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CHRONIC RENAL FAILURE

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Immunization in children with chronic renal failure

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Abstract Infections jeopardize children on immunosuppression after organ transplantation. Immunization is protective in healthy children. The aims of this study were to analyze the rate and efficacy of immunization in 62 children undergoing dialysis and renal transplantation (RTPL) between 1987 and 2000. The analysis was based on clinical findings, vaccination certificates, and measurement of specific serum antibodies. A member of the renal unit administered vaccinations. All 62 patients were immunized against diphtheria, tetanus, pertussis, poliomyelitis, measles, mumps, rubella, and hepatitis B. Since introduction in 1991 and 1995, 44 and 42 children were also vaccinated against influenza and *Hemophilus influenzae* type b, respectively. Of 16 patients with a negative history, 14 were given varicella vaccine; 16 children on peritoneal dialysis (PD) or with nephrotic syndrome were immunized against *Streptococcus pneumoniae*. All vaccinated patients had detectable serum antibodies against measles, mumps, rubella, varicella, hepatitis B, *H. influenzae*, and *S. pneumoniae*. There were 3 infections despite vaccination; 1 patient developed varicella after RTPL and 1 patient on PD had 2 episodes of peritonitis caused by *H. influenzae* and *S. pneumoniae*. In conclusion, monitoring and administration of the vaccines by the renal team enabled a high immunization rate. Whether vaccines, as documented by antibody titers, or by the low prevalence in the general population promoted the low prevalence of infections remains open, as there were at least a few vaccination failures.

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Introduction

The prevention of systemic viral and bacterial infections by effective vaccines represents an essential part of a pediatrician's work. This task is particularly important for those taking care of children with chronic renal failure (CRF) eventually undergoing renal transplantation (RTPL) with life-long immunosuppression. Recommendations for immunization in children with CRF follow the standard primary vaccine protocols. In addition, vaccination against varicella, influenza, and *Streptococcus pneumoniae* is advocated in pediatric transplant candidates [1, 2, 3, 4, 5, 6, 7]. Children with CRF have – in contrast to adult patients – no significant immune impairment, except in a few clinical conditions (e.g., nephrotic syndrome, systemic lupus erythematosus). Reduced serum immunoglobulin concentrations have been found in children on peritoneal dialysis (PD) [8, 9, 10, 11]. Standard vaccination schedules generally induce an antibody response in children with CRF [12, 13, 14, 15, 16, 17], although specific revaccination is recommended [17]. The completion of the vaccination program before RTPL is particularly important, as immunosuppressed infants and young children without specific protection – either after immunization or wild-type infection – are at high risk that benign childhood infections are severe and life threatening [12, 18]. Data on the implementation of the comprehensive vaccination schedule in children with CRF and RTPL are rare. We report the immunization rate and the prevalence of vaccine-preventable infectious diseases after an intensified vaccination program was introduced in our unit in 1987.

Patients and methods

Patients

Sixty-two children, 20 girls (32%) and 42 boys (68%), underwent renal replacement therapy between 1987 and 2000 at the Universi-

Table 1 Immunization protocol (*RTPL* renal transplantation)

Vaccination/ infection	Selection of patients	Schedule	Antibody response	Remarks
Diphtheria, tetanus, pertussis	All	2, 4, 6, 15 months; 5, 10 years	Not done	Since 1999 acellular pertussis vaccine
Poliomyelitis	All	2, 4, 6, 15 months; 5, 10 years	Not done	Before RTPL Sabin oral. After RTPL: Salk (including family members)
Measles, mumps, rubella	All	1st dose at 15–18 months, 2nd dose >1 month later	2 months after vaccination	Not after RTPL
Hepatitis B	All	3 doses within 6 months (0, 1, 6)	2 months after 3rd dose	4th or 5th dose if titer <100 IE /ml
Hepatitis A	Hepatitis C or liver disease	2 doses within 6 months	2 months after 2nd dose	
Varicella	Negative history of wild-type infection	1 dose	2 months after vaccination	Not after RTPL. 2nd dose if IgG negative after 1st vaccination
Influenza	All on transplant waiting list and after RTPL	1 annual dose in autumn	Not done	Introduction 1996: vaccine according to yearly up-to-date recommendation of Swiss Federal Office of Public Health
Hemophilus influenzae type b	All	2, 4, 6, 15 months (>24 months 1 dose)	2 months after 3rd dose	Introduction 1991. Only in patients <5 years
Streptococcus pneumoniae	Patients on peritoneal dialysis or with nephrotic syndrome	1 dose	2 months after vaccination	Vaccine: 23-valent polysaccharide antigens. Only in patients >2 years

ty Children's Hospital, Zurich. Median age at onset of renal replacement therapy and at RTPL was 10.2 years (range 0.5–20 years) and 11.3 years (range 2.0–23.1 years), respectively. The causes of end-stage renal failure were renal malformations, hereditary disorders, and acquired renal diseases in 21, 20, and 21 patients, respectively. Fifty-three children were dialyzed (25 PD, 28 hemodialysis). Of the 55 patients undergoing RTPL (16 live-related donors, 9 preemptive), 47 have a functioning graft after a median follow-up period of 5.0 years (range 1.0–12.0 years). Three patients died of heart failure.

