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Immunization of children with secondary immunodeficiency

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The main causes of secondary immunodeficiency at a pediatric age include infectious diseases (mainly HIV infection), malignancies, haematopoietic stem cell or solid organ transplantation and autoimmune diseases. Children with secondary immunodeficiency have an increased risk of severe infectious diseases that could be prevented by adequate vaccination coverage, but vaccines administration can be associated with reduced immune response and an increased risk of adverse reactions. The immunogenicity of inactivated and recombinant vaccines is comparable to that of healthy children at the moment of vaccination, but it undergoes a progressive decline over time, and in the absence of a booster, the patients remain at risk of developing vaccine-preventable infections. However, the administration of live attenuated viral vaccines is controversial because of the risk of the activation of vaccine viruses. A specific immunization program should be administered according to the clinical and immunological status of each of these conditions to ensure a sustained immune response without any risks to the patients' health.

Introduction

Secondary immunodeficiencies occur when the immune system is damaged by an environmental factor such as an infectious disease, malignancy (that may also cause immunodeficiency itself) and immunosuppressive therapy.[1-3] The primary reasons to administer immunosuppressive drugs at the pediatric age include rheumatologic diseases (RDs), haematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT).[4-6]

Secondary immunodeficiencies are a heterogeneous group of illnesses in which the common factor is the increased risk of developing severe infectious diseases (**Table 1**). Vaccines play a significant role in the prevention of infection-related complications.[7] However, they may evoke little or no protection during a state of severe immunosuppression, and in the case of live attenuated viral vaccines, they could cause adverse effects when the immune system is seriously damaged.[7] The primary aim of this review was to analyze the main causes of severe immunodeficiency in pediatric patients and the recommended vaccines for these conditions.

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HIV Infection

In HIV infection, the immune impairment is related to the depletion of CD4+ T-cells[3] and the dysregulation of B-cells.[8] HIV chronically stimulates the immune system, inducing a higher expression of HLA-DR, CD38 (some activation antigens)[9] and CD95 (a pro-apoptotic receptor)[10] on the membrane of T-cells, leading to the reduction of naive CD4+ lymphocytes. Moreover, the persistent immune activation alters the B-cell subsets, which causes the activation of polyclonal B-cells and hypergammaglobulinemia[11] as well as the loss of memory B-lymphocytes.[12] Highly active antiretroviral therapy (HAART) is the treatment of choice in HIV-infected subjects, and it achieves viral suppression, restores CD4+ T-cells and normalizes the B-cell subsets.[13]

The immunological dysfunction caused by HIV can result in an insufficient and waning immune protection from vaccine-preventable diseases, and early HAART can lead to immune reconstitution, improvement in the immunogenicity of vaccines and the safety of live attenuated viral vaccines.[14]

All the inactivated vaccines included in the national schedules are strongly recommended in HIV-infected children.[15] In addition, influenza vaccination for the risk of influenza-related complications,[16] a booster with the 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent polysaccharide vaccine (PPSV) due to the high chance of invasive pneumococcal disease[17] and the quadrivalent meningococcal conjugate vaccine (MCV4) for the increased risk of meningitis[18] should be administered. Several studies have demonstrated the safety, the lack of an effect on the HIV RNA load and an adequate seroconversion after the administration of inactivated vaccines in HIV-infected children[18-26]; however, a decline in the antibody titers below the protective limit a few years post-immunization has been observed.[27-29] Predictive markers for a reduced persistence of protective antibody titers after vaccination include low CD4+ T-cell counts and the timing of HAART initiation in relation to

Table 1. Main conditions associated with secondary immunodeficiency at a pediatric age

