

Leading Article

Primary immune deficiencies and stem cell transplantation

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Introduction

Primary immunodeficiency disorder (PID) can be broadly grouped into disorders of adaptive immunity (T-cell, B-cell or combined immunodeficiencies) and disorders of innate immunity (phagocyte defects in Toll-like receptor-mediated signalling and complement disorders)^{1,2}. In the European Society for Immunodeficiencies (ESID) Registry 2010, of 10,747 children diagnosed with PID, humoral deficiencies were the most common (Figure 1)³. This is similar to the data from Sri Lanka, where among 73 cases registered, common variable immune deficiency (CVID) was the commonest, followed by X linked agammaglobulinaemia⁴.

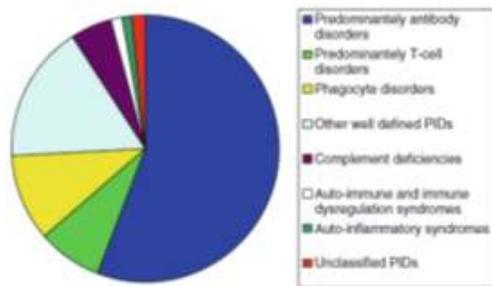


Figure 1: Distribution of PID in Europe according to the ESID registry 2010

PIDs are different to secondary immunodeficiencies which are caused by infections, malnutrition, or immunosuppressive drug therapy. PIDs are associated with recurrent infections and predispose

to autoimmune disorders, lymphomas and other malignancies. It is important that PIDs are diagnosed accurately and in time to reduce morbidity and mortality^{5,6}.

Classification

It may be based on the chief component of the immune system deficient, absent or defective³.

- Predominantly antibody deficiencies:*
 - X-linked agammaglobulinaemia
 - Common variable immune deficiency
 - Selective IgA deficiency
 - Specific antibody deficiency
 - IgG subclass deficiency
- Combined B & T cell immunodeficiencies (predominantly T cell):*
 - Hyper IgM syndrome
 - Severe combined immune deficiency
 - T negative B positive: γ chain deficiency, Janus kinase 3 deficiency
 - T negative B negative: Adenosine deaminase deficiency, Recombination activating gene 1/2 deficiency
- Other well defined immunodeficiency syndromes:*
 - Wiskott-Aldrich syndrome
 - Ataxia telangiectasia
 - Hyper IgE syndrome
- Diseases of immune dysregulation:*
 - Immunodeficiencies with hypopigmentation
 - Familial haemophagocytic lymphohistiocytosis syndromes
 - X-linked lymphoproliferative syndrome
 - Autoimmune lymphoproliferative syndrome
- Congenital defects of phagocyte number, function or both:*
 - Severe congenital neutropenia
 - Cyclic neutropenia
 - X-linked or autosomal recessive chronic granulomatous disease
- Complement deficiencies:*
 - Deficiency in early complement pathway components
 - Deficiency in late complement pathway components

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7. *Defects in innate immunity:*
 - Anhidrotic ectodermal dysplasia with immunodeficiency
 - IL-1 receptor-associated kinase 4 deficiency
 - Chronic mucocutaneous candidiasis
8. *Autoinflammatory disorders:*
 - Familial Mediterranean fever
 - TNF receptor-associated periodic fever
 - Hyper-IgD syndrome
 - Cryopyrin-associated periodic syndromes

Predominantly antibody deficiencies

B cell deficiencies are the most common type of PID. They usually present after 6 months of age with recurrent and severe sino-pulmonary infections mediated by *Streptococcus pneumoniae* and *Haemophilus influenzae*. Diarrhoea and autoimmune manifestations can also occur⁶. These children often have deficient subtypes of immunoglobulin levels. Figure 2 depicts the differentiation of B cells and the genes involved in the various stages of maturation.

