Pediatric Dialysis

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Third Edition

Springer

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ISBN 978-3-030-66860-0 ISBN 978-3-030-66861-7 (eBook)
https://doi.org/10.1007/978-3-030-66861-7

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The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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Introduction

Chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are associated with significant alterations in immune function. On the one hand, CKD is associated with a state of chronic inflammation, which in turn has been associated with increased muscle catabolism, vascular calcification, insulin resistance, and malnutrition [1]. However, patients with CKD and ESKD also have immunodeficiency, as manifested by an increased risk for infection and sepsis and impaired response to vaccinations [1]. Infection is a leading reported cause of death in children with ESKD [2, 3]. Peritoneal dialysis (PD) continues to be plagued with the infectious complication of peritonitis, and hemodialysis (HD) is complicated by the development of catheter-related bacteremia. Excluding transplantation, infection is reported to be the most common reason for dialysis modality termination in children [2]. The treatment and the prevention of infections are therefore important elements in the care of pediatric dialysis patients, both for reduction of mortality and morbidity, and in the setting of PD, for preservation of the peritoneal membrane function. This chapter will provide a brief review of currently available information regarding the immune dysfunction associated with CKD and ESKD. In addition, because delivery of routine childhood and supplemental vaccinations remains a cornerstone of infection prevention, data regarding response to immunizations in children with CKD and alterations to the routine immunization schedule for healthy children required for children with CKD will be presented.

Immune Dysfunction

Information regarding immune function in children with CKD or ESKD is sparse. The incidence of peritonitis and catheter-related infections in children is higher than that found in adults, and infants and children up to 6 years of age develop peritonitis more frequently than older children. Immaturity of the immune system also contributes to the immune system dysfunction in children with CKD and ESKD. Therefore, the results obtained from adults cannot be directly extrapolated to children. A complete review of innate and acquired immunity in CKD is beyond the scope of this chapter; however, the following provides a brief overview of this complex topic.

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© Springer Nature Switzerland AG 2021
B. A. Warady et al. (eds.), *Pediatric Dialysis*, https://doi.org/10.1007/978-3-030-66861-7_33

White Blood Cell Differentiation and Function

Lymphopenia has been noted in adult dialysis patients; however, the percentages of B-cells, T-cells, and T-cell subsets are usually normal [4–11]. Several studies evaluating lymphocyte number and the percentages of B-cells, T-cells, T-cell subsets, and NK cells in the peripheral blood of children with CKD or ESKD have produced conflicting results [12–18]. Children with pre-dialytic CKD have been reported to have alterations in memory T-cell subsets, and reduced numbers of memory B-cells have been reported in children on dialysis [19, 20]. Possible explanations for the reduced numbers of memory B-cells are a general suppression, suboptimal T helper activity, or disturbances in the B-cell migration process caused by uremia or dialysis treatment. Irrespective of the mechanism of memory B-cell reduction, the consequence might be a lower capacity to mount a secondary immune response, resulting in a decreased response to vaccination and predisposition to increased infection rates [20, 21].

In addition to alterations in the number or percentage of T-cells, abnormalities of T-cell-mediated immune responses have been demonstrated in CKD [7, 22–25]. T-cells from dialysis-treated patients show a combination of reduced proliferation and signs of activation [26–28]. The abnormal T-cell proliferation of uremic patients might be due to a defect within the T-cell population itself, to circulating inhibiting factors in uremic serum, or to the function of accessory cells such as monocytes [25, 29–39]. In children, data on this subject are scarce and conflicting. Two studies could not establish a difference in lymphocyte proliferation between children with CKD, dialyzed or not, and healthy children [12, 13]. George et al. performed an analysis of T-cell populations in children with CKD and demonstrated significant skewing toward advanced differentiation phenotypes in both the CD8 and CD4 subsets, which may represent features of advanced immune exhaustion and senescence [40]. Various alterations in cytokine production, particularly IFN-γ (gamma), have been reported in children with CKD, with one study demonstrating normalization of these abnormalities with HD [17, 41, 42].

