Prevention of infection in children and adolescents with primary immunodeficiency disorders

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Summary

Background: **Primary Immunodeficiency diseases (PIDs) are a heterogenous group of inherited disorders that may involve one or multiple components of the immune system. PIDs are uncommon, chronic and severe disorders, in which patients cannot mount a sufficiently protective immune response, leading to an increased susceptibility to infections. This review addresses the current practices for the prevention of infection in children and adolescents with PIDs, in particular covering immunisations and antimicrobial prophylaxis.**

Results: **Over recent years, there have been major advances in molecular and cellular understanding in the field of PIDs. Many different disorders are recognised with variable spectra of infection susceptibility depending on the particular aspects of the immune response that are affected. Immunoglobulin prophylaxis is the mainstay of treatment for PIDs and provides passive protection. Prophylactic antimicrobials are efficacious in children and adolescents with predominant defects in primary T cell immunodeficiency diseases and phagocytic disorders, and also with predominant defects in antibody production. Prophylactic antibiotics are suggested for patients with antibody deficiency diseases if recurrent infections exceed three per year, if severe infections occur despite adequate immunoglobulin replacement and in hypogammaglobulinaemic patients who have bronchiectasis. Certain immunisations are effective in antibody deficiencies, T cell deficiencies, complement deficiencies and phagocytic disorders.**

Conclusion: **There are remarkably few published data relating to clinical management aimed at preventing infectious complications in children and adolescents with PIDs. The cornerstones of the prevention of infection in most PID patients are: antimicrobial prophylaxis, appropriate vaccination, immunoglobulin replacement, for the more severe cases, and regular ongoing follow-up.** ***(Asian Pac J Allergy Immunol 2012;30:249-58)***

Key words: *adolescents, antimicrobial prophylaxis, bronchiectasis, children, immunizations, primary immunodeficiencies*

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Introduction

Primary immunodeficiency diseases (PIDs) are a heterogenous group of inherited disorders that may involve one or multiple components of the immune system. PIDs are classified according to the compartment of the immune system that is primarily involved[1,2] (Table 1). Tremendous progress has been made in the identification and characterisation of genes responsible for PIDs in the past 15 years. Around 200 clinical entities have been described, more than 100 of which now have a known genetic aetiology.[3-5] PIDs are uncommon, chronic and severe disorders in which patients cannot mount a sufficiently protective immune response, leading to an increased susceptibility to infections.[6]

Given the major role of infection in determining the outcome for patients with PID, clearly defined practices for prophylaxis are important and, where possible, should have a sound evidence base.

Table 1. Classification of primary immunodeficiencies

Defects of Adaptive Immunity	Predominantly Major Antibody Deficiencies	XLA CVID IgA deficiency Isolated IgG subclass deficiency THI
	Combined T- cell and B- cell immunodeficiencies	T^-B^+ SCID ADA deficiency T^-B^- SCID ADA deficiency Omenn syndrome $CD8^+$deficiency ZAP-70 deficiency MHC class I, II deficiency PNP deficiency HIGM-CD40 Ligand deficiency
Defects of Innate Immunity	Phagocytic Disorders	CGD Severe Congenital Neutropenia Kostmann syndrome Cyclic neutropenia LAD syndrome type I, II, III Myeloperoxidase deficiency
	Complement Deficiencies	Complement Components 1-9 deficiencies Mannose-binding lectin disorder Properdin deficiency
	Defects of IL12/INF-γ signalling pathway Defects of Toll-Like Receptor Signalling X-linked ectodermal dysplasia	
Immune Dysregulation Disorders	Chediack Higashi syndrome Griscelli syndrome XLP syndrome ALPS IPEX APECED	
Other well defined immunodeficiency syndromes	WAS A-T DiGeorge syndrome Hyper IgE syndromes	

ADA, Adenosine Diaminase; ALPS, autoimmune lymphoproliferative syndrome; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; A-T, Ataxia Telangiectasia; CGD, Chronic Granulomatous Disease; CVID, Common Variable Immunodeficiency; HIGM, Hyper IGM; IPEX, immunedysregulation polyendocrinopathy enteropathy X-linked; LAD, leukocyte adhesion deficiency; MHC, Major Histocompatibility Complex; PNP, purine nucleoside phosphorylase; SCID, Severe Combined Immunodeficiency; THI, Transient Hypogammaglobulinaemia of infancy; WAS, Wiskott Aldrich syndrome; XLA, X-Linked Agammaglobulinaemia; XLP, X-linked lymphoproliferative; ZAP-70 deficiency, zeta chain associated protein 70 deficiency.

