients should be considered for revaccination.

Persistance des anticorps au vaccin pneumococcique chez des insuffisants rénaux chroniques. La réponse anticorps au vaccin avec la capsule pneumococcique à 14 valences a été mesurée par un dosage avec une enzyme liée à un immunoadsorbant (EIA) chez les receveurs de 17 allogreffes rénales, chez 29 malades urémiques, chez 11 dialysés, et chez 33 contrôles. Les anticorps IgG, IgM, et IgA ont été mesurés contre six types d'antigènes pneumococciques: 1, 3, 4, 6A, 8, et 19F. Les malades contrôles avaient les meilleures réponses anticorps pour les classes d'anticorps IgG et IgA, et les receveurs d'allogreffe rénale pour la classe des IgM. Les receveurs d'allogreffe rénale avaient des réponses anticorps significativement plus fortes que les urémiques et les hémodialysés. Les hémodialysés avaient des réponses anticorps significativement plus faibles que les malades contrôles et que les receveurs d'allogreffe rénale, et ils perdaient également leurs anticorps plus rapidement. Ainsi, les hémodialysés, et sans doute certains urémiques, devraient être revaccinés.

Pneumococcal infections are a major problem in patients with chronic renal failure and in renal allograft recipients. Although the mortality from pneumococcal infections has declined remarkably with the advent of antimicrobial agents, the attack rate of such infections remains virtually unchanged. Moreover, bacteremic pneumococcal infections are associated with a high mortality rate, which reaches 28% in patients over 50 years of age, or who are chronically ill despite the administration of appropriate antibiotics [1]. Different risk groups of patients have been vaccinated with the commercially available polyvalent pneumococcal capsular polysaccharide vaccine. The overall antibody responses have been good, but the persistence of antibodies and the duration of protection is still unknown. The early trials with the pneumococcal vaccine in patients with chronic renal failure were very encouraging regarding the antibody response. In those studies, the patients with uremia and those with renal allograft had almost as good responses as the healthy controls [2–5]. We have studied the antibody response and persistence of antibodies to pneumococcal polysaccharide vaccine in patients with chronic renal failure and renal allograft recipients. One of the goals of this study was to find out whether these patients should be revaccinated with the pneumococcal polysaccharide vaccine. We also wanted to find out which antibody class would be the most desirable and most responsible for the protection against pneumococcal infections.

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Methods

The 14-valent pneumococcal polysaccharide vaccine (Pneumovax®-MSD) was administered to 29 patients with chronic renal failure not needing hemodialysis treatment, 11 hemodialysis patients, 17 patients with renal allograft, and 33 control patients. The sex distribution, the mean ages and the age range, mean serum creatinine, and mean hemoglobin values are given in Table 1. The vaccination with the pneumococcal vaccine was initiated in 1980 in our hospital and since then we have vaccinated all new renal patients with this vaccine. The Pneumovax® was administered intramuscularly in a dose of 0.5 ml. Serum samples were taken from each patient and control before vaccination, 4 to 6 weeks, and 12 months after vaccination. All serum samples were stored at −25°C and tested simultaneously. The sera were assayed for antibodies to the capsular polysaccharides of six pneumococcal types 1, 3, 4, 6A, 8, and 19F. The purified pneumococcal polysaccharides were prepared and provided by Merck Sharp & Dohme Research Laboratories (West Point, Pennsylvania, USA). The enzyme immunoassay (EIA) method is described in detail by Koskela, Leinonen, and Luotonen [6]. The titers were expressed as dilutions of serum giving 0.3 absorbence units (405 nm). For the statistical analysis, the natural logarithms of the mean titers were used.

Table 1. Selected characteristics of renal patients and controls immunized with pneumococcal vaccine

Study group	*N*	Females	Males	Mean age	Age range	Mean KREA *μmole/liter*	Mean HB *g/liter*
Controls	33	14	19	56.6	33 to 73	90.6	148
Azotemic	29	13	16	54.1	18 to 73	422	120
Hemodialyzed	11	4	7	48.2	33 to 64	1287	85
Allograft	17	6	11	36.1	19 to 67	176	134

Table 2. Geometric mean antibody titers against six different pneumococcal polysaccharide antigens in the azotemic (AZO), hemodialysis (HEM), renal allograft recipients (ALL), and control (CON) patients before (0), 4 to 6 weeks (I), and 12 months (II) after vaccination. Comparisons between the patient group pairs are indicated by letters