Phagocytic Cells and Receptors

Reduced chemotaxis, adhesion, migration, and phagocytosis characterize the dysfunction of neutrophils and monocytes demonstrated in patients on dialysis [27, 43–46]. Data on the characteristics and function of phagocytes in children with CKD are limited [47, 48]. Interestingly, one study demonstrated that treatment with recombinant human growth hormone enhanced the oxidative burst activity of neutrophils in uremic children [47]. Wasik and colleagues concluded that PD improves phagocytosis and intracellular killing of bacteria by peritoneal macrophages but not by peripheral blood neutrophils in ESKD patients [48]. In another study of pediatric patients with ESKD, marked dysregulation in inflammatory cell chemokine receptor expression and responsiveness was noted and was more pronounced in the subgroup of patients who had multiple serious bacterial infections in the preceding year [49].

Limited information is available on the impact of CKD on IgG receptor (Fcγ(gamma)R) and complement receptor (CR) expression or function [50–54]. These receptors are important components in the interaction between humoral and cellular immunity and facilitate the phagocytic process. Some authors described an increased CD16 (Fcγ(gamma)RIII)-positive monocyte population in adult PD and HD patients when compared to healthy controls, a phenotype that has been linked to tissue macrophages in the context of the state of maturation [50, 51]. In children with pre-dialytic CKD and ESKD, studies have demonstrated a lower expression of Fcγ(gamma)RII (CD32) on peripheral blood monocytes and neutrophils compared to healthy children [41, 55–58]. Furthermore, reduced CR type 1 (CR1) expression, which is important for inducing phagocytosis of complement-coated bacteria, on lymphocytes and increased expression of Fcγ(gamma)R and CR on peritoneal

macrophages and neutrophils have been shown in pediatric CKD patients [41, 55–58].

Immunoglobulins

Low levels of IgG and/or subclasses have been described in patients on PD, attributed to peritoneal loss in most of the studies [59–70]. However, two studies in children reported that the immunoglobulin deficiency was already present before dialysis started, which suggests inhibition of synthesis by the uremic state [63, 64]. In one study, a deficiency of one or more IgG subclasses was present in 40% of children with CKD, with IgG_2 being the major subclass affected [64]. Children receiving PD had the lowest serum Ig levels [64].

The role of serum IgG or subclass deficiency in the pathogenesis of PD-associated peritonitis is unclear. Studies in adults could not establish a relationship between the peritonitis incidence and IgG or subclass deficiency [65, 70]. In children, a study by Kuizon et al. found a significant relationship between IgG and the incidence of peritonitis [71]. In another study, although not all children with IgG deficiency had a high incidence of peritonitis, all of the children with a high number of peritonitis episodes were in the IgG-deficient group [64]. On the contrary, a study by Lalan et al. found that while hypogammaglobulinemia is a frequent complication of peritoneal dialysis during infancy, it was not associated with an increased risk of peritonitis, and some infants developed peritonitis even after therapeutic IVIG administration [72].

In summary, numerous abnormalities in immune function have been described in CKD; however, these deficiencies are not consistently seen in pediatric patients. In addition, although the uremic state is likely a major contributor to this immune dysfunction, it seems plausible that a variety of uremic toxins may impact the individual components of the immune reaction in disparate ways. For the dialysis patient, it follows that a dialysis prescription measured only in terms of small solute clearance cannot be expected to optimize all of the factors that influence immune function. In addition, the impact of the dialysis procedure itself on immune function and activation must be considered. Thus, specific CKD-related treatment strategies to improve immune function, beyond the obvious goals of optimizing nutrition and correcting mineral bone disorder, metabolic imbalance, and anemia, remain elusive. It bears mentioning that despite data demonstrating low IgG levels in children receiving PD, there are no data at this time to support the routine use of intravenous immunoglobulin infusions for peritonitis treatment or prevention. One treatment strategy that is available specifically to minimize risk for infection in pediatric dialysis patients is the timely delivery of routine and supplemental immunizations, and the remainder of the chapter focuses on this topic.