General measures against infections in primary immunodeficiencies

Measures of hygiene are advised to prevent infections in highly sensitive patients with PIDs. Hand and dental hygiene, good nutrition, avoidance of exposure to people who are ill with an infection, and withdrawal from school during periods of chickenpox and measles outbreaks are several useful precautions for immunodeficient children.

In particular, children with severe combined immune deficiencies need strict isolation and filtered air and should be cared for by staff immune to varicella and influenza. Prophylaxis against cryptosporidium infection is needed for some patients with Hyper IgM syndrome type 1 associated with combined immunodeficiency (X-linked Hyper IgM). Measures reducing the risk of cryptosporidium infection are: boiling of all drinking water and/or installation of a professionally fitted filter with <1 micron pore size, avoidance of swimming in ponds and lakes, use of swimming pool only when aged >5 years, avoidance of contact with farm animals (lambs and calves) and with kittens and puppies.[7]

Prophylactic antimicrobials in children and adolescents with primary immunodeficiencies

A recent large survey conducted by the American Academy of Allergy, Asthma and Immunology concluded that the use of prophylactic antibiotics in PIDs is widespread and perceived to be efficacious.[8] However, a sound evidence base for many practices is not available for PIDs. Practice is often based on extrapolation from studies in other immuno-suppressed states (e.g. Human Immunodeficiency Virus or chemotherapy-induced immuno-suppression) or based on expert opinion. The choice of anti-micriobials is based on the particular type of PID and the expected microbial susceptibility.

Predominantly defects in antibody production

They are characterised by chronic or recurrent sino-pulmonary infections with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.[3] Among patients with antibody deficiencies, those with severe illness should be on immunoglobulin (Ig) which is the most important treatment. It has been suggested that prophylactic antibiotics should be used if recurrent infections exceed three per year or if any very severe infection occurs despite adequate Ig replacement.[9] Antimicrobial long-term prophylaxis with Trimethoprim-

sulphamethoxazole (TMP-SMX), amoxicillin or macrolides may then be required.[10]

Common Variable Immunodeficiency (CVID) is the most common symptomatic PID with recurrent infections of the respiratory tract including those caused by Streptococcus pneumoniae, Moxarella catarrhalis, Haemophilus influenzae.[11] Early diagnosis in childhood and close follow-up are required to prevent bronchiectasis. Repeated high resolution computed tomography of the thorax should be considered every 3-5 years, or more frequently if recurrent clinical infections or change in pulmonary tests suggest deterioration in pulmonary function.[9] Antibiotic prophylaxis should depend on the patient's pathogens. Macrolides and TMP-SMX are useful agents for this purpose; they are well tolerated and cover the most relevant pathogens. In some circumstances, quinolones can be used (Table 2). However, the development of antimicrobial resistance needs to be taken into account.[10]

X-Linked Agammaglobulinaemia (XLA) is a humoral immunodeficiency characterised by respiratory infections, mainly due to encapsulated bacteria. It may be associated with neutropenia and it may also predispose to staphylococcal or pseudomonas infections. Giardia, mycoplasma and ureoplasma infections can also occur.[10] Severe viral infections are rare, but patients with XLA have a unique susceptibility to meningoencephalitis caused by *enteroviruses*.[4] To prevent enteroviral and enterococcal infections, particular attention should be given to hand hygiene of healthcare professionals, especially after diaper changing.[12]

XLA patients with infections despite adequate Ig replacement may benefit from antibiotic prophylaxis, although evidence is lacking and variations in practice are observed. Some practitioners add continuous antibiotic prophylaxis (TMP-SMX) [13] (Table 2). In a series of XLA children, prophylactic antibiotics were given to

Table 2. Dosage of prophylaxis therapy in children with Primary Immunodeficiencies