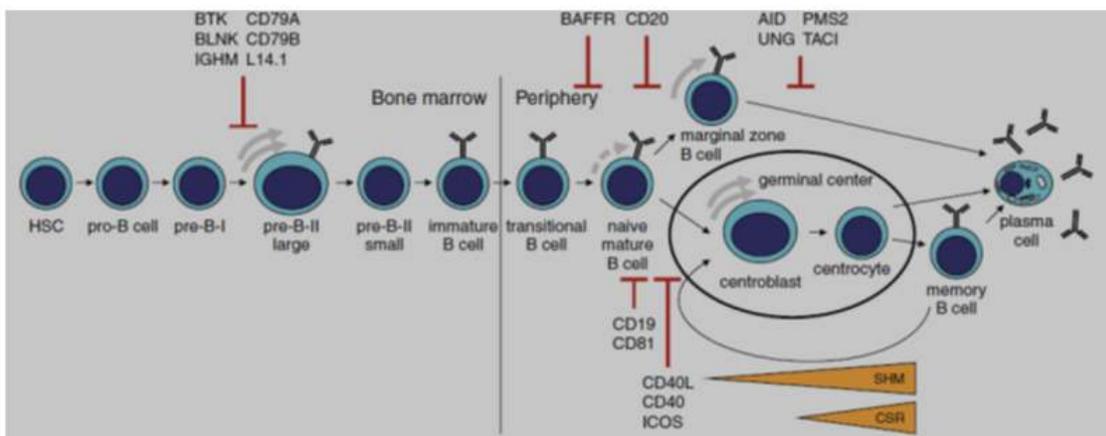


Figure 2: depicts differentiation of B cells and the genes involved in the various stages of maturation

AID - activation induced cytidine deaminase; *BAFFR* - B cell activating factor receptor; *BTK* - Bruton's tyrosine kinase; *CSR* - class switch recombination; *PMS2* - post-meiotic segregation increased 2; *SHM* - somatic hyper mutation; *TACI* - transmembrane activator; *UNG* - uracil-n glycosylase;

Defect in functioning of these genes results in humoral immune deficiency⁷. Antigen (Ag)-independent B cell differentiation occurs in the bone marrow, whilst Ag-dependent B cell differentiation occurs in the periphery. After activation by Ag, B cells develop in a T cell dependent way in the germinal centre and in a T cell-independent way in the marginal zone of the spleen (Figure 2)⁷.

Selective IgA deficiency: This is the commonest PID worldwide and occurs in partial and complete forms. Most forms are asymptomatic, though they can present with recurrent infections, autoimmunity or allergy⁸.

Common variable immune deficiencies (CVIDs): These occur in children older than 2 years and are characterised by hypoglobulinaemia (IgG <2SD of normal), decreased IgA and/or IgM levels, recurrent infections and impaired response to immunization. They should be diagnosed only after defined causes of hypoglobulinaemia are excluded⁹.

X-linked agammaglobulinaemia (XLA): This is due to a defect in the gene for Bruton's tyrosine

kinase which causes an early block in B cell development, resulting in absence of B lymphocytes in peripheral blood and hence absent immunoglobulin production. XLA constitutes 85% of all congenital agammaglobulinaemia. They generally present with recurrent infections of the respiratory tract caused by common bacteria such as *Haemophilus influenzae* or *Pneumococcus*. Chronic lung disease is the commonest long term complication while chronic enteroviral meningoencephalitis is the commonest cause of death¹⁰.

Transient hypogammaglobulinaemia of infancy: In this condition the hypogammaglobulinaemia spontaneously reverts to normal, usually before the child is 2 years old¹¹. Most children remain asymptomatic, though there is an increased risk of viral upper respiratory infections.

Combined B and T cell deficiency

Figure 3 depicts the development of B and T cells and the blocks associated in the process¹².

