20.6 Primary immunodeficiency diseases

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1. Introduction
Primary immunodeficiency (PID) diseases arise from genetic defects that lead to abnormalities in immune cell development or function. Replacement of the defective lineage by HSCT from healthy allogeneic donors remains the curative approach for most patients. Other management options including enzyme replacement therapy and gene transfer into autologous haematopoietic stem cells may provide an alternative approach to HSCT in specific immune deficiencies.

2. Diseases
PID may be broadly divided into severe combined immunodeficiencies (SCID) and non-SCID. Non-SCID can be further subdivided into T-cell deficiencies, CD40 ligand deficiency, Wiskott-Aldrich syndrome (WAS), X-linked lymphoproliferative disorder (XLP), phagocytic cell disorders, haemophagocytic syndromes and autoimmune and immunoregulatory disorders (Table 1).
Overall guidelines for HSCT for SCID and non-SCID diseases together with detailed protocols have been produced by the EBMT inborn Errors Working Party (EBMT IEWP) and can be found online at: [http://www.ebmt.org/5WorkingParties/IEWP/wparties-ie5.html](http://www.ebmt.org/5WorkingParties/IEWP/wparties-ie5.html).

3. SCID
The overall frequency of SCID is around 1 in 75,000 live births although the exact frequency is unclear. The immunological phenotypes of SCID are shown in Table 1 and represents monogenic inherited defects in T, B and NK cell differentiation leading to the absence or inactivity of corresponding mature cells. Over the past two decades, the genetic basis of the different forms of SCID have been identified (Table 1) leading to modifications in transplant strategy dependent on the underlying defect. Clinically, most patients present by age 6 months with unusually severe and recurrent infections or with opportunistic infections, the most common being *Pneumocystis jiroveci pneumonitis*. Other common symptoms include diarrhea, dermatitis, and failure to thrive. Survival in SCID patients depends on expeditious T-cell reconstitution, and in the absence of successful HSCT most children die in first year of life from overwhelming infection. It is recognised that as many of 50% of SCID patients are engrafted with maternal T-cells but in most instances these cells do not initiate GvHD. Transfusion associated GvHD, on the other hand, is frequently lethal in SCID and any patient with a possible diagnosis of SCID should receive irradiated blood products. 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.
3.1 General principles in transplant for SCID
Data from the European registry for SCID transplants (SCETIDE) has now collected data on SCID transplants for over 30 years and a number of important publications have documented the outcomes and important risk factors (1–3).

The major factors influencing outcome include:
1. The type of donor with matched sibling donors having the best outcome
2. The type of SCID, with T-B- forms of SCID having a poorer outcome
3. Preceding co-morbidity (pneumonitis, septicaemia, viral illness, malnutrition) adversely influencing outcome
4. Age at transplant with patients <6 months having an improved outcome.

3.2 Matched sibling donor HSCT for SCID
The outcome for MSD HSCT in SCID is now probably in excess of 90%. Somewhat
remarkably, sibling donor BM may be infused into SCID recipients without the requirement for conditioning or GvHD prophylaxis. Infusion of sibling BM leads to the rapid development of T- and B-cell function post-HSCT, although usually only T-cells of donor origin develop, and myeloid and erythroid cells remain of recipient origin. The majority of patients achieve humoral reconstitution despite lack of donor B-cells, although this is dependent on the type of SCID.

3.3 Other matched family and unrelated donor HSCT for SCID
Successes have also been reported with phenotypically matched related as well as unrelated donors. In comparison to genotypically-identical sibling donors, phenotypically-matched related and matched unrelated transplants have a trend to reduced overall survival (81, 72, 63% respectively) (3, 4). It is generally considered that the risk of rejection/GvHD is too high for simple infusion of phenotypically matched marrow into SCID patients, so conditioning/GvHD prophylaxis is recommended. A variety of conditioning regimes have been used and current recommendations include the use of an i.v. busulfan/fludarabine or treosulphan/fludarabine based protocol (details at: http://www.ebmt.org/5WorkingParties/IEWP/wparties-ie5.html).