Infectious diseases
HIV/AIDS
Malignancy
Hematological malignancies or solid tumors
Transplantation
Bone marrow (HSCT)
Solid organ (SOT)
Autoimmune disease
Miscellaneous (not addressed in this review)
Asplenia
Diabetes mellitus
Inflammatory bowel disease
Renal failure and/or dialysis
Hepatic cirrhosis
Malnutrition
Radiation, toxic chemicals

disease onset.[18,19] Timing of HAART initiation is crucial for effective and durable vaccine-induced protective immunity and precocious waning of vaccine-induced immunity is a phenomenon mostly involving patients treated in the chronic phases of HIV infection.[30,31] In addition, due to HIV-related risks, it is important to ensure adequate vaccination coverage against hepatitis A, hepatitis B and human papillomavirus (HPV) in these patients.[32-34]

Regarding the use of live attenuated vaccines, these immunizations prevent serious complications (principally measles with its complications and varicella dissemination); however, the immunocompromised status can also lead to the activation of vaccine viruses and to the development of more severe diseases. There are some studies about the safety, tolerability and immunogenicity of the measles, mumps and rubella (MMR) vaccine and the varicella vaccine in HIV-infected children.[35-37] These studies demonstrated that to reduce the risk of adverse events, patients should receive these live attenuated vaccines when immune reconstitution has been achieved (CD4+ T-cell counts >15%) by HAART.[35,38] In the presence of immune reconstitution, the safety and immunogenicity of live attenuated viral vaccines in HIV-infected children is similar to that observed in healthy subjects of a similar age.[36-38] Additionally, for live attenuated viral vaccines, CD4+ T-cell counts and the timing of HAART initiation are predictive of the immune response.[39] Likewise, the viral load before vaccination appears to be associated with the immunogenicity of the administered vaccines.[37, 39]

Regarding BCG vaccination, it is contraindicated for persons with HIV infection because it can result in severe disease in this population.[40] In tuberculosis-endemic regions, BCG vaccine is administered soon after birth, before *in utero* and peripartum HIV infection is excluded. Recombinant and engineered vaccines against *Mycobacterium tuberculosis* are under development and hopefully their availability will permit to offer protection also in HIV-infected children. [40]

Overall, the available literature shows that the vaccination schedule recommended in healthy children should be used in HIV-infected children who are adequately treated with HAART.[41] Ideally, vaccines should be administered once children are on HAART, have a good CD4+ count, and have an undetectable viral load. In addition, vaccination against influenza, pneumococcal and meningococcal infections as well as hepatitis A, hepatitis B and HPV should be recommended with booster doses to protect HIV-infected children from possible infectious complications. In these patients, it is important to ensure early and complete immunization, to vaccinate when the immunologic status is preserved and to provide booster doses if immunogenicity is poor. However, further research is required on new predictive markers that can indicate a protective immune response and better identify patients who require a booster.

Vaccination in Children with Cancer

Children with cancer receiving chemotherapy have an impaired immune function. These patients lose some of their acquired defenses and show a reduced immune response after vaccination.[42-44] Consequently, vaccine administration is not recommended during intensive chemotherapy because of the lack of potential efficacy and, in the case of live attenuated viral vaccines, the risk of adverse events. Protection against infectious diseases in this period can only be assured by clinical follow-up and, whenever possible, the prompt treatment of any diseases that may occur.

However, cancer patients who have stopped receiving chemotherapy for 3-6 months can be considered similar to healthy children in their immune response to vaccines.[42-44] Consequently, in absence of previous vaccination, these subjects can be vaccinated according to the schedule usually used for normal children of the same age. They should receive inactivated or recombinant vaccines 3 months after the completion of chemotherapy, whereas live attenuated viral vaccines (e.g., MMR and varicella vaccines) should not be given for an additional 3 months. Moreover, they should receive at least one dose of the *Haemophilus influenzae* type b (Hib) and pneumococcal vaccines regardless of age even though they are not recommended for normal children over 5 years of age.

In case of outbreaks, children with cancer can even be vaccinated with inactivated or recombinant vaccines during the last part of maintenance therapy.[42] However, they should be clinically monitored because their immune response to vaccines is reduced and protection against specific infectious agents will not be complete. In any case, live vaccines cannot be recommended during this period in absence of documented immune recovery because they are potentially dangerous.