Immunizations

Children with CKD and dialysis may have reduced response to and/or reduced duration of antibody after immunization and therefore may be at increased risk for infection from vaccine-preventable diseases. In order to minimize this risk, they require all the recommended childhood immunizations according to the standard schedule and additional vaccines and booster doses [73–77].

The completion of the vaccination schedule before renal transplantation (RTx) is of particular importance. Due to the complexity of clinical care of these children, immunizations can be delayed, overlooked, or not properly recorded. In fact, in a recent retrospective case series, only 22 out of 254 dialysis patients (9%) presented complete vaccination coverage prior to RTx. In particular, vaccination coverage against hepatitis B and MMR was more reasonable compared to varicella and pneumococci (89%, 83%, 59%, and 42%, respectively) [78]. The United States Renal Data System (USRDS) 2013 report revealed that among prevalent pediatric dialysis patients, approximately 40% received seasonal influenza vaccine between 2008 and 2011, and only 16% received vaccination against *Streptococcus pneumoniae* [79].

Although immunization recommendations for dialysis patients slightly vary among countries

[80] and different health authorities [73–76], all inactivated vaccine and toxoids are safe and effective when used in dialysis patients with the same doses and schedules as recommended for immunocompetent persons. There is no contraindication for live vaccines (except a precaution for live-attenuated influenza vaccine) in dialysis patients unless they are on immunosuppressive medications [73–76].

Accordingly, diphtheria, tetanus, acellular pertussis (DTaP), *Haemophilus influenzae* type b, polio, measles-mumps-rubella (MMR), *Streptococcus pneumoniae*, varicella zoster, and hepatitis B vaccines continue to be recommended. Parallel to modifications in standard schedules, rotavirus vaccine, tetravalent conjugated meningococcal vaccine, hepatitis A vaccine, and finally human papillomavirus (HPV) vaccine have been included in the immunization schedule of dialysis patients. BCG vaccine is recommended before the age of 6 years in some countries [73–76, 80].

In the following sections, available data concerning vaccine response in pediatric dialysis patients is provided, and any modification of the standard schedule that may be required for children on dialysis will be discussed.

Diphtheria, Tetanus, and Pertussis Vaccine

Diphtheria/tetanus toxoids and acellular pertussis (DTaP) vaccine should be administered in infants as recommended for healthy children. After three primary dose series, booster doses at 12–23 months (DTaP-containing vaccines), 4–6 years, and 9–15 years of age (tetanus, reduced diphtheria, acellular pertussis – Tdap) are recommended. Thereafter, tetanus and diphtheria toxoids (Td) 10 years apart are given [73–76].

A multicenter study in infants vaccinated while on dialysis revealed protective antibody titers to both diphtheria and tetanus toxoids in 7/8 patients (88%) [81]. Studies in older children and young adults on dialysis showed seroconversion after diphtheria and/or tetanus toxoids at a rate of 69–89% compared to 93–100% in healthy children [82, 83]. On the other hand, in older children, the rates of patients with a positive pretransplant vaccination titer against DTP were 38.5%, 60.0%, and 21.3%, respectively [84]. Thus, in older children on dialysis, efforts should be made to ensure that booster immunizations against tetanus and diphtheria are provided.

Haemophilus influenzae Type b (Hib) Conjugate Vaccine

In a multicenter study performed by the Pediatric Peritoneal Dialysis Study Consortium, antibody levels were measured in ten infants vaccinated with Hib conjugate vaccine while on dialysis [85]. This study found that 9/10 (90%) patients had protective antibody levels after vaccination and that antibody levels remained protective for as long as 22 months postvaccination [85]. In another study, antibody levels measured 2 months after the third dose of Hib conjugate vaccine were protective in all 42 pediatric dialysis patients studied [86]. Thus, this vaccine appears to be highly immunogenic in pediatric dialysis patients, and these children should receive this vaccine according to the standard schedule.

