Vaccines in Cellular Immunodeficiencies

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Abstract

Infectious complications are a major cause of morbidity and mortality in patients with primary immune deficiencies. Prevention of infectious diseases by vaccines is among the most effective healthcare measures mainly for these subjects. As in humoral immune deficiencies, there are some specific aspects that need to be deepened. Firstly, response to vaccine is often seriously compromised in patients affected by cellular immunodeficiencies so that some vaccines result inefficacious or even dangerous in particular conditions. However, subjects affected by a cellular immunodeficiency vary in their degree of immunosuppression and susceptibility to infection depending on the kind of defect and, therefore, represent a heterogeneous population with regard to immunization. Secondly, the susceptibility to specific pathogens has to be considered. Therefore, it becomes very important for clinicians to distinguish which vaccines are useful and not deleterious for patients, depending on the type of cellular defect. The aim of this chapter is to issue recommendations based on published scientific literature and practical experience about how and when vaccines can be used in primary cellular immune deficiencies, in order to facilitate physician decisions and to ensure the best immune protection with the lowest risk to the health of the patient.

Keywords

Vaccine · Cellular · Primary immunodeficiency · Severe · Combined · Syndromic Innate immunity

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18.1 Introduction

In cellular immunodeficiencies, the increased susceptibility to infectious diseases results in extremely high morbidity and mortality and has a major role in determining the prognosis. Due to the generally severe course of infections and to the poor response to conventional antimicrobial treatment, prevention is crucial in this population.

Therefore, vaccination as well as immunoglobulin replacement therapy and antimicrobial prophylaxis represent the most important tools of individual prevention. As in humoral immunodeficiencies, some issues have to be considered carefully, first of all the safety of vaccines. In fact, when the cellular defect is profound, the risk of proliferation and dissemination of live viral or bacterial agents is high.

Secondly, if the cellular defect is severe, most of the vaccines have an extremely low immunogenicity, so that specific protection against pathogen can't be obtained.

Moreover, in most of the cases, these patients are under immunoglobulin substitutive therapy; therefore, besides their primary inability to mount an adequate immune response, the interference generated by infused antibodies has to be taken in account. In view of all this, in patients affected by severe cellular immune defects, the greatest possible immunization of all contacts becomes fundamental in order to take the best advantage of herd immunity effect. Finally, special awareness should be raised about specific pathogen susceptibility in the different types of cellular immunodeficiencies (PIDs) so that certain vaccines could be specifically recommended. The aim of this chapter is to report vaccine schedule recommendations in patients with primary cellular immune disorders, based on the currently available evidence and on the standardized experience and practice. Specific recommendations will be made only regarding well-defined and studied conditions. Viable and nonviable vaccines will be analyzed separately in each disease category; in particular cellular deficiencies will be classified in a simplified manner as follows: severe combined immunodeficiencies, combined immunodeficiencies, and combined immunodeficiencies with associated or syndromic feature.

Moreover, vaccine recommendations in defects of innate immunity in intrinsic immunity with susceptibility to specific organisms, in congenital defects of phagocytes, and in complement deficiencies will be reviewed. Vaccines in particular conditions, as contacts of patients with cellular immunodeficiency and patients undergoing stem cell transplant, will be discussed, as well.

In recent years, thanks to the rapid evolution of diagnostic techniques, more and more genetic defects have been discovered. The chapter will offer general principles that could be applicable also into newly discovered clinical entities instead of focusing on specific defects that are still poorly characterized. Specific recommendations will be made only regarding well-defined and studied conditions. Viable and nonviable vaccines will be analyzed separately in each disease category. It's important to notice that providing specific recommendations for each type of cellular immunodeficiency is difficult for many reasons: the rarity of the single conditions, the

exclusion of immunocompromised individuals from pre-licensure vaccine tests, the lack of high-quality data, and the extreme heterogeneity of clinical expression even among patients with the same molecular defect. Therefore, authors think that a tailor-made approach based on general principles and on specific evaluation of the patient's immune function and a precise assessment of risk-benefits to ensure the greatest protection and to prevent risks of adverse events has to be considered the most appropriate.

18.2 General Principles

The International Union of Immunological Societies (IUIS) Expert Committee for Primary Immunodeficiencies has cataloged and classified all known cellular deficiencies into two main groups, both included in the group named "immunodeficiencies affecting cellular and humoral immunity": severe combined immunodeficiencies (SCID), defined by CD3 T cell lymphopenia (defined by CD3+ T cells <300/μL), and combined immunodeficiencies (CID) generally less profound than severe combined immunodeficiency. Besides these, there is the group of CID with associated or syndromic features [1]. Viable and nonviable vaccines have different general indications and contraindications in the above-cited categories. Inactivated vaccines can be considered safe in all patients. Nevertheless, in patients with profound impairment of cellular immune system, their benefit is unlikely and their use is not fully justified especially when receiving immunoglobulin replacement therapy. On the other hand, live vaccines have always to be avoided in SCID, whether they should be used with greater caution in patients with other cellular defects. In the same classification, just updated, combined immunodeficiencies with associated or syndromic features, congenital defects of phagocyte number or function, defects in intrinsic and innate immunity, and complement deficiencies are cited and constitute different groups. In turn, each group includes multiples genetic defects; in the following discussion, only principal clinical entities will be considered.