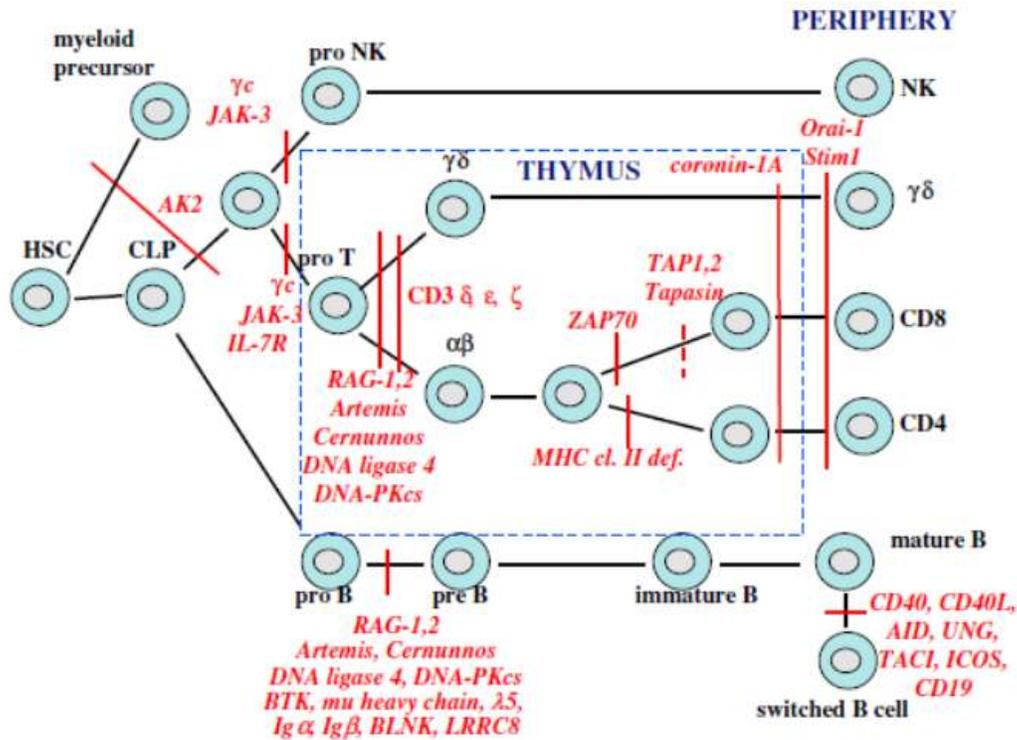


Figure 3: B and T lymphocyte development

Severe combined immune deficiency (SCID): This is the most severe form of PID and can be grouped into cytokine signalling defects, T-cell receptor and signalling defects, V(D)J recombination defects and metabolic defects¹³. Bacille Calmette-Guérin (BCG) vaccination can give rise to disseminated BCG-osis in SCID patients and should be avoided at birth if there is any suspicion or family history of immunodeficiency. Many infants also have chronic diarrhoea and failure to thrive. SCID can lead to early death unless cured by stem cell transplantation¹².

Hyper IgM syndrome (CD40 ligand deficiency): This is inherited as an X-linked trait. Children with CD40L deficiency have a severe defect of all immunoglobulin isotypes other than IgM. They are prone to opportunistic infections by *Pneumocystis carinii* and *Cryptosporidium parvum*¹⁴.

DiGeorge syndrome: This is due to a developmental defect of the third and fourth pharyngeal pouches and arches, resulting in impaired development of the thymus and parathyroids, facial dysmorphism and conotruncal heart defects.

Immunodeficiency with immune dysregulation
Autoimmune regulator (AIRE) protein is expressed by medullary thymic cells which are involved in immune tolerance. Mutations of the AIRE gene

disrupt this protein, causing autoimmune polyendocrinopathy candidiasis ectodermal dystrophy syndrome¹⁵. Mutations of the FOXP3 gene, involved in regulation of Treg cells in the thymus causes immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, with severe and early-onset autoimmune enteropathy, insulin-dependent diabetes, and eczema¹⁶.

Immunodeficiency with impaired cell mediated toxicity

These disorders are characterized by impairment of the mechanisms of transport, docking, or release of the lytic granules in cytotoxic T lymphocytes. Cytotoxicity defects include primary haemophagocytic lymphohistiocytosis (HLH) that results from deficiency of perforin, Munc13-4, and syntaxin 11, which result in defective intracellular killing. There is excessive production of TH1 cytokines and IFN-gamma resulting in the ‘accelerated phase’ with haemophagocytosis.

Phagocytic defects

Children with defects in phagocytosis, typically present with severe pyogenic infections of skin, respiratory tract and internal organs. These include severe congenital neutropenia (SCN) and chronic granulomatous disease (CGD)¹².

SCN: Both X-linked and autosomal recessive forms exist, the most common mutation being in the neutrophil elastase gene at 19p13. G-CSF has significantly improved survival in children with SCN though risk of transformation to acute myeloid leukaemia (AML) does exist¹⁷.

CGD: This is caused by a defect in genes encoding nicotinamide adenine dinucleotide phosphate-oxidase complex leading to insufficient production of free radicals. It is characterized by recurrent pyogenic infections involving deep tissue and sepsis due to catalase positive organisms. The sustained inflammatory response seen in CGD is responsible for the granulomatous manifestations causing gastric outlet obstruction, non-infective colitis, and hydronephrosis¹⁸.