Hepatitis B Vaccine

Suboptimal response to hepatitis B vaccine is well documented among adult dialysis patients, and as such the ACIP recommends that adult patients on dialysis receive an augmented dose of 40 μg of either Recombivax HB or Engerix-B [87]. In children, there are only a few studies. Two small case series of pediatric CKD/dialysis patients and RTx recipients demonstrated that three doses of 5 μg (age <10 years) or 10 μg (age >10 years) or 20 μg hepatitis B vaccines resulted in a protective antibody titer

of ≥10 mIU/mL in more than 90% of cases (91–97%), if checked 2 months after the final immunization [86, 88]. Another prospective study revealed a seroconversion rate of 72% ($n = 26/36$) following three dose series of 10 μg hepatitis B vaccine in children with CKD stages II–V [89]. Revaccination with full doses is recommended for persons who do not develop protective antibody levels. Despite vaccination, 15% of pediatric RTx candidates were seronegative [90].

Current recommendations specify that dialysis patients less than 20 years of age receive 10 μg hepatitis B immunization according to the standard schedule (0–1–6 months), with the caveat that "higher doses might be more immunogenic" in pediatric HD patients [74, 76]. A recent retrospective multicenter study on pediatric HD patients showed that seroconversion rates are highest when administered 10 μg multidose boosters (97%) or 20 μg single- or multidose boosters (86% and 83%) compared to the augmented (40 μg) booster dose(s). Therefore, no specific recommendations have been made for augmented doses for pediatric hemodialysis patients [91].

Regardless of the dose of vaccine given, the ACIP recommends that postvaccination testing be performed 1–2 months after the primary series is completed and that up to three additional doses be given to patients who do not develop protective antibody levels (>10 mIU/mL). Antibody levels should then be measured annually and booster doses provided to patients if antibody levels fall <10 mIU/mL [73–76]. Protective antibody levels waned more rapidly in children who were immunized after starting dialysis (median: 37 months) than in those who received primary hepatitis B immunizations during childhood (106.3 months). Additionally, a lower percentage of patients immunized post-transplant had protective antibody levels than those with pre-dialysis CKD and on dialysis (66.7% vs. 96.4%) [88]. Therefore, vaccination in early stages of CKD is recommended [92] or at least two immunizations be given prior to the point at which dialysis or transplant is necessary, whenever possible [88].

Inactivated Polio Virus Vaccine

Since 1999, the AAP and ACIP recommendations have specified that only inactivated vaccine (IPV), rather than the live-attenuated oral vaccine, be used for routine immunization in all children [93] including dialysis patients. Vaccine coverage rate among pediatric dialysis patients is around 81% in a European multicenter study [78]. Another study performed in older children on dialysis who had antibody levels measured after vaccination with IPV found that 42/49 (86%) patients either had protective antibody levels to all three serotypes prior to vaccination or had at least a fourfold increase in antibody levels following immunization [94]. Because this vaccine contains only inactivated virus, it may be safely given to dialysis patients who are also on immunosuppressive medications.

Measles, Mumps, Rubella Vaccine

Measles, mumps, and rubella (MMR) vaccine is one of the live-attenuated viral vaccines currently on the childhood immunization schedule. There is no contraindication for MMR in children on dialysis unless they are receiving immunosuppressive therapy including corticosteroids [95]. Once corticosteroids are discontinued, it is generally recommended that MMR vaccination be delayed for at least 1 month [95] and it should be given at least 1 month prior to RTx. Additionally, when MMR and varicella vaccines are given shortly before, simultaneously with, or after an antibody-containing blood product, response to the vaccine can be diminished. Therefore, these vaccines either should be administered ≥2 weeks before receipt of a blood product or should be

delayed 3–8 months after receipt of the blood product, depending on the type of product [96].