Methods

A history of previous infections was available from the parents and the referring physicians. Administration of vaccinations was documented according to the vaccination certificate. The immunization protocol included the primary vaccine series as recommended for healthy children by the Swiss Federal Office of Public Health [4]. Additional vaccines included those against hepatitis B and A [19], varicella, influenza and *S. pneumoniae* (Table 1). Only inactivated vaccines were used after RTPL. Once a patient is referred to our unit, the renal team takes over the responsibility for the monitoring and administration of the vaccines. The vaccination status is assessed as part of the primary work-up and is reviewed at least once a year (generally in the autumn together with the administration of the annual influenza vaccine). Parents are strongly advised to have the patients' siblings completely vaccinated by their local physician, according to the standard primary vaccine recommendations.

Antibody response for selected vaccines (Table 1) was assessed either as the presence of specific IgG or by a titer (hepatitis B and *H. influenzae* type b). The following IgG titers have been considered to be long-term protective for healthy children: anti-hepatitis B surface (anti-HBs) >100 IE/ml [20]; *H. influenzae* type b >1.0 µg/ml [21]. The prevalence of vaccine-preventable infections was assessed on clinical findings. Culture (e.g., nasal swabs) or measurements of serum antibodies were performed to confirm the clinical diagnosis. The prevalence among the patients' siblings was assessed on history and reports from the local physician.

Triple immunosuppression after RTPL consisted of cyclosporine A (6–12 mg/kg body weight daily, whole-blood trough concentration 200–250 µg/l during the first 6 months, 100–150 µg/l thereafter), azathioprine (1 mg/kg daily) before 1998 or mycophenolate mofetil (1.2 g/m^2 body surface area daily), and prednisone (1 mg/kg daily). Prednisone was tapered and given on alternate days after 6 months (5 mg/m^2); it was completely withdrawn in 9 patients during the 2nd year after RTPL. Monoclonal or polyclonal antibodies were not used for induction therapy. Graft rejection was treated with methylprednisolone (0.5–1.0 g/1.73 m^2 daily i.v.) for 3 days. If the response was insufficient and renal biopsy confirmed severe rejection (Banff ≥grade II [22]), anti-thymocyte globulin (ATG, n=8) or monoclonal anti-CD3 antibody (OKT3, n=4) was added until 1996; thereafter, patients were switched from cyclosporine A to tacrolimus (0.25–0.3 mg/kg daily, n=13).

Results

Immunization rate

The immunization rate before RTPL is summarized in Table 2. All patients completed the standard vaccination series, including influenza (since 1996) and *H. influen-*

Table 2 Immunization rate, antibody response, and systemic infectious diseases in 62 patients

Vaccination/infection	Before RTPL			After RTPL
	Number immunized	Antibody response	Systemic infectious diseases	Systemic infectious diseases
Diphtheria, tetanus, pertussis	62	Not done	0	0
Poliomyelitis	62	Not done	0	0
Measles, mumps, rubella	62	62	0	0
Hepatitis B	62	62	0	0
Hepatitis A	8	8	0	0
Varicella	14	14	46	2
Influenza	44	Not done	?	?
Hemophilus influenzae type b	42	42	1	0
Streptococcus pneumoniae	16	16	1	0

zae type b (since 1991). Eight patients were also immunized against hepatitis A: 4 with hepatitis C infection and 4 with associated liver disease. Of 16 children without a history of varicella and without IgG, 14 were vaccinated against varicella. In addition, 16 patients either on PD or with nephrotic syndrome were vaccinated with the 23-valent (non-conjugate) vaccine against *S. pneumoniae*. There were no apparent side effects from the vaccines, except mild temperature and swelling at the injection site in some patients.

Antibody response

Specific serum IgG against measles, mumps, rubella, hepatitis A, varicella, and *S. pneumoniae* were detected in all vaccinated patients (Table 2). Sixty patients responded to three doses (dose 5 µg <10 years, 10 µg >10 years) of hepatitis B vaccine with an anti-HBs titer >100 IE/l; only 2 patients required a 4th and 5th vaccination, respectively. Antibody titers against *H. influenzae* type b – measured in all patients on PD – were >1.0 µg/ml.

