



PRIMARY IMMUNODEFICIENCIES

THE VALUE OF SCID NEWBORN SCREENING



ABBREVIATIONS

HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplantation
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency
CMV	Cytomegalovirus
TREC	T-cell receptor excision circles
KREC	Kappa recombining excision circle
IG	Immunoglobulin

Severe Combined Immunodeficiency (1st edition).

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Published by IPOPI: www.ipopi.org

INTRODUCTION

This booklet explains the value of screening newborns for severe combined immunodeficiency (SCID) and how babies diagnosed with SCID should be evaluated and managed.

Primary immunodeficiencies (PIDs) are rare diseases that occur when components of the immune system are either not present or not functioning normally. The immune system protects the body from infections. People without the protection of a properly functioning immune system are prone to catch infections.

SCIDs are a group of rare, life-threatening inherited disorders that represent a paediatric emergency. These disorders are present at birth and manifest as major abnormalities of the immune system leading to extreme susceptibility to serious infections. Early diagnosis is essential to enable early intervention before infections occur. Potentially curative haematopoietic stem cell transplantation (HSCT, previously known as bone marrow transplantation) given during the first 3 months of life has a 96% success rate. Without a successful HSCT or gene therapy, patients are at constant risk of a fatal infection before 1 year of age.

The following sections explain what SCIDs are, the manifestations of SCIDs, how they are diagnosed and the role of newborn screening in achieving an early diagnosis, and how SCIDs are treated and managed.



WHAT IS SCID?

SCIDs are a group of rare, life-threatening inherited disorders in which there is an absence of autologous T-cells (sometimes associated with absence of B-cells and/or NK-cells) leading to a very profound immunodeficiency. These defects in the immune system lead to extreme susceptibility to serious infections. It is a paediatric diagnostic and therapeutic emergency.

HOW IS SCID DIAGNOSED?

CLINICAL PRESENTATION OF SCID

An excessive number of infections and/or opportunistic infections are the most common presenting symptoms in infants with SCID. These infections are not the usual type of childhood infections but are more serious, life-threatening infections that include pneumonia, meningitis and bloodstream infections. Persistent diarrhoea resulting in failure to thrive is a common symptom in children with SCID. In children with SCID, the skin may become chronically infected by the same fungus (*Candida* species for instance) that infects the mouth and causes thrush. Infants with SCID may also have a rash that could have been mistakenly diagnosed as eczema.

DIAGNOSIS OF SCID

In addition to the clinical presentation described above, a family history of SCID may prompt a diagnosis even before a child develops symptoms. One of the easiest ways to diagnose SCID is to count the peripheral (or cord) blood lymphocytes. Infants usually have around 4000 lymphocytes/mm³ of blood in the first year of life, 70% of which are T cells. As infants with SCID do not have T cells, their lymphocyte count can be much lower (on average around 1500 lymphocytes/mm³) in certain types of SCID; however, this is not the case in all types of SCID so it is necessary to perform a lymphocyte subset count (T-cells, B-cells and NK-cells). A low T-cell count should prompt referral to a clinical centre with expertise in managing infants with PID.

Immunoglobulin levels are usually very low in patients with SCID but may be nearly normal in the blood of newborns due to the presence of maternal IgG that are passively transferred through the placenta prior to birth, contrasting with very low to absent IgA and IgM though.

NEWBORN SCREENING FOR SCID

SCID is an absolute paediatric emergency. Without early diagnosis and treatment these infants might not survive, succumbing to a serious infection, usually within the first year of life. Children born with SCID are partially protected from infection in the first few weeks of life because of the presence of maternal antibodies in their blood; those that are breastfed will continue to receive some antibodies through breast milk (although it can also lead to cytomegalovirus [CMV] infection). Once these antibodies disappear from the child's system, they become prone to severe, life-threatening infections.

Newborn screening is the only way to universally detect SCID prior to the onset of an infection (in cases without positive family history of SCID). Systematic screening at birth for SCID allows early identification and intervention with curative HSCT (or gene therapy when possible, as this is still an innovative and experimental treatment possible only in some forms of SCID and in some centres).

