Clinical Focus on Primary Immune Deficiencies

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ISSUES AND INFORMATION ON CURRENT TOPICS

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Immunization Of The Immunocompromised Host

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Immunocompromised persons vary in their degree of immunosuppression, response to immunization, and susceptibility to infection. These differences correspond to three issues of importance in the vaccination of immunocompromised persons: vaccine safety, vaccine efficacy and the potential benefit of particular vaccines in specific immunodeficiency disorders. Vaccine safety correlates with the degree and type of immunosuppression, ranging from mild or limited deficits in immune function to severe abnormalities in multiple arms of the immune system. In general, severely immunocompromised persons should not receive live, attenuated vaccines because of the risk of disease caused by the vaccine strain. Vaccine efficacy also is dependent upon the nature and degree of immunosuppression. For example, persons with X-linked agammaglobulinemia will not develop an antibody response following any immunization. Vaccine benefit relates to the nature of the immunodeficiency and the risks of infection with specific pathogens. For example, persons with asplenia and terminal complement deficiencies are at increased risk of infection with encapsulated bacteria. They may have even more benefit from pneumococcal and meningococcal vaccines than healthy children who do not have the same susceptibility to those infections.

Information on vaccine safety and efficacy in patients with specific immunodeficiency diseases frequently is not available. Most of this information has been extrapolated from studies on persons with HIV infection, cancer and renal failure. Assessment of vaccine efficacy in immunocompromised patients is further complicated because efficacy is often assessed indirectly by measuring antibody responses rather than protection against infection and disease. In the normal population, there often appears to be a correlation between antibody level and protection. Although this would imply that immunization of patients unable to mount an antibody response would have no benefit, this assumption has never been verified.

Not All Immunodeficiencies Are Alike

Primary disorders of the immune system can be divided into four categories: (1) disorders of humoral immunity (antibody), (2) disorders of cell-mediated and humoral immunity, (3) disorders of phagocytes, and (4) disorders of complement. In addition, there are many causes of secondary immunodeficiency, such as treatment with immunosuppressive or chemotherapeutic agents, protein-losing enteropathy and HIV infection. Each group of diseases presents different issues related to the risks and benefits of vaccines.

Disorders of Humoral Immunity

There is a spectrum of disease within this category ranging from patients with an inability to make any type of antibody response to patients whose only defect is making an IgA antibody response. Patients with severe deficiencies of humoral immunity (X-linked agammaglobulinemia and common variable immunodeficiency) have little or no ability to mount antibody responses to vaccines or microbial pathogens. They are highly susceptible to infections caused by encapsulated bacteria and enteroviruses, including polio and coxsackie viruses. Treatment with prophylactic intravenous infusions of gamma globulin (IVIG) is effective at preventing bacterial sepsis and meningitis, but may be less helpful for preventing sinusitis and bronchitis. Less severe forms of humoral immune deficiency include patients with selective inability to produce antibodies of a specific class (IgA deficiency) or subclass (IgG subclass deficiency). They generally have less severe problems with infection since some elements of humoral immunity are intact. IgA deficient patients typically develop infections along mucosal surfaces (otitis, sinusitis and bronchitis) but rarely develop tissue invasive infections because they have normal ability to produce IgG and IgM antibodies.

Disorders of Cell-Mediated and Humoral Immunity

This group of disorders includes the variants of severe combined immunodeficiency disease (SCID). Patients are highly susceptible to all microbial pathogens including encapsulated bacteria such as pneumococci, fungi such as *Candida albicans*, a wide variety of viruses and opportunistic infections such as *Pneumocystis carinii*. Patients with SCID do not develop any antibody or cell-mediated immune response to vaccines or natural infections. Although they have normal numbers of phagocytic cells, bactericidal function is often impaired due to lack of T cell cytokines. Serum complement levels are normal, but antibody-induced activation of complement depends entirely on exogenously administered gamma globulin. Therapy for this group of patients is supportive (passive immunization with intravenous gamma globulin), unless bone marrow transplantation can be performed.

