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Management of Primary Immunodeficiency

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Immunodeficiency diseases increase susceptibility to infection, malignancy, allergy and autoimmunity. They result from the absence or functional failure of one or more elements of the immune system and may be either primary or acquired in origin. Primary immunodeficiency diseases (PIDs) are due to intrinsic defects in the cellular components of the immune system, secondary immunodeficiency diseases result from extrinsic factors such as drugs, irradiation, malnutrition or infection.

CLASSIFICATION

For practical purposes, PIDs are classified into defects of specific immunity, namely T and B lymphocyte function impairment and defects of non-specific immunity, namely impairment of complement components or cells of the mononuclear phagocytic system. In this review, the management of PIDs will be discussed. The approximate relative frequency of various PIDs is shown in figure 1.¹

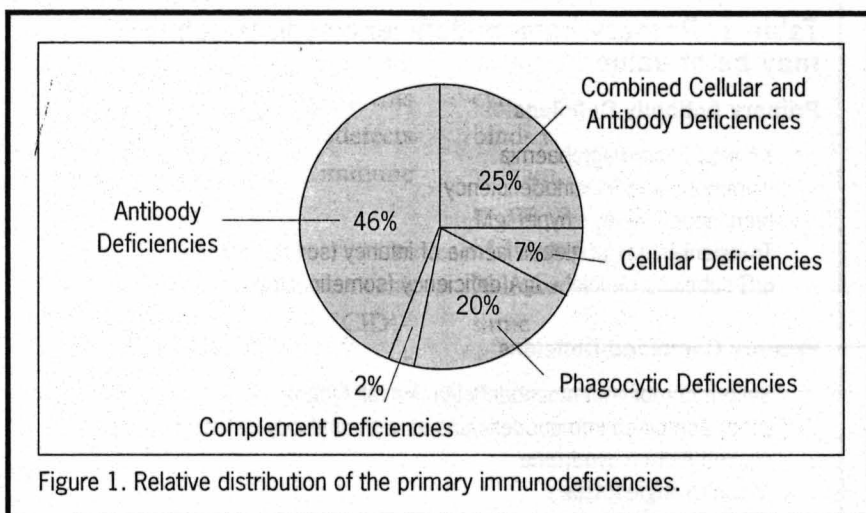


Figure 1. Relative distribution of the primary immunodeficiencies.

GENERAL CONSIDERATIONS

Vaccination and Blood Products

Killed vaccine (eg. inactivated poliomyelitis) should be given if there is evidence of some antibody synthesis. Live attenuated vaccines (eg. live oral poliomyelitis, BCG) should be avoided in all severe antibody or cellular immunodeficiencies to avoid the risk of vaccine-induced infection. Live oral poliomyelitis vaccine (OPV) should not be given to a PID patient's parents, siblings, or other people sharing the same household as the patient may contract

paralytic polio from live OPV. Varicella-zoster immunoglobulin (VZIG) is indicated for T cell and antibody deficient children following chickenpox exposure.

For patients with cellular immunodeficiencies, blood products including packed red cell and platelet concentrates should be irradiated prior to administration to prevent graft-versus-host reaction from heterologous lymphocytes. Because of the risk of cytomegalovirus (CMV) infection from blood products, it is advisable to use CMV-negative preparations or high efficiency

leucocyte filters.

Use of Antimicrobials

One of the mainstays of management in most immunodeficient patients is the use of antibiotics given either in response to infection or on a long term prophylactic basis. PID patients may succumb

rapidly to infection, therefore fevers or other manifestations common to infection are assumed to be secondary to bacterial infection, and antibiotic treatment should be begun immediately. *Pneumocystis carinii* pneumonia (PCP) prophylaxis is recommended for children with significant T cell immuno-

deficiencies. Prophylaxis consists of trimethoprim-sulfamethoxazole (TMP/SMX) - 150mg/m²/day of TMP and 750mg/m²/day of SMX - given orally in divided doses twice per day 3 times per week. Alternative drugs for PCP prophylaxis include pentamidine and dapsone.

Continuous prophylactic antibiotics have an important role to play in the management of certain immunodeficiencies. They are especially useful in disorders characterised by rapid overwhelming infections such as Wiskott-Aldrich syndrome, in antibody immunodeficiencies when recurrent infections still occur despite optimal immunoglobulin therapy, and in certain phagocytic disorders such as chronic granulomatous disease (CGD). However, antibiotics given regularly may encourage the development of fungal infection in patients with CGD.

