

# Vaccination Status of Children Considered for Renal Transplant: Missed Opportunities for Vaccine Preventable Diseases

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## Abstract

**Objectives:** Infectious diseases, even vaccine preventable ones, might affect transplanting and the life course in pediatric solid-organ recipients. Owing to immunosuppression and decreased antibody production, susceptibility to infections is increased in these patients.

**Materials and Methods:** The present study was designed to assess the vaccination and antibody status of the pediatric renal transplant patients. Fifty-one patients who were admitted to the regional transplant center for renal transplant were retrospectively evaluated. Patient's vaccination charts were examined, and their immunization status was determined by antibody titers against hepatitis B, hepatitis A, measles, mumps, rubella, and varicella.

**Results:** The study group was composed of 23 males and 28 females (mean age, 10.8 y; age range, 2-17 y). All patients' vaccination status was appropriate with their ages according to national vaccination program. Antibodies were positive for hepatitis B in 84.3% patients, 76.5% for hepatitis A, 72.5% for measles, 64.7% for mumps, 64.7% for rubella, and 72.5% for varicella.

**Conclusions:** Seronegativity for common childhood diseases may complicate the posttransplant period owing to increased risk of infections. Especially in developing countries, immunization protocols and vaccination program schedules should be reviewed

before transplant to prevent serious complications caused by these diseases.

**Key words:** Children, Renal transplant, Vaccination

## Introduction

Posttransplant immunosuppression increases the risk of infectious disease and its complications. Infectious diseases, even vaccine-preventable ones, are leading causes of morbidity and mortality in solid-organ transplant recipients.<sup>1-3</sup> Infections such as influenza, chickenpox, and measles are more likely to be complicated and even life-threatening in solid-organ transplant recipients.<sup>1-7</sup> During childhood, the possibility of incomplete immunizations at the time of transplant is more frequently observed than during adulthood. Several previous studies have shown inadequate immunization for some vaccines (measles, mumps, rubella [MMR], diphtheria-tetanus-pertussis, and hepatitis B) in liver and kidney transplant candidates.<sup>8,9</sup> Therefore, during this time, especially for vaccine-preventable diseases, a review of vaccination and viral antibody status of patients who are candidates for transplant surgery and management of vaccines are paramount. This study sought to evaluate antibody status against vaccine-preventable diseases in children scheduled for renal transplant.

## Materials and Methods

Fifty-one pediatric renal transplant candidates between January 2008 and December 2011 (age range, 2-17 y), who were referred to Pediatric Nephrology Department or were under regular follow-up were enrolled in this study. Patients, their parents or guardians were informed about the study

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and gave their informed consent to participate in research. Patients' age, sex, living area (urban/rural), dialysis type, underlying disease, tuberculosis skin test results, vaccination status, and antibody titers were recorded.

Thirty-one patients were on peritoneal dialysis, 7 were on hemodialysis, and 13 were in predialysis period. None of these patients had severe proteinuria (> 40 mg/m<sup>2</sup>/h) or had received immunosuppression treatment at the time of their vaccination. Antibody levels against measles, mumps, varicella, and hepatitis B were measured by enzyme-linked immunosorbent assay, and all results were evaluated according to the manufacturer's instructions.

Data on antibody titers against hepatitis B surface antigen, hepatitis A, rubella, measles, mumps, and varicella were obtained from the "Pediatric Renal Transplant Candidate Charts." Patients' vaccination charts were investigated.

Information about other vaccines that are on the Natural Vaccination Schedule such as diphtheria, tetanus, *Bordetella pertussis*, or that are not on the National Vaccination Programme (Table 1), but could be obtained on special advice, like pneumococcus and *Haemophilus influenzae*, were obtained from their vaccination charts. Tuberculosis skin test was considered positive if the induration was ≥ 10 mm.

**Table 1.** National Immunization Program in Turkey (Since January 2008)

Vaccines	Number of Doses	Schedule
BCG	1	2nd mo
HBV	3	Birth, 1st, 6th mo
DTwP-IPV-Hib	4	2nd, 4th, 6th, 18-24 mo
OPV	2	6th mo, 18-24 mo
MMR	2	12th mo, 4-6 y
Td	2	4-6 y, 14-16 y

**Abbreviations:** BCG, Bacille Calmette-Guerin vaccine; DTwP, Diphtheria and tetanus toxoid with whole cell pertussis vaccine; HBV, Hepatitis B vaccine; Hib, *Haemophilus influenzae* type B vaccine; IPV, Inactive polio vaccine; MMR, Measles mumps and rubella vaccine; OPV, Oral polio vaccine; Td, Tetanus and diphtheria toxoid for older children/adults.