Disorders of Phagocytic Cells

The best known examples of these disorders include chronic granulomatous disease (CGD) - a disease of defective bactericidal function of phagocytes, and leukocyte adhesion deficiency (LAD) - a disease of defective phagocytic cell locomotion. Patients with defective phagocytic function are susceptible to bacterial and fungal infections. Intracellular bacterial pathogens such as mycobacteria and fungi can cause abscesses of the spleen and liver, lymphadenitis and chronic granulomatous lesions of the lung.

Another example of phagocytic deficiency is asplenia, either anatomic or functional. In either case, there is a predisposition to bloodborne infections because of a loss of the phagocytic filtering mass of the spleen. The incidence of pneumococcal bacteremia is greatly increased in persons with asplenia, and such infections can progress to fatal bacterial sepsis within hours.

Table 1:
Classification of Selected Primary Immunodeficiency Diseases

Deficiency of humoral immunity
- X-linked agammaglobulinemia
- Common variable immunodeficiency
- Selective IgA deficiency

Deficiency of cell-mediated and humoral immunity
- Severe combined immunodeficiency

Deficiency of phagocyte function
- Chronic granulomatous disease
- Leukocyte adhesion deficiency

Deficiency of complement
- Deficiency of early components (C1-C5)
- Deficiency of late components (C6-C9)

Complement deficiency

The complement system includes approximately two dozen proteins that can be activated by antibody-antigen complexes or microbial products such as polysaccharides. When activated, the complement system recruits phagocytic cells to areas of infection, enhances the ability of B lymphocytes to produce antibody, and causes the formation of lytic pores spanning the cell wall of gram-negative bacteria. Patients with deficiencies of early complement components have a predisposition to develop bacterial sepsis caused by gram-positive encapsulated organisms and a predisposition to develop autoimmune diseases such as systemic lupus erythematosis. Patients with deficiencies of late complement components (C6 to C9) are susceptible to infection caused by *Neisseria* species.

Vaccines Safe for Use in Immunocompromised Persons

Vaccines that are not composed of live viruses or bacteria are generally safe for administration to immunocompromised persons. "Safe vaccines" include toxoid vaccines, polysaccharide vaccines, inactivated bacterial and viral vaccines, viral subunit vaccines and recombinant viral vaccines. Despite their safety, persons with some immunodeficiencies will not respond to these vaccines. Persons with severely impaired humoral immunity, such as X-linked agammaglobulinemia and severe combined immunodeficiency, will not develop an antibody response to these vaccines. However, persons with milder or more limited forms of impaired humoral immunity such as selective IgA deficiency, and persons with defects of phagocytosis and complement usually will respond adequately to these vaccines. Persons with impaired humoral immunity should not be assumed to be protected against infection after vaccination. Measurement of specific antibody titers following vaccination is a reasonable way to assess vaccine efficacy and determine if additional booster doses of vaccine are necessary.

Toxoid Vaccines

Toxoids are inactivated bacterial toxins that induce immunity against toxin-mediated infections. Recommended toxoid vaccines are diphtheria and tetanus vaccines, which are safe in immunocompromised children because they consist of non-infectious, inactivated toxins. Although there is no greater risk for adverse reactions, persons with significantly impaired humoral immunity may not have an adequate immune response to toxoid vaccines to provide protection. Because the only adverse reactions to these vaccines are local discomfort or low-grade fever, and these adverse reactions are no more likely in an immunodeficient patient than

in a normal host, toxoid vaccines can be administered safely to test the function of a patient's immune system. Measurement of pre- and post-immunization antibody levels are useful for this purpose.

Polysaccharide Vaccines

The polysaccharide capsules of bacteria such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae* are virulence factors which inhibit phagocytosis. Polysaccharide vaccines provide protection against infection by inducing opsonic antibodies, enhancing the rate of phagocytosis. Polysaccharide vaccines are generally not immunogenic in children under two years of age, but immunogenicity can be improved by conjugation of polysaccharide antigens with proteins such as the outer membrane protein of *Neisseria meningitidis* and diphtheria or tetanus toxoids. As with toxoid vaccines, polysaccharide vaccines are non-infectious and safe for use in immunocompromised persons. Available polysaccharide vaccines include vaccines for *Haemophilus influenzae* type b, pneumococcus and meningococcus.