Complement defects

Deficiency of early components of the classical complement pathway (C1q, C1r, C1s, C4, C2, and C3) causes autoimmune manifestations resembling systemic lupus erythematosus¹². Defects of late components (C5-C9) are associated with recurrent and invasive neisserial infections. Deficiencies of the regulatory components Factor H and Factor I cause membranoproliferative glomerulonephritis and recurrent atypical haemolytic uraemic syndrome. Deficiency of the C1 esterase inhibitor, a regulatory component of the classical pathway of complement activation, causes hereditary angioedema¹².

Immunodeficiency syndromes

These are disorders where other clinical features are present in addition to immunodeficiency.

Wiskott-Aldrich syndrome (WAS): This is caused by mutations in the gene encoding WAS protein which regulates actin cytoskeleton. It is associated with thrombocytopenia, severe eczema, and susceptibility to autoimmunity and malignancy. Affected males rarely survive beyond the second decade of life¹⁹.

Ataxia telangiectasia: This is an autosomal recessive disease caused by mutations of the ataxia-telangiectasia mutated gene. Patients have ataxia, ocular telangiectasia, increased risk of infections, and tumours. There is a progressive decrease of T-lymphocyte counts and function and hypogammaglobulinaemia. Alpha fetoprotein levels are usually increased²⁰.

Hyper IgE syndrome (HIES): This is characterized by eczema, cutaneous and pulmonary infections by *Staphylococcus aureus* and *Candida* species, and grossly increased IgE levels. Superinfection of pneumatoceles by *Aspergillus* species is not uncommon. Autosomal dominant variant is caused

by mutations of STAT3 gene and is characterized by dental and bone anomalies²¹.

Approach to diagnosis

A detailed history and physical examination supplemented by immune function testing is essential for diagnosis. Pre-natal testing is indicated if there is a family history of immunodeficiency and the mutation has been identified in family members.

History: This should focus on the age of onset, type and severity of infections, immunization history and family history of early deaths. Recurrent infections could give valuable clues to the diagnosis²².

Based on age of onset:

Neonatal period: Omenn Syndrome, severe congenital neutropenia (SCN), DiGeorge syndrome, leucocyte adhesion deficiency (LAD), reticular dysgenesis.

- Delayed separation of the umbilical cord beyond 2 weeks is characteristic of type I LAD.
- Omphalitis is suggestive of a neutrophil disorder such as LAD or SCN.
- Erythroderma with lymphadenopathy and hepatosplenomegaly is highly suggestive of Omenn syndrome, an atypical variant of SCID.
- Cardiac defects with hypocalcaemia and facial dysmorphism suggest DiGeorge syndrome.
- Reticular dysgenesis, a rare form of SCID usually presents in the neonatal period with cytopenia.

Before 6 months of age: SCID, CD40 ligand deficiency.

- Presentation in early infancy is highly suggestive of a significant T lymphocyte or combined immunodeficiency, such as SCID or CD40 ligand deficiency.

6 months to 5 years of age: WAS, DiGeorge syndrome, CGD, chronic mucocutaneous candidiasis and hypogammaglobulinaemia.

- Antibody deficiency presents after 4–6 months once placentally acquired maternal IgG has decayed.
- Defects in neutrophil function, such as CGD, may present in infancy, although the diagnosis is often made later.
- Immunodeficiency associated with DNA repair defects such as ataxia telangiectasia present commonly with gait abnormalities or neurodevelopmental delay.

After 5 years of age: CVID, specific antibody deficiency, complement disorder.

Based on system affected: Pattern of organ involved could give a clue to the type of PID.

Respiratory:

- Infants presenting with persistent or recurrent bronchiolitis may have SCID.
- Prolonged interstitial pneumonia due to *parainfluenza* virus, *cytomegalovirus* or *pneumocystis carinii* is suggestive of human immunodeficiency virus (HIV), SCID or CD40 ligand deficiency.
- Recurrent sino-bacterial infections after 6 months of age is suggestive of a humoral immunodeficiency.
- Staphylococcal lung infection with pneumatoceles, if associated with eczema, should suggest hyper-IgE syndrome.
- Fungal pneumonias could be a presentation of CGD.
- Recurrent sino-pulmonary infection occurring later in childhood could be due to CVID or complement deficiency.

