Efficacy of Pneumococcal Immunization in Patients with Renal Disease – What Is the Data?

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Key Words

Nephrotic syndrome · Pneumococcal immunization · Pneumococcal immunization, adverse reactions · Renal disease transplant, pneumococcal vaccine · Renal allograft recipients

Abstract

Background/Aims: There is an increased incidence of invasive pneumococcal disease in patients with renal allografts, chronic renal insufficiency (CRI), or nephrotic syndrome (NS). Routine pneumococcal immunization (PI) has been recommended for these patients, but the efficacy of PI in this population is not well established.

Methods: A review was done of studies that reported the immunologic response, efficacy, or safety of PI in patients with renal allografts, CRI, or NS. **Results:** On review of 26 published studies of PI in this population, all studies demonstrated a serologic response by the majority of patients to at least some pneumococcal serotypes. Use of steroids did not alter this response. In the studies with a greater than 6-month follow-up, declining antibody titers were consistently reported, and this decline was usually more rapid than in healthy controls. However, because the studies of the efficacy of PI in this population involve small numbers of patients and are not

controlled, the significance of this decline in titers is not known. The incidence of serious adverse reactions to PI is very low. **Conclusion:** Pending more data, patients with renal transplants, CRI, or NS should continue to be offered PI.

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Invasive pneumococcal disease (IPD) is defined as isolation of *Pneumococcus* from a normally sterile body site [1]. There is an increased risk of IPD in children and adults with renal allografts, chronic renal insufficiency (CRI), or nephrotic syndrome (NS) [2]. The magnitude of this increased risk has not been quantified, but in a study of 556 Navajo adults with IPD, 11.5% had CRI [1], with the risk of IPD presumed to be even higher in patients with NS [2]. Common presentations of IPD in patients with CRI or transplants are bacteremia with no focus or pneumonia. Patients with NS commonly seed their ascitic fluid while bacteremic, and present with peritonitis [2].

Pneumococcal disease is preceded by colonization of the nasopharynx [3]. Disease occurs if organisms are carried from the nasopharynx to normally sterile body sites, and replicate in these sites. This process is prevented if serotype-specific anticapsular antibody is present, opsonophagocytosis occurs, and the spleen is able to clear the

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opsonized particles [3]. Contributing factors to IPD in patients with renal disease include impaired leukocyte function in patients with CRI, immunosuppressive drugs in recipients of renal transplants, and hypogammaglobulinemia, urinary loss of factors B and D of the alternate complement pathway, impaired leukocyte and splenic function, and immunosuppressive drugs in patients with NS [4].

Possible options for prophylaxis of IPD include antibiotics, passive immunization, and active immunization. The risk of IPD is not sufficiently high in patients with renal disease to justify the routine use of prophylactic antibiotics, and the increasing incidence of antibiotic-resistant pneumococci over the past decade has undoubtedly decreased the efficacy of this option. It has been suggested that prophylactic antibiotics be considered in children with new-onset NS who are less than 2 years of age, have relapsing or steroid-resistant NS, or have already had IPD [4], but this option has not been studied, and differs from published guidelines. Passive immunization with intravenous immune globulin is a very expensive option that has also not been studied. With regard to active immunization, polysaccharide pneumococcal vaccines (PPV) have been available for decades. There are 90 known serotypes of *Pneumococcus* [5]. Pneumovax (Merck & Co. Inc., West Point, Pa., USA), a widely used PPV, contains the 23 pneumococcal serotypes most commonly associated with IPD (Danish serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F), and replaced the 14-valent vaccine in 1983. Protein-conjugated pneumococcal (PCV) vaccines are much more immunogenic than PPV in healthy children under 2 years of age as they induce a T-cell-dependent response with immunological memory and increased antibody avidity [6], but there is limited data on their immunogenicity in other populations. The PCV that is currently licensed in Canada and the US (Prevnar, Wyeth-Ayerst, Philadelphia, Pa., USA) is conjugated to a genetically engineered diphtheria protein (CRM 197), and contains 7 pneumococcal serotypes (Danish serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F). These serotypes account for about 80% of IPD in children and 50% of IPD in adults in the US [5].