Infants diagnosed with SCID and who receive curative treatment before 3.5 months of age without any active infection at time of therapy (HSCT and/or gene therapy) might have a greater than 96% chance of survival. A delay in the diagnosis of SCID reduces the success of a curative option and impairs survival or quality of immune reconstitution and quality of life due to sequelae.

Screening for SCID immediately after birth is possible and can be performed on dried blood spot samples that are currently collected in a standardised fashion from all newborn babies almost worldwide. SCID screening test is based on a T-cell receptor excision circles (TREC) measurement assay. Some may also include kappa recombining excision circle (KREC) analyses. These tests also allow identification of infants with severe forms of PID characterised by T- and/or B-cell lymphopenia, which will require proper management in referral centres.

WHAT TREATMENT IS SUGGESTED FOR SCID?

HAEMATOPOIETIC STEM CELL TRANSPLANTATION

HSCT is the main curative therapy for SCID. Haematopoietic stem cells (HSC) from a suitable healthy donor with a good human leucocyte antigen (HLA) match are given to replace the HSC of the recipient that will ultimately produce normal immune cells (i.e. T cells).

The ideal donor for an infant with a PID and requiring HSCT is a perfect HLA-type matched normal sibling (success rate >96% if performed before 3.5 months of life and without any active infection at time of HSCT). Half-matched related donors or cord blood units have also been used with fairly good success. Unlike HSCT for cancer patients, depending on the type of SCID and the type of donor, and also the clinical state of the recipient, pre-transplant chemotherapy might not be necessary as the goal is to correct the immune dysfunction rather than to eradicate cancer cells.

GENE THERAPY

Gene therapy is used to correct the underlying genetic defect in SCID and other severe PIDs. A licensed gene therapy is now available for SCID-ADA in some world regions. Several clinical trials are ongoing, some with very encouraging results for other conditions such as X-SCID, WAS and X-CGD. In the future, other PIDs are candidates for gene therapy such as LAD, AR-SCID, IL-7 receptor deficiency, SCID Rag-I and Rag-2, SCID Artemis, Omenn Syndrome, hyper-IgM deficiency among potential others.

OTHER THERAPIES

Infants with SCID are not able to fight off bacterial, viral or fungal infections as effectively as those with fully functioning immune systems. This is the result of the low levels of IgG and IgM as well as the low count or absence of T lymphocytes. Patients need to be placed in a sterile room in a hospital, be put under maintenance anti-infectious therapies including antifungal and antibacterial prophylaxis (usually cotrimoxazole, except for infants aged < 28 days since this molecule has a liver toxicity on immature liver at this very young age) and Ig replacement therapy as a minimal mainstay therapy while waiting for curative treatment. For patients with SCID due to adenosine deaminase (ADA) deficiency, replacement therapy with a modified form of the enzyme has been used with some success but is not a curative approach.

VACCINATIONS AND BLOOD TRANSFUSIONS

Live vaccines (e.g. BCG, MMR, Rotavirus...) are absolutely contraindicated. Patients with SCID requiring blood or platelet transfusion should always get irradiated (CMV-negative, leukocyte-depleted) products.

CARING FOR AN INFANT WITH SCID PRIOR TO CURATIVE TREATMENT

An infant with a suspected SCID needs to be isolated from children outside the family, especially from young children. Older siblings attending daycare or school can bring home infections that might potentially be life-threatening for the infant with SCID (e.g. chicken pox). An infant with SCID should not be taken to public places and contact with relatives should be limited, especially for those with young children. Home hygiene is essential and although nutrition is important, no special diets have been shown to be helpful. Once SCID has been diagnosed, the patient should be hospitalised and cared for under sterile conditions while waiting for curative treatment.

IMPACT OF SCID NBS

Newborn screening for SCID saves lives. Without early diagnosis and treatment children born with SCID usually do not survive beyond their first year of life. It is well established that active infection and older age at the time of transplantation worsen the chances of survival of affected babies. With curative treatment and cost-effective newborn screening tests available, it is imperative to implement SCID newborn screening in as many countries as possible.



FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations in 67 countries worldwide, please visit www.ipopi.org.



Supported by an educational grant from Takeda.