**Results**

Of fifty-one patients who participated in our study, 54.9% were girls and 45.1% were boys (mean age, 10.86 y; range, 2-17 y). The underlying diseases comprised 7 neurogenic bladder (13.7%), 5 reflux nephropathy (9.8%), 4 nephronophthisis (7.8%), 4 membranoproliferative glomerulonephritis (7.8%), 3 Alport syndrome (5.9%), 3 polycystic kidney disease (5.9%), 3 hemolytic uremic syndrome (5.9%), 2 focal segmental glomerulosclerosis (3.9%), 2 posterior urethral valve (3.9%), and 18 of an unknown cause (35.3%). Thirty-six patients (70.6%) came from rural areas. All patients received Bacille Calmette-Guerin and poliovirus vaccine along with diphtheria-tetanus-pertussis on a scheduled vaccination protocol.

Of 51 patients, 47 (92.2%) had at least 1 dose of hepatitis B vaccine. Three-dose schedule of hepatitis B vaccine was completed in 18 patients (35.2%). In all, 84.3% patients were seropositive for hepatitis B. As a result of routine controls of hepatitis B antigen, hepatitis B core antibody and anti-hepatitis B surface antibody, there was no patient with a positive antibody owing to hepatitis B infection. All patients had at least 1 dose of measles vaccine.

Of 51 patients, 31 (60.8%) had a single dose of measles vaccine, 7 (13.7%) had 2 doses of measles vaccine, 11 (21.6%) had 1 dose of measles vaccine, and single dose of MMR vaccine, 2 patients (3.9%) had a single dose of measles and 2 doses of MMR vaccine. Of all patients, 12 (23.5%) had a history of measles eruption. Antibody status of all patients revealed seropositivity for measles in 72.5%, for mumps in 64.7%, and for rubella in 64.7% patients (Table 2). In addition, antibodies against measles were found in 75% (n=15) of patients who received a single dose of measles vaccine and 77.4% of patients who received more than 2 doses of measles vaccine.

**Table 2.** Seropositivity Status of Renal Transplant Patients

Patients	Measles	Rubella	Mumps	Varicella	Hepatitis B	Hepatitis A
All patients' antibody status (n=51)	37/51 (72.5%*)	33/51 (64.7%*)	33/51 (64.7%*)	37/51 (72.5%*)	43/51 (84.3%*)	39/51 (76.5%*)
Children less than 6 years old with seropositivity	9/12 (75%*)	9/12 (75%*)	5/12 (41.7%*)	7/12 (58.3%*)	11/12 (91.7%*)	8/12 (66.7%*)
Children more than 6 years old with seropositivity	30/39 (76.9%*)	25/39 (64.1%*)	30/39 (76.9%*)	30/39 (76.9%*)	32/39 (82.1%*)	31/39 (79.5%*)

\*seropositivity rates

Varicella and hepatitis A vaccinations, which are not freely provided vaccines from Ministry of Health, were not performed in any of our patients before admission. Nonetheless, in our study, of 51 patients, antibodies against hepatitis A were found in 76.5% patients and antibodies against varicella were found in 72.5% patients. Both hepatitis A and varicella are common childhood infections in Turkey and patients might have seroconverted through "natural" ways.

None of our patients had hepatitis B surface antigen (HBsAg) positivity. Three patients (5.9%) had injections for *Haemophilus influenzae*, and 5 (9.8%) had pneumococcal vaccine. Purified protein derivative tests were positive in only 2 patients (3.9%) who were subsequently given isoniazid prophylaxis.

## Discussion

National vaccination program in Turkey at the moment covers vaccines for Bacille Calmette-Guerin, diphtheria-tetanus-pertussis, polio, MMR, pneumococcus, and *Haemophilus influenzae* type B free of charge (excluding vaccines for hepatitis A and varicella), albeit the results of this study revealed a low seropositivity against several vaccine-preventable diseases in renal transplant patients.

Inadequate immunization before solid-organ transplant is a problem worldwide.<sup>4, 10</sup> In a recent study conducted in 35 children, antibody titers against measles, mumps, rubella, varicella, hepatitis, and tetanus were determined. It was shown that protective antibodies were present in only 26% of patients.<sup>9</sup> Children with chronic renal failure generally miss immunizations owing to frequent hospitalizations, or consideration of their chronic conditions as a contraindication for immunization by primary care practitioners. Besides, vaccines that are not provided by the government cannot be obtained by many families owing to their relatively high costs. Limited information of families and health care providers regarding the importance of these vaccines might be another reason for incomplete immunization status of renal transplant patients.