The purpose of this review is to summarize studies of the immunogenicity and efficacy of pneumococcal vaccines in patients with renal allografts, CRI, or NS. The barriers to interpreting the studies include the following:

(1) Most studies of pneumococcal immunization in renal patients were done prior to 1985, and pneumococcal antibody titers were generally measured using a radioim-

munoassay (RIA). This assay cannot distinguish between antibodies to the common pneumococcal cell wall C-polysaccharide (which are not protective against IPD) and protective antibodies to type-specific pneumococcal capsular polysaccharide [7]. The absolute numbers obtained by the RIA differed from one study to another [8–10] and from one time period to another within a study [11] because of lack of standardization of this assay. A serotype-specific enzyme-linked immunoabsorbent assay (ELISA) is now available, which is superior to the RIA as it measures only protective antibodies to the pneumococcal capsular polysaccharide [3]. However, a protective titer is not yet firmly established for the ELISA (although 0.20 µg/ml has been suggested [6]) and may even differ for different serotypes.

(2) Opsonization must occur for an antibody to be effective. The capacity for pneumococcal IgG to opsonize pneumococci for phagocytosis varies [3]. Therefore, functional opsonization assays would provide the best information regarding protective antibody titers, but these assays are currently not well standardized [6].

(3) In assessing the response of a patient to pneumococcal immunization, it is not clear if the rise attained in antibody titers or the absolute value attained is of greater importance, and some studies report only one or the other. It is not clear if titers obtained following immunization are equivalent to titers attained following natural disease. In assessing the durability of immunity, it is not clear if loss of antibodies always indicates loss of immunity, or if there sometimes is an anamnestic response.

Methods

A search was done of the English-language literature from 1966 to the present. Studies where patients with renal allografts, CRI, or NS were immunized with a pneumococcal vaccine were included, but studies that were presented only in abstract form were excluded. Studies or case reports that described possible adverse events related to pneumococcal vaccine in renal patients were noted. The bibliographies of relevant articles were also searched.

Results

Renal Allograft Recipients

There are 11 published studies where renal transplant patients were given PPV and had follow-up serology (table 1). Only one study definitely included patients who were less than 15 years of age [7]. Although different assays and protective titers were used to assess the

Table 1. Response of renal allograft recipients to pneumococcal capsular polysaccharide vaccine

Author (ref.), year, type of PPV	Number and type of renal transplant patients immunized	Response to immunization	Follow-up serology
Silberman [12], 1979, 14-valent	27 adults 7–108 months post-transplant (2 with asplenia)	Percentage of patients with a 4-fold increase in titer was equivalent to 24 healthy adults for 12/13 serotypes	NR
Marrie & Bortolussi [9], 1981, 14-valent	63 patients 3–99 months post-transplant	Mean 2.8-fold increase in titer, versus 3.4-fold for 8 healthcare workers Opsonization to types 3 and 6B was equivalent in cases and controls	GMT in cases 872 post-immunization and 659 at 12 months
Cosio [14], 1981, 14-valent	25 patients ≥ 15 years old and 3–118 months post-transplant (14 with asplenia)	55% of patients with a spleen, 78% of asplenic patients, and 93% of 14 healthy adults achieved a protective titer and a 2-fold increase in titer	NR
Linnemann [8, 15], 1981, 1986, 14-valent	104 adults on < 60 mg/day prednisone with stable renal function	93% achieved a protective titer and a 1.4-fold increase in titer	GMT in cases 440 post-immunization and 385 at 24 months, then increased to 536 with reimmunization of 33 cases
Arnold [16], 1985, 14-valent	75 adults > 1 year post-transplant with serum creatinine < 3 mg/dl (32 with asplenia)	59% developed opsonizing antibody and a 2-fold increase in titer for > 6 months to serotype 12F, and 76% to serotype 14F	NR
Nikoskelainen [17], 1985	17 adults	Higher IgM but lower IgG and IgA titers than in 33 healthy adults	Follow-up titers at 1 year lower than in controls
Rytel [11], 1986, 14-valent	61 patients > 6 months post-transplant (57 with asplenia)	Trend towards lower antibody titers than in 9 healthy adults and 10 adults with chronic disease, but equivalent number achieved a protective titer	Rate of decline in antibody levels was equivalent to that in healthy controls at 1, 2, and 3.5 years
Furth [7], 1996, 23-valent	41 children (17 with transplants, 24 CRD)*	93% achieved a protective titer for serotype 3, and 76% for serotype 14 76% achieved a 2-fold increase in titer for serotype 3 and 61% for serotype 14	93% maintained a protective titer for serotype 3 at 12 months, and 59% for serotype 14
Fuchshuber [18], 1996, 23-valent	7 patients a mean of 22 months post-transplant with an antibody titer < 200 **	88% achieved a protective titer and a 2-fold increase in titer	57% still had a protective titer and a 2-fold increase in titer from pre-immunization at 6 months, and 43% at 12 months
Kazancioglu [19], 2000, 23-valent	21 adults > 2 months post-transplant with no anti-rejection therapy in preceding 2 months	All but 1 patient had a response***	NR
Kumar [20], 2003, 23-valent	30 adults 3 months to 3 years post-transplant with a spleen, a serum creatinine < 2.8 mg/dl, and no pneumococcal vaccine in previous 5 years	Most pre-immunization titers protective, so a 2-fold increase occurred for a median of 1/7 serotypes 83% had a response to at least 1 serotype by opsonophagocytic assay	NR