3.4 HLA-mismatched family donor for SCID
Virtually all children have an haploidentical parental donor and this is an alternative option especially as the donor is readily available. HLA-disparity necessitates rigorous T-cell depletion in order to avoid GvHD. With the introduction of PBPCs as a preferred stem cell source most centres now employ CD34+ cell selection or large scale CD3/CD19 negative depletion methods to achieve a 4–5 log T-cell depletion achieving a threshold of 1–5 x 10^4/kg CD3+ cells, below which GvHD prophylaxis is not required. Some centres advocate performing transplants without the use of any conditioning and survival rates of over 80% have been reported (5). However, the best results are seen in those transplanted at <3.5 months of age and also this does not seem to be equally efficient in all forms of SCID with the best results seen in the T-B+ phenotype. Even in these cases, B-cell function is only restored in ~20% of patients. Alternatively conditioning regimes can be used but the use of myeloablative conditioning regimes in children often <1 yr of age and with significant co-morbidity, leads to survival figures of 50–60%.

3.5 Unrelated cord blood transplantation for SCID
There are now in excess of 450,000 cord blood units stored worldwide. There are some theoretical advantages for the use of cord blood stem cells for SCID, namely: 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 which might be particularly important in such young recipients. 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 HSCT. Of 20 SCID patients who have undergone CBT reported in the literature and reviewed recently, 16 (80%) are surviving with good immune reconstitution including B-cell reconstitution (6).

3.6 HSCT for radiosensitive SCID
Patients with T-B- SCID due to radiosensitive disorders such as DNA ligase 4 deficiency, Cernunnos deficiency, DNA-PKcs deficiency are increasingly being identified and being considered for haematopoietic stem cell transplant. As many of the conditioning regimens are particularly damaging to DNA, less toxic regimens are required to successfully treat these patients. No definitive studies are available but a low dose fludarabine/cyclophosphamide regime has been suggested by the EBMT IEWP (http://www.ebmt.org/5WorkingParties/IEWP/wparties-ie5.html).

4. Non-SCID immunodeficiency
The major difference with non-SCID patients in comparison 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 may be associated with significant treatment-related toxicity as well as long-term sequelae. Recent alternatives have:
1. Replaced cyclophosphamide with fludarabine, as the combination of busulfan and fludarabine appears better tolerated in these patients
2. Replaced busulfan with a structural analogue, treosulphan, which is similarly immuno- and myelo-suppressive, but does not cause hepatic veno-occlusive disease (VOD) (7)
3. Used reduced intensity HSCT to achieve stable engraftment of immunocompetent donor cells with reduced procedure-related morbidity and mortality (8). Sufficient long-term donor chimerism needs to be confirmed following these new approaches.

The latest outcome data for HSCT in non-SCID patients comes from Europe (3). In the 2000–2005 period, HSCT using an unrelated donor (n=124) gave a 3-year survival rate similar to a genoidentical donor (n=73), 79% for both. Survival was 76% in phenoidentical transplants (n=23) and worse in mismatched related donor
transplants (n=47; 46%; p=0.016), in contrast to SCID patients (see above). Ten year survival was significantly better for patients with WAS, phagocytic and haemophagocytic disorders than for patients with T-lymphocyte immunodeficiencies (71, 63, 58, 47% respectively). Unrelated CB donors appear to also give promising results in non-SCID immunodeficiency with 29/32 (91%) patients surviving CBT matched for 4-6/6 HLA antigens (6).

4.1 Wiskott-Aldrich syndrome
WAS is an X-linked disorder characterised by thrombocytopenia with small platelets, eczema, and progressive immunodeficiency. Without HSCT, WAS patients have a poor prognosis with the major causes of death being infection, bleeding and lymphoproliferative disease (LPD). The outcome of 194 WAS patients undergoing HSCT in the period 1980–2009 has recently been reported (9). Overall survival was 84%, and even higher 89% for those undergoing HSCT since 2000. Good clinical status at the time of HSCT resulted in better survival. Younger age at HSCT(<2 yrs vs >5 yrs) was associated with better survival in children undergoing unrelated donor HSCT. Use of mismatched family donors or mismatched cord blood as a source of stem cells was associated with reduced survival and more post-HSCT complications. Mixed chimerism was associated with an increased risk of incomplete reconstitution of lymphocyte count and post-HSCT autoimmunity, and myeloid donor cell chimerism <50% was associated with persistent thrombocytopenia. Splenectomy pre- or post-HSCT was associated with an increased risk of fatal sepsis. A flow chart for management of WAS is shown in Figure 1.