Antiviral therapy is useful for certain viral infections. Severe infections due to herpes simplex virus (HSV), or herpes zoster virus (HZV) can be treated with acyclovir. Acyclovir resistant strains of HSV can be controlled by foscarnet while CMV infections may be treated with ganciclovir. The author has also used lamivudine and famciclovir as combination therapy for hepatitis B virus infection in patients with PID. Ribavirin aerosols have been used in the treatment of infections due

Table 1. Primary Immunodeficiencies in Which IVIG may be of Value

Primary Antibody Deficiencies

- X-linked agammaglobulinaemia
- Common variable immunodeficiency
- Immunodeficiency with hyper-IgM
- Transient hypogammaglobulinaemia of infancy (sometimes)
- IgG subclass deficiency + IgA deficiency (sometimes)

Primary Combined Deficiencies

- Severe combined immunodeficiencies (all types)
- Other combined immunodeficiencies with antibody defects
- Wiskott-Aldrich syndrome
- Ataxia telangiectasia
- Short-limbed dwarfism
- X-linked lymphoproliferative syndrome

Table 2. Proven and Possible Side Effects of IVIG Administration

Common	Rare (Multiple Reports)	Very Rare (Isolated Reports)
Chills	Chest pain or tightness	Anaphylaxis
Headache	Dyspnoea	Arthritis
Backache	Migraine headaches	Thrombosis
Malaise	Aseptic meningitis	Cryoglobulinaemia
Fever	Renal failure	Neutropenia
Pruritis	Hepatitis C	Alopecia
Rash		Uveitis+retinal vasculitis
Nausea		Noninfectious hepatitis
Tingling		Hypothermia
Hypo- or hypertension		Pulmonary insufficiency
Fluid overload		Desquamation

to respiratory syncytial virus and parainfluenza virus. A much more prolonged course than the standard 5 days may be necessary in these patients. As these viral infections can be extremely severe and very resistant to therapy an early, aggressive approach is warranted.

Use of Intravenous Immunoglobulin (IVIG)

IVIG is indicated in the management of several PIDs as shown in table 1. The side effects of IVIG administration have recently been reviewed and are summarised in table 2.^{2,3} Two side effects which are particularly serious and not uncommon are hepatitis C and aseptic meningitis.

Bone Marrow Transplantation (BMT)

Patients with potentially fatal PIDs are candidates for BMT. However, because this is a procedure that may result in immediate mortality, the risk:benefit ratio must first be assessed carefully. Theoretically, if a PID is a result of defects that are intrinsic to cells of one or more haemopoietic lineage, it is correctable by BMT. Table 3 shows the different types of PID for which BMT has been performed.^{4,5} The majority of transplants have been performed in patients with severe combined immunodeficiency (SCID) or Wiskott-Aldrich syndrome (WAS).

CURRENT MANAGEMENT OF PIDs

We shall review the recent advances in the management of six PIDs: severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome (WAS), X-linked agammaglobulinaemia (XLA), X-linked hyper-IgM syndrome (XHIM), chronic granulomatous disease (CGD) and congenital neutropenia. These are discussed in this paper as they illustrate defects of different arms of the immune system.

Severe Combined Immunodeficiency Disease (SCID)

SCID comprises a heterogeneous group of diseases. In an analysis of 108 infants with this syndrome, approximately half of the cases had been inherited as X-linked recessive and the remaining as

autosomal recessive.⁶ The affected infants could be classified into two groups: those without T cells and B cells (T-B-) and those with B cells only (T-B+). T-B+ patients have a defect in the common γ chain of the IL-2 receptor, which is shared with the receptors for IL-4, IL-7, IL-9 and IL-15. The gene for the common γ chain is on the X chromosome. When T cells are activated by any of these cytokines, Jak 3, a tyrosine kinase, binds to the cytoplasmic tail of the γ chain. The gene encoding Jak 3 is on an autosome. Thus T-B+ SCID is commonly inherited as an X-linked recessive trait, but the same phenotype may be inherited as an autosomal recessive trait. On the other hand, T-B- SCID occurs equally in male and female infants. These infants, in contrast to those with T-B+ SCID, usually have normal and elevated numbers of

Table 3. Survey of Bone Marrow Transplantation for Immunodeficiency Disease From 1968 to 1995