		Type 1						Type 3						Type 4					
		IgG	dGMT	IgM	dGMT	IgA	dGMT	IgG	dGMT	IgM	dGMT	IgA	dGMT	IgG	dGMT	IgM	dGMT	IgA	dGMT
CON	0	1160[a]		90[c]		60[de]		480[i]		110		120		2140[l]		250[o]		140[r]	
	I	2200	1.9	180	2.0	320	5.3	770	1.6	130	1.2	200	1.6	4290	2.6	350	1.4	550	3.9
	II	1630	1.4	100	1.1	150	2.5	590	1.2	90	0.8	140	1.1	2950	1.4	250	1.0	300	2.1
AZO	0	990[b]		150		50[dfg]		460		110		90		2120[m]		380[p]		140[sr]	
	I	1760	1.8	220	1.5	160	3.2	640	1.4	110	1.0	160	1.8	3360	1.6	440	1.2	310	2.2
	II	1170	1.2	140	0.9	60	1.2	490	1.1	80	0.7	90	1.0	2050	1.0	360	0.9	190	1.4
HEM	0	310[ab]		70[c]		40[efh]		540[ik]		50		110		840[lm]		170[nop]		60	
	I	830	2.7	90	1.3	80	2.0	530	1.0	70	1.4	170	1.5	1270	1.5	200	1.2	180	3.0
	II	370	1.2	90	1.3	70	1.8	390	0.7	50	1.0	180	1.6	660	0.8	130	0.8	160	2.7
ALL	0	830		120		50[gh]		480[k]		100		80		1780		350[n]		80[s]	
	I	1670	2.0	250	2.1	220	4.4	940	2.0	150	1.5	170	2.1	3210	1.8	560	1.6	370	4.6
	II	1140	1.4	170	1.4	110	2.2	540	1.1	90	0.9	100	1.3	2080	1.2	430	1.2	170	2.1

b, c, i, m, n, o, p, r, s: $P < 0.05$; a, d, e, f, g, h, k, l: $P < 0.005$

		Type 6A						Type 8						Type 19F					
		IgG	dGMT	IgM	dGMT	IgA	dGMT	IgG	dGMT	IgM	dGMT	IgA	dGMT	IgG	dGMT	IgM	dGMT	IgA	dGMT
CON	0	1930[t]		250		120[yB]		1490[D]		250[H]		90[MN]		1120[RS]		170		90[UVX]	
	I	3550	1.8	320	1.3	300	2.5	3050	2.0	360	1.4	480	5.3	2230	2.0	230	1.4	260	2.9
	II	2640	1.4	230	0.9	190	1.6	2300	1.5	230	0.9	240	2.7	1640	1.5	180	1.0	170	1.9
AZO	0	1550[u]		310		70[zB]		1750[EF]		160[JK]		60[MOP]		1020[T]		240		80[U]	
	I	2160	1.4	370	1.2	150	2.1	2650	1.5	200	1.3	150	2.5	1560	1.4	330	1.4	170	2.1
	II	1730	1.1	310	1.0	90	1.3	1830	1.0	160	1.0	80	1.3	1280	1.1	190	0.8	80	1.0
HEM	0	600[tuv]		190[x]		60[yzA]		1130[DEG]		60[HJL]		50[NOQ]		280[RT]		130		60[V]	
	I	940	1.6	170	0.9	70	1.1	2310	2.1	70	1.3	70	1.4	530	1.9	150	1.2	80	1.3
	II	620	1.0	170	0.9	110	1.8	570	0.5	80	1.3	100	2.0	420	1.5	100	0.8	60	1.0
ALL	0	1460[v]		360[x]		70[A]		1430[FG]		140[KL]		50[PQ]		760[S]		130		50[X]	
	I	2420	1.7	510	1.4	220	3.1	2750	1.9	310	2.2	310	6.2	1430	1.9	190	1.5	120	2.4
	II	1850	1.3	460	1.3	110	1.6	1790	1.3	240	1.7	160	3.2	1130	1.5	150	1.2	60	1.2

u, v, x, y, z, B, F, J, O, S, T, U: $P < 0.05$; t, A, K, L, P, R, V, X: $P < 0.005$; D, E, G, H, M, N, Q: $P < 0.001$ by the 2-factor analysis of variance. dGMT: fold increase in geometric mean titers between the sera 0 and I and 0 and II, respectively.