Gastrointestinal:

- Recurrent infectious diarrhoea, malabsorption and failure to thrive might suggest SCID.
- Persistent non-infective diarrhoea in boys, with associated eczema and recurrent respiratory infection, should suggest IPEX syndrome.
- Hepatic abscesses, or abscesses due to *Staphylococcus aureus* or fungal infection are characteristic of CGD.
- Shwachman–Diamond syndrome should be considered in children with exocrine pancreatic insufficiency associated with neutropenia.
- Sclerosing cholangitis due to *Cryptosporidium parvum* is associated with CD40 ligand deficiency.

Haematological:

- Lymphocyte counts are comparatively higher in infancy and an absolute lymphocyte count less than $2.8 \times 10^9/L$ is 2 standard deviations below the mean until 1 year of age. Lymphopenia on more than 2 occasions is highly suggestive of SCID.
- Erythrophagocytosis might be suggestive of familial HLH, Chediak Higashi syndrome or Griscelli syndrome.
- Neutropenia occurring every 3–4 weeks, often with an associated fever, infection or mouth ulcers, is suggestive of cyclical neutropenia.

- Thrombocytopenia, small platelets and eczema occurring in boys suggests WAS.
- Autoimmune cytopenia might suggest DiGeorge syndrome, autoimmune lymphoproliferative syndrome (ALPS) or IPEX syndrome.

Skin:

- Eczema, associated with thrombocytopenia and small platelets suggests WAS.
- Eczema associated with staphylococcal pneumatoceles suggests hyper IgE syndrome.
- Mucocutaneous albinism may be a sign of disorders of cell-mediated killing, such as Griscelli syndrome or Chediak–Higashi syndrome.
- Perianal ulceration in the newborn, associated with a high neutrophil count but a lack of pus is indicative of LAD.
- Systemic lupus erythematosus (SLE) is a feature of complement deficiency.
- Persistent mucosal candida infection may be suggestive of SCID, chronic mucocutaneous candidiasis or hyper-IgE syndrome.
- Telangiectasia or photosensitivity with recurrent infection is suggestive of ataxia telangiectasia.

Neurological:

- Unsteady gait might be associated with ataxia telangiectasia.
- Spastic diplegia with dysarthria is a common presenting feature of purine nucleotide phosphorylase-deficient SCID.
- DiGeorge syndrome may be associated with developmental and speech delay.
- Neurological deterioration is a late feature of Chediak–Higashi syndrome.
- Enteroviral meningoencephalitis may be a feature of humoral immunodeficiency.

Lymphoreticular malignancy:

- EBV-associated lymphomas are described in XLP and Wiskott–Aldrich syndrome.
- Non-Hodgkin's lymphoma is described in ALPS and CVID.

Based on type of infections:

The spectrum of infections in a child could also give a clue to the suspected diagnosis of PID. Table I presents the type of infections that occur in various subtypes of PIDs¹².

Organism	Antibody deficiencies	CIDs	Phagocytic defects	Complement deficiencies
Viruses	Enteroviruses	All, especially: CMV, respiratory syncytial virus, EBV, parainfluenza type 3	No	No
Bacteria	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Neisseria meningitidis</i> , <i>Mycoplasma pneumoniae</i>	As for antibody deficiencies, also: <i>Salmonella typhi</i> , <i>Listeria monocytogenes</i> , enteric flora	<i>S aureus</i> , <i>P aeruginosa</i> , <i>Nocardia asteroides</i> , <i>S typhi</i>	As for antibody deficiencies especially <i>N meningitidis</i> in deficiency of late components
Mycobacteria	No	Nontuberculous, including BCG	Nontuberculous, including BCG	No
Fungi	No	<i>Candida</i> species, <i>Aspergillus</i> species, <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i>	<i>Candida</i> species, <i>Aspergillus</i> species	No
Protozoa	<i>Giardia lamblia</i>	<i>Pneumocystis jirovecii</i> , <i>Toxoplasma gondii</i> , <i>Cryptosporidium parvum</i>	No	No

Table I: Pattern of infections in various primary immunodeficiency disorders

Whom to investigate?

A high index of clinical suspicion is needed to diagnose PID. Child having recurrent infections in a single anatomic location will more probably have an anatomic defect than an immune deficiency. Unusually severe or long lasting recurrent infections or failing to respond to standard therapy, or infection with unusual organisms makes one to suspect PID. The European Society of Immunodeficiencies (ESID) has suggested 10 warning signs for suspicion of PIDs²³.

1. Four or more new ear infections within one year.
2. Two or more serious sinus infections within one year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within one year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicaemia.
10. A family history of PID

How to investigate?