4.2 T-cell immunodeficiency

4.2.1 Omenn’s syndrome
Omenn’s syndrome (OS) is characterised by SCID typically associated with the triad of erythroderma, hepatosplenomegaly, and lymphadenopathy. There is a marked eosinophilia and a variable number of autologous, activated, and oligoclonal T-lymphocytes (leaky SCID/CID), that infiltrate target organs and are generally poorly responsive to mitogens. Experience with HSCT in OS has been difficult with high levels of mortality in some studies. A recent study examining the use of alternative donor HSCT in a single centre reported survival in 9/11 patients with OS patients who were alive with immune reconstitution 30–146 months after HSCT (11). The overall mortality in this study was lower than previously reported and was due to early recognition of OS, and rapid initiation of treatment with topical/systemic immune suppression with steroids and/or cyclosporin A to control immune dysreactivity before proceeding to HSCT.
4.2.2 HLA class II (MHC II) deficiency

MHC II deficiency patients seem to do particularly poorly through BMT (12); in a summary of 23 patients who underwent BMT for MHC II deficiency in Europe up to 1996, disease free survival was 40% for HLA-matched transplants (n=9) but only 20% from HLA-mismatched transplants (n=14). Of the eight patients who remained
well post HSCT, all had persistently low CD4+ T-lymphocytes consistent with impaired thymic maturation caused by defective HLA class II expression on thymic epithelia, making the patients particularly susceptible to ongoing opportunistic infection. Importantly in this condition reconstitution of antigen presenting cells, i.e. B-cells, monocytes, dendritic cells, and not just T-cells is essential for disease correction.

### 4.3 CD40 ligand deficiency (X-linked hyper-IgM syndrome)

CD40 ligand deficiency is a rare X-linked T-cell immunodeficiency caused by mutations in the gene encoding CD40 ligand glycoprotein (CD154) which is critical in initiating immunoglobulin isotype class switching from IgM to IgG, IgA and IgE in B-cells, and for monocyte/macrophage activation. Patients present recurrent bacterial sino-pulmonary infection leading to bronchiectasis and are particularly susceptible to gastrointestinal infection with protozoa such as *Cryptosporidium parvum*, leading to sclerosing cholangitis. Without HSCT about 50% of patients survive to the fourth decade. The largest HSCT series reported 38 patients from 8 European countries between 1993 and 2004 (13). HSCT cured 58% of the patients and 72% of those without hepatic disease. 32% died from infection-related complications, including severe cryptosporidiosis.

### 4.4 X-linked lymphoproliferative syndrome

X-linked lymphoproliferative syndrome (XLP) is a rare immunodeficiency characterised by a dysregulated immune response to Epstein-Barr virus and other pathogens. The clinical presentation includes fulminant infectious mononucleosis, haemophagocytic histiocytosis (HLH), lymphoma, hypogammaglobulinemia and aplastic anaemia. The advent of better treatment strategies for HLH and malignancy has greatly reduced mortality for these patients; survival following HSCT is 81% and similar with different donor sources, however, survival falls to 50% in patients with HLH as a feature of disease (14). It is logical to use EBV positive donors for EBV+ patients and if T-cell depletion is required for the HSCT procedure careful monitoring of the EBV viral load by EBV-specific RQ-PCR is advisable. The generation and use of EBV-specific CTLs may be beneficial, as well as depletion of donor/recipient B-lymphocytes by the administration of rituximab.

### 4.5 Phagocytic cell disorders

#### 4.5.1 Kostmann syndrome

Severe congenital neutropenia (CN) (Kostmann syndrome) is a haematological disorder characterised by a maturation arrest of myelopoiesis at the promyelocyte/myelocyte stage of development. This arrest results in severe neutropenia leading to absolute neutrophil counts (ANC) below 0.2 x 10^9/L associated with severe
bacterial infections from early infancy. The availability of recombinant human granulocyte colony-stimulating factor (r-HuG-CSF) in 1987 dramatically changed the prognosis and quality of life of patients with CN. More than 90% of CN patients respond to r-HuG-CSF with an increase in ANC >1.0 x 10^9/L, requiring fewer antibiotics and reduced hospitalisation. In G-CSF less-responsive patients followed up for 10 years, 40% develop MDS/AML and 14% die of sepsis. This is the best group to target for HSCT as outcomes of HSCT have been poor when leukaemic transformation has already taken place.

4.5.2 Leucocyte adhesion deficiency
Leucocyte adhesion deficiency (LAD) is an autosomal recessive disorder characterised by impaired migration of neutrophils from the intravascular space, due to defective β2 leukocyte integrin (CD11/CD18) expression. Complete absence of CD11/CD18 leads to a severe phenotype usually presenting in early infancy and characterised by deep tissue infections, leukocytosis with impaired formation of pus, and delayed wound healing. The worldwide BMT experience was recently reviewed (15): amongst 36 patients the overall survival rate was 75%. Myeloablative conditioning regimens were used in 28 patients, and reduced-intensity conditioning in 8 patients, with no deaths in the latter subgroup. Survival rates after matched family donor and unrelated donor transplants were similar; mortality was greatest after haploidentical transplants.

