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# Perspectives on Hepatitis B Infections and the Efficacy of Vaccination (Hepatitis B and Pneumococci) in Dialysis Patients

G Almroth,[1] F Uhlin,[1] B Ekermo,[2] B Isaksson,[3] B Kaijser,[4] B Andersson,[5] M Hahn-Zoric[5] and M Sällberg[6]

*Departments of Nephrology,[1] Transfusion Medicine and Clinical Microbiology[2] and Hospital Infection Control,[3] University Hospital of Linköping, Departments of Clinical Bacteriology[4] and Clinical Immunology,[5] Sahlgren´s University Hospital, Göteborg University and Department of Clinical Virology,[6] Huddinge University Hospital, Stockholm, Sweden.*

## ABSTRACT

Hepatitis B is a well known problem in dialysis units. We therefore examined the historical frequency of hepatitis B carriers in our unit, our vaccination program to hepatitis B virus (HBV), the response to hepatitis B vaccine, the IgG subclass response of anti-HBs and the response and IgG subclass response to pneumococcal vaccination (another vaccine) in dialysis patients. From 1970 and onwards 23 HBV carriers were found, but no new cases of hepatitis B occurred during the study period, i.e. from 1980 and onwards.Only one of the carriers was alive by the end of 2001. In four patients liver disease(in one of them liver cirrhosis) may have been a concomitant cause of death. The antibody response to hepatitis B vaccine was significantly lower in patients than in staff. In four patients a fourth injection was cancelled due to transplantation and bad health, while such data were lacking in 8 cases. In anti-HBs positive patients and controls a significant difference in the response of healthy adults was observed in anti-HBs IgG1 ($p<0.001$) vs all other IgG subclasses. Dialysis patients had low levels, or negative findings, in all cases, with IgG1 as the highest proportion found (3/11 patients). An antibody response to pneumococcal vaccination was registered in 25 out of 29 dialysis patients (in all 86 %). The IgG-subclass vaccination response to pneumococci in 28 dialysis patients was mainly IgG2 and IgG1 but also occurred in IgG3 and IgG4. Prevaccination antibody levels of the controls were higher in IgG1 and IgG2 ($p< 0.01$) (n=21) than in dialysis patients (n=28).

Hepatitis B is nowadays a rare, but still dangerous disease in nephrology units. Dialysis patients have a reduced response to hepatitis B vaccine and vaccination schedules should be started early as some patients otherwise may not receive a

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fourth injection. The adequate antibody response to pneumococcal vaccination mainly due to IgG2 and IgG1 antibodies indicates that the antigen involved is important in vaccination responses in dialysis patients.

## INTRODUCTION

Dialysis patients are considered to be at increased risk of acquiring hepatitis B virus (HBV) infection, and have a reduced response to vaccination (1). The responses to other vaccinations as tetanus and pneumococci have also been found to be reduced (2). Changes in the dialysis regime chosen are not infrequent, and both patients with hemodialysis (HD) and those with peritoneal dialysis (PD) should be vaccinated to HBV. The mode of dialysis chosen does not seem to affect the response to hepatitis B vaccination (3). A difference in response has, however, been shown for other vaccines as in influenza immunisation, where patients with continuous ambulatory peritoneal dialysis (CAPD) had a response similar to that of healthy adults, while HD patients had a lower response rate (4). Although influenza vaccination is not as effective as in healthy adults renal patients seem to benefit from it (5). Antibodies of immunoglobulin G (IgG) class are important in the response to foreign antigens. IgG has four different subclasses (IgG1, IgG2, IgG3 and IgG4) with different biological properties.

The IgG subclass response to vaccinations may reflect the antigen involved and the mechanisms of response (6). The IgG-subclass distribution of antibodies to hepatitis B surface antigen (anti-HBs) has earlier been determined in sera from healthy adults but not in dialysis patients (7, 8). Also it is not known whether the impaired response to HBV vaccines in dialysis patients is caused by the lack of a specific IgG subclass or a general deficit. A limited vaccination schedule to HBV, which only concerned patients who awaited renal transplantation had been adopted, since 1983, in accordance with instructions from the local hygiene committee.