18.3 Vaccination in Severe Combined Immunodeficiencies

No live viral or bacterial vaccines should be given to SCID patients before immune reconstitution who should otherwise receive passive immunization with immunoglobulins [2]. Immunodeficient patients who have received hematopoietic stem cell transplantation (HCT) but who continue to have incomplete immune reconstitution or are undergoing immunosuppression should not be given live viral or bacterial vaccines [3]. In particular, no live viral (oral poliovirus, measles, mumps, rubella, varicella, yellow fever, herpes zoster, smallpox, rotavirus, or live attenuated influenza virus) or live bacterial (BCG or *S. typhi* Ty21a) vaccines should be administered in SCID patients. In fact, in these subjects the impaired generation of a diverse repertoire of mature T lymphocytes leads to a severe T lymphopenia with a lack of a T- and B-dependent-specific

antibody response. Even if B cell counts may be normal or increased in some patients with SCID, their maturation is incomplete and fail to produce specific antibodies. For these reasons, there is a very high risk of vaccine-induced infection. Disseminated vaccine-acquired varicella and vaccine-acquired rubella have been reported in a 13-month-old female with an atypical SCID due to IL7R mutation [4]. All patients receive immunoglobulin substitutive therapy and have exogenous protective antibody titers. Oral polio vaccine (OPV) should not be administered to SCID patients. In most countries, inactivated poliovirus vaccine (IPV) has replaced OPV vaccine. Recently in the United States a case of vaccine-associated paralytic poliomyelitis has been described in a child with SCID and a history of OPV vaccination in India [5]. Other cases of oral vaccine-derived poliovirus infections have been reported in subjects with SCID [6, 7]. Live-attenuated *M. bovis* bacille Calmette-Guérin (BCG) is routinely administered in most countries within the first month of life. However, only a small number of SCID patients receive diagnosis before the age of 1 month, as the median age at diagnosis is 138.5 days [8]. BCG complications, including disseminated BCG infections, have been observed in patients with all of the underlying genetic types of severe combined immunodeficiency (SCID). However, it is not known which type of SCID is more susceptible to BCG complications, which prohibits BCG administration to any patient with SCID [9–11]. Moreover, in countries where newborn screening for SCID is available, BCG vaccination should be shortly postponed. Oral rotavirus vaccine is also a live vaccine that is recommended at 2 months of life in the United States and in several European countries. In the United States from February 3, 2006, to January 15, 2010, nine cases of SCID and rotavirus vaccination in infants between 3 and 9 months of age have been reported. All but one presented with diarrhea among other symptoms. Stool rotavirus testing was positive in all the children, and the virus was identified as the vaccine strain in six cases. Prolonged viral shedding was documented in five patients. Fortunately, no death occurred [12]. Thus, as for other live vaccines, SCID is a contraindication for rotavirus vaccination [13]. However, a delay in rotavirus vaccination cannot be considered because rotavirus vaccination must be administered early in life to prevent the first yet most severe infection in children. The only strategy to avoid rotavirus vaccination in SCID patients is early diagnosis through newborn screening. Killed or inactivated vaccines are safe because they cannot replicate. Nevertheless, their effectiveness is very limited. Bacterial conjugate polysaccharide vaccines, including pneumococcal, meningococcal, and *H. influenzae* vaccines, and influenza-inactivated vaccine are recommended even in patients with complete T cell defect, but immune response to those vaccines is likely to be poor. However, whereas patients are passively protected by donors' immunoglobulins against diphtheria, poliomyelitis, tetanus, hepatitis B, and pertussis, they are not by capsulated bacteria since most of the population is not immunized. Thus, it is worth vaccinating them against these pathogens [14] (Table 18.1).

Table 18.1 Vaccination in primary cellular immunodeficiencies and in defects of innate immunity

	TDP	IPV	Hib	HBV	Influenza	Pneumococcus in S. pneumoniae	Meningococcus in N. meningitidis	MMR Varicella	Rotavirus	BCG *S. typhi*
SCID	No[a]	No[a]	Yes[b]	No[a]	Yes[b]	Yes[b]	Yes[b]	No	No	No
CID	Yes[b]	Yes[b]	Yes	Yes[b]	Yes	Yes	Yes	No[c]	No[c]	No
MSMD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Invasive bacterial infections	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
CMCD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
TLR deficiency	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
IL-12/IFN-gamma pathway deficiency	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Complement deficiency	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No data available
Congenital defects of phagocytes (CGD, LAD, MPO neutropenia)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[d]	Yes[d]	No

[a]Not recommended: these vaccines are safe but probably ineffective
[b]May be administered, the response to these vaccines is likely to be poor
[c]Generally contraindicated but they could be considered according to patient's immune system function
[d]Not recommended in LAD and CHs

18.4 Vaccination in Combined Immunodeficiencies

In this group of patients, inactivated viral and bacterial vaccines are always safe and are generally indicated; however, the immunological response could be poor. Vaccines against *S. pneumoniae, H. influenzae,* and *N. meningitidis* are recommended because they are T cell-independent antigens.

Influenza-inactivated vaccine is recommended, as well. In patients with impairment of T-cell functions, live bacterial vaccines are always contraindicated. Live viral vaccines are generally contraindicated, but live measles, mumps, rubella, and varicella vaccines could be considered in patients according to the immune system function: if CD4 + T lymphocytes are greater than or equal to 500 cells/μL, CD8+ T lymphocytes are greater than or equal to 200 cells/μL and proliferative response to mitogens is normal, and they can be administered safely.