Disease	Agent	Dose	Route	Regimen
Common Variable Immunodeficiency	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
	Azithromycin	10 mg/kg	P.O	Once daily
X-linked Agammaglobulinaemia	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
Di George Syndrome	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
	Fluconazole	3 mg/kg	P.O	Once daily
Wiskott-Aldrich Syndrome	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
	Acylovir	80 mg/kg	P.O	Four times daily
	Fluconazole	3mg/kg	P.O	Once daily
	Penicillin if splenectomy	125 mg(<5years) 250 mg(>5years)	P.O	Twice daily
Chronic Granulomatous Disease	Trimethoprim-Sulphamethoxazole	6 mg/ kg of Trimethoprim	P.O	1-2 divided doses daily,
	Itraconazole	5 mg/kg	P.O	Once daily
Hyper IgE Syndrome STAT3 deficiency	Trimethoprim-Sulphamethoxazole	6 mg/kg of Trimethoprim	P.O	1-2 divided doses daily,
	Flucloxacillin	125-250 mg	P.O	Twice daily
	If bronchiectasis :			
	Azithromycin	10 mg/kg	P.O	Once daily
	Inh Tobramycin	300 mg	Inhalation	Twice daily
	If pneumatoceles:			
	Itraconazole	5 mg/kg	P.O	Once daily
Ataxia Telangiectasia	Azithromycin	10 mg/kg	P.O	3 days/week

3 days/week, consecutively or on alternate day; P.O, per os; TMP-SMX, 30mg/Kg total daily dose

those who suffered upper respiratory tract infections more than once a month, despite Ig therapy. TMP-SMX, amoxicillin or penicillin were used during frequent infection periods. Fewer infections and the prevention of the development of microorganism resistance were reported.[14]

In general, the effect of prophylactic antibiotics on the frequency and severity of infections in hypogammaglobulinaemic patients is beneficial. Nevertheless, there is variation in the need for antibiotics according to the patient and the type of antibody deficiency.

Primary T cell immunodeficiencies

Severe Combined Immunodeficiency (SCID) represents a group of genetic defects causing severe deficiencies of the number and/or function of T, B and natural killer cells. Patients with SCID are highly susceptible to infections with a variety of pathogens, such as *Pneumocystis jiroveci, Candida albicans,* Cytomegalovirus (CMV), respiratory syncytial virus (RSV), Herpes simplex virus (HSV), Adenoviruses, Influenza, Parainfluenza viruses and Mycobacteria.[4] As infections are the major cause of morbidity and mortality in this group of PIDs, the cornerstone of management is the prevention of viral, bacterial and fungal infections. Prophylaxis should be started early and continue until the definitive treatment, hematopoietic stem cell transplantation (HSCT), is performed.[4,10] If SCID is likely and/or lymphopenia is severe, all protective isolation measures should be undertaken and Ig replacement with a loading dose of 1g/kg should be initiated whilst awaiting diagnostic test results, followed by 0.4-0.5g/kg every three weeks. Patients are recommended to have regular monitoring by nasopharyngeal aspirates for respiratory viruses (RSV, Influenza, Parainfluenza) and in those countries where the resources are available, blood polymerase chain reaction (PCR) monitoring for CMV, Epstein Barr Virus (EBV) and Adenovirus. However, this recommendation may not applicable in many countries, especially developing countries.

Palivizumab is a humanised monoclonal antibody against RSV which is licensed for preventing serious lower respiratory-tract disease caused by RSV in children at high risk. Its usage varies a lot because many countries have different seasonal pattern of RSV infection. It has been recommended that Palivizumab be used in children under 2 years with SCID and a $CD4^+$ count <200, on a monthly basis during the RSV season, October through February, typically in North America and Western Europe.[15,16]

TMP-SMX is the drug of choice in prophylaxis of pneumonia from *Pneumocystis jiroveci*, known as *Pneumocystis Carinii* Pneumonia (PCP). Pentamidine isetionate in a nebuliser solution can be used for prophylaxis against PCP in older children unable to tolerate TMP-SMX. Dapsone can be used as an alternative. Fluconazole is given to prevent mucocutaneous candidiasis and is considered generally tolerable. Acyclovir is used in HSV family virus prophylaxis (Table 3).