* Data not analyzed separately for transplant patients; ** units not specified; *** not clear if they achieved a protective titer, a 1.4-fold rise in titers, or both.

CRD = Chronic renal disease; GMT = geometric mean titer in nanograms antibody nitrogen/ml (calculated using all serotypes that were analyzed); NR = not reported; PPV = pneumococcal capsular polysaccharide vaccine.

response to immunization, patients had a serologic response to the majority of serotypes measured with the exception of one study where even controls often did not attain protective titers to most serotypes with the assay that was used [11], and one study where the majority of

patients had protective titers pre-immunization [20]. In four of the five studies that included a control group [11–14, 17], post-immunization titers were lower in renal allograft recipients, but the difference was usually only statistically significant for individual serotypes. Follow-up se-

rology was performed in six of the studies 1–3.5 years later [7, 11, 13, 15, 17, 18], with two of these studies also having follow-up data on controls [11, 17]. There was always a drop in antibody titers in the renal allograft recipients at follow-up. The follow-up titers were lower than in controls in one study [17], but it was noted that the rate of decline in titers was equivalent to controls in the other study [11].

Asplenia was associated with a poorer response to PPV in two studies [8, 11], an improved response in one study [12], and an equivalent response in another study [11]. There was no relationship between the age of the graft and the response to PPV [8, 11, 14, 16, 17]. Poor renal function seemed to impair the response to PPV in one study [11] but not in another [8]. No relationship was found between the age of the patient [16, 17] or the dose [8] or number [19] of immunosuppressive drugs and the response to PPV.

There is only one published study comparing PPV to PCV in renal allograft recipients (adults only) [20]. Although the antibody response as measured by ELISA was better with PCV than with PPV for all except serotype 14, the difference was only statistically significant for serotype 23 F. There were no differences for the functional opsonization assays.

Only one of the studies reported vaccine efficacy, with 2 of the 104 transplant patients immunized with 14-valent PPV developing IPD over 5 years [15]. However, the incidence of IPD in all the renal transplant patients in their program dropped from 28.4/1,000 patient years to 2.3/1,000 patient years ($p < 0.01$) once they introduced routine pneumococcal immunization with boosters every 2 years [15].

Chronic Renal Insufficiency with or without the Need for Dialysis

In the nine published studies where adults or children with CRI were given PPV and had follow-up serology, over half the patients had a serologic response to the majority of serotypes (table 2). Antibody titers tended to be lower in CRI patients than in controls at baseline [11, 18, 21]. Responses were less robust than were those of controls in four studies [11, 14, 17, 21], but the differences were not always statistically significant. In a fourth study with controls, response was reported to be equivalent to controls [22] but no data was presented. Follow-up serology was obtained 6 months to 3.5 years later in six of the studies [7, 11, 15, 17, 18, 21]. The titers in patients with CRI continued to rise between 1 and 6 months post-immunization in one study [21], were stable at 12 months

in another study [7], and declined by 6 months in a third study [18]. Antibody titers in patients on hemodialysis showed a marked decline at 1 year [17] and 2 years [15] post-immunization, with less of a decline in patients with CRI who were not on dialysis [17]. Another study showed that the rate of decline in antibody titers was greater in the CRI patients than in either transplant patients or a control group at 1, 2, and 3.5 years [11].