The Centers for Disease Control and Prevention (CDC) recommends higher values of CD4+ T cells if the child is less than 6 years old: at least 1000 CD4+ T cells/μL if between 1 and 6 years, at least 1500 CD4 T cells/μL under the year if age [2, 15, 16]. Patients affected by mild DiGeorge syndrome can have a CID immunological phenotype. Before administering a live viral vaccine, in order to reduce the risks, it is worth evaluating the lymphocyte count and mitogen responsiveness [17, 18]: those with ≥500 CD4 cells/ L, ≥200 CD8 cells/ L and a normal mitogen response or, more simply according to Hofstetter et al. [18], those with CD4 cells/L ≥ 25% can receive measles-mumps-rubella (MMR) and varicella vaccines. Focusing on mild DiGeorge syndrome, Perez et al. retrospectively analyzed adverse events following MMR and varicella vaccine administration in these patients [19] and found that only 9% experienced adverse events, none of which was severe. A comparison of the patients who tolerated the vaccine and those who reported adverse events showed that there was no statistically significant difference in current age, age at the time of vaccination, or T cell subset counts. Similar immunogenicity and safety findings have been reported by Al-Sukaiti et al. [18, 20] (Table 18.1).

18.5 Vaccination in Combined Immunodeficiencies with Associated or Syndromic Features

18.5.1 Hyper-IgE Syndrome

In hyper-IgE syndrome (HIES) patients, all killed/inactivated/recombinant vaccines are recommended, and in particular anti-*H. influenza*e, anti-pneumococcal, and all the anti-meningococcal are indicated, since they don't evoke a T-mediated immune response. Anti-influenza-inactivated vaccine is recommended as well, as it can't be dangerous. Nevertheless, these vaccines could not be protective totally, depending on variable immune defect.

A variable capacity to produce protective antibody response has been demonstrated in these patients [21]. In particular, the administration of two doses of

conjugate vaccines (13-valent pneumococcal and tetravalent anti-meningococcal MenACWY vaccines) at 12-month interval may be useful.

Live attenuated viral vaccines can be used without risks in AD-HIES patients. Conversely, live vaccines should not be administered in HIES patients with DOCK8 or PGM3 mutations with T immune defects, as evaluated by CD4+ T cell counts ≥500 cells/μL, CD8+ T cells ≥200 cells/μL, and normal T cell response to mitogen. Conversely, live attenuated bacterial vaccines (BCG and *Salmonella typhi* vaccines) are always contraindicated because of the common association with a functional defect of antibacterial response [14].

18.5.2 Wiskott-Aldrich Syndrome

Killed, inactivated, and recombinant vaccines are all recommended, using the conjugated forms preferably in Wiskott-Aldrich syndrome (WAS). In particular patients aged 2–5 years should receive one dose of 13-valent pneumococcal conjugate vaccine (PCV13) if they have received three doses of PCV (either 7-valent PCV [PCV7] or PCV13) before age 24 months and two doses of PCV13 (8 weeks apart) if they have received an incomplete schedule of ≤2 doses of PCV7 (PCV7 or PCV13) before age 24 months [17]. Live attenuated viral and bacterial vaccines are contraindicated, as a defective number or function of T lymphocytes is common in these patients [22].

18.5.3 Ataxia-Telangiectasia

Patients affected by ataxia-telangiectasia can receive all killed/inactivated/recombinant vaccines and conjugated vaccines against *S. pneumoniae, H. influenzae*, and *N. meningitidis*, are recommended. Although there is reduced specific antibody production against polysaccharides, conjugated vaccines are effective. Inactivated influenza vaccine is strongly suggested, as well. Regarding live attenuated vaccines, they can be administered only after a careful evaluation of number and function of T lymphocytes, in particular only if CD4+ T lymphocytes are ≥500 cells/μL, CD8+ T lymphocytes are ≥200 cells/μL, and T lymphocyte mitogen response is normal [23, 24].

18.5.4 DiGeorge Syndrome

When the form is complete, patients share the same recommendations of patients affected by SCID regarding vaccines: all live attenuated viral and bacterial vaccines are contraindicated because of the potential risk of vaccine-related diseases. Conversely, vaccines against capsulated germs and inactivated influenza vaccine are recommended [14, 15].

Regarding "partial" syndrome, as mentioned before, the same recommendations observed in CID are to be followed. Vaccines against *S. pneumoniae, H. influenzae*, and *N. meningitidis* and influenza are recommended. Live attenuated viral vaccines can be administered if CD4+ T cells are ≥500 cells/μL, CD8+ T cells are ≥200 cells/μL, and T cell response to mitogen is normal. If these criteria are not satisfied, delaying the vaccination with immunological monitoring is advised [14, 15].

18.5.5 IPEX Syndrome (Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked)

In IPEX patients none of killed/inactivated/recombinant vaccines can provoke damage, so that all can be administered [25]. However, studies on response to those vaccines are not available. Regarding live attenuated vaccines, some cautions are needed. It's well known that immunoglobulins, number, and distribution of lymphocyte subpopulations are normal. T repertoire is polyclonal and naïve, and memory cells are comparable to those of control subjects of the same age. T lymphocyte mitogen response is normal or increased. Life vaccines could then be used, theoretically. Nevertheless, every single case has to be carefully evaluated and a complete immunologic evaluation is needed before any vaccine. In fact, sometimes cytokine production can be altered. Moreover, many patients are treated with immunosuppressive agents because of autoimmunity and that prohibits live vaccines [14].