To minimise CMV transmission, all blood products that have to be given should be CMV-negative and irradiated. Breast feeding is contraindicated until the CMV status of both mother and child is known.

Any SCID infant who received the Bacille Calmette Guerin (BCG) vaccine at birth must be commenced on chemoprophylaxis because of the risk of disseminated BCG infection. Isoniazid 10 mg/kg and rifampicin 10mg/kg are given once daily until HSCT and then until immunological reconstitution.

Hyper IgM syndrome (HIGM) is characterised by recurrent infections, usually of the ear, throat and chest, which may be severe and/or frequent. In contrast to other hypogammaglobulinaemias, patients with X-linked HIGM are susceptible to

Table 3. Prophylaxis therapy in children with severe combined immunodeficiency

Against	Agent	Dose	Route	Regimen
Respiratory syncytial virus	Palivizumab	15 mg/kg	IM	Once monthly•
Pneumocystis jiroveci	Trimethoprim-Sulphamethoxazole	5 mg/kg of Trimethoprim	P.O	1-2 divided doses daily, 3 days/week
Pneumocystis jiroveci	*Pentamidine isetionate	300 mg	Inh	Once every 3 weeks
Pneumocystis jiroveci	*Dapsone	2 mg/kg	P.O	Once daily
Candida	Fluconazole	3 mg/kg	P.O	Once daily
Herpes family viruses	Acyclovir	80 mg/kg	P.O	Four times daily

IM, intramuscular; P.O, per os; Inh, Inhalation, • during respiratory syncytial virus season for children <2years * alternative to Trimethoprim-Sulphamethoxazole; TMP-SMX, 30 mg/kg total daily dose

PCP, which can be the first manifestation. Therefore, PCP prophylaxis is necessary and it requires antibiotic prophylaxis with TMP-SMX (5 mg/kg/day of Trimethoprim) three days per week, which is useful for other pyogenic infections as well. Chronic diarrhoea caused by *cryptosporidium* that is involved in the development of sclerosing cholangitis is common. To reduce the risk of cryptosporidium infection, certain measures need to be taken, as mentioned above.

For the majority of DiGeorge syndrome (DGS) patients who are not severely immunodeficient, prophylaxis is often not necessary.[10] Thymic aplasia and profound T cell lymphopenia occurs in <1% of all DGS cases and can present as a SCID-like phenotype[10,17]. These patients are at risk of opportunistic infections such as *Pneumocystis jiroveci* and CMV and should be treated with prophylactic broad spectrum antibiotics and fluconazole, as for other SCID patient[18] (Table 2, 3).

Wiskott-Aldrich syndrome (WAS) is a rare X-linked disease characterised by thrombocytopenia, eczema and increased susceptibility to infections caused by mutations in the WAS gene. Purulent otitis media, pneumonia and skin infections are common. Infections by opportunistic agents including CMV, HSV, EBV, and Adenovirus may occur. PCP pneumonia is a possible life-threatening complication. Splenectomy is sometimes necessary in non-transplanted patients with significant bleeding when the platelet count cannot be improved with other measures. Ig replacement is indicated for WAS patients with frequent bacterial infections. Some studies report the use of prophylactic antimicrobials, mostly TMP-SMX and also acyclovir or fluconazole.[19] In addition, patients should receive penicillin following splenectomy (phenoxymethylpenicillin by mouth every 12 hours: 125mg for children <5 years, 250 mg for children >5 years)[19] (Table 2).

Phagocytic disorders

Children with Chronic Granulomatous Disease (CGD) present with recurrent and severe bacterial and fungal infections. The major clinical manifestations are lymphadenitis, pyoderma, pneumonia, inflammation of the gastrointestinal tract, liver abscesses, osteomyelitis, and septicaemia. The pathogens for the majority of the infections are bacteria: Staphylococcus aureus, Mycobacteria species, Salmonella species, Serratia marcescens, Nocardia, Burkholderia cepacia and/or fungi, Aspergillus predominantly fugimatus, although Aspergillus species may also be involved.[20,21] The mainstay of clinical care prior to possible bone marrow transplantation is antibiotic and antifungal prophylaxis with drugs which are highly lipophilic, are taken up by phagocytes, and are active intracellularly. TMP-SMX at a dose of 6 mg/kg/day of the Trimethoprim portion twice daily is the common practice. In cases with intolerance, ciprofloxacin can be used.[20,22,23] Itraconazole oral solution at a single daily dose of 5 mg/kg is the drug of choice for antifungal prophylaxis, because of its activity against Aspergillus, although breakthrough infections may occur, possibly due to resistance (Table 2).