4.5.3 Chronic granulomatous disease
Chronic granulomatous disease (CGD) is an inherited disorder of phagocyte function, characterised by recurrent, often life-threatening bacterial and fungal infections and by granuloma formation in vital organs. Neutrophils, monocytes/macrophages, and eosinophils cannot generate microbicidal oxygen metabolites owing to a defect in one of the four subunits of the NADPH oxidase of phagocytes. Despite prophylactic treatment with cotrimoxazole, itraconazole and/or gamma interferon, there is an annual mortality between 2 and 5%, with 25% of the deaths due to invasive aspergillosis. Recent BMT outcomes targeting iv busulfan to 75% of myeloablative dose + fludarabine + ATG or alemtuzumab (to suppress inflammation and GvHD) has produced excellent outcomes (>90% in 28 patients - Gungor T, personal communication 2011) with MSD or MUD donors respectively, prompting the suggestion that all children with CGD should undergo a BMT procedure if a matched donor is available.

4.6 Haemophagocytic syndromes

4.6.1 Familial haemophagocytic lymphohistiocytosis
Familial haemophagocytic lymphohistiocytosis (FHL) is a genetically determined
autosomal recessive disorder characterised by the early onset of fever and hepatosplenomegaly, associated with pancytopenia, hypertriglyceridaemia, and hypofibrinogenemia, and haemophagocytosis in the bone marrow. In addition, central nervous (CNS) involvement may be severe and cause permanent CNS dysfunction. The pathogenesis of FHL has been associated with the impairment of the cytotoxic pathway in lymphocytes, where uncontrolled activation of T-lymphocytes results in raised levels of inflammatory cytokines. Mutations within the perforin (PRF1) gene accounts for 30% of cases, while mutations of MUNC and SYNTAXIN genes account for another 40% or so. HLH is also a significant feature of other disorders including XLP 1 and 2, Chediak-Higashi and Griscelli syndromes. The condition is fatal without adequate treatment including HSCT. Initial therapy consists of cycles of therapy with etoposide, dexamethasone and cyclosporin A (CsA) (HLH 2004) or anti-thymocyte globulin (ATG), steroids and CsA with intrathecal methotrexate for CNS disease to achieve control of HLH, and followed by HSCT from the best available donor. Conventional BMT with busulfan and cyclophosphamide ± VP16 gives an overall 3 year survival rate of 64%: matched-related donor 71%; matched unrelated donor 70%; familial haploidentical donor 54%; and mismatched unrelated donor 54%. The odds ratio for mortality were 2.75 for those with active disease after 2 months of therapy compared with inactive disease, and 1.8 for children with active as opposed to inactive disease at the time of HSCT. Veno-occlusive disease is the major toxicity associated with transplants in HLH and because donor lymphocyte chimerism >20% is associated with sustained remission, reduced intensity conditioning (RIC) may be an alternative and perhaps better approach for FHL (16).

4.6.2 Chediak-Higashi syndrome
Chediak-Higashi syndrome (CHS) is a rare autosomal recessive syndrome characterised by oculo-cutaneous albinism, recurrent infections, microscopic finding of large granules in haematopoietic and other cells, neurologic abnormalities and a bleeding diathesis. In survivors of infectious complications an accelerated phase, manifested by life threatening haemophagocytosis, occurs within the first or second decade. Thirty-five children with CHS underwent HSCT and were reported to the CIBMTR (17), the 5-year probability of overall survival was 62%, suggesting that HSCT is effective therapy for the accelerated phase of CHS. However, progressive neurological dysfunction has been reported in long-term survivors of HSCT for CHS who had neither recurrent infections nor manifestations of haemophagocytic syndrome after HSCT. This suggests a steady long-term progression, despite HSCT, of the lysosomal defect in neurons and glial cells, and may question the appropriateness of HSCT in non-accelerated CHS.
5. Alternative therapies

Alternative treatments to HSCT have been developed for specific immunodeficiencies over the last two decades.