Patients were followed for 5 years in one study, and seven of the 33 CRI patients immunized with 14-valent PPV developed IPD, which is a much higher incidence than in renal allograft recipients in the same study [15]. Another study of the efficacy of PPV in preventing IPD in all high-risk populations found approximately 27% efficacy in patients with CRI, but the confidence intervals were very wide (–152% to 78%) as the number of CRI patients was small [24].

Pneumococcal immunization prior to transplantation is often considered in patients with CRI [25]. Two studies found that patients with CRI responded better to PPV than did patients with renal transplants [14, 15], but two others found the opposite [11, 17]. There are no published studies on the response to PCV in CRI patients.

Nephrotic Syndrome

In the six published studies where patients with NS were given PPV and had follow-up serology, age range was from 2 to 20 years (table 3). Three of the four studies that included a control group showed an excellent serologic response to PPV in children with NS that was comparable to that in controls [27, 29, 31]. The fourth study showed equivalent IgM production in the children with NS, but decreased IgG production to one of only two serotypes analyzed [30]. Although the number of patients was small in all studies, it appeared that use of corticosteroids [26, 31] or dose of corticosteroids [10, 31] did not alter the response to PPV, or decreased the response to a single serotype only [28]. One study that divided patients into subgroups based on their type of NS found that the 5 patients with NS that was not steroid-responsive had a very poor response to PPV, despite no mention of use of other immunosuppressive agents [28], but another study found no difference in children with NS that was not steroid-responsive [31]. One study reported that 2 children on cyclophosphamide and chlorambucil respectively did not respond to PPV [28], and none of the other studies reported data separately for children on immunosuppressive agents other than corticosteroids. Two studies had long-term follow-up, with one reporting that 78% of patients maintained a response to PPV for 6 months, and

Table 2. Response of patients with chronic renal disease (with or without dialysis) to pneumococcal capsular polysaccharide vaccine

Author (ref.), year, type of PPV	Number and type of patients immunized	Response to immunization	Follow-up serology
Simberkoff [21], 1980, 14-valent	21 adults (HD)	Protective titer achieved for 10/11 serotypes and mean 2.7-fold increase in titer achieved versus 3.3-fold for 21 healthy adults 50% of cases had opsonic titer for serotype 1 versus 56% of controls, and 36% of cases had opsonic titer for serotype 3 versus 82% of controls ⁺	GMT in cases 364 post-immunization and 499 at 6 months GMT in controls 851 post-immunization and 763 at 6 months
Friedman [22], 1980, 14-valent	18 adults (8 CRI, 10 HD)	Equivalent response to 5 healthy adults	NR
Cosio [14], 1981, 14-valent	21 adults (7 CRF, 14 HD)	a) CRI – 43% achieved a protective titer and a 2-fold increase in titer, versus 93% of 14 healthy adults b) HD – 79% achieved a protective titer and a 2-fold increase in titer	NR
Linnemann [8, 15], 1981, 1986, 14-valent	33 adults (HD)	88% achieved a protective titer and a 1.4-fold increase in titer	GMT in cases 592 post-immunization and 215 at 24 months, then increased to 757 after reimmunization of 17 patients
Nikoskelainen [17], 1985, 14-valent	50 adults (29 CRI, 11 HD)	Increase in IgA, IgG, and IgM titers, but post-immunization titers in HD patients all lower than in CRI patients or in 33 healthy adults	At 12 months, faster decline in HD patients than in controls, CRI patients, or renal transplant patients with some titers in HD patients being lower than pre-immunization
Rytel [11], 1986, 14-valent	23 adults on HD (4 with asplenia)	Rise in titers similar to controls (9 healthy adults and 10 adults with chronic disease), but lower GMT for 12/12 serotypes than in controls	Faster decline than in controls or transplant patients at 1, 2, and 3.5 years
Fuchshuber [18], 1996, 23-valent	11 patients with CRI, 7 on HD, and 6 on PD with antibody titer <200 ⁺⁺	91% with CRI, 71% on HD, and 83% on PD had a protective titer and a 2-fold increase in titer	At 6 months, 73% with CRI, 43% on HD, and 83% on PD still had a protective titer and a 2-fold increase in titer At 12 months, 55% with CRI, 43% on HD, and 33% on PD still had a protective titer and a 2-fold increase in titer
Furth [7], 1996, 23-valent	41 children (14 CRI, 10HD, 17 renal transplants) ⁺⁺⁺	93% achieved a protective titer for serotype 3, and 76% for serotype 14 76% achieved a 2-fold increase in titer for serotype 3 and 61% for serotype 14	93% maintained a protective titer for serotype 3 at 12 months, and 59% for serotype 14
Laube [23], 2002, 23-valent	16 children with CRD	All had a rise in titers	NR

⁺ Statistically significantly lower than controls ($p < 0.05$); ⁺⁺ units not specified; ⁺⁺⁺ data not analyzed separately for CRI and HD patients.