Haemophilus influenzae type b conjugate vaccine is recommended for all children and has greatly diminished the risk of invasive infections such as sepsis and meningitis. Older children and adults at high risk of *Haemophilus influenzae* type b infections who were not immunized previously should also be considered candidates for *Haemophilus influenzae* type b vaccine. This vaccine may not be useful in patients with severe antibody deficiency, but should be used for all immunodeficient patients who are not receiving regular prophylactic infusions of gamma globulin.

Although ninety pneumococcal serotypes have been identified, a limited number of serotypes most commonly cause invasive pneumococcal disease. The available pneumococcal vaccine contains capsular polysaccharide antigens of 23 pneumococcal serotypes, including the majority of serotypes likely to cause infection in children and adults. Pneumococcal immunization is not recommended for all children, but is reserved for children two years of age or older who are at increased risk of acquiring pneumococcal infection or at increased risk of serious disease if infected. This includes persons with complement deficiency, defects of phagocytic function, asplenia, HIV-infected persons, those receiving immunosuppressive medications including long-term, systemic corticosteroid therapy, and persons with chronic lung or renal disease. The current 23-valent pneumococcal vaccine is not immunogenic in children less than two years of age, but evaluation of protein conjugate vaccines is underway. Revaccination with pneumococcal vaccine is recommended after 3 to 5 years in asplenic children who are less than 10 years of age, and at 5-10 year intervals for high risk older children and adults.

The primary meningococcal serotypes causing infection in the United States are serogroups B and C, but the licensed meningococcal vaccine is a tetravalent polysaccharide vaccine against serogroups A, C, Y and W-135. Serogroup B is not a component of the current vaccine because of the poor immunogenicity of the group B polysaccharide. Serogroup A polysaccharide is immunogenic in children 3 months of age and older; however, the immunogenicity of the other vaccine serogroups is poor under 2 years of age. Meningococcal vaccine is recommended at 2 years of age or older for persons with asplenia and terminal complement deficiencies.

Inactivated Bacterial Vaccines

Inactivated bacterial vaccines resemble toxoid and polysaccharide vaccines in being non-infectious and safe for administration in immunocompromised persons, but differ in containing multiple, bacterial-derived antigens.

Table 2:
Vaccine Safety and Efficacy in Immunocompromised Persons

Vaccine	Safety	Efficacy
Toxoid vaccines Tetanus toxoid Diphtheria toxoid Polysaccharide vaccines Haemophilus influenzae b Pneumococcus Meningococcus Inactivated bacterial vaccines Pertussis Inactivated and subunit viruses Inactivated poliovirus (IPV) Influenza virus whole-cell split-virus Recombinant viral vaccines Hepatitis B	Safe for use.	Not efficacious for persons with severe defects of humoral immunity (X-linked agammaglobulinemia, common variable immunodeficiency and severe combined immunodeficiency). Probably not necessary for patients receiving regular prophylactic infusions of human immunoglobulin (IVIG). Of potential benefit in persons with selective IgA deficiency, asplenia, disorders of complement and impaired phagocytic function.
Live virus vaccines Live poliovirus (OPV) Measles Mumps Rubella Varicella	Not safe for use in persons with severely impaired humoral or cellular immunity	
Live bacterial vaccines BCG	Not safe for use in persons with disorders of cell mediated immunity or phagocytic function.	Rarely indicated in the United States.

Whole-cell pertussis vaccine is a suspension of inactivated *Bordetella pertussis* cells containing multiple antigens, including endotoxin. The latter is responsible for many of the adverse reactions following pertussis immunization. Acellular pertussis vaccine contains a limited number of *Bordetella pertussis* antigens, including pertussis toxin, but little or no endotoxin. Diphtheria and tetanus toxoid vaccines are administered in combination with whole cell pertussis vaccine (DTP) and acellular pertussis vaccine (DTaP). There is no data related to risk for adverse reactions to either of these vaccines among substantial numbers of patients with primary immunodeficiencies, but there are no theoretical reasons to believe that adverse reactions would be more severe or more frequent than in immunocompetent individuals.

