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ORIGINAL ARTICLE

Lack of serologic immunity against vaccine-preventable diseases in children after thoracic transplantation

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Summary

We investigated whether children after heart- (HTx) or heart–lung transplantation (HLTx) show protective antibody levels against recommended vaccinations, whether vaccination schedules are completed and which factors influence serologic immunity. We performed a cross sectional ELISA – quantification of specific antibodies in 46 patients after pediatric thoracic Tx. Findings were correlated to vaccination history, age at Tx, clinical course and immunosuppressive regimen. We found protective antibody levels against diphtheria in 74% of patients, against tetanus in 22%, against *Haemophilus influenzae* type b in 30% and against *Streptococcus pneumoniae* in 59%. Antibody concentrations against live attenuated vaccines were significantly lower in children transplanted in the first 2 years of life. Antibodies were absent for measles in 55% of late – and 81% of early transplanted children, for mumps in 66%/94%, for rubella in 30%/56% and for *Varicella* in 34%/63%. We found significant correlation of low antibody concentrations and age at Tx. Patients without protective antibody concentrations had significantly longer use of steroids. Vaccination schedules were incomplete or delayed in the majority of patients associated with more days in hospital pre-Tx. Our study shows that closer adherence to pre-transplantation vaccination schedules and also post-transplantation monitoring of antibody levels are required in transplant patients.

Introduction

Heart transplantation (HTx) and heart–lung transplantation (HLTx) have become more common in children in the recent years. Outcome and long-term survival have markedly improved, enabling children to lead a fairly normal life. The threat of infectious disease, however, remains imminent. The immature pediatric immune system has to deal with a variety of infectious agents to which it is exposed for the first time. Because of this, and age-specific social and hygienic behaviour, the probability of acquisition of infections is higher [1]. Pediatric patients requiring thoracic transplantation are in a particularly dangerous situation. Prior to transplantation, the majority have a history of severe illness – sometimes for years and starting from birth – resulting from congenital heart disease or dilated cardiomyopathy [2,3]. This history frequently includes hospital stays with interventions requiring repeated mechanical ventilation and invasive treatments. It is easy to imagine that parts of general pediatric care such as vaccination can be missed or delayed in such severely ill children. It is therefore questionable whether the recommendation of the infectious disease societies to complete vaccination schedules prior

to transplantation can be accomplished in this patient group, especially as vaccination is considered a contraindication in advanced heart failure.

After transplantation, immunosuppression is required, therefore live attenuated vaccinations are not recommended because of the risk of symptomatic infection with the vaccine virus and severe sequelae [4,5]. Inactivated or recombinant vaccines can be administered, however, the efficacy of some vaccinations in terms of antibody development was found to be reduced [6,7]. Long-term persistence of protective antibodies and memory cells may also be impaired by immunosuppressive therapy [8]. In countries with no mandatory vaccination schedules, some vaccine-preventable diseases remain endemic or have become so, because of insufficient vaccination of parts of the population [9,10].

We investigated the serologic immunity towards vaccine-preventable diseases in our thoracic transplantation patients to determine whether they are in danger to acquire these infections when naturally exposed. We further sought to investigate the level to which the generally proposed vaccination schedules were completed in our patients prior to transplantation and determine the factors in patient history that may have affected serologic protection as well as individual vaccination policy.

Patients and methods

Following approval from institutional ethical review board, informed consent to participate in the study was obtained from parents and patients followed after pediatric HTx or HLTx. Patients were included in the study between June 2005 and June 2006 if they were at least 6 months post-transplantation and did not currently show evidence of rejection or receive rejection treatment. Patients treated with immunoglobulin preparations within 6 months prior to blood collection were excluded, as well as children with congenital immunodeficiency or total protein or immunoglobulin G levels below two standard deviations of normal value. Clinical and vaccination history was acquired from vaccination passports, clinical files, and personal communication. We documented age, age at transplantation, type of transplantation, underlying cardiopulmonary disease and further disorders. Regarding immunosuppressive regimen we analysed current and prior used drugs and doses as well as target trough levels if defined, days on steroid treatment and cumulative dose. We documented date, type and brand name of each applied vaccination and calculated the number of achieved doses for each component. History of infection with vaccine-preventable diseases was documented, as well as all episodes of clinical or biopsy-proven rejection.

The vaccination schedule for 2005 as recommended by the German national vaccination commission (STIKO) [11] is shown in Table 1.