Of vaccine-preventable diseases, measles remains one of the most-important causes of childhood morbidity and mortality in developing countries. Of our patients, 60.8% were vaccinated against measles with a single dose, whereas the rest were vaccinated with > 2 doses. The discrepancy in vaccination schedule reflects the change in the National

Vaccination Programme in Turkey. Measles vaccination in Turkey started in 1970 and until 1998, children were given only 1 dose of measles vaccine in the ninth month of life. In 1998, a second dose of measles was added to the National Vaccination Programme. In 2003 and 2005, nationwide measles vaccination campaigns were performed. After several modifications for the measles vaccination program, in 2006, the measles vaccination policy changed to receiving MMR vaccine at 12 months and a booster dose at 6 years of age,<sup>11, 12</sup> but for a time, some children were immunized with MMR at 15 months along with 1 dose of measles vaccine administered at 9 to 12 months.

In our study, the seronegativity rate was 25% in children immunized with a single dose of measles vaccine, and 22.6% in children immunized with > 2 doses. When taken together, 23.5% of the study population was susceptible to measles, which can lead to high morbidity and mortality after transplant.<sup>7, 13, 14</sup> Seronegativity in 22.6% of children despite > 2 doses of measles vaccine can be explained by reduced immunogenicity of vaccine owing to impaired immune function caused by underlying conditions such as uremia or dialysis.<sup>15</sup> A reduced number of memory B cells have been reported in children with chronic renal failure.<sup>16</sup> Such immunologic defects also might impair immunologic memory.

Vaccination coverage for measles was 80% in 2000 and 91% in 2005. With successful vaccination campaigns, it rose to 97% in 2009. Accordingly, measles was thought nearly to be eradicated from Turkey, but in the winter of 2011, 40 cases of measles were reported.<sup>12</sup> Similar information on measles outbreaks had been reported around the world in 2010 and 2011 from many countries like Ireland, Germany, and Switzerland, as well.<sup>17-19</sup> Measles have been shown to be associated with severe complications like encephalitis (requiring mechanical ventilator treatment in children with renal transplants) and atypical presentation may complicate the diagnosis and treatment issues.<sup>20, 21</sup> So, we advise that anti-measles antibodies should be checked in every transplant candidate, even if the patient declares a complete immunization schedule for measles.

Seropositivities for rubella and mumps are also quite low (69.2% and 61.5%). This low ratio of seropositivity can be explained by the fact that the

MMR vaccine has been provided by the government free of charge since 2006. Therefore, 7 patients who were born before 2006 were not vaccinated by MMR during their routine vaccination program. Rubella is still endemic in Turkey; with an estimated incidence of 3.1/100 000 in 2005.<sup>22</sup> Immunization against rubella also should be offered to seronegative children before transplant.

Although both varicella and hepatitis A vaccines are available in Turkey, none of the patients in the study declared to be vaccinated with those vaccines. This could be expected because the National Vaccination Programme does not cover varicella and hepatitis A vaccines. Despite the lack of vaccination by these vaccines, 72.5% of patients had varicella and 76.5% hepatitis A antibodies, which were probably acquired by natural infections. Considering the high prevalence of these 2 diseases in our country (like other developing countries), it is likely that these patients will encounter these diseases.<sup>23, 24</sup> Varicella is reported to be an important cause of hospital admissions and severe disease in solid-organ transplant recipients including renal transplant patients.<sup>25</sup> Therefore, it is of paramount importance to vaccinate susceptible individuals before transplant.

Seroconversion ratios after hepatitis B vaccination in dialysis patients are expected to be lower than healthy individuals. Therefore, to achieve protective antibody levels, booster doses are recommended.<sup>26, 27</sup> In a meta-analysis, it was revealed that patients with HBsAg seropositivity have poorer outcomes in terms of morbidity and mortality after transplant.<sup>28</sup> Chaves and associates<sup>10</sup> reported that 63% of patients had 3 doses of hepatitis B vaccine before transplant. In our country, hepatitis B vaccine was added to the national vaccination program in 1998. Most dialysis centers routinely check the patients' antigen/antibody status, and patients are vaccinated against hepatitis B, as well. In our study, 47 patients (92.2%) received at least 1 dose of hepatitis B vaccine and 84.3% patients had seroconverted.

Limitations of this study include the fact that the patients were not tested for diphtheria-tetanus-pertussis, *Haemophilus influenzae*, and *Streptococcus pneumoniae* antibody levels because these tests are not routinely available in our hospital.

Our results revealed a low rate of adequate immunization in our transplant candidates. Therefore, antibody titers for vaccine-preventable

diseases should be checked in children who are candidates for transplant before placing them on a waiting list, and those who are seronegative should be vaccinated and immunization status should be regularly re-evaluated. Despite the governmental vaccination strategies, inadequate immunization can be an important problem, especially for the vaccines that are not provided by the government free of charge, such as hepatitis A and varicella in developing countries. Parents should be encouraged to immunize their children with vaccines not provided by the national vaccination program without charge and if possible, governmental policies for vaccination should be made for solid-organ recipients, so that this selective group can be properly vaccinated before transplant.

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