18.5.6 APECED Syndrome (Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy)

All killed, inactivated, and recombinant vaccines are safe in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome.

Since lymphocytic defect is not always specific for *C. albicans*, live attenuated vaccines could be contraindicated; their use has to be carefully evaluated and immunologic tests have to be performed: lymphocyte subpopulations and T lymphocyte mitogen response. Nevertheless, live attenuated vaccines are at present contraindicated for the lack of studies [14] (Table 18.2).

18.6 Vaccines in Defects of Innate Immunity

Inborn errors of innate immunity encompass a wide group of congenital immunodeficiencies mainly characterized by recurrent bacterial invasive infections and viral and fungal infections often in the absence of a significant inflammatory response. Recently, the International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency (PIDs) classified these disorders in three main groups: intrinsic defects of innate immunity including Mendelian susceptibility to mycobacterial disease (MSMD), herpes simplex encephalitis, Toll-Like

Table 18.2 Vaccination in syndromic immunodeficiencies

	TDP	IPV	Hib	HBV	Influenza	Pneumococcus in S. pneumoniae	Meningococcus in N. meningitidis	MMR varicella	Rotavirus	BCG *S. typhi*
Complete DiGeorge syndrome	No[a]	No[a]	Yes[b]	No[a]	Yes[b]	Yes[b]	Yes[b]	No	No	No
Partial DiGeorge syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[c]	Yes[c]	No
Ataxia-telangiectasia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[c]	No data available	No
Wiskott-Aldrich syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Hyper-IgE syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[c,d]	Yes[c,d]	No
IPEX syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No data available	No data available	No data available
APECED syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No data available	No data available	No data available

[a]Not recommended: these vaccines are safe but probably ineffective
[b]May be administered, the response to these vaccines is likely to be poor
[c]Can be administered only if T CD4+ lymphocytes ≥500 cells/μL, T CD8+ lymphocytes ≥200 cells/μL and T lymphocytes mitogen response is normal. Center for Disease Control and Prevention recommends higher CD4+ levels if children are under 6 years: al least 1000 CD4+ cells/μL between 1 and 6 years, at least 1500 cells/μL under 1 year of life (*Red Book, 31st Edition 2018, Report of the Committee on Infectious Diseases*)
[d]Can be administered only in AD-HIES, generally

receptor (TLR) signaling pathway deficiencies, and disorders with predisposition to invasive fungal infections; congenital defect of the phagocyte number, function, or both; and complement pathway deficiencies [1] (Table 18.1).

18.6.1 Vaccination in Defects in Intrinsic Immunity with Susceptibility to Specific Organisms

In patients with defects in innate immunity that predispose to invasive bacterial infections, all the killed/inactivated/recombinant vaccines are safe and indicated. In particular, inherited mutations in IRAK4, NEMO, and MYD88 make patient susceptible to invasive bacterial infections, mostly caused by *S. pneumoniae*, *S. aureus*, and *P. aeruginosa* [1]. Thus, patients have to be vaccinated with both 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23), *Haemophilus* type b conjugate vaccine, and *Neisseria meningitidis* conjugate (MenACWY) and subcapsular protein (MenB) vaccine [14]. Moreover, patients require repeated vaccination. However, a fatal pneumococcal meningitis despite PCV13 vaccination 6 weeks before and a satisfactory IgG response to vaccine antigens in a 7-year-old girl with IRAK-4 deficiency has been reported [26]. Patients that present Mendelian susceptibility to mycobacterial disease (MSMD), due to mutations in genes involved in the IL-12/IFN-γ axis, can't receive live bacterial vaccines. In fact, after BCG vaccine, patients with MSMD can develop localized (such as lymphadenitis or osteomyelitis) or disseminated (fever, weight loss, anemia, and hepatosplenomegaly) complications. In 1996, a case of fatal disseminated BCG infection led to the identification of the IFN-γ receptor deficiency [27].

In 1998, inherited IL-12 deficiency was identified in a patient with a history of BCG lymphadenitis and *Salmonella enteritidis*-disseminated infection [28]. Disseminated BCG osteomyelitis was found in a patient with heterozygous mutation in STAT1 [29].

In patients affected by chronic mucocutaneous candidiasis disease (CMCD), killed/inactivated/recombinant vaccines can generally be administered, while live attenuated pathogens are contraindicated. In fact, in a cohort of 274 patients with STAT1 GOF mutations, Toubiana et al. reported localized and disseminated disease caused by BCG vaccine and severe disease due to live viral vaccine (smallpox and measles) [30].