The first-line investigations include a full blood count with a differential count, lymphocyte subset analysis for enumeration of CD3+, CD4+, CD8+ T lymphocytes, B lymphocytes (CD19+, CD20+) and

natural killer (NK) cells (CD16+, CD56+), and serum immunoglobulins (Ig).

Absence of B lymphocytes is associated with congenital agammaglobulinaemia. Serum Ig levels lower than age-appropriate reference values suggest B-cell immunodeficiency. However, serum specific antibody titres (usually IgG) in response to vaccine antigens is ideal to confirm an antibody-deficiency disorder. In this method, a patient is immunised with protein antigens (e.g. tetanus toxoid) and polysaccharide antigens (e.g. pneumococcus) and pre- and post-immunization antibody levels are assessed. Most PIDs have diminished or absent antibody responses to these antigens⁶.

Age specific lymphopenia, along with markedly reduced T-lymphocyte counts, is characteristic of SCID. Absolute lymphocyte count below 3000 per cu mm in a neonate is a useful cut off for T cell disorder. A lymphocyte count less than 2 standard deviations below the age-specific mean is abnormal²⁴. T-cell receptor excision circles (TRECs), a by-product of V(D)J recombination, are exported to the periphery by newly generated thymic T lymphocytes. TRECs levels in circulating lymphocytes are especially high in neonates and infants and reduce with age. TRECs less than 30 copies per µL is 100% sensitive for T-cell disorder. Assessing TREC levels by PCR may be used for neonatal screening of SCID²⁵. Markedly decreased levels of serum IgG and IgA together with normal or high serum IgM levels, suggests CSR defects due to either intrinsic B cell problems or impaired cross-talk between T and B lymphocytes¹².

Absolute neutrophil count (ANC) is greatly decreased in all types of SCN. Nitroblue tetrazolium test (NBT) is widely used as the screening test for CGD, whereas neutrophil function assays like dihydrorhodamine response helps in confirming a diagnosis of CGD. Diagnosis of LAD1 is straightforward and is based on flow cytometric evaluation of CD18 expression on the leucocyte surface. Measuring haemolytic activity of the classical and alternative pathways of complement, along with C3 and C4 levels may help in the diagnosis of complement deficiencies. Increase of TCRαβ+CD4 neg CD8 neg T cells suggests ALPS.

Treatment

The treatment of patients with PID is based on: (1) timely recognition, (2) adequate treatment and surveillance and (3) nature of the underlying disease. Immunoglobulin replacement and prophylactic antibiotics used judiciously may prevent significant end organ damage and improve long-term outcome and quality of life²⁶. Broadly, the supportive and definitive treatment options of the various groups of PID are summarized in Table 2²⁷.

	Supportive	Definitive
CID/SCID	<ul style="list-style-type: none"> • Ig replacement therapy (IV or SC) • Antibiotic prophylaxis • Antifungal prophylaxis • Aggressive management of established infections • Infectious precautions when hospitalized • Withhold all live vaccines 	<ul style="list-style-type: none"> • BMT • HSCT • Gene therapy a possibility for some SCIDs
B-cell disorders	<ul style="list-style-type: none"> • Ig replacement therapy (IV or SC) • Antibiotic prophylaxis • Antifungal prophylaxis depending upon etiology • Hearing assessment • Assessment of pulmonary status and function • Close monitoring for co-morbidities 	<ul style="list-style-type: none"> • Gene therapy is a potential future treatment in some patients
Innate disorders	<ul style="list-style-type: none"> • Antibiotic prophylaxis • Antifungal prophylaxis • Cytokine replacement (IFNγ) for CGD • Vaccinations (e.g. meningococcal) • Ig replacement is sometimes indicated 	<ul style="list-style-type: none"> • BMT, e.g. for CGD • Gene therapy is a potential future treatment

Ig, immunoglobulin; IV, intravenous; SC, subcutaneous; CID, combined immunodeficiency; SCID, severe combined immunodeficiency; IFNγ, interferon-gamma; BMT, bone marrow transplantation; CGD, chronic granulomatous disease; HSCT, hematopoietic stem cell transplantation

Table 2: Outline of treatment of PID

However, definitive cure can only obtained through haematopoietic stem cell transplantation (HSCT), though gene therapy may be a viable alternative in the future. In fact, prognosis of SCID has altered from invariably fatal to more than 90% survival with timely HSCT with an HLA-matched donor²⁸.