Antibody levels were determined using commercial ELISA-kits following manufacturers' manuals: VaccZyme™ Tetanus-toxoid IgG, VaccZyme™ Diphtheria-toxoid IgG, for *Haemophilus influenzae* type b VaccZyme™ Hib IgG, for *Streptococcus pneumoniae* the VaccZyme™ PCP IgG ELISA-kit, detecting the capsular antigens of all 23 *S. pneumoniae* serotypes used in the polysaccharide vaccine, including all seven serotypes of the conjugate vaccine (all kits manufactured by The Binding Site GmbH, Schwetzingen, Germany). Antibodies against *Varicella zoster*, measles and mumps were tested using ELISA Kits (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany). Rubella antibodies were tested by hemagglutination inhibition test with human erythrocytes from Siemens Dade Behring.

As the literature reports no clear correlation of plasma antibody levels and probability of acquiring infection

Table 1. National recommendations for general vaccination in the period analysed as released by the STIKO in summer 2005 [11].

	Age (months)						
	3	4	5	12	24–72	60–84	Every 10 years
Tetanus	x	x	x	x		x	x
Diphtheria	x	x	x	x		x	x
Acellular pertussis	x	x	x	x		x	
Haemophilus influenzae b	x	x	x	x			
Poliomyelitis (SALK)	x	x	x	x			
Hepatitis B	x	x	x	x			
Measles				x	x		
Mumps				x	x		
Rubella				x	x		
Varicella	Indication or if no prior natural infection between 12 and 15 years						
Streptococcus pneumoniae	Indication (e.g. chronic lung disease, cystic fibrosis)						

[12,13], we did not determine the antibody response towards *Bordetella pertussis* antigens.

For live attenuated vaccines, no thresholds indicating safe immunity exist in the literature except for Rubella, but here the initially determined thresholds did not prove to be reliable [14]. Therefore, antibody levels were only compared regarding absence versus presence of specific antibodies.

The thresholds for safe, intermediate and unsafe immunity were taken from national recommendations, literature [6,13,15,16] and manufacturers guidelines (Table 2). These thresholds were determined based on observations in people with a healthy noncompromised immune system and therefore may not represent a state of actual safe immunity in a setting of immunosuppression. The categorization of patient groups into those transplanted at age below and above 2 years was founded on the fact that the basic immunization schedule including live attenuated vaccines should be completed by this age in healthy children.

Statistical analysis was performed using Sigma PLOT®/STAT® (Systat Software Inc., San Jose, CA, USA) and SPSS® (SPSS Inc., Chicago, IL, USA) with the help of a biostatistician. Quantitative values were analysed using Wilcoxon test for comparison of two groups and Kruskal–Wallis test for comparison of more than two groups. Qualitative parameters were compared using Fisher's exact test; correlations were determined using linear regression and Spearman correlation.

Results

Patient cohort

The demographic and clinical characteristics of the 46 patients included are shown in Table 3.

Serologic immunity towards inactivated vaccines

The percentages of patients presenting with antibody concentrations indicating safe, intermediate or unsafe immunity regarding infections preventable with inactivated vaccines are shown in Fig. 1.

We found no significant correlation of age at transplantation or sample collection and antibody concentration. The analysis of patients transplanted in the first 2 years of life compared with those transplanted after the second birthday showed no significant differences. The

Table 2. Threshold levels of antibody concentrations indicating unsafe, intermediate or safe protection for the different vaccine preventable diseases.

	Unsafe	Intermediate	Safe
Diphtheria (U/ml)	<0.01	0.01–0.1	>0.1
Tetanus (IU/ml)	<0.1	0.1–1.0	>1.0
Haemophilus influenzae b (μg/ml)	<0.1	0.1–1.0	>1.0
Streptococcus pneumoniae (μg/ml)	<21.6		>21.6

Table 3. Patient characteristics.