Inactivated and Subunit Viral Vaccines

Inactivated and subunit viral vaccines are not infectious and are safe for administration in immunocompromised persons. Inactivated poliovirus vaccine (IPV) contains poliovirus types 1, 2 and 3 grown in monkey kidney or human diploid cell lines and inactivated with formaldehyde. IPV is safe for use in immunocompromised persons and must be used in place of the live, attenuated oral poliovirus vaccine (OPV) in persons with profound defects of humoral and cellular immunity, and in infants born to HIV-infected mothers. Since there can be person-to-person transmission of the attenuated poliovirus, OPV should not be used in any member of a household with an immunodeficient patient. *In fact, because many patients with primary immune deficiency diseases are not diagnosed in the first year of life and have a negative family history, the Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP) recommends that IPV be used exclusively for immunization of all children less than 12 months old.*

Trivalent influenza vaccines are prepared annually based on the anticipated viral subtypes for the coming epidemic season, and contain antigens from two influenza A subtypes and one influenza B subtype. Influenza vaccines are either formalin-inactivated, whole-virus vaccines or "split-virus" vaccines, and are safe for administration in immunocompromised persons. "Split-virus" vaccines contain either purified surface antigens or subvirions prepared by disrupting the lipid membrane. Only "split-virus" vaccines should be administered to children younger than 13 years because of the high rate of local and febrile reactions with whole-virus vaccines. Protection against influenza in healthy children and adults following vaccination ranges from 50% to 95%, but the duration of protection is short lived, usually less than one year. Persons receiving chemotherapy or high-dose corticosteroids have a diminished antibody response to influenza vaccine, as do HIV-infected persons with low CD4+ T-lymphocyte cell counts. However, because of the potential severity of influenza in immunocompromised persons and the small risk of adverse effects, influenza vaccine is recommended except in patients with severe hypogammaglobulinemia who are receiving IVIG therapy. Booster vaccinations may be necessary to sustain protective immunity through the influenza season.

Recombinant Viral Vaccines

The available hepatitis B vaccine is a recombinant DNA vaccine consisting of hepatitis B surface antigen (HBsAg) expressed in the yeast *Saccharomyces cerevisiae*. Because the protein is not normally glycosylated, the recombinant vaccine is less immunogenic than the plasma-derived HBsAg vaccine, but high-level antibody response to hepatitis B recombinant vaccine occurs in 90-95% of healthy adults. Many nonresponders develop sufficient antibody titers after a second complete course of vaccination, but persons with severely impaired humoral immunity will not develop an antibody response to hepatitis B vaccine. Adults and children receiving chemotherapy have a 75% response rate to hepatitis B vaccine, whereas HIV-infected persons have only a 25-50% response rate. Additional or larger doses of hepatitis B vaccine can induce immunity in some patients. For example, patients receiving hemodialysis treatment should receive two to four times the standard dose of hepatitis B vaccine, depending upon the vaccine manufacturer. In addition, annual anti-HBsAg testing is recommended for hemodialysis patients, and booster doses should be administered if the antibody concentration is less than 10 mIU/ml.

Potentially Harmful Vaccines in Immunocompromised Hosts

Live, attenuated viral and bacterial vaccines induce immunity by causing a limited infection. Persons with some immunodeficiency disorders, generally those with impaired humoral or cellular immunity, may not be able to contain infection with live, attenuated vaccine strains. Severe disease can result. However, persons with selective IgA deficiency, asplenia, disorders of complement, and impaired phagocytic function do not appear to be at higher risk of complications than the general population. Clinicians should weigh the risks and benefits of live, attenuated vaccines in the care of individual immunocompromised patients.