Leukocyte Adhesion Deficiency (LAD) type 1 is a very rare autosomal recessive immunodeficiency, caused by defects of the CD18β-integrin molecule that result in impaired leukocyte adhesion and migration.[24] It presents with impaired pus formation and wound healing, delayed umbilical stump separation and omphalitis, marked leukocytosis and recurrent infections of the skin, airways, and bowel, usually caused by Staphylococcus aureus or gram-negative bacilli. Amoxicillin/clavulanic acid or fluoroquinolones have been used as prophylaxis prior to transplantation.[10,25,26]

Patients with INF-γ/IL-12 pathway defects typically present with persistent infections with intracellular microbes such as mycobacteria and salmonella. INF-γ receptor 1 deficiency is characterised by infections with the Mycobacterium avium complex and Mycobacterium bovis. Once the infection is treated, long-term prophylaxis against environmental mycobacteria with azithromycin or clarithromycin is recommended.[27,28]

X-Linked ectodermal dysplasia with immunodeficiency is characterised by signalling defects to the NFκB essential modulator (NEMO) and is due to mutations in the IKBKG (inhibitory κB kinase γ) gene. Patients are predisposed to infections due to Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella and Pseudomonas species, as well as Mycobacterium avium, CMV, HSV and Pneumocystis jiroveci. Prophylaxis should be considered for non-tuberculous mycobacteria with azithromycin; for PCP with TMP-SMX; and for Herpes family viral infections with acyclovir.[29,30,31]

Autosomal dominant Hyper IgE syndrome due to mutations in STAT3 is characterised by a variety of connective tissue and skeletal system abnormalities, eczema, and extreme elevation of IgE. Affected patients experience chronic candidiasis of mucosal

sites and nail beds and recurrent staphylococcal skin abscesses. They present predominantly with recurrent bacterial pneumonias, typically due to Staphylococcus aureus, but also with Streptococcus pneumonia and Haemophilus influenzae. Antibiotic prophylaxis against Staphylococcus is beneficial and also covers encapsulated pneumoniae pathogens. Flucloxacillin and azithromycin are used. Pneumatoceles, formed secondary to bacterial pneumonias, may subsequently become colonised with gram-negative bacteria (Pseudomonas), fungal and opportunists (Aspergillus species); however, PCP is occasionally seen. TMP-SMX prophylaxis is ideal for community-acquired MSSA, which is a very common organism infecting patients with Hyper IgE syndrome. If bronchiectasis develops, long-term therapy for fluoroquinolone-sensitive Pseudomonas *aeruginosa* appears beneficial. Azithromycin and inhaled tobramycin may be considered. Antifungal prophylaxis with itraconazole, especially for patients with pneumatoceles, may also be advantageous. Autosomal recessive Hyper IgE syndrome due to DOCK8 deficiency is characterised by recurrent bacterial and viral infections. Prophylaxis with TMP-SMX and Acyclovir is indicated[32,33, 34] (Table 2) .

The immunodeficiency in Ataxia Telangiectasia (A-T), caused by mutations in the A-T gene, is variable. Opportunistic infections are unusual, but sino-pulmonary infections are common and can contribute to pulmonary insufficiency. Prophylactic azithromycin is commonly used at a dose of 10mg/Kg once a day every alternate day over 2 weeks, although an evidence base is lacking[35] (Table 2).

Prophylactic antibiotic treatment of bronchiectasis in primary immunodeficiencies

Immunoglobulin replacement and broad spectrum antibiotics have significantly reduced the frequency and severity of acute bacterial infections in patients with primary antibody deficiency syndromes, delaying the development and also altering the natural course of bronchiectasis. However, bronchiectasis is the most severe complication of recurrent respiratory infections in hypogammaglobulinaemic patients, which can occur despite apparently appropriate Ig replacement.