The aim of the study was to determine the antibody response to hepatitis B and pneumococcal vaccine in dialysis patients and to evaluate the adequacy of the vaccination program we used. We therefore reviewed the records of all patients who were known to have had hepatitis B at our unit. A further aim was to compare in retrospect the findings of a group of dialysis patients vaccinated at least three times and tested after the third and/or fourth injection with the conditions found in healthy vaccinated adults, as the latter usually need only three injections to fulfil the vaccination programme, and to suggest future vaccination strategies. We also determined the IgG-subclass distribution of anti-HBs in sera from healthy adults and dialysis patients as this may reflect the mechanisms of the known reduced response to hepatitis B vaccination in dialysis patients as well as the antibody response to pneumococcal vaccination, also in IgG-subclasses, in a group of dialysis patients.

The latter vaccination is of importance in the protection against invasive pneumo-

coccal infections and is recommended in the elderly, in splenectomized patients and in various forms of immunodeficiency (9, 10). An initially low, but later more adequate, antibody response to pneumococcal vaccination has earlier been demonstrated in dialysis patients (11).

## PATIENTS AND METHODS

The records of all patients who were known to have been carriers of hepatitis B virus (Au Ag or HBsAg positive) from 1970 to the end of 2001 were reviewed to evaluate the historical frequency of HBV carriers at our unit. We also examined the antibody responses to hepatitis B and pneumococcal vaccines and the IgG subclass response to anti-HBs and pneumococci after vaccination.

Dialysis patients; group A. To determine the response to vaccination to hepatitis B we tested sera from 25 dialysis patients (16 with continuous ambulatory peritoneal dialysis (CAPD) and 9 with hemodialysis (HD) (18 males and 7 females with a mean age of 49) vaccinated at least three times to hepatitis B during 1986–93. Eight of them were tested after three as well as four vaccinations and 17 after three vaccinations only.

All patients were negative for hepatitis B surface antigen (HBsAg) in ELISA (enzyme linked immunosorbent assay) (Organon Teknika Oss, the Netherlands, commercially available kit) before entering dialysis. Later analysis was performed by ELISA from ABBOTT Murex (Murex Biotech Ltd, Dartford, Kent, England) and from December 1995 Axsym from Abbot, Abbot park; Il., Chicago, US.

Follow-up with HBsAg-testing was performed every 6–12th month in HD-patients and every 12th month in PD-patients according to clinical routines. No positive findings were observed. Alanine aminotransferase (ALT) levels were, as a rule, tested every 2–4 weeks in HD-patients and once per two months in PD-patients. None of the patients who were vaccinated had clinical or laboratory signs of ongoing hepatitis B.

Vaccination was until February 1990 performed with HB-Vax and then switched to Engerix B 1 ml i.m. at a time schedule of 0, 1, 2 and 6 months thereafter, which was used until the end of 1993 (doubling the dose schedule is nowadays performed in dialysis patients).

*Anti-HBs analysis* was performed with ELISA-technique (Organon qualitative/semiquantitative ELISA in 9 cases + Abbot IMX quantitative microparticle enzyme immunoassay in positive cases and in the remaining 16 cases). Positive and negative findings and levels of 10–100, (100)– 100–1000 and > 1000 were determined according to the manufacturer´s instructions.

As a rule, samples were drawn three to five weeks (20 days to 6 months) after vaccination and stored frozen at –20 C until analysis, which was performed within two years. In the 9 patients tested with Organon samples were drawn within 6–49 months after vaccination. In anti-HBs positive patients antibodies to hepatitis B core antigen (anti-HBc ) or prevaccination levels of anti-HBs were determined with

ELISA technique, to confirm that all individuals were unprotected before vaccination. These tests were found to be negative in all cases.

*Staff; group B.* Data from 53 healthy adults, 52 females and one male, mean age 37, vaccinated at least three times, were obtained by testing anti-HBs 1–3 months after i.c. vaccination with HB-vax. One person (female 55 years) who received two injections only was also tested.

*IgG-subclasses in anti-HBs positive patients (group C),* were determined with ELISA with microplates coated with plasma- derived HbsAg (Murex, England) and monoclonal mouse antibodies to human IgG1–4 (Sigma, S:t Louis, MO, USA) as previously described for anti-HBc (12–14) in sera from 11 anti-HBs positive dialysis patients (6 males and five females with a mean age of 51 years). Ten of these patients were from the time period studied (see above). Serum from one patient, who tested positive, was collected afterwards and used for subclass analysis. The anti-HBs levels were 10–100 in two cases, 100–1000 in 7 cases and > 1000 in three cases.