Diseases	Total Number of Patients	
	Transplanted	Surviving
Severe combined immunodeficiency	517	341
Wiskott-Aldrich syndrome	143	91
Major histocompatibility complex antigen deficiency	30	13
Leukocyte adhesion defect type I	26	21
Chediak-Higashi syndrome	18	13
Chronic granulomatous disease	10	6
Purine nucleoside phosphorylase deficiency	8	4
DiGeorge anomaly	8	2
Cartilage hair hypoplasia	6	3
Hyper-IgM syndrome	6	3
X-linked lymphoproliferative syndrome	5	2

natural killer cells and are of autosomal recessive inheritance. Some of the cases are due to defects in one of two purine degradation enzymes, adenosine deaminase or purine nucleoside phosphorylase. This may account for about half of the patients with T-B- SCID. Rare cases of SCID, for example, TCR-CD3 abnormalities, ZAP70 defects, have also been described. In many cases the cause remains unknown.

Early recognition of SCID should be considered as a paediatric emergency, because a diagnosis before the onset of opportunistic infections permits lifesaving unfractionated HLA-identical or T cell depleted haplo-identical BMT. A combination of persistent oral thrush, pneumonia, and/or diarrhoea with persisting lymphopenia should alert paediatricians to this diagnosis. The absolute lymphocyte count is the most useful screening diagnostic test, because lymphopenia is present in almost all patients with SCID from the time of birth.⁷

The best transplantation results have been achieved with related HLA-identical donors: for patients with SCID, the survival rate is about 84%. If there are no related HLA-identical donors, the alternatives include related haplo-identical donors or matched unrelated donors (MUDs). However the results of such BMT were inferior to those of related matched BMT.

Survival rates of around 60% and 68% for patients with SCID, have been achieved using haplo-identical donors and MUDs respectively.⁸ In the last few years, umbilical cord-blood stem cells have been established as an alternative source of allogeneic stem cells for transplantation. Patients with SCID have been transplanted using sibling umbilical cord blood.⁹ For families with a previous child diagnosed as having PID, in-utero transplantation has also been attempted. Full donor chimerism is not necessary for a favourable transplant outcome in patients with SCID.¹⁰

Wiskott-Aldrich Syndrome (WAS)

WAS is an X-linked recessive PID characterised by thrombocytopenia, eczema, and increased susceptibility to infections. Abnormalities include defective T cell function, poor antibody responses to polysaccharide antigens, and a characteristic serum immunoglobulin pattern of markedly elevated levels of IgA and IgE and low levels of IgM. The gene responsible for the disease has recently been cloned.¹¹ Findings of small platelets, almost exclusive to WAS, sometimes facilitate a laboratory diagnosis of the condition. However, in a multi-institutional survey of 154 unselected patients with WAS, the classic triad of thrombocytopenia with small platelets, recurrent otitis media, and eczema was seen

in only 27% of the study population;¹² 5% of the study population had only infectious manifestations, and 20% had only haematological manifestations (thrombocytopenia) before diagnosis. WAS is also associated with autoimmunity.¹³

For WAS, BMT is the treatment of choice if an HLA-identical donor is available. The survival rate for patients receiving transplants from related HLA-identical donors is about 90% compared to 34% and 65% for haplo-identical donors and MUDs respectively.^{8,14,15} If stem cell transplantation is not possible, the alternative supportive treatment is intravenous immunoglobulin (IVIG) and antibiotic prophylaxis in combination with splenectomy. In a review of 21 WAS patients, thrombocytopenia was cured in 14 of 15 patients who had splenectomy, with intermittent recurrence in three of the 'cured'.¹⁶ Mean platelet volume (MPV) was normal transiently in some patients, but all MPV values were subnormal 8 to 23 months after splenectomy. Antibiotic and IVIG prophylaxis may have contributed to the lack of a detectable increase in the number of severe acute bacterial infections in the 451 months after splenectomy. Four patients died, two of cerebral B cell lymphoma, one of progressive multifocal leucoencephalopathy, and one with severe chronic chest disease of pneumonia. Patients with platelet

counts $< 10 \times 10^9/L$ at the time of diagnosis are at high risk of bleeding, and patients with autoimmune disorders are at increased risk of suffering a malignancy.

Adequate supportive treatment with IVIG and antibiotic prophylaxis together with splenectomy enables good survival and quality of life in the short and medium term for patients with WAS. Persistence of infection, bleeding, vasculitic and allergic symptoms; and the risk of development of lymphoma, in a significant minority of patients suggest that BMT is indicated if an HLA-identical donor is available. If immunological reconstitution is successful, the outlook for prolonged life is excellent. Whether the BMT diminishes the risk of haematopoietic malignancies is not known; so far no such cases have been reported in those with successfully reconstituted immune systems.