18.6.2 Vaccines in Phagocytic Defects

Even in the absence of controlled trials, vaccines with inactivated germs are useful, safe, and well tolerated in patients with phagocytic defects [17]. Nevertheless, immunologic response can be compromised. In fact, it has been reported that patients affected by chronic granulomatous disease (CGD) display significantly lower antibody titers against measles and not fully characterized abnormalities of

the B cell compartment, hence a suspect defect in long-term maintenance of the memory response [31]. Regarding the administration of vaccines with live viruses, an increased risk of bacterial complication of viral infections (such as staphylococcus infections on varicella lesions) should be considered in patients with neutropenia, so that these vaccines are recommended in those patients. However, in a few cases affected by leukocyte adhesion deficiency (LAD) or Chediak-Higashi syndrome (CHs), which is characterized by a failure in releasing the cytolytic granules, severe side effects have been reported as a consequence of the impairment of cell-mediated and cytolytic activity [32]. Thus, live viral vaccines are contraindicated in these categories of patients [14]. As for attenuated live bacterial vaccines, an increased risk to develop a disseminated form of mycobacteriosis following BCG vaccination has been reported even a long time after the vaccination. Multiple BCG reactivations have been described, as well [32]. Several studies show that 62–75% of the CGD patients with mycobacterial complications had BCG-related disease [33–35]. Therefore, BCG vaccination is contraindicated in patients with a diagnosis of CGD. Despite the lack of data, live *Salmonella typhi* vaccines should be avoided, due to the high occurrence of such infections in CGD patients, while inactivated *Salmonella typhi* vaccines can be used [14].

18.6.3 Vaccines in Complement Deficiency

All types of vaccines are generally safe in patients with complement deficiency (CD). Post-vaccine immunocomplex-mediated glomerulonephritis has been described in a patient with C2 deficiency who had received the first dose of the combined vaccine with purified antigens; but, the presence of specific antigens was not detected in glomerular immunocomplexes [36]. Concerning the effectiveness of vaccination, all vaccines, including viral vaccines, can be considered sufficiently immunogenic. In particular, conjugate vaccines (pneumococcal, anti-*Haemophilus,* and anti-meningococcus) are strongly recommended in patients suffering from both early component and late component deficiency. Few studies are available on immunogenicity of these vaccines: the serum bactericidal and opsono-phagocytosis activity of patients with CD, who had received an anti-meningococcal tetravalent polysaccharidic vaccine (MPSV), was similar or only slightly lower than those of healthy subjects. However, a significantly increased risk of meningococcal disease persisted in the years following the vaccine administration, especially in the cohort of children who had developed a lower antibody titer [37, 38]. A subsequent study, performed on 22 C2-deficient patients, who had received a tetravalent polysaccharide vaccine, reported a normal antibody response against the serogroups C, Y, and W, but lower against the serogroup A [39]. For these reasons, additional immunization against these pathogens is indicated: a booster dose of tetravalent conjugate meningococcal vaccine every 3 years for 2-month- to 6-year-old patients or every 5 years for patients older than 6 years of age [17]. Furthermore, pneumococcal conjugate vaccine (PCV13) should be followed by pneumococcal polysaccharide 23 vaccine (PPV23) at least 6 months later, to retain protection levels of antibodies [40, 41].

18.7 Vaccinations for Household Members and Caregivers of Patients with Cellular Immunodeficiency

It is mandatory that all close contacts of a patient with cellular defect are immunized against all vaccine preventable diseases, whenever this is possible. In fact, when the patient is forbidden to receive any vaccine, the only way to protect him is through protection of the related people. It is then fundamental to verify that all the contacts are vaccinated: if not already protected, they can receive all killed, inactivated, and recombinant vaccines. In particular, in older household members, it is suggested to administer a booster of anti-pertussis vaccine, since protection obtained through a previous infection is likely to decrease over time. The booster should be repeated every 10 years. In the case of bacterial infection, such as pertussis or meningitis, isolating the patient, observing all the hygienic measures, and, in case of meningitis due to *Neisseria meningitidis or Haemophilus influenzae*, administering antibiotic prophylaxis to the subject are advised. Regarding live attenuated vaccines, OPV should be avoided in household contacts of patients with cellular immunodeficiency because of documented risk of transmission and possible vaccine-related complications [15]. Only inactivated vaccine IPV should be administered.

Measles, mumps, rubella, varicella, and rotavirus can be administered to family members or other close contacts susceptible to infection, since the risk of developing the disease is extremely rare.

Yellow fever and *Salmonella typhi* (Ty21a) can be administered to contacts, as well. Particularly, adults with primary immune deficiency should avoid changing the diaper to children vaccinated with rotavirus in the 4 weeks following the immunization. It is also recommended to verify the immune status against varicella in adult contacts, since they could be not vaccinated and not protected by natural immunization. If a household member had a rash after varicella vaccine, the risk of transmission of infection to an immunosuppressed patient would be very low. The only risky case would be if blisters appeared in correspondence of the inoculation site: in that case it would be better to isolate the patient and to treat him with prophylactic specific immunoglobulins (a single dose within 96 h after exposure) and to treat the contact with antiviral therapy. In the rare case of measles in a household member, patient must receive specific immunoglobulins within 6 days from exposure [2, 17]. As reported by the ACIP, live attenuated influenza vaccine should not be administered in people who care for patients affected by cellular immunodeficiency, in particular SCID, patients who received hematopoietic stem cell transplantation (HSCT) within 2 months, and patients receiving treatment for graft versus host disease (GVHD). Otherwise, the contact with immunosuppressed patients within 7 days after vaccination should be avoided due to the risk of virus transmission [42]. On the contrary, inactivated influenza annual vaccine is recommended in household contacts [2, 17].