Statistical methods

The differences between the patient groups were analyzed using the 2-factor analysis of variance with repeated measures. The correlation of antibody titers to the clinical parameters of the patient groups was analyzed using the one-way analysis of covariance.

Results

The EIA antibody titers against the types 1, 3, 4, 6A, 8, and 19F pneumococcal polysaccharide antigens were analyzed separately for IgG, IgM, and IgA class-specific antibodies. The results are given in Table 2 and Figures 1 through 3. The control patients had the highest post-vaccination mean IgG titers against all but type 3 antigens (Fig. 1, Table 2). On the other hand, the hemodialysis patients had very low pre-vaccination titers and the antibody response was lower than in all the other patient groups. The azotemic patients had higher pre- and post-vaccination IgG antibody titers than the allograft recipients against antigen types 1, 4, and 19F, and to the other types the titers were very close to each other. When the antibody responses were expressed as antibody increase between the pre- and post-vaccination antibody titers, the results were very similar, but the hemodialysis patients had the strongest rise in titers against types 1 and 8 due to the low pre-vaccination level (Table 2). When the IgG antibody titers were compared 12 months after vaccination in different groups, the control patients had the most stable antibody levels and the hemodialysis patients had the most rapid fall in titers. The IgG antibody levels of the azotemic patients and the renal allograft recipients were very close to each other. When the antibodies and changes

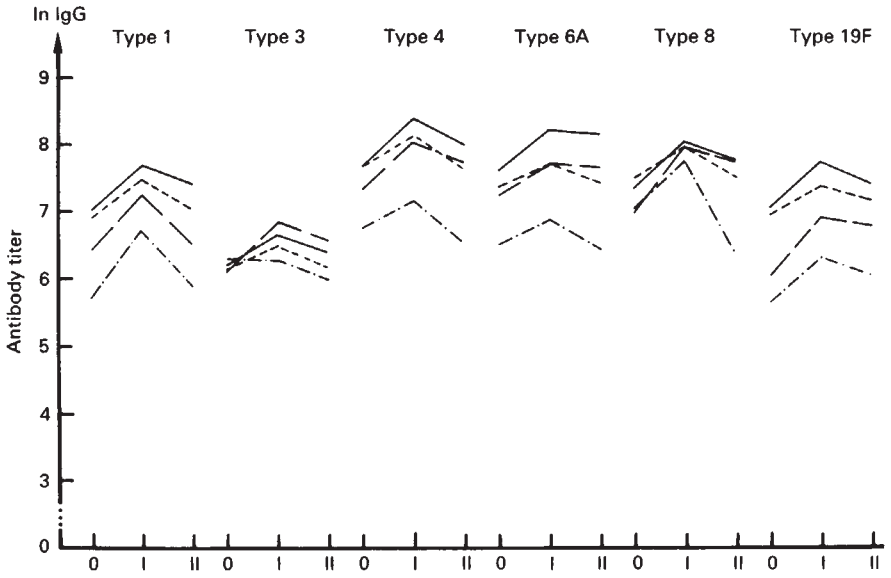

Fig. 1. *Geometric mean IgG antibody titers expressed as natural logarithms against six different pneumococcal polysaccharide antigens in the azotemic, hemodialysis, renal allograft recipients, and control patients before* (0), *4 to 6 weeks* (I), *and 12 months* (II) *after pneumococcal vaccination.* Symbols are: ——, control; ------, azotemic; — · —, hemodialyzed; — —, allograft.