MMR vaccine can be used as early as 6 months of age. If transplant has not occurred by the age of 12 months, the schedule for the MMR vaccine should be restarted with two doses at a minimal interval of 4 weeks between doses [97, 98].

There have been several studies evaluating response to MMR in pediatric dialysis patients. In a study performed by Schulman et al., ten dialysis patients 15–33 months of age were vaccinated with MMR after which only 70% developed protective titers to measles, 50% to mumps, and 80% to rubella [99]. Furthermore, only 3/10 (30%) had protective titers to all three viruses [99]. A subsequent study performed by Flynn et al. vaccinated nine infants, six of whom were on dialysis, at a mean age of 11.6 months [100]. Eight of these patients were subsequently transplanted at a mean age of 16 months, and at the time of transplantation, 89% had protective titers to measles, 88% to mumps, 100% to rubella, and 88% to all three viruses [100]. Another study performed in Germany measured antibody levels in 62 pediatric dialysis patients 2 months after immunization with MMR and found that all patients had positive antibody titers [86]. However, a recent European survey showed that only 77.4% and 73.0% of RTx candidates (age at transplantation: 9.9 ± 5.8 years) were seropositive against measles and mumps, despite a complete childhood vaccination schedule [78]. Furthermore, another recent European multicenter study showed that one third of pediatric nephrology centers reported not checking MMR antibodies during dialysis period or pre-RTx preparations [80]. Although these data suggest that many pediatric patients on dialysis may respond well to MMR vaccine, because immunization posttransplant is contraindicated, antibody titers should be measured prior to proceeding to transplant, and repeat vaccination given to patients with negative titers [95] . It should be kept in mind that children who were seronegative or not vaccinated against measles during pretransplantation period may experience severe measles infection and fatal measles complications after RTx [101].

Varicella Zoster Vaccine

Varicella zoster virus (VZV) vaccine is also a live-attenuated viral vaccine and is therefore contraindicated in dialysis patients on immunosuppressive medication and status post RTx [102]. Because of the significant risk for morbidity and mortality from varicella zoster infection posttransplant, there have been several studies to evaluate the immunogenicity of this vaccine in children with kidney failure and on dialysis. Early studies using the previously recommended single immunization with VZV vaccine in children with chronic kidney failure and on dialysis demonstrated seroconversion rates of 85–88%, compared to a rate of 99% in healthy children [103, 104]. Subsequently, two multicenter, prospective studies evaluated antibody levels after a two-dose regimen of VZV vaccine in children with pre-dialysis CKD and on dialysis [105, 106]. Both studies revealed that nearly all patients seroconverted after the second dose of vaccine, with a 98% seroconversion rate in one study and 100% in the other [105, 106]. Unfortunately, very few infants were included in these studies, and thus seroconversion rates in infants and toddlers on dialysis after either a one- or two-dose regimen are not known. Given these data, it is reasonable to consider measuring antibody levels prior to RTx and to provide supplemental vaccination if positive antibody titers are not demonstrated. In line with this, two recent studies from Europe showed that pretransplant rate of positive varicella titers was 79.2% and VZV antibodies were measured during dialysis period or pre-RTx preparations as a policy in 15 out of 18 pediatric nephrology centers [80].

Growing experience suggests that MMR and varicella vaccines can be administered at least 1 year after RTx, in clinically stable patients without a recent (within 2 months) rejection episode. Even though these patients are under minimal immunosuppression, the vaccination option should be evaluated on an individual basis [97].