Type of transplantation	
Heart ABO compatible	35 (76%)
Heart ABO incompatible	3 (7%)
Heart–lung	8 (17%)
Age (median and range, years)	
At transplantation	6.71 (0.01–17.80)
At transplantation (HLTx)	9.49 (4.07–11.15)
At sample collection	13.6 (0.92–24.33)
Interval between transplantation and sample collection	
Median and range, years	4.8 (0.51–13.41)
Transplanted in the first 2 years of life	16 (35%)
Date of transplantation (range)	03/1992–03/2005
Cause of transplantation	
Cardiomyopathy	18 (39%)
Congenital heart disease	17 (37%)
Myocarditis	4 (9%)
Primary pulmonary hypertension	4 (9%)
Kawasaki disease	1 (2%)
Pulmonary veno-occlusive disease	1 (2%)
Arrhythmogenic right ventricular dysplasia	1 (2%)
Immunsuppressive medication at sample collection	
Tacrolimus	37 (80%)
Mycophenolate	36 (78%)
Sirolimus	4 (9%)
Cyclosporine	3 (7%)
Azathioprine	1 (2%)
Steroids	9 (20%)

Standard immunosuppressive therapy was a dual drug regimen of tacrolimus and mycophenolate (mycophenolate mofetil or mycophenolic acid, not separately analysed) in some patients with additional steroid treatment (methylprednisolone 0.1 mg/kg).
Different combinations were used in individual patients.

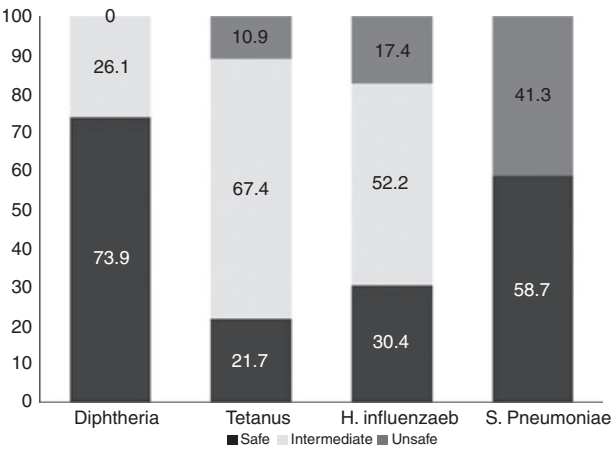

Figure 1 Proportion of all included patients (n = 46) presenting with antibody levels indicating safe, intermediate or absent (definitions see Methods) serologic protection towards diseases prevented with inactivated vaccines.

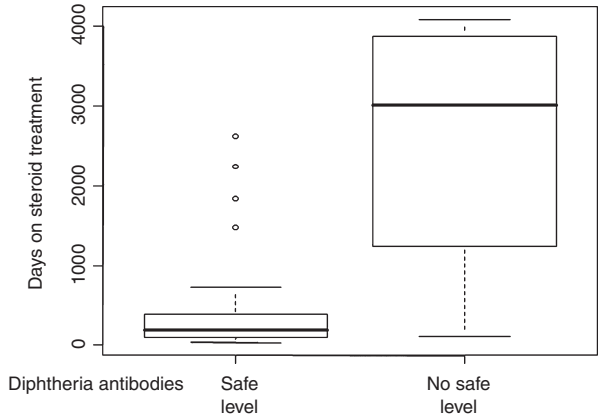

Figure 2 Days on steroid treatment comparing patients with antibody levels indicating safe immunity versus patients with levels below threshold (0.1 IU/ml). The box represents 25th, 50th and 75th percentile, the whiskers indicate 10th and 90th percentile and the circles show single outliers. Difference significant (Kruskal–Wallis test $P < 0.05$, one-way ANOVA $P < 0.001$).

detected antibody levels were not significantly different comparing underlying disease for solitary HTx or number of previous acute rejection episodes. Comparing HTx versus HLTx patients, we found a significantly lower number of patients presenting with safe immunity towards diphtheria in the HLTx group ($P < 0.05$), while safe immunity towards *S. pneumoniae* was present in significantly more patients after HLTx ($P < 0.05$). All other inactivated vaccines did not differ significantly regarding the type of transplantation.

To determine the influence of the immunosuppressive regimen, we analysed antibody status in relation to the use of cyclosporine versus tacrolimus and mycophenolate versus azathioprine as used at sample collection. The only significant difference was a higher prevalence of patients with safe protection towards diphtheria in the cyclosporine treated group than in the tacrolimus treated patients. However, while the tacrolimus group contained 40 of 46 patients (87%) only four of 46 (9%) patients were on cyclosporine treatment with the latter representing the long-term stable patients without side-effects who were not switched to Tacrolimus as per institutional protocol. Although we collected data on number of days with each treatment and cumulative dose, we found that the high variability in inter- and intra-individual dose, target trough levels and changing combinations with pauses because of side-effects, did not allow reliable statistic analysis.