It is more difficult to define the best solution for children who have started or completed their vaccination schedules before the diagnosis of cancer. In these patients, a possibility is to test residual immunity and then decide whether to administer all the scheduled doses of a certain vaccine, only a booster, or nothing at all. However, the antibody titers for each vaccine antigen are not always assessable and for some vaccines the protection correlates have not been already available.[45,46] Moreover, protection can be

present even with low antibody levels. One possibility is that these children receive a booster dose of all the vaccines, including the Hib and pneumococcal vaccines. Once again, they can receive inactivated or recombinant vaccines 3 months after the end of chemotherapy, and live attenuated viral vaccines after a post-chemotherapy interval of 6 months. However, due to herd immunity in countries in which more than 90% of the total pediatric population has been vaccinated against MMR, some experts suggest that the MMR vaccine can be avoided in children who have received very prolonged and powerful chemotherapy (for whom live vaccines can be dangerous).[47]

However, data are lacking on the best approach for children who have received some but not all the doses of a specific vaccine at the time of the cancer diagnosis and more information is required regarding these children. Experts suggest to administer them all the doses usually required to confer protection, regardless of those they have already received.[42] Moreover, research priorities include the evaluation of immunogenicity and safety of pneumococcal and meningococcal conjugate vaccines as well as the best vaccination schedule for HPV.

Vaccination in Children with Haematopoietic Stem Cell Transplantation (HSCT) or Solid Organ Transplantation (SOT)

A number of studies demonstrated that children who have undergone HSCT lose the protective immunity to vaccine-preventable infectious diseases that was achieved after childhood immunization.[48] Moreover, after HSCT, the recovery of cellular immunity may require months or even years, and in the absence of re-immunization, antibody titers to pathogens for which vaccines had been administered decreases during the 1–10 years after HSCT.[49] Consequently, repeating the primary vaccine series after HSCT is critical to prevent life-threatening infections.

As for other causes of immunosuppression, inactivated and recombinant vaccines are not contraindicated, and the vaccines should be administered 6–12 months after HCST.[50,51] Influenza vaccine is recommended for all HSCT candidates and recipients, and it should be repeated annually.[52] Although the immune response may be suboptimal in these patients, it has appeared satisfactory, with no observed safety issues. Also a booster with PCV13 and PPSV is recommended.[52]

As for other immunodeficiencies, live attenuated viral vaccines are generally contraindicated because of the risk of disease caused by the vaccine strains. Revaccination with MMR should be delayed for at least 24 months after HSCT in children who no longer have a need for pharmacological immunosuppression and do not have graft versus host disease (GVHD).[53,54] Considering that patients with HSCT have an increased risk of developing herpes zoster mainly after the first 2 years, varicella vaccine with a 2 doses one month apart should be given 24 months after HSCT to varicella seronegative patients with neither GVHD nor ongoing immunosuppression and 8–11 months after the last dose of intravenous immunoglobulins.[54,55]

Children who are candidates for SOT are at an increased risk of infectious complications, and every effort must be made to complete the appropriate vaccinations before SOT.[56] However, children may not receive the complete vaccinations before the SOT for medical reasons or because of parental refusal of vaccination.[57]

Additionally, after SOT, inactivated vaccines are generally safe with no evidence to link rejection episodes to vaccination, whereas live attenuated viral vaccines are contraindicated.[56] The timing of the vaccines after SOT is a matter of debate: most centers restart vaccination approximately 3–6 months after SOT once maintenance immunosuppression levels have been reached.[56] The routine seasonal administration of an inactivated influenza vaccine is recommended annually for these patients as well as a booster with PCV13 and PPSV.[58]