CRD = Chronic renal disease; CRI = chronic renal insufficiency (not on dialysis); GMT = geometric mean titer in nanograms antibody nitrogen/ml (calculated using all serotypes that were analyzed); HD = hemodialysis; NR = not reported; PD = peritoneal dialysis; PPV = pneumococcal capsular polysaccharide vaccine.

56% for 12 months [18]. The other study reported that all 9 patients with minimal change NS maintained presumptive protective titers to 12 serotypes after 5 years, but the 9 patients with other types of NS did not [27].

In analyzing the efficacy of PPV in NS, it was reported that 2 of 19 children developed IPD over a 10-month period (1 with serotype 4, which is contained in the vaccine, and 1 with serotype 19A, which is not) [32]. In another

study, 16 patients with NS were followed for 5 years after receiving PPV, and 1 developed IPD, versus 8 of 20 other NS patients who were not immunized with PPV ($p < 0.05$) [27]. There are no published studies on the serologic response to PCV in patients with NS.

Table 3. Response of patients with nephrotic syndrome to pneumococcal capsular polysaccharide vaccine

Author (ref.), year, PPV used	Number of patients immunized and type of NS	Use of steroids	Response to immunization	Follow-up serology
Fikrig [26] and Tejani [27], 1978, 1984, 13-valent	21 children – 12 MCNS and 9 others	Some patients were on steroids – no details provided	Equivalent to 23 healthy children	9 patients with MCNS all had GMT > 300 at 5 years 7 patients with other forms of NS all had GMT < 300
Spika [28, 29], 1982, 1986, 14-valent	32 children: a) 13 steroid-responsive and in remission, but still on steroids b) 12 steroid-responsive and in remission off steroids c) 2 steroid-responsive but received cyclophosphamide or chlorambucil in previous month d) 5 steroid-resistant and not in remission (all FGSC)	13 patients on steroids	Response rate (defined as protective titer and a 2-fold increase in titer): a) 93% b) 83% c) 0% d) 20%	At 12 months, the 27 patients with steroid-responsive NS had a mean decline in GMT of 2.4% per month in cases with no relapses, and 5.3% in cases with relapses Percentage of patients with protective titer higher for all 12 serotypes in patients with no relapses
Wilkes [10], 1982, 14-valent	20 children with steroid-responsive NS in remission No biopsies done	5 patients on 1–2 mg/kg/day prednisone and 15 patients on alternate day prednisone	4.1- to 23.4-fold increase in titers for different serotypes (mean 8.4-fold increase)	NR
Garin [30], 1988, 14-valent or 23-valent	11 children with steroid-resistant NS in relapse On no immunosuppressive drugs	None for 10–26 months	Good IgM and IgG responses to serotypes 3, and good IgM but poor IgG response to serotype 19* 15 healthy adults had good IgM and IgG responses to both serotypes	NR
Lee [31], 1995, 23-valent	48 children with NS	Some patients were on steroids – no details provided	Mean 3.0-fold increase titers in cases, versus 2.6-fold increase in 21 healthy children	NR
Fuchshuber [18], 1996, 23-valent	9 patients with steroid-responsive NS in remission and antibody titer <200**	4 patients were on steroids or cyclosporine	89% achieved a protective titer and a 2-fold increase in titer	78% still had a protective titer and a 2-fold increase in titer at 6 months, and 56% at 12 months 3 patients with low titers were then reimmunized, and 67% achieved a protective titer and a 2-fold increase in titer, but none maintained this response 6 months after the second immunization

* Statistically significantly lower than controls ($p < 0.05$); ** units not specified.

FGSC = Focal glomerulosclerosis; GMT = geometric mean titer in nanograms antibody nitrogen/ml (calculated using all serotypes that were analyzed); MCNS = minimal change nephrotic syndrome; NR = not reported; NS = nephrotic syndrome; PPV = pneumococcal capsular polysaccharide vaccine.