X-Linked Agammaglobulinaemia (XLA)

XLA is inherited as an X-linked recessive trait. Generally, symptoms of XLA have their onset after 6 months of age, when maternally transmitted immunoglobulin has largely been depleted. Subsequently, patients experience recurrent pyogenic infections such as otitis media, sinusitis, conjunctivitis, pneumonia, and pyoderma. These infections are mainly due to *Haemophilus influenzae* and

Streptococcus pneumoniae and less frequently to *Staphylococcus aureus* and *Streptococcus pyogenes*. Although readily controlled by antibiotics, these recurrent infections lead to anatomical destruction, particularly of the lungs; chronic obstructive lung disease and bronchiectasis invariably results when proper prophylactic treatment is not undertaken. There have been reports of paralytic poliomyelitis and progressive encephalitis following immunisation with live polio vaccine or exposure to a wild virus. Chronic progressive panencephalitis also occurs in association with XLA. Enteroviruses, particularly echoviruses, are commonly implicated. *Giardia lamblia* infestation leads to chronic diarrhoea, weight loss, protein-losing enteropathy and steatorrhoea. Other occasional features of XLA include autoimmune haemolytic anaemia, joint disease resembling juvenile rheumatoid arthritis, neutropenia, and dermatomyositis.

Prophylaxis with IVIG is the standard therapy for XLA. Starting doses of IVIG range from 400mg/kg to 600mg/kg every 2 to 4 weeks. Depending on the patient's response to the therapy, the amount and frequency of administration must be individualised to achieve trough levels at the upper level of the normal range.³ Lung disease is the most common morbidity and regular

lung function assessment should be done.

Immunoglobulin is a safe biological product. Nevertheless, the risk of transmitting hepatitis C virus is ever present and does occur with IVIG.¹⁷ Although immunoglobulin therapy has been a major advance in the treatment of patients with XLA, it has some limitations. IVIG only replaces IgG and is unable to correct the defect in secretory immunity. In addition, the use of non-selected lots of IVIG does not provide high levels of specific antibody and, by definition, does not establish active immunity. Therefore, although IVIG significantly lowers the frequency and severity of infections in patients with XLA, it cannot prevent all infections in every patient.¹⁸ Treatment of acute bacterial infections with specific antibiotics may be necessary in some patients. In other patients, especially those in whom structural damage to the sinuses and/or lungs develops before treatment can be instituted, chronic infections may necessitate long term, broad-spectrum antibiotics and postural drainage.

X-Linked Hyper-IgM Syndrome (XHIM)

Immunodeficiency with hyper-IgM is a rare genetic disorder characterised by recurrent infections in association with markedly decreased serum IgG, IgA and IgE

levels but normal or elevated serum IgM levels.¹⁹ Genetic heterogeneity is indicated by the occurrence of both X-linked and autosomal recessive variants. The molecular defect of the X-linked form of HIM has been elucidated as defective expression of T cell CD40 ligands.^{20,21} CD40 ligand molecules are required for B cell activation and the production of IgG, IgA and IgE in response to T cell-dependent antigens, as well as for the formation of germinal centres. Consequently, patients with XHIM show an inability to mount IgG, IgA and IgE responses to T cell-dependent antigens and lack germinal centers, but their ability to produce IgM is preserved. In addition to severely depressed antibody responses, patients with XHIM have a defect in antigen-specific T cell proliferation, which may explain their susceptibility to pathogens such as *Pneumocystis carinii*.²²

In a review of 56 patients with XHIM, upper and lower respiratory tract infections, chronic diarrhoea and liver involvement, eg. sclerosing cholangitis, were common.²³ Many patients had chronic neutropenia associated with oral and rectal ulcers. The marked prevalence of infections caused by intracellular pathogens suggests some degree of impairment of cell-mediated immunity. Although lymphocyte counts and in vitro proliferation due to mitogens were

normal, a defective in vitro proliferative response to specific antigens was observed in some patients, and additional defects of the cell-mediated immunity may be presumed on the basis of current knowledge of CD40 ligand function.

IVIG at a dose 500 mg/kg per month is indicated in XHIM. Patients should also receive prophylactic trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonia. Some patients with persistent neutropenia despite regular IVIG have responded to granulocyte colony-stimulating factor (G-CSF) therapy.²⁴ Since XHIM is now considered a cellular immunodeficiency characterised by the disruption of multiple cellular interactions (T cells and B cells; T cells and macrophages), more aggressive therapeutic approaches, including BMT have been prompted.^{8,23} It appears reasonable to consider BMT as a therapeutic option if HLA-matched family donors are available.