5.1 Enzyme replacement therapy for adenosine deaminase deficiency (ADA-SCID)

Enzyme replacement has been used in the treatment of ADA deficiency since 1987 (18). PEG-ADA is administered weekly or twice weekly by intramuscular injection and leads to rapid metabolic correction with normalisation of metabolic parameters which is then followed by cellular and humoral immune reconstitution. The extent of immune recovery is variable and a significant number (~50%) remain on immunoglobulin replacement (19). Over a longer time period, patients show a decline in T-cell numbers and remain lymphopenic (20). Long term follow-up shows that patients remain clinically well but a number of cases of EBV related lymphoma have been reported, suggesting decreased immune surveillance with time.

5.2 Gene therapy for specific immune deficiencies

Possibly the greatest advance has been the development of stem cell gene therapy for the treatment of defined genetic defects. The first human condition for which gene therapy has shown unequivocal benefit is X-linked severe combined immunodeficiency (SCID-X1). Using retroviral mediated transfer of the IL-2RG gene into autologous CD34+ cells, successful reconstitution of cellular and humoral immunity has been demonstrated in the majority of patients treated in two trials in Paris and London (21, 22). Since gene transduced cells have a significant survival advantage, this procedure can be undertaken without prior cytoreductive therapy and thus the short term morbidity of the procedure is low. Twenty patients have now been treated and nearly all have a shown significant improvement of T-cell numbers and ~50% show humoral reconstitution.

A number of gene therapy trials for ADA deficiency have also been initiated using gamma retroviral vectors. In contrast to the SCID-X1 studies, a mild non-myeloablative conditioning regime (in most cases iv busulfan 4 mg/kg) was used to allow engraftment of a greater number of gene modified cells. Over 30 patients have now been treated in 3 trials worldwide. All patients have survived and ~70% have been able to stop enzyme replacement therapy suggesting that gene therapy is able to effectively detoxify the system and allow immune reconstitution. Approximately 50% of patients have been able to stop immunoglobulin replacement no adverse events have been seen so far. In 3 patients with X-CGD, a similar retroviral vector based protocol using a non-myeloablative conditioning regime prior to the return of gene transduced autologous cells, showed substantial gene transfer into neutrophils leading to a large number of functionally corrected phagocytes and notable clinical
improvement (23). Gene therapy for WAS using a gamma retroviral vector and a busulfan based conditioning regimen have also shown considerable success in correcting both the platelet and immunological defects. These gene therapy studies show clearly that gene transfer into autologous stem cells can result in functional immune correction. However, side-effects related to insertion of the retroviral vector into a proto-oncogene (LMO2) have resulted in the development of T-cell leukaemia in 5 of 20 patients treated in the two SCID-X1 gene therapy studies (24). The reasons for oncogenesis relate to the integration profile of retroviral vector and their ability to activate transcription of neighboring genes. Modifications to vector design are in progress and may overcome the problems associated with these initial trials. The role of gene therapy alongside conventional HSCT (or enzyme replacement therapy for ADA–SCID) is shown in the figures designed by the EBMT-IEWP (Figure 2 and Figure 3).

Figure 2: Treatment options in SCID-X1
**References**


18. Hershfield MS, Buckley RH, Greenberg ML et al. Treatment of adenosine deaminase deficiency


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**Multiple Choice Questionnaire**

To find the correct answer, go to [http://www.esh.org/online-training/handbook/](http://www.esh.org/online-training/handbook/)

1. **X-linked SCID classically leads to which of the following immunological phenotypes?**
   a) T^−^ B^−^ NK^−^ ........................................................................................................................................... [ ]
   b) T^−^ B^−^ NK^+^ ........................................................................................................................................... [ ]
   c) T^−^ B^+^ NK^−^ ........................................................................................................................................... [ ]
   d) T^−^ B^+^ NK^+^ ........................................................................................................................................... [ ]

2. **Which one of the following is a radiosensitive form of SCID and requires careful use of alkylating agents?**
   a) ADA deficiency ....................................................................................................................................... [ ]
   b) JAK 3 deficiency ..................................................................................................................................... [ ]
   c) RAG deficient SCID ................................................................................................................................. [ ]
   d) Cernunnos deficient SCID ....................................................................................................................... [ ]

3. **Gene therapy is now available for which of the following forms of SCID?**
4. In HSCT for WAS:
   a) Mixed donor chimerism is preferred over full donor chimerism.
   b) In patients with WAS platelets are typically large.
   c) Unrelated donor HSCT has better outcome in patients <5 yrs.
   d) Splenectomy should be performed pre-HSCT.

5. Familial haemophagocytic lymphohistiocytosis:
   a) Is typically an X-linked disorder.
   b) Reduced intensity conditioning is contraindicated.
   c) The CNS is never involved.
   d) Patients do better when HSCT is performed with inactive disease.