The experts recommend waiting a minimum of 4 weeks between live virus vaccine administration and SOT.[54] All children should ideally receive a 2-dose series of the MMR vaccine, with at least 4 weeks between doses.[56] Although the MMR vaccine is most effective after one year of age when maternal antibodies have waned, to immunize pediatric SOT candidates younger than one year of age prior to transplantation, the MMR vaccine can be given as early as 6 months of age in infants not receiving immunosuppression. If transplantation has not occurred by one year of age, another dose should be given, provided that a minimum of 4 weeks has elapsed since the previous dose.[54,56] Given the risk of severe varicella infection in non-immune SOT recipients, the varicella vaccine should be administered before transplant.[54,56]

Only new data will allow us to draw up evidence-based recommendations to ensure that all these high-risk patients are adequately protected against infectious diseases.

Vaccine Recommendations for Children with Rheumatologic Disease (RD)

An analysis of the international literature shows that there are few data on vaccination in children with RD.[59] The available studies show that conventional RD therapy does not significantly influence the immune responses to vaccines, whereas the new biological drugs can reduce antibody production. However, it is not possible to establish whether immunogenicity to vaccines is reduced by certain biological drugs more than by others, what doses can influence antibody responses, or whether active disease (*per se* or because of its required treatment) justifies the reduced immune responses. Moreover, some case reports in adults have suggested possible associations between vaccinations and the induction or exacerbation of autoimmune reactions, but these data have not been confirmed by prospective investigations or thorough case-control studies. Due to these unanswered issues, approximately one-third of children with RDs are incompletely vaccinated.[59,60]

The available evidence is sufficient to encourage vaccines use in children with stable AD.[61,62] This is the recommendation for inactivated and recombinant vaccines regardless of the degree of

Table 2. Suggested vaccination according to underlying secondary immunodeficiency

Underlying secondary immunodeficiency	Inactivated vaccines	Live attenuated vaccines	Advice
HIV infection	All those included in the national schedules (including HPV) are strongly recommended In addition, annual influenza vaccination, a booster with PCV13 and PPSV, a dose of MCV4, hepatitis A and hepatitis B vaccines are recommended due to HIV-related risks	MMR and varicella vaccines are recommended due to available studies on their immunogenicity, safety, and tolerability Other live attenuated vaccines (including BCG) are controindicated	Vaccines should be administered once children are on HAART, have a good CD4+ count, and have an undetectable viral load
Cancer	Administration of the primary schedule or booster dose in patients off-therapy for 3 months These patients should receive at least one dose of Hib and PCV13 regardless of age when they are off-therapy since 3 months n addition, annual influenza vaccination is recommended	MMR vaccine should be administered in patients off-therapy for 6 months Varicella vaccine should be administered in patients in continuous remission for at least one year, with a lymphocyte count of $>700/\mu L$ and a platelet count of $>100,000/\mu L$; if still being treated in an epidemic period, they should stop drug administration one week before and for one week after vaccination Other live attenuated vaccines can be administered in patients off-therapy for 6 months	In the presence of outbreaks, inactivated or recombinant vaccines can even been administered during the last part of maintenance therapy
Haematopoietic stem cell transplantation (HSCT)	All those included in the national schedules (including HPV) are strongly recommended 6–12 months after HSCT In addition, lifelong annual influenza vaccination and a booster with PCV13 and PPSV are recommended	MMR should be delayed for at least 24 months after HSCT in children who no longer have a need for pharmacological immunosuppression and do not have graft versus host disease Varicella vaccine should be given 24 months after HSCT to varicella seronegative patients with neither GVHD nor ongoing immunosuppression and 8–11 months after the last dose of intravenous immunoglobulin Other live attenuated vaccines are generally contraindicated	Repeat primary vaccine series with inactivated vaccines 6–12 months after HSCT
Solid organ transplantation (SOT)	Inactivated vaccines can be administered 3–6 months after SOT In addition, lifelong annual influenza vaccination and a booster with PCV13 and PPSV are recommended	Live attenuated vaccines are generally contraindicated	Vaccines should be administered once maintenance immunosuppression levels have been reached MMR and varicella vaccines should be administered 4 weeks before SOT
Rheumatologic diseases (RDs)	All those included in the national schedules (including HPV) are strongly recommended In addition, annual influenza vaccination and a booster with PCV13 and PPSV are recommended due to RD-related risks	MMR vaccine can be safely administered Other live attenuated vaccines should not be administered in the presence of severe immunosuppression	Vaccinations should be postponed only in the case of severe active RD (and then only until the child has stabilized), and a vaccine should be avoided if it has previously caused a disease relapse In patients on rituximab treatment, vaccines should be avoided until B cell levels return to normal values