Response to Reimmunization

Reimmunization of patients with renal allografts or CRD with PPV resulted in higher geometric mean titers than with the first immunization [15]. However, response was poor when patients with renal allografts, CRI, or NS and a poor immunologic response 12 months after the first dose of PPV were reimmunized [18].

Adverse Events Related to Pneumococcal Immunization

Serious adverse reactions such as anaphylaxis are very rare with pneumococcal immunization in renal patients, or in any other patient group. Local reactions are common with reimmunization with PPV in all patient groups, especially if the interval is short. However, one small study found a 25% incidence of local reactions in children

with NS who had not received previous PPV [33], with rates of 3–50% being reported in adults receiving their first dose of PPV [34]. There are single case reports of NS [35] and crescentic glomerulonephritis [36] in adults that may have been precipitated by PPV, but there is otherwise no evidence that pneumococcal immunization has any effect on renal function. There is no published data supporting an association between immunization and rejection in renal allograft recipients [37].

Discussion

There is no evidence of significant adverse events when pneumococcal vaccines are given to patients with renal allografts, CRI, or NS. There is insufficient data to be certain about the efficacy of PPV or PCV in these patients. However, it appears that the majority of patients will have a serologic response to at least some of the serotypes contained in the vaccine. Use of corticosteroids has no consistent effect on this response. It is unfortunate that most studies of pneumococcal immunization in renal allograft recipients were done prior to 1990, and few of the children with NS in previous studies were on non-steroid regimens, as modern immunosuppressive regimens may alter the chance of these patients responding to PPV.

The decline in pneumococcal antibody titers appears to be more rapid in patients with renal disease (especially those on hemodialysis) [17, 18] than in healthy patients, and can even occur in the first year after PPV [18, 19]. Reimmunization is likely indicated, but there is no data showing what interval is ideal. There is insufficient evidence to determine if PCV offers any advantages over PPV, and if there are advantages in giving both vaccines as there is only one study published to date that analyzed the response to PCV in this population [20]. Further studies of PCV need to be done in all ages of patients with renal allografts, CRI, and NS.

The American Academy of Pediatrics recommends that all children who have received renal transplants, have CRI, or have NS receive PCV as appropriate for age if they are ≤ 24 months of age, receive 2 doses of PCV if they are 24–59 months of age, and possibly receive a single dose of PCV if they are older than 59 months of age [38]. They should also all receive a single dose of PPV if they are at least 24 months of age, with a single booster 3–5 years later if they were ≤ 5 years old when they received the first dose [38]. Immunizations should be given prior to a renal transplant where possible, or resumed a

minimum of 6 months post-transplant [25]. The Advisory Committee on Immunization Practices (ACIP) guideline differs in that it recommends a single booster with PPV after ≥ 5 years in all adults or children who received their first dose of PPV after 10 years of age and have renal allografts, have CRI, or have NS, and a single booster after 3 years if they received the first dose of PPV prior to 10 years of age [39]. The Canadian National Advisory Committee on Immunizations recommends the booster dose of PPV after 3–5 years only if the patients were < 10 years of age when they received PPV, or are renal allograft recipients [40]. The minor discrepancies concerning reimmunization in these three guidelines do not appear to be evidence-based. Guidelines for other countries do not appear to have been published. Despite the fact that renal disease has been an indication for pneumococcal immunization in ACIP guidelines since 1989, pneumococcal immunization was recommended for allograft recipients by only 59% of North American pediatric renal transplant programs surveyed in a 1997 study [41], and for new-onset NS in 52% of respondents to the Pediatric Nephrology Forum Bulletin in a 1998 study [4]. A 1994 survey of North American nephrologists found that half withheld all immunizations in children with NS until they were in remission and off steroids [42]. Pneumococcal immunization was recommended for children on dialysis in 64% of programs and for children with CRI in 58% of programs in a 1994 study [42]. A 2000 survey of patients in chronic dialysis programs in the USA estimated that only 27% of patients had received pneumococcal vaccine [43]. Further efforts need to be expended in determining the reasons for this discrepancy between guidelines and practice.

Acknowledgment

The author would like to acknowledge Gregory Tyrell, MD, who reviewed the manuscript.

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