Stem cell transplantation in primary immune deficiencies

The first allogeneic human leucocyte antigen (HLA)-matched sibling bone marrow transplants for SCID and WAS was performed in 1968, adenosine

deaminase deficiency (ADA) and SCID in 1975, unrelated donor transplant in 1977 and haplo-identical related donor transplants in 1983²⁹. HSCT involves identifying a HLA matched donor, conditioning chemotherapy to enable recipient to accept new stem cells, infusion of donor stem cells into recipient, providing optimal supportive care until engraftment and continuing immunosuppression for around 6 months to prevent graft rejection and graft versus host disease³⁰. The potential immune deficiencies treated with HSCT are shown in Table 3³¹.

Absent T- and B-lymphocyte function	Defective T and B lymphocytes	Dysfunctional T lymphocytes with predisposition to HLH	Absent or dysfunctional granulocytes
SCID	Wiskott-Aldrich syndrome HIGM1	Familial HLH (defects in <i>perforin</i> , <i>MUNC</i> , etc.) Chodak-Higashi syndrome Griscelli syndrome XLP	Severe congenital neutropenia Leukocyte adhesion disorder Chronic granulomatous disease

Abbreviations: HIGM1 – hyper IgM syndrome (CD40 ligand deficiency); HLH – hemophagocytic lymphohistiocytosis; XLP – X-linked lymphoproliferative disease.

Table 3

Severe Combined Immune Deficiency

The only curative therapy for SCID is allogenic HSCT, except ADA for which a replacement

enzyme exists. Major factors influencing outcome post HSCT are:

1. Type of donor, matched sibling donors having best outcome.

2. Type of SCID, T-B- forms having poorer outcome.
3. Preceding co-morbidity (pneumonitis, septicaemia, viral illness, malnutrition) adversely affecting outcome.
4. Age at transplant, infants less than 6 months having improved outcome.

In children with SCID, HSCT is warranted as soon as possible after diagnosis, preferably before 6 months of age, when outcomes are very good^{32,33}. According to *Buckley et al.* HSCT prior to 3.5 months of age has 95% survival, compared to 76% in older patients³⁴. Transplants in the first 30 days of life are associated with superior T cell reconstitution³⁵. T-cell negative, B-cell negative, NK cell-positive SCID (T- B- NK+ SCID, the commonest subtype, is caused by a defect in the common gamma chain or is due to Janus kinase 3 (JAK3) deficiency and is associated with good T cell reconstitution after engraftment³⁶. T- B- NK+ SCID, due to defects in recombination activating gene 1 (RAG1) or RAG2, has an inferior overall survival compared to the B+ subtypes with decreased chance of engraftment, increased incidence and severity of GVHD and slower T cell reconstitution^{37,38}. The presence of NK cells also mediates graft rejection.

Source of stem cells

The best results following HSCT are seen with a HLA identical sibling where overall survival rates are more than 90%³⁴. In children where a HLA matched sibling is not available, the choices are between a T cell deplete haplo-identical parent, a matched unrelated donor or unrelated cord blood. Virtually all children have haplo-identical parental donors and this is an alternative option especially as the donor is readily available. If performed early before the onset of severe infections and with effective T cell depletion strategies available, overall survival rates of 50-70% are seen with haplo-identical transplantation. The mother is ideally utilized as the stem cell source since the child is already tolerant to maternal cells. However, there is an increased likelihood of GVHD due to the maternally engrafted T lymphocytes. The potential risk with haplo-identical transplantation is the delayed T cell reconstitution and increased risk of opportunistic infections³². Few studies have shown overall survival with matched unrelated transplantation to be superior to mismatched related transplantation with faster immune reconstitution²⁸. But the long term results are not clear.

Cord blood transplantation offers some theoretical advantages including rapid availability, as with haplotype-matched parental donors but with no requirement for T-cell depletion, less risk of GVHD compared to adult unrelated donors, no medical risk to the donor and a greater proliferative life span. There are also some specific disadvantages

including: slower engraftment; lack of viral specific cytotoxic T-cells; and lack of availability of the donor for a boost HSCT³⁴. However, both matched unrelated transplantation and using cord blood would need high dose chemotherapy for successful engraftment.