Sera selected from 45 vaccinated anti-HBs positive persons with levels of 10–100 IU in four cases, 100–1000 IU in 31 cases and > 1000 IU in 10 cases, as well as sera from 12 unvaccinated individuals, served as positive and negative controls, respectively. Cut-off levels were defined as the mean absorbance of unvaccinated individuals+3 SD.

*Response to pneumococcal vaccination (group D).* Twentynine HD patients ( 20 males and 9 females with a mean age of 67 years) were vaccinated with Pneumovax® (Pasteur-Merieux, MSD) 0.5 ml subcutaneously against pneumococci during 1998. The vaccine Pneumovax®, which contains a mixture of the 23 most common capsular polysaccharides from pneumococci, was used as antigen.

Antibody titres were measured before vaccination and four weeks afterwards with ELISA-technique. An antibody response was, with the method used (9), defined as an increase by 50% or more in optical density (OD).

*The IgG-subclass response to pneumococci in dialysis patients (group E).* Twentyeight HD patients (17 males and 11 females) with an mean age of 61.3 years, who, in the year 2002 were vaccinated to 23 pneumococcal antigens with Pneumo-23®; Pasteur Mérieux, France and 21 healthy controls (4 males and 17 females) with a mean age of 29.5 years were studied with respect to anti-pneumococcal antibodies of all subclasses.

The tests were performed with an ELISA-technique using a commercially available kit for determination of IgG2 antibodies to a mixture of pneumococcal polysaccharides (Bindazyme anti-PCP IgG2 Eia, the Binding Site LTD, Birmingham, UK). For IgG2 antibodies the test performed as described by the manufacturer and for the other IgG subclasses using sheep anti-human IgG1, IgG3 and IgG4 (0.5mg/ml, 1/5000) (The Binding Site Ltd, UK) conjugated to peroxidase. The dialysis patients were tested both before and one month after vaccination, while all controls were tested unvaccinated measuring naturally occurring antibodies to pneumococci only. An antibody response (OD elevation) of 50% or more was considered as a positive vaccination response.

Table 1. Patients infected with hepatitis B virus at the Nephrology unit of Linköping from 1970–2001.

| Patient no Sex/born | Year of HBsAG pos | Treat-ment form | Cause of death/ Diagnosis/alive (uremia in all cases except no. 7) | Year of death/ Autopsy/ | Kidney Disorder |
|---|---|---|---|---|---|
| 1 M/ –29 | –71 | HD-70 | Bleeding ulcer/hepatitis | –77/No | CGN |
| 2 M/ –23 | –71 | HD-69 | Pneumonia/Septichemia | –73/Y | PCK |
| 3 M/ –36 | –71 | HD-69 | Hematemesis/hepatitis/ ascites | –71/Y | CGN |
| 4 M/ –16 | –71 | HD-70 | Hepatitis/myocarditis | –71/Y | CIN |
| 5 M/ –33 | –71 | HD-70 | Subdural hematoma | –71/N | CGN |
| 6 M/ –23 | –71 | HD-71 | Pancreatitis/cachexia | –71/N | CGN |
| 7 M/ –45 | –76 | HD-71/Tx-72 | Coronary sclerosis/ Pulmonary Oedema | -91/Y | CIN/ cong.ano |
| 8 F/ –27 | –73 | HD-72 | External shunt bleeding | –76/Y | CGN |
| 9 M/ –19 | –75 | HD-73/Tx-74 | Septicemia | –79/N | CGN |
| 10 F/ –14 | –71 | HD-68 | Susp. coronary infarction | –72/N | PCK |
| 11 M/ –46 | –71 | HD-69 | Pulmonary oedema | –83/Y | PCK |
| 12 F/ –27 | –71 | HD-65, Tx/HD | Constrictive pericarditis | –75/Y | CIN |
| 13 M/ –45 | –75 | HD-72 | Gastrointestinal bleeding | –77/Y | AGN |
| 14 F/ –24 | –75 | HD-73 | Uremia | –83/Y | CIN |
| 15 M/ –14 | –71 | Tx/HD-71 | Septichemia | –72/N | Nefroscl. |
| 16 F/ –30 | –71 | HD-70 | Pericarditis/pulmonary oedema | –71/Y | CIN |
| 17 M/ –35 | –70 | HD-69 | Rectal cancer with metastases | –80/N | CIN |
| 18 M/ –27 | –79 | Tx/HD-77 | Meningitis/septiche-mia | –79/Y | PCK |
| 19 M/–25 | –73 | HD-72 | Pneumonia/septiche-mia | –74/N | PCK |
| 20 M/ –33 | –75 | HD-73 | Intracerebral haemorrhage | –79/N | CGN/CIN |
| 21 M/ –26 | –70 | HD-65 | Pneumonia | –76/N | CGN |
| 22 F/ –59 | –73 | Tx–72–73 | Cachexia, uremia liver cirrhosis | –01/N | CIN |
| 23 F/ –51 | –72 | HD-68/Tx | Alive (HBsAg pos HBeAg neg, Anti-HBe pos.) | | CIN |