Live Viral Vaccines

Live, attenuated oral poliovirus vaccine (OPV) can cause vaccine-associated paralytic poliomyelitis (VAPP), particularly in persons with severely impaired humoral or cellular immunity. For example, the risk of VAPP is ten thousand times greater in patients with hypogammaglobulinemia than in healthy persons. VAPP can be the initial presentation of congenital or acquired immunodeficiencies, warranting caution in the administration of OPV to siblings of children with a known immunodeficiency. The risk of VAPP in HIV-

Table 3:
Immunization of Household Contacts of Immunocompromised Persons

Vaccines recommended for household contacts

- Influenza vaccine
- Measles vaccine
- Mumps vaccine
- Rubella vaccine
- Varicella vaccine

Vaccines contraindicated in household contacts

- Live, attenuated poliovirus vaccine

infected children who have received OPV appears to be low; nevertheless, HIV-infected children should receive IPV. In fact, since the newer generation IPV vaccine has increased immunogenicity, there is no need to incur the risk of OPV in a patient with any immunodeficiency or in a household contact of such a patient.

Measles vaccination is generally contraindicated in immunocompromised persons because of the risk of infection with vaccine virus. However, infection with wild-type measles virus can be severe in persons with defective cell-mediated immunity. Measles in HIV-infected adults and children frequently results in giant cell pneumonitis and has a high case-fatality rate. Use of measles vaccine in patients with deficiencies of humoral and/or cell-mediated immunity is controversial. Early in the HIV epidemic, measles vaccine was not recommended for symptomatic HIV-infected patients in the United States. Measles epidemics from 1989 to 1991 resulted in severe and fatal measles in HIV-infected children and adults, prompting the use of measles vaccine in symptomatic HIV-infected persons. No serious adverse effects were noted, and measles immunization of HIV-infected children became routine. However, in 1996, the CDC reported the first known death due to measles vaccine virus in a 20 year old HIV-infected man. He had a very low CD4 count but no HIV-related symptoms, and was not receiving antiretroviral therapy at the time of vaccination. Ten months after immunization he developed fatal giant cell pneumonia due to measles vaccine virus. Because of this case, the ACIP recommends measles vaccine not be administered to HIV-infected persons with severe immunosuppression based on age-specific CD4+ T-lymphocyte counts.

Mumps and rubella vaccines are usually administered with measles vaccine (MMR); all are live, attenuated virus vaccines. Vaccination with mumps and rubella vaccines is generally contraindicated in persons with severe defects of humoral or cellular immunity and in those receiving immunosuppressive therapy, although reports of adverse events are uncommon. Symptomatic HIV-infected persons who are not severely immunocompromised may receive mumps and rubella vaccines. The immunogenicity of mumps and rubella vaccines in immunocompromised persons has not been well studied. Antibody responses to mumps and rubella vaccines were decreased in HIV-infected children and bone marrow transplant recipients.

Varicella can be severe in immunocompromised persons, particularly those with defective cellular immunity. In addition, children with varicella have an increased risk of invasive group A streptococcal infection. Both of these problems can be reduced by use of varicella vaccine. The immunogenicity and safety of this live, attenuated viral vaccine has been extensively studied in children with acute lymphocytic leukemia (ALL). In spite of extensive experience in children with ALL, varicella vaccine is not recommended for other immunocompromised persons, including those with "congenital immunodeficiencies." However, as stated previously, not all immunodeficient patients are alike. The risk of complications from varicella vaccine is probably greatest in persons with defective cell-mediated immunity, and minimal in persons with selective IgA deficiency, asplenia, complement deficiencies and disorders of phagocytic function. Children with ALL in remission for at least one year can