Organisms such as *Haemophilus influenzae, Streptococcus pneumoniae* and *Staphylococcus aureus* may colonise the lungs of these patients. *Pseudomonas aeruginosa*, Aspergillus species and non-tuberculous mycobacteria are infrequent in antibody deficiency-associated bronchiectasis. They may be a complication in any PID-patient with structural lung disease. Infection with mycoplasma species has also been demonstrated in patients with bronchiectasis.

High resolution computed tomography is specific for the diagnosis and monitoring of bronchiectasis. It is more sensitive than the measurement of pulmonary function, although the latter is useful for monitoring the progression of chronic disease. It is indicated at 2 yearly intervals in chronic lung disease. Some physicians scan at regular intervals, every 3-5 years, to detect those patients with progressive damage.[9]

Although there are no published guidelines to manage antibody-deficient patients with bronchiectasis, it is common practice to achieve high through IgG level along with antibiotic prophylaxis.

Macrolide antibiotics have anti-inflammatory as well as anti-microbial properties. The efficacy of long-term low dose azithromycin and its beneficial effects on exacerbation frequency and suppression of airway pathogens, including *Pseudomonas aeruginosa* and *mycoplasma* has been demonstrated.[9,36] Azithromycin administration for 3 days, either consecutively or on alternate days each week, is efficient as long-term prophylaxis. Sputum cultures before and after starting prophylaxis, as well as clinical and lung function review, have to be repeated at regular intervals. Significant changes in the volume and colour of sputum, cough, fatigue, exercise tolerance, wheeze and breathlessness have been noted.[37] In CVID patients with bronchiectasis, consideration should be given to patient-held antibiotics for rapid administration at first sign of respiratory symptoms.

In patients who are colonised chronically with *Pseudomonas*, inhaled antibiotics may be considered. Their use is particularly attractive, as this mode of administration has the potential to deliver high concentrations to the site of infection. A pilot study in non-cystic fibrosis patients with bronchiectasis demonstrated that inhaled tobramycin resulted in a significant improvement in respiratory symptoms. The use of aerosolised tobramycin has clinical benefits, although an increase in pulmonary function is more difficult to determine in this population of patients.[38] Patients with bronchiectasis should be managed by or in conjunction with a physician with appropriate respiratory skills and further options such as corticosteroids may be used.[39]

Immunisations in children and adolescents with primary immunodeficiencies

The impaired immunity of patients with PIDs can be improved either with passive or active immunisation. *Immunoglobulin prophylaxis* is the mainstay for PIDs as has been stated elsewhere.[6,40] Most of them are on life-long Ig replacement (intravenously or subcutaneously), which provides passive protection against infections using antibodies present in the pool of healthy donors. Live vaccines, either viral: oral Polio, Measles, Mumps, Rubella (MMR), Varicella, Rota, or bacterial: BCG, Ty21a *Salmonella typhi* are contraindicated in many PIDs and should be used with caution in others because of the risk of disease from vaccine strains. The attenuated vaccines, such as Diphteria, Tetanus, Pertusis (DTP) and the conjugated *Haemophilus influenzae* type b (Hib), Meningococcal, and pneumococcal, can be given routinely in PIDs.

Immunisation is effective because the immune system generates specific adaptive responses usually with immunological memory. In patients with PID, the immune response to vaccines may be abnormal and the efficacy of vaccinations is therefore sub-optimal. However, the potential for some response, either through T cells or antibody production, means that vaccinations could be considered as a beneficial management tool in these patients. Experience with vaccine administration in children with PID is limited. Certain general principles can be stated.

Predominantly defects in antibody production

In minor antibody defects, such as IgA and IgG subclasses and Transient Hypogammaglobulinaemia of Infancy, all routine vaccines in the childhood schedule should be given.[41] Specifically, selective IgA-deficient patients can receive MMR, Varicella, and BCG vaccines, but should not receive live oral polio (OPV) because of reported prolonged excretion for months and even years.[42] The use of Inactivated Polio Vaccine (IPV) instead of OPV is indicated. OPV is no longer recommended for routine use in many countries. There is insufficient experience with the Rota virus vaccine for a recommendation.