HD = Hemodialysis, Tx = transplanted, CGN = Chronic glomerulonephritis, CIN = Chronic interstitial nephritis, PCK = polycystic kidney disease, cong. ano = congenital anomalies. Nefroscl. = nefrosclerosis.

* In two further patients intermittent unspecific HBsAg reactivity was shown during 2001.

## RESULTS

Twentythree patients were known to have been affected with hepatitis B at the unit, Table 1. No new case of hepatitis B was detected after 1979 (after the start of the vaccination program). Only one of the 23 patients infected in 1971–79 was alive at the end of the year 2001. In four of the patients hepatitis B liver disease may have been a concomitant cause of death (Table 1). One of them acquired a liver cirrhosis (a long time complication of the disease) before she died in 2001.

*Vaccinations.* In *dialysis patients (group A)* ten out of the 25 CAPD/ HD patients (40%) were positive and 15 were negative for anti-HBs when both testings after the third and fourth injection were considered. Among the twenty-one patients who were tested after the third injection nine patients were positive and 12 were negative for anti-HBs. In those tested after four vaccinations, four were negative and four were positive for anti-HBs. One patient who received a fourth injection was tested too close to this injection (five days thereafter) and the result was considered invalid. This patient was tested after the third injection and was found to be positive.

Positive tests after three vaccinations were in the level of 10–100 units (U) in six cases and 100–1000 U in three cases.

After four vaccinations the anti-HBs levels were 10–100 U in one case and 100–1000 U in three cases. None of the patients had a level above 1000 U (Table 2 a).

One serum found to be positive in a level of 100–1000 with semiquantitative test was however later retested with Abbot IMX and had then a level above 1000 U. In the nine patients tested with Organon anti-HBs no additional serologic follow up was performed after the third injection and post-vaccination test. Five of these patients received renal transplants while three had transplantation postponed due to bad health. In one of these nine patients a fourth injection was omitted as the patient was transferred to another unit.

In three out of the remaining 16 patients the fourth vaccination was inhibited as renal transplantation was performed. In one patient transplantation was stopped for medical purposes and the fourth vaccination was inhibited. In one patient the blood sample was taken only five days after the 4th vaccination, but testing was per-

Table 2 a. Antibody responses to hepatitis B vaccine in patients and staff (groups A, B and C).

| Group A (N=25) | Negative <10U | Low level 10–100 U | Intermediate level 100–1000 U | High level >1000 U |
|---|---|---|---|---|
| A1; all | 15 | 5 | 5 | (1 retested) |
| A2; 3 inj. (n=21) | 12 | 6 | 3 | (1 retested) |
| Group B (N=53) | 2 | 10 | 38 | 3 |
| (Group A2 vs B; Level > or 10 U p<0.001***). | | | | |
| Number of subclass-positive anti-HBs positive patients and controls (group C). | | | | |
| | IgG1 | IgG2 | IgG3 | IgG4 |
| Patients (n=11) | 3 | 1 | – | – |
| Controls (n=45) | 25 | 2 | 4 | 5 |

formed after the third injection (see above). In three cases post vaccination test after the fourth injection is lacking for unknown causes.

In the nine patients tested with Organon anti-HBs three had antibodies while seven of the remaining 16 patients had positive tests. No statistical difference was observed in age and sex of patients who had positive and negative tests respectively. Out of the 16 patients with CAPD six were positive and ten were negative for anti-HBs. Four of the nine HD patients were positive and five were negative for anti-HBs.

In *staff (group B)* three persons had levels above 1000 IU, 38/53 persons (72%) had levels of (100)–100–1000 IU, eight persons had levels of 10–100 IU. In two persons who had levels of 10 IU a fourth, booster, injection gave levels of 10 IU in one case and 100 IU in one case. Two persons had levels below 10 IU. The person who received two injections was also negative. Only 2/53 (3.7%) of the persons who received three injections were anti-HBs negative. A significant difference in response was thus shown to be present after the third injection in the staff group vs dialysis patients (49/53 persons vs 9/21 patients, $p< 0.001$, Chi-square test) (Table 2a).