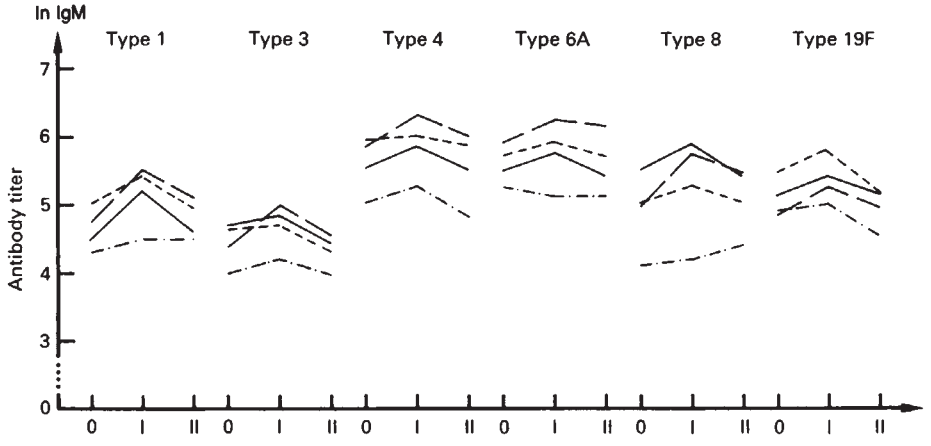

Fig. 2. *Geometric mean IgM antibody titers expressed as natural logarithms against six different pneumococcal polysaccharide antigens in the azotemic, hemodialysis, renal allograft recipients, and control patients before* (0), *4 to 6 weeks* (I) *and 12 months* (II) *after pneumococcal vaccination.* Symbols same as Fig. 1.

in titers were compared to each other, the control patients differed significantly from the hemodialysis patients for type 3 ($P < 0.05$), for types 1, 4, 6A, 19F ($P < 0.005$), and for type 8 antibodies ($P < 0.001$). Also, the azotemic patients had significantly better response and persistence of antibody levels than the hemodialysis patients for type 1, 4, 6A, 19F ($P < 0.05$) and type 8 antigens ($P < 0.001$).

The IgM antibody responses in the different patient groups and the controls are given in Table 2 and Figure 2. In this analysis, the renal allograft recipients had the best IgM antibody responses against types 1, 3, 4, and 6A antigens. The control patients had the best responses against type 8, and the azotemic patients against type 19F antigens. The hemodialysis patients had the poorest IgM antibody responses for all different antigen types. The renal allograft recipients had the strongest increases in antibody titers against all antigen types (Table 2). When the antibody levels and changes in titers were compared, the hemodialysis patients differed significantly from the controls for types 1 and 4 ($P < 0.05$) and type 8 ($P < 0.001$). The renal allograft recipients had significantly stronger IgM antibody responses than the hemodialysis patients for types 4, 6A, ($P < 0.05$), and 8 ($P < 0.005$) antigens.

The IgA antibody responses to the different antigen types are expressed in Table 2 and Figure 3. Here the control patients had the highest pre- and post-vaccination mean antibody titers for all antigen types. The renal allograft recipients had the second best responses for type 1, 4, 6A, and 8 antigens. And again, the hemodialysis patients had the lowest antibody responses for all antigen types except type 3. The controls and the renal allograft recipients had the strongest increases in antibody titers against most of the antigen types (Table 2). When these antibody responses and changes in titers were compared, the control patients differed significantly from the hemodialysis patients for type 6A ($P < 0.05$), type 1 and 19F ($P < 0.005$), and for type 8 ($P < 0.001$). The control patients also differed significantly from the azotemic patients for type 4, 6A, and 19F ($P < 0.05$), for 1 ($P < 0.005$), and for type 8 ($P < 0.001$).

When the persistence of antibodies was studied by comparing the ratio of geometric mean titers 12 months after vaccination in different groups to the corresponding pre-vaccination titer of the controls, the differences between the patient groups were clear (Table 3). The controls had the highest IgG ratios, the renal allograft recipients had the second highest, and the hemodialysis patients had the lowest ones. In IgM antibodies,