As shown in Fig. 2 we found a significantly shorter course of steroid treatment in patients showing safe immunity towards diphtheria and tetanus than in those with intermediate or absent immunity ($P < 0.05$).

Serologic immunity towards live attenuated vaccines

The IgG antibody concentration towards measles, mumps, *Varicella* and reciprocal values of rubella hemagglutination titers are shown in Fig. 3. For all four diseases the levels were significantly lower in children transplanted in the first 2 years of life ($P < 0.05$).

For live vaccines there is no clear correlation between antibody levels and protection from disease, we therefore determined presence versus absence of antibodies in our patients (Table 4). We found complete absence of specific

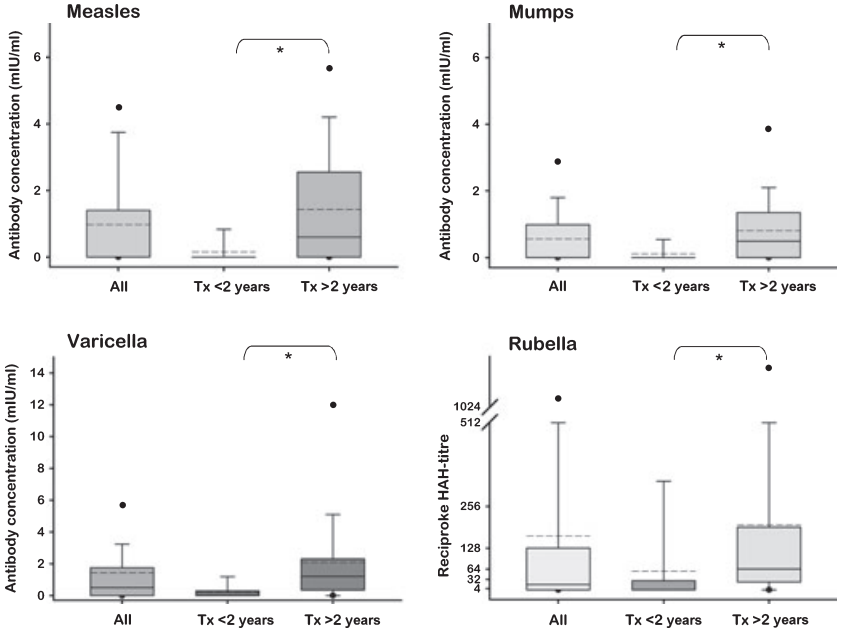

Figure 3 Antibody concentrations and reciprocal values for rubella hemagglutination test (The box represents 25th, 50th and 75th percentile, the whiskers indicate 10th and 90th the circles show the 5th and 95th percentile, the dashed line represents the mean). Significantly lower levels for children transplanted in the first 2 years of life compared with patients transplanted later (*Wilcoxon test $P < 0.05$).

Table 4. Absence of specific antibodies.

	All (n = 44)	Transplantation before 2 years of age (n = 16)	Transplantation after 2 years of age (n = 28)
Measles	24 (54.5)	13 (81.3)	11 (39.3)
Mumps	29 (65.9)	15 (93.8)	14 (50.0)
Varicella	13 (29.5)	9 (56.3)	5 (17.9)
Rubella	15 (34.1)	10 (62.5)	4 (14.3)

Values in parenthesis are expressed in percentage.
Proportion of patients without detectable specific antibodies towards infections preventable with live attenuated vaccines comparing patients transplanted in the first 2 years of life versus transplanted at older age.
Differences significant for all four diseases (Fisher's exact test $P < 0.01$).

antibodies towards all four pathogens in a majority of our cohort and significantly more frequent in children transplanted in the first 2 years of life ($P < 0.01$).

No significant differences were found regarding age at time of sample collection or current immunosuppressive treatment. Days on steroids did not significantly influence the antibody levels. There was a tendency for HLTx patients to have higher antibody levels and to be more likely to have antibodies present than patients with HTx alone but these trends were not significant.

Vaccination history

The vaccination history was assessed complete and reliable in 41 patients. Five were excluded because of incomplete documentation (e.g. missing vaccination passports). The majority of patients presented with incomplete vaccination schedules for both inactivated and live attenuated vaccines at the time of transplant.