Pneumococcal Vaccine

All children on dialysis should be vaccinated with the 13-valent conjugated pneumococcal vaccine (PCV13) as is recommended for healthy children to decrease the risk of invasive pneumococcal infection [73–75]. Despite adequate antibody response to conjugated vaccine in children and adults on dialysis [107, 108], due to the increased risk for pneumococcal disease in dialysis patients, they should also receive supplemental immunization with the 23-valent polysaccharide vaccine (PPSV23) after the age of 2 to expand serotype coverage [73–76, 109, 110]. In Europe, only 42% of children received a complete vaccination schedule against pneumococcus before RTx [84]. The timing of the supplemental immunization with PPSV23 vaccine varies depending on the age of the patient and the number of previous immunizations with PCV13 (for specific recommendations, see Table 33.1, CDC and ECDC websites [73–75, 109, 110]). Briefly, at least 8 weeks after primary immunization with PCV13, PPSV23 can be given and repeated after 5 years. Revaccination is important as several studies have suggested that although PPSV23 vaccine produces a reasonable antibody response in children on dialysis, there may be a rapid decline in antibody levels [84, 86, 111]. A recent study showed that only 69.4% of patients exhibited a positive vaccination titer against pneumococci serotypes before transplantation [78].

Hepatitis A, Meningococcal, Human Papillomavirus, and Rotavirus Vaccines

Children on dialysis may receive these vaccines as recommended for healthy children with the caveat that the live-attenuated rotavirus vaccine be avoided in children on immunosuppressive therapy. There are currently no data available on response to hepatitis A or rotavirus vaccines in children on dialysis. Because of the low prevalence of hepatitis A infections, its vaccine is not widely applied in Europe [80]. Although meningococcal and HPV vaccines are included in many countries' standard vaccination schedules [73–75, 80], a recent study from Europe showed that only 27.3% and 47.9% of pediatric RTx candidates had vaccination coverage against HPV and meningococcus [78]. Another study from the USA evaluated antibody response to the standard three-dose vaccine series of the HPV in 57 girls aged 9–21 years old with CKD, on dialysis, or with status post Rtx. Seropositivity was 100% in the CKD and dialysis groups, but a less robust response to the vaccine was observed among those with a RTx [112], which highlighted the importance of immunization before transplantation.

Influenza Vaccine

Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications [73, 113]. The influenza vaccine is available either as an inactivated vaccine (IIV) or a live-attenuated vaccine (LAIV). The CDC has a precaution about usage of LAIV in persons with kidney dysfunction, including those on dialysis. Therefore, only the inactivated vaccine should be given to patients on dialysis [73–75, 113]. The composition of the influenza vaccine changes each year based

Table 33.1 Recommended immunization schedule in children with chronic kidney disease and on dialysis

Vaccine	Age	Dose	Schedule	Route of administration	Booster doses
HBV	0–10 years 11–19 years	5 mcg/dose 10 mcg/dose	Three-dose schedule	IM	Postimmunization testing for anti-HBs is recommended for dialysis patients 4–8 weeks after completion of schedule. If immunization completed before, determine anti-HBs at time of diagnosis. If anti-HBs <10 UI/l 4–8 weeks after the last dose of primary vaccination series, repeat the series: 0–10 years: 10 mcg/dose three dose *series* 11–19 years: 20 mcg/dose three dose *series* Annual anti-HBs should be checked; booster doses should be given when anti-HBs <10 mIU/ml
Inactive influenza	6–35 months 3–8 years ≥9 years	0.25 or 0.5 ml[a] 0.5 ml 0.5 ml	Two annual doses in autumn Two annual doses in autumn (two annual doses for the first time immunization <9 years of age, thereafter one annual dose) One dose	IM/SC	Repeat every year during influenza season
Varicella	>12 months	0.5 ml	12 months to 12 years Two doses minimum 3 months apart >12 years two doses minimum 4 weeks apart	SC	Complete the immunization series or check the IgG level for varicella at the time of diagnosis[b]
Hepatitis A	>12 months	0.5 ml	Two doses 6 months apart	IM	Immunization recommendation depends on epidemiology of disease in the region. Complete the immunization series or check the IgG level for hepatitis A at the time of diagnosis
MMR	>12 months (6–9 months under specific circumstances)	0.5 ml	Two doses (min 4 weeks apart)	SC	Timing of doses depends on the epidemiology in the region Complete the immunization series or check the IgG level for MMR at the time of diagnosis[b]
IPV	2, 4, 6, 12–15 months 15 months to 18 years, unvaccinated	0.5 ml 0.5 ml	Four dose series Three doses with an interval of 1–2 months	IM IM	Booster dose between 5 and 10 years of age Revaccination 1 year after the third dose
Diphtheria, tetanus, acellular pertussis (DTaP)-containing vaccines	Min 6 weeks to 6 months	0.5 ml	Three primary dose series	IM	Booster doses at 12–23 months (DTaP-containing vaccines), 4–6 years, and 9–15 years of age (tetanus, reduced diphtheria, acellular pertussis – Tdap) Thereafter, Td 10 years apart