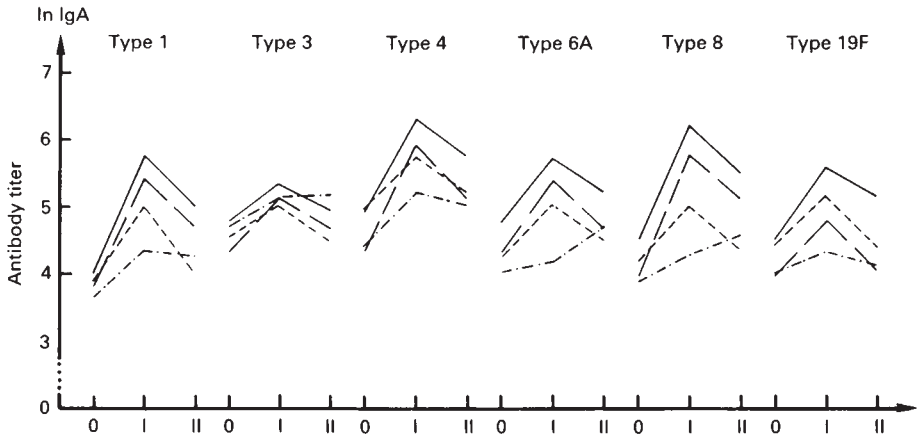

Fig. 3. *Geometric mean IgA antibody titers expressed as natural logarithms against six different pneumococcal polysaccharide antigens in the azotemic, hemodialysis, renal allograft recipients, and control patients before* (0), *4 to 6 weeks* (I) *and 12 months* (II) *after pneumococcal vaccination.* Symbols same as Fig. 1.

Table 3. Ratio of the geometric mean antibody titers of the renal patients and controls 12 months after vaccination to the corresponding pre-vaccination titer of the controls

Patient group	Antibody class	Antigen type					
		Type 1	Type 3	Type 4	Type 6A	Type 8	Type 19F
CON	IgG	1.4	1.2	1.4	1.4	1.5	1.5
AZO		1.0	1.0	1.0	0.9	1.2	1.1
HEM		0.3	0.8	0.3	0.3	0.4	0.4
ALL		1.0	1.1	1.0	1.0	1.2	1.0
CON	IgM	1.1	0.8	1.0	0.9	0.9	1.0
AZO		1.6	0.7	1.4	1.2	0.6	1.1
HEM		1.0	0.5	0.5	0.7	0.3	0.6
ALL		1.9	0.8	1.7	1.7	1.0	0.9
CON	IgA	2.5	1.1	2.1	1.6	2.7	1.9
AZO		1.0	0.8	1.4	0.8	0.9	0.9
HEM		1.2	1.4	1.1	0.9	1.1	0.7
ALL		1.8	0.8	1.2	0.9	1.8	0.7

Abbreviations same as Table 2.

the renal allograft recipients had the highest ratios for types 1, 4, 6A, and 8, the azotemic patients the second highest for types 1, 4, 6A, and 19F, and the hemodialysis patients had the lowest ratios against all types. In IgA antibodies, the controls had the highest ratios against all except type 3 and the renal allograft recipients the second highest ratios for types 1 and 8. The azotemics and the hemodialysis patients were quite close to each other.

When the antibody responses were correlated to the kidney function, the antibody response was significantly lower in IgG type 2 and 8 ($P < 0.05$), in IgA type 1, 6A, 19F ($P < 0.05$), and 8 ($P < 0.005$) when the serum creatinine increased. When the persistence of the antibody levels was correlated to the kidney function, the fall in antibody titers was stronger in IgG type 1 ($P < 0.05$) and 8 ($P < 0.001$) and in IgM type 1 and 6A ($P < 0.05$) when the serum creatinine increased.

When the age of the patients was correlated to the antibody response, with increasing age the antibody response was lower in IgG type 1 and 19F ($p < 0.05$), in IgM type 1 and 8 ($P < 0.05$) and in IgA type 1, 4, 6A, 19F ($P < 0.05$), and 3 ($P < 0.001$). Also, with increasing age the fall in antibody titers was faster in IgG type 3 ($P < 0.05$) and 19F ($P < 0.005$), and weaker in IgM type 6A and 8 ($P < 0.05$), in IgA type 1, 3, and 4 ($P < 0.05$), and in 6A ($P < 0.005$).

Discussion

The indications for pneumococcal vaccination have been clearly settled during the recent years. The candidates for vaccination are those who have an increased risk for pneumococcal infections. This includes patients who are scheduled for splenectomy or have had splenectomy. Also, patients with diabetes and chronic renal failure and renal allograft recipients are at high risk for pneumococcal infections [7–8]. The patients with insulin-dependent diabetes respond adequately to the pneumococcal vaccination [9]. The splenectomized patients have been observed to have impaired immune response to the polyvalent pneumococcal vaccine [10, 11]. Thus, the vaccination should be given before a planned splenectomy, especially in patients with Hodgkin's disease [12]. There are groups of patients who have an increased risk for pneumococcal infections, such as patients with multiple myeloma, but the antibody response in these patients has been poor and without any protective effect [13–15]. The protective effect of pneumococcal vaccination is probably not very good and long-lasting because pneumococcal diseases have been observed in vaccinated patients 1 to 18 months after vaccination [16]. There are several reports of pneumococcal vaccination in patients with chronic renal disease and renal allograft recipients

with somewhat conflicting results. Overall, the antibody responses in the hemodialysis patients have been quite good; in some series, even better than those of the renal allograft recipients [5, 17]. In these studies, however, only the total and not the class-specific antibody response had been determined.