Table 4:
Guidelines for Immunization in Specific Immunodeficiency Disorders

Immunodeficiency	Vaccine Efficacy	Vaccine Safety	Vaccines of Special Benefit
X- Linked Agammaglobulinemia Common Variable Immunodeficiency	Doubtful efficacy of vaccines for which antibody provides protection.	Live viral vaccines are contraindicated.	
IgA Deficiency	Killed and live vaccines are probably efficacious.	Inactivated viral vaccines are preferred. Live viral and bacterial vaccines are probably safe.	Patients may benefit from pneumococcal and influenza vaccines.
Severe Combined Immunodeficiency	Doubtful efficacy of vaccines for which humoral or cellular immunity important for protection.	Live viral and bacterial vaccines are contraindicated.	
Chronic Granulomatous Disease	Killed and live viral vaccines are probably efficacious.	Live viral vaccines are safe. Live bacterial vaccines (BCG) are contraindicated.	Influenza and varicella vaccines may decrease the risk of secondary bacterial infections.
Asplenia	Killed and live viral vaccines are probably efficacious.	Live viral vaccines are safe.	Polysaccharide vaccines against pneumococcus and meningococcus are recommended.
Complement Deficiencies	Killed and live viral vaccines are probably efficacious.	Live viral and bacterial vaccines are safe.	Meningococcal vaccine is recommended in persons with deficiencies of terminal complement components.

receive varicella vaccine as part of a study protocol. Our usual practice is to administer this vaccine even to immunodeficient patients if they have documented normal cell-mediated immunity and ability to produce normal IgG antibody responses to a "test vaccine" such as tetanus toxoid. Varicella vaccine virus can be transmitted to household contacts. The varicelliform rash is usually mild, transmission to household contacts is infrequent, and those household contacts usually have very mild illness. Therefore, the risk of administering varicella vaccine to the household contacts of an immunodeficient patient may be smaller than the risks associated with natural infection. Thorough investigation of the nature of the immune deficiency is warranted before making the decision to immunize an individual patient with varicella vaccine.

Live Bacterial Vaccines

No live bacterial vaccines are recommended for routine use in the United States. The bacillus Calmette-Guerin (BCG) vaccine, derived from an attenuated strain of *Mycobacterium bovis*, is used in many other countries to prevent meningeal and miliary tuberculosis in infants and young children. Indications for the use of BCG in the United States include health care workers in high-risk settings and children with intimate and prolonged exposure to a person with contagious tuberculosis, particularly if the isolate is resistant to isoniazid and rifampin. BCG should never be given to persons with impaired cellular immunity or defective phagocytic function because of the risk of severe local or disseminated mycobacterial infection.

Guidelines for Immunization of Patients with Selected Immunodeficiency Diseases

Severe Deficiency of Humoral Immunity

Patients with severe deficiency of humoral immunity, for example X-linked agammaglobulinemia and common variable immunodeficiency, generally have no ability to mount an antibody response to any vaccine, and are treated with prophylactic doses of pooled human gamma globulin. Since the efficacy of most of the currently licensed vaccines appears to require the production of pathogen-specific antibodies (BCG vaccine is an exception), the value of immunization in these patients is doubtful. Other than the issues of cost and the discomfort of an injection, there is no contraindication to immunization with killed vaccines. However, there is a serious risk of harm from the use of live, viral vaccines in this patient group. Due to the inability to produce neutralizing antibodies, immunization with live vaccines such as oral polio vaccine (OPV) may lead to a prolonged state of viral colonization. This can occur in the absence of direct immunization, as person-to-person transmission of vaccine poliovirus has been documented. An immunologically normal infant immunized with live, oral polio vaccine can transmit vaccine virus to an agammaglobulinemic adult through fecal-oral contamination. Within the hypogammaglobulinemic host, attenuated poliovirus can mutate and revert to a wild type virus that is capable of causing acute paralytic polio and/or chronic meningoencephalitis. For these reasons, OPV and all other live viral vaccines are absolutely contraindicated in patients with severe deficiencies of humoral immunity. In fact, largely because of OPV complications in this patient population, expanded use of the inactivated polio vaccine (IPV) is recommended in the United States.