18.8 Vaccination in Patients with Cellular Immunodeficiency Undergoing HSCT or Gene Therapy

The loss of vaccine immunity that occurs after SCT is affected by many factors: the strength of pretransplant immunity of the patient and the donor's immune status, the age of the patient at the time of transplantation, the combination of pretransplant chemotherapy regimens and/or radiation therapy, the occurrence of GVHD, and the immunosuppressive therapy following transplantation.

The risk of losing the vaccine immunity is similar after allogeneic and autologous SCT so that recommendations about vaccines are the same. In both cases, vaccination schedule has to be started from the beginning after transplant, considering the patient naïve for any antigens.

In literature, data regarding the effectiveness of vaccines in patients undergoing allogeneic hematopoietic stem cell transplantation for a primary immunodeficiency are limited. It is known that the count of B cells takes 3–12 months to return to normal values. Furthermore, newly generated B cells often show defective Ag-specific response during the first year after transplantation, due to a limited capacity of naïve B cells to undergo isotype switching and somatic mutations [43]. The majority of circulating T cells in the first year after transplantation are T memory/effector, derived from the graft and able to respond to antigens encountered by the donor before transplantation. The naïve T cells capable of responding to new antigens are generated only 6–12 months after transplant, and this occurs earlier in young children than in older ones [44].

Inactivated/recombinant vaccines are safe and are not associated with an increased risk of side effects compared to healthy patients. In general, these vaccines have to be scheduled starting from 1 year after transplant. However, they should be considered in every single case and should be given 6 months after stopping any immunosuppressive therapy.

Three doses of DTP-Polio-Hib-HBsAg, separately or in combination according to age (hexavalent can be used up to the 7th year), two doses of conjugate pneumococcal vaccine, two doses of MenB, and two doses of conjugate MenACWY vaccine should be given. Inactivated influenza vaccine should be given annually [17]. In particular, this vaccine is recommended for all SCT patients at least 4–6 months after SCT [17]. Live vaccines should not be used within 24 months from SCT or in patients with GVHD or immunosuppressive therapy ongoing [45].

Specifically, two doses of MMR and varicella vaccines should be given 24 months after HSCT, but a preliminary immunologic evaluation including lymphocyte subset count and T cell proliferation test is always highly recommended [14].

Moreover, the last Ig infusion must have been drawn up at least 11 months before, no GVHD has to be present, and immunosuppressive therapy must have been stopped at least 3 months before [46].

Donor who has not received recommended vaccinations should be vaccinated for his/her own health; in fact, vaccination of donor aimed to the recipient's benefit is not recommended. Vaccination of donor with live vaccines should be avoided within 4 weeks of donation [17].

Regarding vaccination in patients who had undergone gene therapy, there is no literature available, yet. Nevertheless, we could assume that the same rules of the transplant apply: vaccines will be safe and fully effective when immune reconstitution will be complete.

References

1. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, Ochs HD, Oksenhendler E, Picard C, Puck J, Torgerson TR, Casanova JL, Sullivan KE (2020) Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol 40(1):24–64. https://doi.org/10.1007/s10875-019-00737-x
2. Shearer WT, Fleisher TA, Buckley RH, Ballas Z, Ballow M, Blaese RM et al (2014) Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts. J Allergy Clin Immunol 133:961–966
3. American Academy of Pediatrics (2012) Immunization in special clinical circumstances. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS (eds) Red Book: 2012 Report of the committee on infectious diseases. American Academy of Pediatrics, Elk Grove Village (IL), pp 74–90
4. Bayer DK, Martinez CA, Sorte HS, Forbes LR, Demmler-Harrison GJ, Hanson IC, Pearson NM, Noroski LM, Zaki SR, Bellini WJ, Leduc MS, Yang Y, Eng CM, Patel A, Rodningen OK, Muzny DM, Gibbs RA, Campbell IM, Shaw CA, Baker MW, Zhang V, Lupski JR, Orange JS, Seeborg FO, Stray-Pedersen A (2014) Vaccine-associated varicella and rubella infections in severe combined immunodeficiency with isolated CD4 lymphocytopenia and mutations in IL7R detected by tandem whole exome sequencing and chromosomal microarray. Clin Exp Immunol 178:459–469
5. Trimble R, Atkins J, Quigg TC, Burns CC, Wallace GS, Thomas M, Mangla AT, Infante AJ (2014) Vaccine-associated paralytic poliomyelitis and BCG-osis in an immigrant child with severe combined immunodeficiency syndrome—Texas, 2013. MMWR Morb Mortal Wkly Rep 63:721–724
6. Shaghaghi M, Parvaneh N, Ostad-Rahimi P, Fathi SM, Shahmahmoodi S, Abolhassani H, Aghamohammadi A (2014) Combined immunodeficiency presenting with vaccine- associated paralytic poliomyelitis: a case report and narrative review of literature. Immunol Invest 2013 43(3):292–298
7. Canessa C, Romano F, Lippi F, Bianchi L, Kashef S, Rezaei N, Moriondo M, Nieddu F, Martini M, Azzari C (2013) Bcgitis and vaccine-derived poliovirus infection in a patient with a novel deletion in RAG1 binding site. Int J Immunopathol Pharmacol 26:511–515
8. Pai S-Y, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, Kapoor N, Hanson IC, Filipovich AH, Jyonouchi S, Sullivan KE, Small TN, Burroughs L, Skoda-Smith S, Haight AE, Grizzle A, Pulsipher MA, Chan KW, Fuleihan RL, Haddad E, Loechelt B, Aquino VM, Gillio A, Davis J, Knutsen A, Smith AR, Moore TB, Schroeder ML, Goldman FD, Connelly JA, Porteus MH, Xiang Q, Shearer WT, Fleisher TA, Kohn DB, Puck JM, Notarangelo LD, Cowan MJ, O'Reilly RJ et al (2014) Transplantation outcomes for severe combined immunodeficiency, 2000–2009. N Engl J Med 371:434–446