HIB	6 weeks (min) to 59 months	0.5 ml	One to four dose series depending on the age of first vaccination	IM	Complete and check the immunization series
Conjugated meningococcal vaccines (monovalent-A, C, bivalent-CY, quadrivalent– ACYW) MenB	Min 2 months of age >10 years in the USA >2 mo in Europe	0.5 ml	Dose series depends on starting age and the type of conjugate vaccine used (follow manufacturer recommendations)	IM	Follow national immunization recommendations[c]
HPV	As soon as possible from 9 years of age		Two doses 6 months apart (least 5 months apart)	IM	Older age groups ≥15 years three doses (0, 2, 6 months)
Rotavirus	First dose 6–14 weeks 6 days Last dose at 8 months		Two to three doses depending on vaccine with an interval of 4–8 weeks	PO	–
BCG	As soon as possible after birth	0.05 ml (<12 months) 0.1 ml (>12 months)	One dose One dose	ID	Follow the national immunization recommendations
Pneumococcal vaccine					
PCV13	2–23 months 24–71 months with no previous PCV13 6–18 years with no previous PCV13	0.5 ml	Two to four doses for completion of immunization depending on the age of first immunization Two doses of PCV13 One dose of PCV13	IM	
PPSV23	>2 years	0.5 ml	One dose 8 weeks after completion of PCV13 series	IM or SC	Booster dose 5 years later

IM intramuscular, *SC* subcutaneous, *ID* intradermal, *PO* per oral

[a]Dose volume is based on manufacturer

[b]MMR and varicella vaccine administration should be avoided within 4 weeks of organ donation and after renal transplantation

[c]If there is an ongoing risk, booster doses should be given

on the strains of viruses likely to circulate in the upcoming year, and, therefore, this vaccine must be given annually, typically in the fall [113]. Children under the age of 9 years who are receiving the influenza vaccine for the first time should receive two doses, given at least 1 month apart [74, 113].

Because of the significant risk for morbidity and mortality associated with influenza infection in pediatric patients with CKD and dialysis, there have been several studies evaluating vaccine response in this population that reported very good vaccine responses [114, 115]. Although these studies suggest that influenza vaccine produces a reasonable response in pediatric dialysis patients, because of the significant risk for morbidity and mortality from influenza infection in these patients, household contacts should receive vaccination in an effort to decrease the risk for exposure to influenza [73, 74, 113].

Bacille Calmette-Guerin (BCG) Vaccine

Children with CKD may receive BCG vaccine as recommended for healthy children at 2 months. Alternatively, it can be performed before the age of 6, according to PPD test results [73]. There is a significant variation about BCG vaccine administration among European countries [75]. A recent survey showed that BCG vaccine is routinely performed in only five countries (Greece, Lithuania, Poland, Turkey, and the UK), while PPD or Quantiferon test is applied to CKD patients in 12 centers from eight countries [80]. The difference among national immunization programs may be partly due to the low prevalence or eradication of tuberculosis in some European countries, so that health authorities do not recommend BCG vaccine.