In major antibody defects, such as CVID and XLA, live vaccines are generally not considered. BCG is not strictly contraindicated in pure B cell deficiencies such as XLA. However, experimental work in mice suggests that it might show reduced efficacy in the absence of B cells. BCG is contraindicated in CVID because of possible accompanying T cell dysfunction and because of the possibility of triggering inflammatory complications.[43]

Children with CVID are at enhanced risk of pneumococcal infections if they are not on Ig replacement. They should be immunised initially with the conjugated pneumococcal vaccine followed later by a dose of polysaccharide pneumococcal vaccine in order to boost the response and also to provide some protection against serotypes not included in the conjugated vaccine (Table 4).

Table 4. Immunisations of Children and Adolescents with Primary Immunodeficiencies

	Immune Deficiency Syndrome	Vaccine Contraindications	Vaccine Recommendations
B-lymphocyte defects	X-linked agammaglobulinaemia	All live vaccines	
	Common Variable Immunodeficiency	All live vaccines	Pneumococcal conjugated
	Selective IgA Deficiency	OPV	Haemophilus, meningococcal
	IgG subclass Deficiency	None	Trivalent influenza (non live)
T-lymphocytes defects	Severe Combined Immunodeficiency	All live vaccines	
	DGS	All live vaccines (except partial cases)	MMR if CD4+>400
	WAS	All live vaccines	Trivalent influenza (non live)
	HIGM-CD40 Ligand deficiency, A-T	All live vaccines	
Complement defects	Deficiency of Components C1-C9, properdin, factor B	None	Meningococcal, pneumococcal conjugated
Phagocytic defects	Chronic granulomatous disease Leukocyte Adhesion defects	Live bacterial vaccines	Annual non live influenza
Cytotoxicity Defects	Chediak-Higashi syndrome Griscelli syndrome Familial Haemaphagocytic lymphohistiocytosis X-linked lymphoproliferative disease	All live vaccines	
	Hyper IgE Syndrome	BCG	

DGS, Di George syndrome; WAS, Wiskott-Aldrich syndrome; HIGM, Hyper IgM syndrome; A-T, Ataxia Telangiectasia; MMR , Measles mumps rubella; BCG, Bacille Calmette Guerin vaccine, all live vaccines: live viral and bacterial vaccines

Primary T cell immunodeficiencies

In general, all live vaccines, either viral or bacterial, should be avoided. In patients with full SCID, it is not considered worthwhile to give non-live vaccines because it is extremely unlikely that they will produce a response. BCG is a live attenuated bacterial vaccine and must be avoided in subjects with T cell problems, because it can cause severe disseminated infection. If BCG has been given before the diagnosis of SCID, or given near birth in some high risk communities, then anti-mycobacterial treatment should be initiated. Babies with a family history of SCID should not be given BCG until carefully assessed.[10]

Infants with DiGeorge syndrome may have substantial thymic defects, an absence of the thymus and profound T-cell lymphopenia, along with impaired T-cell function (complete DGS). These patients should not be given live viral vaccines. Some studies suggest the administration of MMR and Varicella vaccine to patients with partial DGS who have documentation of adequate cellular immune function (CD4+ >500 cells/mm^3 and adequate proliferative response to polyclonal mitogens) is safe.[44,45]

WAS patients have an increased risk of mortality due to bacterial sepsis from encapsulated organisms. Therefore, they may benefit from pneumococcal, meningococcal and haemophilus vaccines, particularly before undergoing splenectomy.[19] Live virus vaccines are not recommended.

Phagocytic disorders

Children with phagocytic disorders, such as CGD, can receive all immunisations except live bacterial vaccines: BCG and Ty21a *Salmonella typhi*.[46] All live vaccines should be also avoided in immunodeficient patients with impaired cell-mediated cytotoxicity including LAD, because they cannot eliminate viruses due to defective cytotoxicity of T and NK cells (Table 4).