9. Norouzi S, Aghamohammadi A, Mamishi S, Rosenzweig SD, Rezaei N (2012) Bacillus Calmette-Guérin (BCG) complications associated with primary immunodeficiency diseases. J Infect 64:543–554
10. Stephan JL, Vlekova V, Le Deist F, Blanche S, Donadieu J, De Saint-Basile G, Durandy A, Griscelli C, Fischer A (1993) Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients. J Pediatr 123:564–572
11. Yeganeh M, Heidarzade M, Pourpak Z, Parvaneh N, Rezaei N, Gharagozlou M, Movahedi M, Shabestari MS, Mamishi S, Aghamohammadi A, Moin M (2008) Severe combined immunodeficiency: a cohort of 40 patients. Pediatr Allergy Immunol 19:303–306
12. Bakare N, Menschik D, Tiernan R, Hua W, Martin D (2010) Severe combined immunodeficiency (SCID) and rotavirus vaccination: Reports to the Vaccine Adverse Events Reporting System (VAERS). Vaccine 28:6609–6612
13. Centers for Disease Control and Prevention (CDC) (2010) Addition of severe combined immunodeficiency as a contraindication for administration of rotavirus vaccine. MMWR Morb Mortal Wkly Rep 59:687–688
14. Martire B, Azzari C, Badolato R, Canessa C, Cirillo E, Gallo V, Graziani S, Lorenzini T, Milito C, Panza R, Moschese V, with Italian Network for Primary Immunodeficiencies (IPINET) (2018 Jun 7) Vaccine 36(24):3541–3554
15. Red Book 2018–2021 (2018). 31st Edition. Report of Pediatrics Committee on Infectious Diseases American Academy of Pediatrics
16. Centers for Disease Control and Prevention (1994) Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. Official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. MMWR Recomm Rep 43(RR-12):1–19
17. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I (2014) 2013 IDSA clinical practice guideline for vaccination in the immunocompromised host. Clin Infect Dis 58:e44–e100
18. Hofstetter AM, Jakob K, Klein NP, Dekker CL, Edwards KM, Halsey NA, Baxter R, Williams SE, Graham PL 3rd, LaRussa P (2014) Live vaccine use and safety in DiGeorge syndrome. Pediatrics 133:e946–e954
19. Perez EE, Bokszczanin A, McDonald-McGinn D, Zackai EH, Sullivan KE (2003) Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Pediatrics 112:e325
20. Al-Sukaiti N, Reid B, Lavi S, Al-Zaharani D, Atkinson A, Roifman CM et al (2010) Safety and efficacy of measles, mumps, and rubella vaccine in patients with DiGeorge syndrome. J Allergy Clin Immunol 126:868–869
21. Leung DYM, Ambrosino DM, Arbeit RD, Newton JL, Geha RS (1988) Impaired antibody responses in the hyperimmunoglobulin E syndrome. J Allergy Clin Immunol 81:1082–1087
22. Albert MH, Notarangelo LD, Ochs HD (2011) Clinical spectrum, pathophysiology and treatment of the Wiskott–Aldrich syndrome. Curr Opin Hematol 18:42–48
23. Giovannetti A, Mazzetta F, Caprini E, Aiuti A, Marziali M, Pierdominici M, Cossarizza A, Chessa L, Scala E, Quinti I, Russo G, Fiorilli M (2002) Skewed T-cell receptor repertoire, decreased thymic output, and predominance of terminally differentiated T cells in ataxia telangiectasia. Blood 100(12):4082–4089
24. Staples ER, McDermott EM, Reiman A, Byrd PJ, Ritchie S, Taylor AMR, Davies EG (2008) Immunodeficiency in ataxia telangiectasia is correlated strongly with the presence of two null mutations in the ataxia telangiectasia mutated gene. Clin Exp Immunol 153:214–220
25. Cesaro S, Giacchino M, Fioredda F, Barone A, Battisti L, Bezzio S et al (2014) Guidelines on vaccinations in paediatric haematology and oncology patients. Biomed Res Int 2014:707691
26. Issekutz A, Top K, McKelvie B, Issekutz T, Letenyi D, McCusker C (2012) Fatal pneumococcal sepsis/meningitis in seven-year-old girl with IRAK-4 deficiency despite antibiotic prophylaxis and repeated pneumococcal vaccination. J Clin Immunol 32:S93