In *anti-HBs positive patients ( group C)* a statistically significant difference was present among the anti-HBs levels of the controls vs the dialysis patients ($p<0.05$, Wilcoxon's rank sum test).

Twentyfive out of 45 healthy controls were positive in tests for IgG1, two for

Table 2b. Patients with reactivity and subclass reactivity to pneumococcal vaccine.

| Patients with reactivity to pneumococcal vaccine. Group D (n=29) | Increased levels 25 | Unchanged (high) levels 3 | Low levels 1 | |
|---|---|---|---|---|
| IgG subclass levels in controls (n=21) and patients (n=28) (AU) before vaccination to pneumococci (group E) (** = p<0.01) | IgG1<br>0.3±0.14<br>0.2±0.07** | IgG2<br>1.05±0.67<br>0.6±0.3** | IgG3<br>0.17±0.1<br>0.15±0.07 | IgG4<br>0.12±0.01<br>0.11±0.01 |
| IgG subclass levels in patients (AU) (n=28) before and after vaccination in group E (* = p<0.05, *** = p<0.001) | 0.2±0.07<br>0.45±0.3*** | 0.6±0.3<br>2.04±1.02*** | 0.15±0.07<br>0.25±0.24* | 0.11±0.01<br>0.13±0.02*** |
| Number of responders to pneumococcal vaccination in each subclass. Group E (n=28) | IgG1<br>19 | IgG2<br>23 | IgG3<br>13 | IgG4<br>3 |

IgG2, four for IgG3 and five for IgG4. IgG1 was the most abundant subclass ($p< 0.001$, Chi-Square test) in healthy adults. In dialysis patients three patients were positive for IgG1, one for IgG2 and none for IgG3 or IgG4 (Table 2a).

Neither a difference among the different IgG subclasses in dialysis patients (Fischer´s exact test), nor among the classes of controls vs those of dialysis patients, was observed (Chi Square test).

The absorbances of positive tests for IgG1 and IgG2 were low (between cut off and 1.0) in dialysis patients, while healthy controls had low (cut off to 1.0) or intermediate (1.0–2.0) levels in all cases but one (an IgG1 with an absorbance of 2.8).

*Group D ( hemodialysis patients vaccinated to pneumococci)*

An antibody response equal to or increased by more than 50 % was seen in 25 patients.In three cases conditions were unchanged (high levels before and after vaccination).In one patient antibody levels remained low before and after vaccination (Table 2b).

*Group E (hemodialysis patients vaccinated to pneumococci and staff)*. In both patients and staff antibodies to pneumococci occurred in all IgG-subclasses. The controls were not vaccinated measuring naturally occurring antibodies to pneumococci only.

The mean anti-pneumococcal IgG2 level of unvaccinated controls was 8 ± 5.6mg/L. In patients the mean prevaccinated level was 4.4±2.5 mg/L and the mean post-vaccination level was 16.4±9.1 mg/L. A standard curve according to optical density in arbitrary units was constructed för all IgG-subclass antibodies to pneumococci. The test results are shown in Table 2b.

The antibody levels of IgG1 and IgG2 were higher in staff than in patients (IgG1 0.3±0.14 arbitrary units (AU) in staff and 0.2±0.07 AU in patients ($p<0.01$, Student's t-test); IgG2 1.05±0.67 AU in staff and 0.61±0.3 AU in patients ($p<0.01$)) before vaccination. In patients prevaccination antibody levels of IgG2 were higher than IgG1 ($p<0.0001$). IgG2 levels were also highly significantly higher than IgG3 and IgG4 ($p<0.0001$). The levels of IgG1 were higher than those of IgG4 ($p<0.05$). The IgG2 and IgG1 responses were thus the most prominent ones.

In hemodialysis patients 23/28 patients (82%) had an increase of OD for IgG2 of more than 50% after vaccination. In the case of IgG2 the OD was doubbled or more for all responders.