We have studied the antibody responses to 14-valent pneumococcal polysaccharide vaccine in patients with chronic renal failure, either hemodialyzed or not, and in renal allograft recipients. The antibody responses were analyzed for IgG, IgM, and IgA antibody classes for the types 1, 3, 4, 6A, 8, and 19F polysaccharide antigens. From these pneumococcal types, 3, 6A, and 19F are relatively common, and types 1, 4, and 8 rare, but cause serious infections in humans [18, 19]. The differences between the patient groups were very clear; the controls and the renal allograft recipients had the best and the hemodialysis patients had the poorest antibody responses. However, the hemodialysis patients had a good response to vaccination when measured by increase in titer, but the antibody levels were low and decreased very rapidly. In IgG antibodies, the control patients had the best responses for all except type 3 and for IgA antibodies for all antigen types. However, in IgM antibodies the renal allograft recipients had the best responses for all except two (8 and 19F) antigen types. This is an interesting finding that suggests that the immunosuppressive treatment given to the renal transplant recipients modifies the antibody response toward a primitive direction. The hemodialysis patients had the poorest antibody responses in all antibody classes and to almost all antigen types.

The antibody response correlated clearly to the kidney function and to the age of the patients. With increasing serum creatinine, the rise in IgG and IgA antibodies was lower for several antigen types. With increasing age, the rise in IgG, IgM, and IgA antibodies was lower, and the decline in IgG antibodies was faster for some antigen types. There were some variations between the different antigen types, type 3 giving the weakest and type 8 giving the strongest differences between the patient groups. On the basis of these results we cannot yet conclude which antibody class would be the most protective and most desirable, but the IgG and IgA antibodies correlated best to the kidney function. As to the protective effect of these antibodies, none of our patients has had any diagnosed pneumococcal infections during the observation time.

There are reports of side effects of pneumococcal vaccination in which the younger patients had more local and systemic adverse effects after vaccination than the older ones. Our patients received the pneumococcal vaccination intramuscularly and, according to Pönkä and Leinonen [20], the patients receiving the vaccine subcutaneously had fewer side effects.

There are very little data available about the duration of the protective effect against serious pneumococcal infections after vaccination. The original recommendation was not to revaccinate patients sooner than 5 yrs after the primary vaccination because of possible local and systemic side effects of the vaccine. The newest published recommendation is not to revaccinate at all [21]. In the present study, the IgG class antibodies had declined to the pre-vaccination level already 1 yr after vaccination in the hemodialysis patients and also in some azotemic patients, especially in the older ones. There were, however, some differences between the antigen types. Also, the antibody levels of the hemodialysis patients were clearly below the corresponding pre-vaccination titers of the controls, suggesting that there would be no protection left at all 1 yr after vaccination. In the IgM and IgA class antibodies this difference was not so clear. As to the protection against pneumococcal infections, probably the IgG class antibodies are the most important ones because they are known to promote the opsonophagocytosis more efficiently than the IgM class antibodies. The protective role of the serum IgA class antibodies against pneumococcal infection is poorly documented. It is not known whether the pneumococcal vaccination stimulates production of secretory IgA class antibodies to pneumococcal antigens, which might play an important role in the protection against infections. Because in this study the IgG class antibodies correlated best to the kindey function and to the other clinical parameters, it seems that this antibody class might play the most important role in the protection against serious pneumococcal infections.

On the basis of the present results, it seems that the hemodialysis patients and probably some azotemics, especially the older ones, should be revaccinated with the new 23-valent pneumococcal vaccine. We presently recommend routine vaccination of all renal patients with polyvalent pneumococcal vaccine because there were no side effects in the present patient material. It seems that early in illness the patients have a better antibody response. All renal patients are potential candidates for future kidney transplantation; thus, it should be preferable to vaccinate them all well before transplantation since the immunosuppressive treatment given after transplantation might modify the antibody response. The same recommendation has been given recently by the Centers for Disease Control [21].