Selective IgA Deficiency

Patients with selective IgA deficiency have an inability to produce antibodies of the IgA class, but have normal ability to produce IgG and IgM antibodies in response to vaccines and natural infection. There is no contraindication to the use of any killed vaccine in persons with selective IgA deficiency. In fact, those IgA deficient patients who suffer from recurrent sinopulmonary infections may derive benefit from immunization with pneumococcal polysaccharide and influenza virus vaccines. No formal studies of live viral vaccines have been performed in this group, but the lack of case reports of vaccine complications suggests that immunization with varicella and measles/mumps/rubella vaccines is safe. After documenting that a child with IgA deficiency has normal serum antibody responses to killed vaccines such as tetanus toxoid or one of the *Haemophilus influenzae* type b conjugate vaccines, we recommend live attenuated varicella and measles/mumps/rubella vaccines as a safer alternative to natural infection. There is no need to use OPV since IPV is highly immunogenic and carries no risk for mutation to wild-type virus.

Severe Combined Immunodeficiency

Infants with any of this group of disorders have no humoral or cell-mediated immune function and are highly susceptible to the complications of all live vaccines. They suffer from the same high risk of chronic or severe infection caused by live poliovirus, varicella or measles/mumps/rubella vaccines as patients with severe humoral immune deficiency. In addition, the lack of T cell function leads to deficiencies in interferon-gamma production and secondary deficiencies of bactericidal function of phagocytic cells. These patients can develop disseminated infection with the attenuated BCG strain of mycobacteria that can be difficult if not impossible to treat. In addition to the prohibition of direct immunization with live viral or bacterial vaccines, patients with severe combined immunodeficiency should be isolated from immunologically normal individuals who have recently been immunized with any of these vaccines.

Chronic Granulomatous Disease

Patients with disorders such as chronic granulomatous disease have normal ability to mount humoral and cell-mediated lymphocyte responses to vaccines, and phagocytic cells such as monocytes and polymorphonuclear neutrophils appear to have little or no role in host defense against most viruses. Therefore, there does not appear to be a contraindication to live viral vaccines in this patient population. In fact, immunization with varicella vaccine may prevent a more severe cutaneous infection with the wild-type virus and protect patients with phagocytic defects from secondary skin infections. The live, bacterial vaccine BCG poses the same risk to CGD patients as it does to patients with defects of cell-mediated immunity. An interaction between T lymphocytes and monocytes is required for successful control and eradication of intracellular pathogens such as mycobacteria. If either the T cell or phagocytic compartment is defective, there is significant risk for chronic and sometimes fatal infection with BCG.

Asplenia

Individuals may have anatomic asplenia (congenital asplenia or splenectomy following abdominal trauma) or functional asplenia (sickle cell disease). In either case, they have an increased risk of bloodstream infections due to lack of phagocyte mass within the circulation. The pneumococcus is the most important pathogen in asplenic individuals, and it is well documented that immunization with pneumococcal polysaccharide vaccines can elicit levels of anti-pneumococcal antibodies that can compensate in part for the lack of splenic tissue. Anti-pneumococcal antibodies are opsonins which enhance the phagocytosis of the organisms by other phagocytes such as Kuppfer cells in the liver. Asplenic individuals do not have difficulty with immune responses to viruses, so live attenuated viral vaccines are not contraindicated.

Complement deficiency

Complement, as demonstrated in the laboratory, functions as an opsonin for host defense against viral pathogens. In addition, patients with C3 deficiency have impaired antibody responses compared to individuals with normal levels of C3. However, these contributions of complement seem not to be clinically important because viral infections are not especially virulent in complement deficient patients. We do not believe that there are any contraindications to live viral vaccines in complement deficient patients. Patients with deficiencies of the early complement components C2 and C3 are at increased risk for pneumococcal and to lesser extent meningococcal infections, and should be immunized against these pathogens. Similarly, patients with deficiencies of late complement components (C6 to C9) are at risk of infection with *Neisseria* species. For this group of patients, meningococcal vaccine can elicit high titers of antibody against the meningococcal capsule and help compensate for the problem of complement deficiency.

Vaccination of Household Contacts

Vaccines Recommended for Household Contacts

Immunocompromised persons are at risk of acquiring infection through person-to-person transmission from household contacts and nosocomial acquisition from health care workers. Therefore, it is reasonable to consider vaccination of household contacts and health care workers against contagious and pathogenic organisms to provide an additional means of protecting immunocompromised persons from infection.