In IgG1 19/28 patients (68%) had more than 50% increase of the OD level. 13/28 patients (46%) had a doubling of the OD level or more for this subclass. In IgG3 a 50 (100) % increase of the OD level was seen in 13/28 patients (46%) while only 3/28 patients (11%) esponded with IgG4-antibodies (50% increase of the OD-level). The number of patients reacting with IgG2 antibodies was significantly higher ($p<0.01$ ) than the number reacting with IgG3 and IgG4 antibodies (chi-square test) (Table 2b). Postvaccination antibody levels were higher than prevaccination anti-

body levels for all subclasses in the patients ( n=28) $p < 0.001$ for IgG1, IgG2 and IgG4, $p < 0.05$ for IgG3 (Table 2b).

## DISCUSSION

Only one of the 23 HBV carriers who had been cared for at the unit from 1970–2001 was alive by the end of the year 2001.

The efficacy of the vaccination program, and the hygienic precautions used in the dialysis unit, in the early part of the period with a separate unit for HBV carriers, are demonstrated by the absence of new cases of hepatitis B from 1980 and onwards.The importance of such measures is indicated by the presence of acute liver disease as a possible concomitant (secondary) cause of death in four of the 23 patients affected by hepatitis B and the occurence of a late liver cirrhosis in the fourth patient who was transplanted and died in 2001 (patient n:o 22) (Table 1). Also the occurrence of other blood-born diseases as hepatitis C in our unit made hygienic precautions necessary (15). The low survival rate among the infected patients is notable, but may be due to a worse prognosis for dialysis patients in the 1980ths than nowadays apart for the conditions stated above. Also the mortality of dialysis patients is still high (16).

The study has also shown an adequate response to pneumococcal vaccination in the majority of the patients studied, mainly due to IgG2 and IgG1 antibodies, but occurring in all subclasses, and a reduced response to hepatitis B vaccination in dialysis patients vs staff.

Dialysis patients are known to have a reduced response to hepatitis B vaccine and are recommended four vaccinations at the time schedule of 0, 1, 2 months and a fourth injection 6 months later (3). This schedule was used in our patients, but the efficacy was hampered by renal transplantation in 3 of the dialysis patients (group A), after which a fourth injection was not performed. In one patient in this group vaccination was cancelled due to bad health, while one patient was referred to another unit. Data concerning the fourth injection was missing in 8 patients, five of whom, however, underwent transplantation, which suggests that the fourth injection may have been given.

If vaccination is started too late, transplantation or bad health may thus hamper the fourth injection in some cases. This questions the adequacy of the vaccination schedule used, as transplantation (operation) in a larger transplantation center, where patients from different dialysis units are nursed, may be considered as a risk factor for hepatitis B.

In the patients vaccinated to hepatitis B the relatively high number of patients tested after the third (and not a fourth) injection (17/25) and the long time until blood samples were drawn (6–49 months) in the patients tested with Organon anti-HBs (9 patients), may have reduced the number of anti-HBs positive patients after vaccination.

The number of responders was higher in staff than in dialysis patients after the

third injection of hepatitis B vaccine. This is in accordance with earlier studies on hepatitis B vaccination in dialysis patients (1) and healthy adults (17). The number of patients vaccinated and tested after the fourth injection was considered too small for such a comparison but the response of dialysis patients was low (4/8, 50%). HD and CAPD patients had a similar ratio of response; 4/9 and 6/16 respectively had positive tests. The low level or negative responses found in the various IgG-subclasses of anti-HBs in dialysis patients may reflect the low total anti-HBs levels in this group. This may be due to B-cell mediated- as well as T-cell mediated- (reduced T-helper response) abnormalities (18). The dominance of IgG1 anti-HBs shown in healthy adults is consistent with the findings in the literature, where healthy adults, however, were shown to have mainly IgG1 and IgG3 responses or IgG1 and IgG2 responses (7, 8, 19). Protein antigens, e.g. viral proteins, are known to elicit mainly IgG1 and sometimes IgG3 responses, whereas IgG2 response is seen mainly to carbohydrate antigens (2, 6). Skvaril et al (8) demonstrated a predominant IgG1 response in individuals newly vaccinated against HBV, which also is consistent with our findings. Our findings also suggest that the inability of dialysis patients to respond adequately to HBV vaccination is due to a general anti-HBs IgG deficit rather than a restricted IgG subclass deficit. A more prominent IgG1 anti-HBs response would have been expected.The adequate response to pneumococcal vaccination in 86 % of our patients studied, which was shown to be due mainly to IgG1- (68 %) and IgG2- (82 %) responses to carbohydrate antigens, but with responders also in IgG3 (46%) and IgG4 (11%) (2, 20, 21), indicates however that the subclass response to the antigen involved may be of importance. The antibody levels of IgG1 and IgG2 were also higher in staff than in dialysis patients before vaccination.