Table 5 shows the proportion of patients that had or had not completed the vaccination schedule at the time of transplantation separately for patients transplanted in the first 2 years of life or later. It further shows what proportion of patients had received a basic immunization (as defined by WHO) towards the different pathogens at the time of transplantation. Significantly less of the early transplanted children had received a basic immunization course against diphtheria, pertussis and hepatitis B and all live attenuated vaccines ($P < 0.001$). Patients transplanted in the first year of life are not expected to be vaccinated with live attenuated vaccines, so even if they were on schedule, <10% of these patients had received any live attenuated vaccine.

We found a significant correlation of age at transplant and received doses of tetanus and diphtheria vaccines for both early transplanted and all patients (Spearman-correlation for all patients: correlation coefficient = 0.47, $P < 0.001$, for early transplanted patients: correlation

Table 5. Adherence to recommended vaccination schedules.

	Transplantation before 2 years of age					Transplantation after 2 years of age				
	Complete schedule	Incomplete schedule	Basic immunization	No basic immunization	Natural infection	Complete schedule	Incomplete schedule	Basic immunization	No basic immunization	Natural infection
Tetanus	3 (23)	10 (77)	**8 (50)***	8 (50)	0	8 (32)	17 (68)	**22 (88)***	3 (12)	0
Diphtheria	3 (23)	10 (77)	**8 (50)***	8 (50)	0	8 (32)	17 (68)	**22 (88)***	3 (12)	0
Pertussis	3 (23)	10 (77)	5 (31)	10 (69)	0	6 (24)	19 (76)	12 (48)	13 (52)	2 (8)
Haemophilus influenzae b	5 (38)	8 (62)	3 (19)	13 (81)	N/A	7 (28)	18 (72)	7 (28)	18 (72)	N/A
Hepatitis B	2 (15)	11 (85)	**0***	16 (100)	0	7 (28)	18 (72)	**8 (32)***	17 (68)	0
Measles	1 (33)	2 (67)	**1 (6)***	15 (94)	0	7 (28)	18 (72)	**19 (76)***	6 (24)	4 (16)
Mumps	1 (33)	2 (67)	**1 (6)***	15 (94)	0	7 (28)	18 (72)	**19 (76)***	6 (24)	3 (12)
Rubella	1 (33)	2 (67)	**1 (6)***	15 (94)	0	9 (36)	16 (64)	**18 (72)***	7 (28)	5 (20)
Poliomyelitis (Salk)	**5 (38)$^{\$}$**	8 (62)	**3 (19)***	13 (81)	0	**21 (84)$^{\$}$**	4 (16)	**21 (84)***	4 (16)	0
Varizella	x	x	1 (6)	15 (94)	0	x	x	1 (4)	24 (96)	19 (76)
Streptococcus pneumoniae	x	x	1 (6)	15 (94)	0	x	x	0	25 (100)	2 (8)
Neisseria meningitidis	x	x	0	16 (100)	0	x	x	0	25 (100)	0

Values in parenthesis are expressed in percentage.
Proportion of patients with complete or incomplete vaccination schedule and presence or absence of a basic immunization cycle (one dose of live attenuated, three doses of inactivated vaccines) at date of transplantation.
Bold print indicates significant difference comparing patients transplanted in the first 2 years of live versus after second birthday in Fisher's exact test (*$P < 0.001$, $^{\$}P < 0.05$).
The total patient numbers differ accordingly because patients transplanted prior to first recommended vaccination (<3 months for inactivated, <1 year for live attenuated) were excluded from analysis.

Table 6. Influence of days in hospital on adherence to vaccination schedule.

Vaccination	Incomplete schedule (days in hospital)	Complete schedule (days in hospital)
Diphtheria	45 (0–218)	25 (0–65)
Tetanus	45 (0–218)	25 (0–65)
Pertussis	40 (0–218)	38 (0–65)
Hep B	37 (0–135)	46 (0–218)
HiB	37 (0–125)	44 (0–218)
Measles	29 (0–218)	10 (0–39)
Mumps	28 (0–218)	11 (0–39)
Rubella	27 (0–218)	16 (0–39)
Varicella	28 (0–218)	20 (0–39)
Poliomyelitis	61* (0–135)	29* (0–218)

Comparison of days in hospital for patients with complete versus incomplete vaccination schedule at date of transplantation (mean and range).

*Difference significant for poliomyelitis (Kruskal–Wallis test and one-way ANOVA, $P < 0.05$).

coefficient = 0.87, $P < 0.0001$). We observed a marked delay in the vaccination schedule, especially when looking at the early transplanted children.