Varicella vaccine is recommended for all children and susceptible young adults. Varicella vaccine is specifically recommended for susceptible health care workers and household contacts of immunocompromised persons. Because varicella vaccine is a live viral vaccine, transmission of vaccine virus can occur. However, the risk of transmission of vaccine virus is very low and disease caused by vaccine virus in immunocompromised persons is mild. Recipients of varicella vaccine who develop a rash should avoid direct contact with immunocompromised persons for the duration of the rash. Varicella-zoster immune globulin is not indicated should contact occur between an immunocompromised person and a varicella vaccine recipient with a varicelliform rash.

Immunization of household contacts against other contagious and potentially serious infections is important in protecting immunocompromised persons. Specific recommendations for household contacts include vaccination against influenza, measles, mumps and rubella (MMR). The latter vaccine, although consisting of attenuated, live viruses, is not contraindicated in household contacts of immunocompromised persons because transmission of vaccine viruses does not occur.

Vaccines Contraindicated in Household Contacts

Due to the potential transmission of live vaccine virus from vaccinated household contacts to immunocompromised persons, vaccination of the household contact is sometimes contraindicated. Household contacts of persons with severe impairment of humoral or cellular immunity should not receive live, oral polio vaccine (OPV) because of the risk of transmitting virulent poliovirus and development of vaccine-associated paralytic poliomyelitis (VAPP). Instead, inactivated poliovirus vaccine should be used. If live, oral polio vaccine is inadvertently given to a household member, close contact should be limited for 4 to 6 weeks after vaccination, the duration of poliovirus shedding. Increased attention to good hygiene, particularly hand washing, may also reduce the risk of poliovirus transmission. The risk of VAPP from household transmission of poliovirus in persons with selective IgA deficiency, asplenia, complement deficiencies and phagocytic defects is probably no greater than the general population although no studies have been done to assess this.

Immunization of Siblings of Immunocompromised Children

Siblings of children with severe humoral or cellular immunodeficiencies, or siblings of children with perinatally-acquired HIV infection, should not receive potentially harmful vaccines until their own immune status is established.

Special Considerations

Immune Activation and HIV Replication

Efficient replication of HIV in CD4+ T lymphocytes and monocytes is dependent on cellular activation. The activation of CD4 lymphocytes and monocyte/macrophages that occurs as part of the immunologic response to immunization has the potential for directly enhancing HIV replication. Transient increases in HIV plasma viremia have been documented following vaccination with tetanus toxoid, influenza vaccine and pneumococcal polysaccharide vaccine. At present, it is thought that among patients receiving effective anti-retroviral therapy, the transient increase in HIV plasma viremia is not of clinical significance and is not a contraindication to immunization.

Immunosuppression Following Measles Vaccine

Measles virus infection is associated with a prolonged suppression of cell-mediated immunity, manifested by loss of delayed type hypersensitivity reaction to purified protein derivative (PPD) and increased risk of secondary bacterial infections. Transient immunosuppression may also occur after measles vaccination. Loss of delayed type hypersensitivity and leukopenia can occur after immunization with live, attenuated measles vaccine. The clinical significance of transient immunosuppression following immunization with live, attenuated measles vaccine in unclear, but may be important in persons whose immune function is compromised.

This situation most frequently arises in the administration of the primary vaccine series to a young infant whose sibling has a severe immunodeficiency or perinatally-acquired HIV infection. Live, attenuated MMR vaccine should be withheld from the infant until his/her immune status is known. If the infant is determined to have no immunodeficiency, the MMR vaccine can be administered at the appropriate age. Regardless of the infant's immune status, inactivated poliovirus vaccine, and not OPV, should be administered because the infant is the household contact of a person with severe immunodeficiency.

Conclusions

Vaccine safety, efficacy and potential benefit are critically dependent upon the nature and degree of immunodeficiency in an individual patient. Not all immunodeficiencies are alike, and broad recommendations for the vaccination of immunocompromised persons may not be universally applicable. The risks and benefits of vaccination should be considered in the context of the specificity and magnitude of the immune deficits within the individual patient.

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