Summary

In conclusion, several abnormalities of the immune system have been reported in children with CKD. Given the complexity of the multifactorial processes involved as well as the heterogeneity of the patients studied, it is difficult to elucidate the exact mechanisms leading to the increased risk of infection. In the meantime, in an effort to minimize risk for vaccine-preventable disease, pediatric patients on dialysis should receive all age-appropriate vaccines currently recommended for healthy children according to the standard schedule, with the exception of the avoidance of the live-attenuated influenza vaccine in all dialysis patients and avoidance of the other live vaccines (rotavirus vaccine, MMR, VZV) in CKD and dialysis patients treated with immunosuppressive medications. Because MMR and VZV vaccines are contraindicated posttransplant, every effort to provide immunization prior to the introduction of immunosuppressive medication posttransplantation should be made. Supplemental and/or augmented doses of hepatitis B vaccine should be given as indicated. Additional vaccination against *Streptococcus pneumonia, Neisseria meningitides, and HPV* should be performed. Antibody levels should be monitored regularly to evaluate protection.

Practical points around vaccine administration in children with CKD/Dialysis [73, 74, 76, 97, 98]

- Children with CKD/dialysis should receive all the recommended childhood immunizations according to the standard schedule whenever possible. Vaccination in early stages of CKD has better seroconversion rates than late vaccination.
- Inactive vaccines should be given at least 2 weeks prior to transplantation. Live vaccines (MMR and Varicella) should be administered at least four weeks prior to renal transplantation.
  - If an organ becomes available within 4 weeks of receiving MMR vaccine, a clinical decision must be made by weighing the risks of proceeding with transplant and starting immunosuppression in the face of recent live viral vaccine administration, and the efficacy of post-exposure prophylaxis such as IVIG, vs. the risk of remaining on the wait list.
  - For varicella vaccine, using antiviral treatment (usually IV acyclovir) and proceeding with transplant may be considered even if the patient received varicella vaccine within 3-4 weeks.
- Live attenuated influenza vaccine should not be given to CKD/dialysis patients.
- Live vaccines may be given 1 month after discontinuation of steroid therapy, 3 months or more after completion of other immunosuppressive chemotherapy, or 6 months after treatment with anti-B-cell antibodies.
- MMR and varicella vaccines should be administered ≥2 weeks before receipt of a blood product or should be delayed 3–8 months after receipt of the blood product, depending on the type of product.
- MMR and varicella vaccines can be administered at the age of 6 months, if early transplantation is desired. If transplant has not occurred by the age of 12 months, the schedule for the MMR vaccine should be restarted with two doses at a minimal interval of 4 weeks between doses.

Which vaccines cannot be administered simultaneously?

- The immune response to one live-virus vaccine might be impaired if administered within 28 days of another live-virus vaccine. If MMR and varicella vaccines are not administered simultaneously, administration should be separated by 28 day interval.
- PCV13 and PPSV23 should not be administered simultaneously and preference is for PCV13 first, followed by PPSV23.
- Since Men-ACWY decreases seroconversion of PCV13, it should be delayed at least four weeks after completion of PCV series (in those with asplenia).

Which primary/booster vaccinations can be postponed to after transplantation?

- Any of the inactivated virus vaccines can be postponed to post-transplantation period for the sake of timely transplantation, but ideally want to get it done prior for better seroconversion rates.
- Standard age-appropriate inactivated vaccine series should be administered 3 to 6 months after transplantation

For which vaccines should antibodies be measured routinely after vaccinations to verify an adequate immune response?

Ideally, CKD patients or those on dialysis should be tested for seroconversion 1-3 months after complete vaccination series for Hepatitis B (3 doses), varicella (2 doses) and MMR (2 doses). If antibody titers are positive, they can go into renal transplantation. If anti-HBs <10 mIU/ml, an augmented dose series should be administered. If still seronegative for MMR and Varicella, an extra dose may be administered.

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