To determine the influence of the pretransplantation course, we analysed patients with complete versus incomplete schedule with regard to days spent in hospital and on the intensive care unit prior to transplantation. We found that children with incomplete schedules for poliomyelitis were significantly more days in hospital ($P < 0.05$). The same trend was observed for tetanus, diphtheria, pertussis and all live attenuated vaccines (see Table 6), but failed to reach significance. In contrast, patients with completed schedules for *Hib* and hepatitis B tended to have more pretransplantation days in hospital but not significantly.

Discussion

Our study is the first cross-sectional analysis of serologic immunity and vaccination history with regard to all generally recommended vaccinations in a cohort of patients after thoracic transplantation in childhood. With the experience of a *Varicella*-infection causing severe acute and accelerated chronic rejection leading to re-transplantation in one of our patients, as well as the awareness of the emerging presence of vaccine preventable diseases in the general population in Europe, we thought it to be vital to know whether we can assume protection towards these diseases in our patients. We found a frighteningly low number of our patients safely protected against tetanus, which can be acquired ubiquitously. The level of protection against diphtheria, which had several epidemic phases in Eastern Europe throughout the recent decade [17] was better, but still not complete. Patients with intermediate titers may still be protected by memory cells persisting in a standby-state that can be reactivated when exposed to the antigen. However, to which extent this occurs in the setting of immunosuppression is subject to speculation. As the thresholds for levels considered as protective were defined in people with noncompromised healthy immune systems the actual level of protection they provide in a setting of immunosuppression are unclear. Specific thresholds for this patient group are not available which emphasizes the need for careful evaluation and consideration of the vaccination history.

Children transplanted in the first 2 years of life were significantly more likely to lack protection towards vaccine-preventable diseases than patients transplanted later, especially regarding live attenuated vaccines. The main reason for the latter is that live vaccinations are not recommended prior to the 12th month of life [18] as they do not effectively induce immunity because of persisting serologic immunity transferred from the mother. Beyond that we found a marked delay in the individual vaccination schedule, leading to incomplete immunization despite adequate age at transplantation. In Germany vaccination is not mandatory and there is no strong administrative regulation mechanism, consequently vaccination rates of the general population are lower than in other developed countries [19] and delay in vaccination schedule was recognized also for healthy children [20]. Schedules were reported to be complete for inactivated vaccines in 86.0–98.5% of all 6-year-old children and for live attenuated vaccines in 75.6–76.5% [21]. With 38% or less of the early transplanted children having received their recommended vaccines and, excluding the high coverage for Poliomyelitis, 36% or less of the later transplanted patients presenting with complete vaccination schedule, we have found a critical deficit in pretransplantation care in this patient group. Regarding the presence of a basic immunization regimen as documented in the WHO registry, with at least three doses of inactivated vaccines and one dose of a live vaccine, the overall coverage in the later transplanted group appears reasonable. In contrast its absence in the early transplanted group in 50% or more for the inactivated and 94% for the live vaccines points out a serious problem.

Because of the cross-sectional design, our study cannot answer the question whether inactivated post-transplant vaccinations can sufficiently replace what has been missed prior to vaccination. In trend only the number of pretransplantation vaccinations showed a positive correlation to the antibody-levels. However, single patients acquired full protection with post-transplant vaccinations only. In prospective studies it was demonstrated that some vaccinations such as hepatitis B [22] and influenza [23,24] are

less effective when applied to immunosuppressed patients after solid organ transplantation and live vaccinations are generally not recommended for immunosuppressed persons. Therefore adequate vaccination prior to transplantation is of imminent importance.

To determine possible causes for the delay in vaccine application we analysed days in hospital and on ICU prior to transplantation and found significantly more inpatient days in children with incomplete schedule for poliomyelitis, and identical tendencies for nearly all other vaccinations. This may indicate that the patients with incomplete schedules were sicker and more likely to suffer from advanced heart failure. Care-takers might then outweigh the benefit of the vaccination with the risk of deterioration of the cardiac situation and avoid vaccinations despite the recognized necessity. Furthermore, especially for early transplanted patients who are mainly in hospital care, attention may be lost to the issues of community-based health care, and specialized cardiologic wards may be less aware of the necessity of basic measures such as vaccination. A minority of our patients may have received immune modulating treatment prior to transplantation related to the underlying cardiac disease (e.g. immunoglobulin infusions in myocarditis or Kawasaki disease). As this was not systematically analysed a potential impact on the vaccine response remains unclear. Interestingly, children with complete schedule for hepatitis B showed a trend to more days in hospital, indicating either that these patients were thought to be potentially more endangered by this infection or that hospital physicians perceive this vaccination as more important.