Chronic Granulomatous Disease (CGD)

CGD results from the absence or malfunction of NADPH oxidase in neutrophils, monocytes, macrophages and eosinophils. NADPH oxidase is a complex enzyme consisting of at least five different components, individual components are found to be abnormal in

different forms of CGD. Deficiency of this oxidase, responsible for the production of microbicidal oxygen metabolites, results in susceptibility to recurrent infections by bacteria and fungi.

The major clinical manifestations of CGD are pyoderma, gastrointestinal infections, lymphadenitis, liver abscess and osteomyelitis. Growth retardation is also a problem in chronically infected CGD patients. A variety of bacterial pathogens have been isolated from the lesions of CGD patients. *Staphylococci* (*aureus* and *epidermidis*) and *Enterobacteriaceae* predominate. Commonly found gram-negative bacteria include *Escherichia coli*, *Salmonella*, *Pseudomonas* (*aeruginosa* and *cepacia*), *Klebsiella*, *Proteus* and *Serratia marcescens*. Infections of *Nocardia* species and *Mycobacteria* are of particular concern in CGD patients. Fungal pathogens in CGD patients include *Aspergillus* species as well as *Candida albicans*. *Mycobacterium tuberculosis* has been noted to be a common pathogen in Chinese patients with CGD.²⁵

Several retrospective studies have shown the beneficial effects of long term trimethoprim-sulfamethoxazole administration in patients with CGD.^{26,27} A marked reduction in the number of major bacterial infections and of surgical interventions (mainly abscess drainages) required and conse-

quently a considerable reduction in the period of hospitalisation are among the advantages.

In contrast to bacterial infections, fungal (*Aspergillus*) infections remain frequent and represent a major cause of morbidity and mortality in patients with CGD. Itraconazole has been used to treat aspergillosis, and a double-blind trial is under way using oral itraconazole prophylactically to prevent fungal infections.²⁸

An international placebo-controlled study involving 128 patients with CGD showed a 67% reduction in the relative risk of serious infection in the interferon gamma treated group.²⁹ Patients benefited regardless of their age or mode of inheritance. No serious life-threatening toxicity was observed. Adverse reactions included headache, fever, chills, myalgia and injection site erythema. A Phase IV study has confirmed and extended the findings of this study. Interferon gamma has been used either intermittently as required or continuously as prophylaxis.

BMT has been performed in patients with CGD.³⁰ Interestingly, a mixed chimerism of at least 10 to 15% of donor cells suffices for host defence against infections.³⁰ The mortality of HLA-identical BMT is difficult to assess since only a few transplants have been performed. BMT remains a treat-

ment option as there is, as yet, no unequivocal evidence to suggest that *Aspergillus* infections could be wholly prevented by conventional itraconazole or interferon gamma prophylaxis.

Congenital Neutropenia

Neutropenia is defined by the presence of fewer than 1500 neutrophils per mm³ blood. When the absolute neutrophil count (ANC) falls below 1000 per mm³, stomatitis, gingivitis and cellulitis dominate the clinical picture. More severe infections occur when the ANC is below 500 per mm³, when perirectal abscess, pneumonia and sepsis are particularly common. Different types of congenital neutropenia include Kostmann syndrome, cyclic neutropenia, Shwachman-Diamond syndrome, reticular dysgenesis, myelodysplasia and Chediak-Higashi syndrome.³¹

It is essential that severe neutropenic patients with acute bacteraemic infections receive appropriate doses of β lactam and aminoglycoside antibiotics given for a sufficient duration. A continuing febrile course and persistent neutropenia despite potent broad spectrum antibiotics suggests fungal super-infection, which necessitates empirical amphotericin B therapy.

Granulocyte CSFs (eg. GM-CSF or G-CSF) seem to be useful in several types of chronic neutropenia. Severe chronic neutropenia

has been successfully managed with maintenance G-CSF administration, resulting in improvements of infection-related problems.³²

CONCLUSION

PID is relatively rare but early and accurate diagnosis is of utmost importance for planning specific management for individual patients with PID as well as offering genetic counselling including prenatal diagnosis and even in utero treatment for the family.

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• PAEDIATRIC QUIZ •

This is a one day old male borderline preterm neonate admitted for preterm care.

1. What does the picture show?
2. What is the most likely diagnosis?

Answers given on page 30.