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References

1. Austrian R: Pneumococcal infection and pneumococcal vaccine. *N Engl J Med* 297:938–939, 1977
2. Friedman EA, Beyer MM, Hirsch SR, Schiffman G: Intact antibody response to pneumococcal capsular polysaccharides in uremia and diabetes. *JAMA* 244:2310–2311, 1980
3. Linnemann CC Jr, First MR: Risk of pneumococcal infections in renal transplant patients. *JAMA* 241:2619–2621, 1979
4. Silberman H, Overturf GD, Field RJ, Butler J, Berne TV, Witt R: Response of renal allograft recipients to pneumococcal vaccine. *Ann Surg* 192:199–201, 1980
5. Cosio FG, Giebink GS, Le CT, Schiffman G: Pneumococcal vaccination in patients with chronic renal disease and renal allograft recipients. *Kidney Int* 20:254–258, 1981
6. Koskela M, Leinonen M, Luotonen J: Serum antibody response to pneumococcal otitis media. *Pediatr Infect Dis* 1:245–251, 1982
7. Bourgault A-M, van Scoy RE, Wilkowske CJ, Zincke H, Sterioff S: Severe infection due to *Streptococcus pneumoniae* in asplenic renal transplant patients. *Mayo Clin Proc* 54:123–126, 1979
8. Schwartz JS: Pneumococcal vaccine: Clinical efficacy and effectiveness. *Ann Intern Med* 96:208–220, 1982
9. Beam TR, Crigler ED, Goldman JK, Schiffman G: Antibody response to polyvalent pneumococcal polysaccharide vaccine in

diabetics. *JAMA* 244:2621–2624, 1980
10. HOSEA SW, BURCH CG, BROWN EJ, BERG RA, FRANK MM: Impaired immune response of splenectomised patients to polyvalent pneumococcal vaccine. *Lancet* I:804–807, 1981
11. GIEBINK GS, FOKER JE, KIM Y, SCHIFFMAN G: Serum antibody and opsonic responses to vaccination with pneumococcal capsular polysaccharide in normal and splenectomized children. *J Infect Dis* 141:404–412, 1980
12. ADDIEGO JE, AMMANN AJ, SCHIFFMAN G, BAEHNER R, HIGGINS G, HAMMOND D: Response to pneumococcal polysaccharide vaccine in patients with untreated Hodgkin's disease. *Lancet* II:450–453, 1980
13. BIRGENS HS, ESPERSEN F, HERTZ JB, PEDERSEN FK, DRIVSHOLM A: Antibody response to pneumococcal vaccination in patients with myelomatosis. *Scand J Haematol* 30:324–330, 1983
14. LAZARUS HM, LEDERMAN M, LUBIN A, HERZIG RH, SCHIFFMAN G, JONES P, WINE A, RODMAN HM: Pneumococcal vaccination: The response of patients with multiple myeloma. *Am J Med* 69:419–423, 1980
15. SCHMID GP, SMITH RP, BALTCH AL, HALL CA, SCHIFFMAN G: Antibody response to pneumococcal vaccine in patients with multiple myeloma. *J Infect Dis* 143:590–597, 1981
16. BROOME CV, FACKLAM RR, FRASER DW: Pneumococcal disease after pneumococcal vaccination: An alternative method to estimate the efficacy of pneumococcal vaccine. *N Engl J Med* 303:549–552, 1980
17. LINNEMANN CC, FIRST MR, SCHIFFMAN G: Response to pneumococcal vaccine in renal transplant and hemodialysis patients. *Arch Intern Med* 141:1637–1640, 1981
18. GRAY BM, CONVERSE GM III, DILLON HC JR: Serotypes of *Streptococcus pneumoniae* causing disease. *J Infect Dis* 140:979–983, 1979
19. KALIN M, LIDBERG AA: Distribution of pneumococcal types in the Stockholm region 1976–1978. *Scand J Infect Dis* 12:91–95, 1980
20. PÖNKÄ A, LEINONEN M: Adverse reactions to polyvalent pneumococcal vaccine. *Scand J Infect Dis* 14:67–71, 1982
21. Centers for Disease Control, Department of Health and Human Services, Atlanta, Georgia: Update: Pneumococcal polysaccharide vaccine usage—United States. *Ann Intern Med* 101:348–350, 1984