GVHD: graft vs. host disease; HAART: highly active antiretroviral therapy; Hib: *Haemophilus influenzae* type b; HPV: human papillomavirus; HSCT: haematopoietic stem cell transplantation; MCV4: quadrivalent meningococcal conjugate vaccine; PCV13: 13-valent pneumococcal conjugate vaccine; PPSV: 23-valent polysaccharide vaccine; RD: rheumatologic disease; SOT: sold organ transplantation.

immunosuppression and for all disease subgroups regardless of the treatments given. Vaccinations should be postponed only in the case of severe active RD (and then only until the child has stabilized) to avoid any misunderstandings related to safety issues (i.e., adverse events attributed to a vaccination but actually due to the underlying disease), and a vaccine should be avoided if it has previously caused a disease relapse.[61,62] In patients on rituximab treatment, vaccines should be avoided until B cell levels return to normal values,[62,63]

Studies are lacking on the immune response and adverse reactions to live attenuated vaccines in children with RD. Although the available studies show that the MMR vaccine is safe, children with RD should not receive other live vaccines in the presence of severe immunosuppression.[61,62] On the contrary, in these patients pneumococcal and annual influenza vaccinations should be strongly recommended because of the increased risk of these infections associated with immunosuppressive therapy.[61,62]

However, priorities for future research include a number of areas. First, there is an urgent need for studies on the persistence of immunity induced by the 13-valent pneumococcal conjugate vaccines to determine how frequently booster doses are required. There is also a need for studies of HPV vaccines (usually administered after RD diagnosis) because immunocompromised patients are at an increased risk of HPV infection. Moreover, it is essential to clarify how long HPV vaccine-induced immunity lasts and whether 2 vaccine doses are enough to protect RD patients. Finally, educational programs on the risks associated with vaccine-preventable diseases in patients with RDs are required for healthcare workers, the patients and their.

Conclusions

In children with secondary immunodeficiency status, vaccination has a key role in protecting against infectious diseases and preventing their complications. **Table 2** summarizes the suggested vaccination according to underlying secondary immunodeficiency. By analyzing the data from the literature, the inactivated and recombinant vaccines appear safe and well-tolerated in these conditions. Their immunogenicity is comparable to that of healthy children at the moment of vaccination, but it undergoes a progressive decline over time, and in the absence of a booster, the patients remain at risk of developing vaccine-preventable infections. For this reason, in children with secondary immunodeficiency, minimum protective antibody levels against vaccine antigens should be monitored, and these children should receive booster doses if the immune response falls under the protective line. However, the administration of live attenuated vaccines is controversial because of the risk of the activation of vaccine viruses and the development of disseminated infections. A specific immunization program should be performed according to the clinical and immunological status for each of these conditions to ensure a higher, sustained immune response with the lowest risk to the health of the patients. In addition, there is the concern for immunodeficient patients to acquire infections from healthy subjects who have not been immunized or who are shedding live vaccine-derived viral or bacterial organisms, especially nowadays with the progressive increased rates of unvaccinated individuals due to vaccine refusal.[64] This highlights the importance to ensure adequate vaccination coverage in close contacts of patients with immunodeficiency in order to protect these vulnerable subjects and to permit them to integrate into society, attend school, and benefit from peer education.

Disclosure of Potential Conflicts of Interest

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