Vaccination failures and prevalence of infectious diseases

Varicella

Two patients manifested mild varicella 8 months and 3 years, respectively, after RTPL. They were treated with i.v. acyclovir and transient reduction of immunosuppression. One patient had detectable serum IgG after vaccination 1 year before, but serum IgG was negative at the onset of disease. The other was 1 of the 2 patients who had "escaped" vaccination. Both developed serum anti-varicella IgG within 1 month of the disease. Forty-six patients had mild wild-type varicella before RTPL.

H. influenzae *type b and* S. pneumoniae

One patient with Denys-Drash syndrome had four episodes of peritonitis on PD. One episode was caused by *H. influenzae* type b despite a "protective" serum IgG titer (3.0 µg/ml) at the onset of disease; the IgG concentration in the dialysate was <0.2 µg/ml. A second peritonitis episode was caused by *S. pneumoniae* type b, despite a previous antibody response after vaccination. Two further infections were due to *H. influenzae* non-type b. Bacterial peritonitis in PD patients of our unit was mainly caused by *Staphylococcus aureus*, with a rate of 0.7 episodes per treatment year.

Influenza

From a clinical point of view, none of the patients developed a "flu-like" syndrome necessitating hospital admission. As serum antibodies and nasal swabs were not routinely performed, milder cases have been missed.

Prevalence of vaccine-preventable infectious diseases among siblings

Varicella was common, whereas other infections were not recorded. As the reporting was based on clinical findings, mild cases of, e.g., influenza or pertussis have been missed.

Discussion

We report the comprehensive implementation of the immunization protocol in a pediatric renal replacement program. All patients were vaccinated before RTPL against diphtheria, tetanus, pertussis, poliomyelitis, measles, mumps, rubella, hepatitis B, *H. influenzae* (since 1991), and influenza (annually since 1996). Most of the patients on PD or with nephrotic syndrome were also vaccinated against *S. pneumoniae*. Only 2 varicella-naïve patients "escaped" vaccination against varicella before RTPL.

The high immunization rate in our small single-center series contrasts with that of 80% or less reported in healthy children in the United States [23], Switzerland [24], and the local community [25]. Reasons for the high rate

were the fact that the renal team was responsible for the administration and surveillance, and repeated information on both the risks of systemic infections after RTPL and the potential protection induced by the available vaccines [12, 13, 14, 15, 16, 17, 18, 19, 20]. Children with CRF are often looked after by several physicians (e.g., general practitioner, pediatrician, nephrologist, urologist) and vaccinations might be overlooked as "minor" problems compared with growth, nutrition, dialysis, and social difficulties. Some parents also fear that vaccinations may aggravate CRF.

The low prevalence of vaccine-preventable infectious diseases in this series is based on two observations. Firstly, the low prevalence of these infections (except varicella) among healthy children (and the patients' siblings) in Switzerland [24], and secondly, the high immunization rate producing detectable serum antibodies. The proof of vaccine efficacy is the absence of disease, which can only be confirmed in large cohort studies, but not in individual patients. A few vaccinations failed in our series despite initial antibody production (varicella, *H. influenzae* type b, and *S. pneumoniae*). Antibody titers reflect the immediate immune response to a vaccine, but are only surrogate markers for potential long-term protection. Titers considered to be protective for healthy children may not prevent infections in children with CRF (e.g., peritonitis on PD) or immunosuppression after RTPL. Some children on PD have been shown to have hypogammaglobulinemia either due to loss of IgG in the dialysate or due to impaired IgG production [26, 27, 28].

Preventive strategies in children with CRF include repeated measurement of serum antibodies (e.g., varicella, *H. influenzae* type b, and *S. pneumoniae*) and appropriate revaccination if titers decline [17, 26, 27, 28]. In addition, the vaccination program of their siblings and household contacts should not only include the standard primary vaccines, but also influenza, varicella, *H. influenzae*, and *S. pneumoniae*. Continuous updating of the vaccination schedule is mandatory. Since 2001, the inactivated poliomyelitis vaccine has replaced the oral live vaccine, and the conjugate pneumococcal vaccine has been introduced for children less than 2 years of age. Whether live vaccines should be avoided or not after RTPL, is still under debate, but most centers do not recommend their use after RTPL [1, 2, 3, 4, 5, 6]. Unfortunately, vaccinations against cytomegalovirus and Epstein-Barr virus, the main causes of serious and life-threatening infections after RTPL, are not yet available.

In conclusion, we report a high immunization rate and a low prevalence of vaccine-preventable infectious diseases in children with CRF before and after RTPL. Monitoring of the vaccination program is part of the primary care of children with CRF.

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