Conditioning

Conditioning prior to HSCT in SCID is not an absolute requirement. For those patients requiring conditioning, a myeloablative regime of 16 mg/kg of busulfan and 200 mg/kg of cyclophosphamide is widely used³². Bertrend *et al* has shown good outcomes with reduced intensity conditioning of 8mg/kg of busulfan and 200mg/kg of cyclophosphamide³⁹. Myeloablative therapy increases the chance for complete chimerism but there is also an increased risk of transplant related mortality and morbidity. Current EBMT recommendations include use of busulfan/fludarabine or treosulfan/fludarabine based protocols.

Non-SCID Immunodeficiency

The major difference with non-SCID patients compared to SCID patients is the usual requirement for a conditioning regimen to achieve engraftment. Many children with non-SCID PID have significant co-morbidities at the time of HSCT and conventional myeloablative preparation with busulfan/cyclophosphamide based regimes can be associated with significant toxicity as well as long term sequelae. Recent alternatives have:

1. replaced cyclophosphamide with fludarabine, as the busulfan/ fludarabine combination appears to be better tolerated.
2. replaced busulfan with a structural analogue, treosulfan, which is similarly immuno- and myelo-suppressive, but does not cause hepatic veno-occlusive disease⁴¹.
3. used reduced intensity HSCT to achieve stable engraftment of immunocompetent donor cells with reduced procedure-related morbidity and mortality.

Wiskott-Aldrich syndrome (WAS)

Only curative treatment is HSCT. A collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program showed transplant outcomes in 170 males with WAS. The overall 5-year probability of survival was 70%. HLA-identical sibling donor transplants had a superior overall survival of 87%. Unrelated donor transplants less than 5 years of age had an overall survival of 85%, while all children more than 5 years of age who underwent unrelated transplantation died⁴⁰. Haplocompatible-related transplants were less successful with an overall survival of 45-52%⁴⁰. Umbilical cord blood transplants had a higher risk of post-transplant complications such as graft

failure, GVHD, autoimmunity and malignancy. Myeloablative conditioning was preferred earlier since mixed chimerism due to reduced intensity conditioning might lead to development of autoimmune diseases. UK experience using treosulfan/ fludarabine in WAS suggests that good immune reconstitution with 100% donor chimerism can be achieved without the need to use full myeloablative conditioning⁴¹.

Chronic granulomatous disease (CGD)

The only curative treatment available for CGD is HSCT. Regimens ranging from full myeloablation to non myeloablative conditioning cured CGD⁴². Even mixed chimerism attained with reduced intensity conditioning has sufficed to cure CGD.

Severe congenital neutropenia (SCN)

Early referral for HSCT is important if there is poor response to G-CSF, considering the high risk for AML transformation. A study from SCN International Registry has shown overall survival of 82% in 11 children who underwent HSCT⁴³.

Familial haemophagocytic lymphohistiocytosis (HLH)

This autosomal recessive disease is characterized by defects in genes encoding NK and T cell cytotoxicity. It is invariably fatal, unless treated by HSCT. A report from HLH-94 showed a 62% 3 year event free survival in 65 children who underwent HSCT⁴⁴.

Chediak Higashi syndrome

Children, often die during the accelerated phase of the disease. A study by Eapen *et al.* showed that 35 children who underwent HSCT had a 5 year overall survival of 62%⁴⁵.

CD40 ligand deficiency (Hyper-IgM syndrome)

Without HSCT about 50% of children with hyper IgM syndrome survive to the fourth decade. A survey of the European experience, 1993-2002 showed that HSCT cured 58% of patients overall and 72% of those without hepatic disease⁴⁶.

Leucocyte adhesion deficiency (LAD)

In a review of worldwide BMT experience amongst 36 children with LAD, overall survival was 75%. Mortality was greatest after haplo-identical transplants³¹.

Future perspectives

To conclude, it is important that children with PIDs are transplanted as early as possible before the onset of severe infections. In families with a history of PID and an identified genetic mutation, prenatal diagnosis should be emphasized. Recently, in utero HSCT for SCID have also been performed, though survival rates are variable⁴⁷. A screening programme

at birth is also warranted to identify children with T cell lymphopenia and SCID and allows for early HSCT. Newer developments like reduced intensity conditioning and tailoring the conditioning regime based on the type of PID like avoiding alkylating agents or radiation might go a long way in improving outcomes with haplo-identical and unrelated donor transplantation. Newer methods of T cell depletion are being increasingly used to facilitate haplo-identical transplantation. Finally, the advent of gene therapy for these disorders might even prompt us to move away from HSCT in the years to come⁴⁸.

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