27. Jouanguy E, Altare F, Lamhamedi S, Revy P, Emile JF, Newport M, Levin M, Blanche S, Seboun E, Fischer A, Casanova JL (1996) Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guérin infection. N Engl J Med 335:1956–1961
28. Altare F, Lammas D, Revy P, Jouanguy E, Döffinger R, Lamhamedi S, Drysdale P, Scheel-Toellner D, Girdlestone J, Darbyshire P, Wadhwa M, Dockrell H, Salmon M, Fischer A, Durandy A, Casanova JL, Kumararatne DS (1998) Inherited interleukin 12 deficiency in a child with bacille Calmette- Guerin and Salmonella enteritidis disseminated infection. J Clin Invest 102:2035–2040
29. Boudjemaa S, Dainese L, Heritier S, Masserot C, Hachemane S, Casanova JL, Coulomb A, Bustamante J (2017) Disseminated bacillus Calmette-Guerin osteomyelitis in twin sisters related to STAT1 gene deficiency. Pediatr Dev Pathol 20:255–261
30. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC, Ouachée-Chardin M, Fouyssac F, Girisha KM, Etzioni A, Van Montfrans J, Camcioglu Y, Kerns LA, Belohradsky B, Blanche S, Bousfiha A, Rodriguez-Gallego C, Meyts I, Kisand K, Reichenbach J, Renner ED, Rosenzweig S, Grimbacher B, van de Veerdonk FL, Traidl-Hoffmann C, Picard C, Marodi L, Morio T, Kobayashi M, Lilic D, Milner JD, Holland S, Casanova JL, Puel A, International STAT1 Gain-of-Function Study Group (2016) Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood 127(25):3154–3164
31. Cotugno N, Finocchi A, Cagigi A, Di Matteo G, Chiriaco M, Di Cesare S, Rossi P, Aiuti A, Palma P, Douagi I (2015) Defective B-cell proliferation and maintenance of long-term memory in patients with chronic granulomatous disease. J Allergy Clin Immunol 135:753–761. e2
32. Oyachi N, Obana K, Suzuki T, Kimura S, Chino K, Oyama T, Takano K (2013) Costal BCG osteomyelitis developing 1 year after BCG vaccination. Pediatr Int 55:641–643
33. Lee PP, Lee P (2015) Disseminated bacillus Calmette-Guérin and Susceptibility to Mycobacterial Infections—Implications on Bacillus Calmette-Guérin Vaccinations *
34. Bustamante J, Aksu G, Vogt G, de Beaucoudrey L, Genel F, Chapgier A, Filipe-Santos O, Feinberg J, Emile JF, Kutukculer N, Casanova JL (2007) BCG-osis and tuberculosis in a child with chronic granulomatous disease. J Allergy Clin Immunol 120:32–38
35. Winkelstein JA, Marino MC, Johnston RB, Boyle J, Curnutte J, Gallin JI, Malech HL, Holland SM, Ochs H, Quie P, Buckley RH, Foster CB, Chanock SJ, Dickler H (2000) Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 79:155–169
36. Kersnik Levart T (2013) Post-vaccine glomerulonephritis in an infant with hereditary C2 complement deficiency: case study. Croat Med J 54:569–573
37. Schlesinger M, Kayhty H, Levy R, Bibi C, Meydan N, Phagocytic Killing LJ (2000) Antibody response during the first year after tetravalent meningococcal vaccine in complement-deficient and in normal individuals. J Clin Immunol 20:46–53
38. Fijen CA, Kuijper EJ, Drogari-Apiranthitou M, Van Leeuwen Y, Daha MR, Dankert J (1998) Protection against meningococcal serogroup ACYW disease in complement-deficient individuals vaccinated with the tetravalent meningococcal capsular polysaccharide vaccine. Clin Exp Immunol 114:362–369
39. Brodszki N, Skattum L, Bai X, Findlow H, Borrow R, Jönsson G (2015) Immune responses following meningococcal serogroups A, C, Y and W polysaccharide vaccination in C2-deficient persons: Evidence for increased levels of serum bactericidal antibodies. Vaccine 33:1839–1845
40. Eibl MM, Wolf HM (2015) Vaccination in patients with primary immune deficiency, secondary immune deficiency and autoimmunity with immune regulatory abnormalities. Immunotherapy 7:1273–1292
41. Poolman J, Borrow R (2011) Hyporesponsiveness and its clinical implications after vaccination with polysaccharide or glycoconjugate vaccines. Expert Rev Vaccines 10:307–322
42. Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA (2015) Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2015–16 Influenza Season. MMWR Morb Mortal Wkly Rep 64:818–825

43. Olkinuora H, Käyhty H, Davidkin I, Roivainen M, Ölander R-M, Kantele JM, Siitonen S, Vettenranta K (2012) Immunity after (re)vaccination of paediatric patients following haematopoietic stem cell transplantation. Acta Paediatr 101:e373–e377
44. Kennedy LB, Li Z, Savani BN, Ljungman P (2017) Measuring immune response to commonly used vaccinations in adult recipients of allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 23:1614–1621
45. Hilgendorf I, Freund M, Jilg W, Einsele H, Gea-Banacloche J, Greinix H, Halter J, Lawitschka A, Wolff D, Meisel R (2011) Vaccination of allogeneic haematopoietic stem cell transplant recipients: Report from the International Consensus Conference on Clinical Practice in chronic GVHD. Vaccine 29:2825–2833
46. Ljungman P, Cordonnier C, Einsele H, Englund J, Machado CM, Storek J, Small T (2009) Vaccination of hematopoietic cell transplant recipients. Bone Marrow Transplant 44:521–526. https://doi.org/10.1038/bmt.2009.263