As consequence of these findings, we think a higher awareness of the need for pretransplant vaccinations must evolve in pediatricians taking care of patients that are likely to require organ transplantation early in childhood. The dramatic deficit in achieved vaccines could be improved by earlier initiation of the vaccination schedule for infants at high risk. It was proven that hepatitis B vaccination is effective as soon as the first day of live [25], so from the immunological perspective there are few arguments against starting with application of inactivated vaccines as early as 4–6 weeks of age. For live attenuated vaccines the situation is more complicated. Too early administration is not likely to induce immunity because of transplacental acquired maternal antibodies [18]. However, early studies and data from developing countries suggest that administration as early as 9 months may be beneficial [26,27]. The potential benefit of live vaccination as early as 6 months of age as proposed by some centres currently lacks published evidence. Live-vaccination while waiting for HTx may be dangerous. As the highest viremia is found 10–18 days post vaccination it could coincide with the induction immunosuppression and enhanced risk of severe complications. It should therefore only be admitted if a delay of the transplantation for 28 days appears justified regarding the clinical state.

In patients who have received live attenuated vaccines after solid organ transplantation, small size studies have shown absence of severe adverse events despite relatively high frequency of vaccine-induced rashes [28,29]. However, the safety after household exposure was low [30,31] and long-term follow-up data are not available. Therefore with the absence of larger and longer studies to demonstrate the benefits outweighing the risks of post-transplant live vaccination it cannot be recommended as general approach. Also the use of absolute lymphocyte counts to determine eligibility for live vaccination [30] seems not helpful. It was shown for bone marrow transplanted [32] and HIV-infected patients [33] that higher T-cell counts correlate with actual protection against infectious diseases. However, this cannot simply be transferred to the setting of solid organ transplantation, in which function of T cells is impaired by the immunosuppression regardless of their absolute number. To protect the post-transplant patients it is more helpful to make sure the close environment is completely vaccinated to minimize the risk of transmission within the household.

We tried to determine further factors influencing the low serologic protection of our patients. The trend to higher levels in HLTx-patients, especially for live-attenuated vaccines is most likely explained by their higher age at transplant. The finding of significantly higher antibody levels in patients treated with cyclosporine versus tacrolimus must be interpreted carefully because our cohort included only four patients on cyclosporine therapy, which represented patients with long-term stable courses at low immunosuppression levels. More relevant is the result of significantly more days of steroid treatment in patients with insufficient diphtheria antibody levels, with similar trends observed for other inactivated vaccines. Our findings support, within the limits of a retrospective analysis, the evolving trend to minimize steroid use in post-transplant immunosuppressive regimens [34–36].

In conclusion, our study shows severe lack of serologic immunity towards vaccine-preventable diseases and incomplete vaccination schedules prior to pediatric thoracic transplantation in the majority of patients. Major risk factors are young age at transplantation, more pretransplantation days in hospital and prolonged use of steroids. Closer adherence to vaccination schedules prior to transplantation is required and possibly modification to earlier application of the vaccines in high-risk children. The discovered deficits are to be expected in patient groups with similar demographics, as children undergoing liver transplantation, but are likely present in many

patients following organ transplantation. Therefore, higher awareness of this issue needs to evolve in professionals taking care of patients in health conditions with a possible need for subsequent transplantation. Vaccination history and evaluation of serologic immunity needs to be part of every pretransplantation workup. As an antibody titer which would be considered to be protective in a nonimmunosuppressed person may not provide safe immunity in a post-transplant patient, schedules need to be completed regardless of the status of serologic immunity. Beyond this, antibody levels towards these infections should be monitored regularly after transplantation to recognize the necessity for additional inactivated booster vaccines or passive prophylaxis in case of exposure.

Authorship

SU: designed prepared and partly performed the study, analysed data and wrote the manuscript. SC: performed data and sample collection, data analysis and edited the manuscript. JB, RDP, AF and CS: helped with patient recruitment, sample collection and edited the manuscript. GJ: performed the virologic testing and edited the manuscript. BHB and HN: helped design and performing of the study and edited the manuscript.

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