Complement deficiencies

In complement deficiencies, encapsulated pyogenic bacteria are the most frequent causes of infections. Meningococcal infections are the most common in this group of patients and are frequently caused by unusual serogroup organisms, including Y and W135. All immunisations, including those with live organisms, are used. Conjugated Pneumococcal, Haemophilus Influenzae and Meningococcal vaccines are particularly recommended. MeningoC conjugated vaccine, which protects against infection by serogroup C, is indicated and the quadrivalent vaccine A, C, Y, W135, ideally the new conjugate quadrivalent vaccine. If this is not available, then the polysaccharide version of the vaccine can be used.[47]

In Ataxia Telangiectasia, the normal protocol should be followed for Hib and tetanus toxoid, as well as for pneumococcal conjugate and influenza vaccines. MMR and Varicella vaccines should be administered unless there is profound CD4 lymphopenia. BCG is not recommended for use in A-T patients.[35]

Patients with Hyper IgE syndrome, STAT3 deficiency, can be immunised with the common vaccines, but BCG should be avoided, as disseminated Bacillus Calmette Guerin infection has been reported in Hyper IgE syndrome children after BCG vaccination.[48] Patients with DOCK8 deficient hyper-IgE syndrome should be given neither BCG nor live viral vaccines.

Special situations

Influenza vaccine

Influenza may cause severe illness in immunodeficient children and also predispose to secondary bacterial infections. Trivalent non-live seasonal influenza vaccines should be offered during each influenza season. Live attenuated influenza vaccine (nasal spray) should not be given to patients with PID. Instead, annual influenza vaccination with inactivated virus or viral sub-units is advised. Priority immunisation with newly developed vaccine strains, as available during an influenza epidemic or pandemic, is also recommended. All PID patients should be immunised with both seasonal and pandemic vaccine even if they are on Ig treatment, except for SCID patients. A child with PID who is not effectively protected by influenza vaccine and has been exposed to someone with an influenza-like illness, should be given immediate prophylaxis with oseltamivir within 48 hours of exposure.[49]

Human Papilloma Virus Vaccine

Both quadrivalent and bivalent Human Papilloma Virus (HPV) vaccines are non-infectious vaccines. They derive from virus-like particles of HPV virus type's capsid proteins, which are prepared using the recombinant DNA technique. The HPV vaccine can be administered to females with PIDs. However, the immune response and vaccine efficacy might be less than in persons who are immunocompetent.[50]

Travel vaccines

These can be used for travel purposes when required. Non-live vaccines (hepatitis A, cholera, rabies) are safe. The live attenuated oral typhoid vaccine (Ty21a) should be avoided and the Vi capsular polysaccharide typhoid vaccine can be given instead. In major antibody and combined deficiencies, the live yellow fever vaccine is absolutely contraindicated.

Household contacts and clinical staff

Siblings and household contacts of PID patients should receive all of the national immunisation schedule vaccines, particularly IPV and influenza. Yearly influenza vaccination of family members is recommended in order to reduce the risk of household-social transmission. The administration of live OPV that can be transmitted from person to person should be avoided. MMR vaccine should be given to siblings because transmission of these vaccine viruses has not been reported. The varicella vaccine can be given to susceptible contacts of immunodeficient children, because transmission of varicella vaccine virus from healthy persons is rare. Besides, indirect protection is provided. However, it should be avoided in siblings of children with suspected SCID while confirming the diagnosis.

Monitoring antibody titres

In some circumstances, PID children who have received an appropriate vaccine may require monitoring of post-immunisation antibody titres to confirm vaccine immunogenicity. Most immunodeficient children are on immunoglobulin (Ig) replacement therapy. Therefore, vaccine administration should be deferred until at least 3 months after cessation of such treatment. The only exception is the influenza vaccine, which is indicated even if the patient is on Ig replacement therapy.

Conclusion

Identification of the genetic basis of PIDs has provided better diagnostic and therapeutic practices along with better understanding of their pathophysiology. In the past decade, significant progress has been made in both supportive and curative therapies. It is clear that persons with PIDs are living much longer due to Ig replacement and stem-cell corrective therapies. This makes the judicious use of antimicrobial prophylaxis and vaccines more important than ever.

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