Soininen et al (22) found the antibody response to pneumoccocal polysaccharide antigens mainly to be restricted to the IgG2 subclass.

Such a vaccination response may be of importance in the protection of invasive pneumococcal infections as pneumonia and bacteremia (septicemia) (23). It has also been used in the protection of infants against otitis media (24).The risk of acquiring hepatitis B is very low in Sweden (17, 25). Despite this, hospital staff is recommended hepatitis B vaccination (25). Dialysis patients in Sweden are probably not at the same risk as in many other countries, but transmission of HBV may occur (26, 27).

Moreover patients not responding to the vaccine or those with an unaccomplished vaccination schedule, without anti-HBs response, may benefit from vaccination, as a milder hepatitis may occur if they are infected (27).

Other factors than B-cell-mediated mechanisms, e.g. T-cell and cytokine reactions, may be important for such vaccination responses (28).

The poor response to vaccination in dialysis patients may be related to different factors connected to the immunodeficiency of uremia (2, 29). It is, however, notable that our dialysis patients vaccinated to hepatitis B were older than our staff ($p < 0.001$, Student's t-test), which might have affected the response to vaccination. Walz et al (18) found age to be unrelated to the response to vaccination.

The inconveniences of the patients (the risk of allergic reactions and other adverse effects as fatigue and myalgia) and the low risk of acquiring hepatitis B in Sweden (less than 10 cases/100 000 inhabitants per year 1990–94) (17) questions the necessity of hepatitis B vaccination in Swedish dialysis patients. So do the low rate of success, the low levels of response shown by us and others as well as a low persistence in time of antibodies in low level antibody responders (30) and the expense of such programs. Renal patients have been shown to have a low persistence of antibodies also with vaccine to pneumococci (31). Docci et al (32) found an acceptable persistence of antibodies with a recombinant hepatitis B vaccine in dialysis patients with 85% of the responders still positive after 18 months. The response to pneumococcal vaccination seen in our patients may however reflect a better vaccination-response to carbohydrate antigens than to protein antigens in dialysis patients.

The risk of developing chronic persistent hepatitis B is known to be high after renal transplantation if transmission occurs (33). Transmission of hepatitis B in dialysis units has been shown to occur also in Sweden in recent years (27). The ratio of hepatitis B in hemodialysis units in a few other countries in Europe, as well as in more distant countries, has been demonstrated to be a considerable risk and has to be considered in patients who travel and have dialysis abroad (34).

Future vaccination schedules may include anti-HBs determination, a fifth (booster) dose in some cases, e.g. patients who travel much, as well as new types of recombinant vaccine (35, 36). Determination of anti-HBs with longer follow-up, e.g. three months after vaccination, may show a better vaccination response than the one seen in our patients 3–5 weeks after the third to fourth injection. The efficiency of an earlier fourth injection, e.g. at three months to precede renal transplantation, might be studied further. Vaccination schedules in potential renal transplant recipients should be started as early as possible as transplantation or bad health might hamper the fourth injection. Also liver disease, due to hepatitis B, is a well known complication affecting morbidity and mortality in renal transplant recipients (37). Erythropoetin might enhance the vaccination response and should be used whenever needed (38). The HLA-haplotype present in the patient population may affect antibody responses and could possibly explain variations in the response rate in different patient populations where the same dosing schedule is employed (39). Hygienic precautions may be of the same importance as vaccination in preventing the spread of hepatitis B in dialysis units (40). A reduced response to hepatitis B vaccination has been shown to be associated with high mortality and morbidity in dialysis patients, e.g. due to malnutrition in the non-responding category (41). In a worldwide perspective hepatitis B vaccination has been shown to reduce the frequency not only of hepatitis B but also of hepatocellular carcinoma (42, 43).

The adequate antibody response to pneumococcal vaccination mainly due to IgG2 and IgG1 indicates that the antigen involved is important in vaccination responses in dialysis patients.

The mechanisms of the reduced response to vaccinations in dialysis patients, in

our study affecting all IgG subclasses of hepatitis B vaccinated patients, should be studied further.


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*Address correspondence to:* G Almroth, MD.
Department of Nephrology
University Hospital of Linköping
S-581 85 Linköping, Sweden.
Fax +4613224514,
Telephone +4613222000
E-mail: gabriel.almroth@lio.se