# Toolkit for Parents

SCID compass

An educational program of the Immune Deficiency Foundation

# About SCID Compass

SCID Compass offers educational materials, access to family networking, and advocacy on a national level, with the goal of improving outcomes for children born with SCID.

SCID is a genetic disorder in which an infant is born without a functioning immune system. The immune system is unable to protect the infant against infection. As a result, a child with SCID has recurrent and persistent illnesses that are life threatening.

SCID Compass provides information on SCID diagnosis, treatment, and support through: www.scidcompass.org, printed materials, and links to SCID communities through social media and mailing lists.

A program of the Immune Deficiency Foundation, SCID Compass is funded through a federal grant from the Health Resources and Services Administration, an agency of the U.S. Department of Health and Human Services.

*HRSA Acknowledgement/Disclaimer: This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $2.97 million with 0% financed with nongovernmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, HRSA, HHS, or the U.S. Government*

# Table of Contents

## YOUR SCID JOURNEY



## ADDITIONAL RESOURCES

# WHERE ARE YOU ON YOUR SCID JOURNEY?

Learning that your newborn child has severe combined immunodeficiency, or SCID, can be overwhelming and you are likely feeling anxious. It's perfectly normal at this point to feel confused and afraid about the diagnosis. After all, SCID is probably not a medical condition you've ever heard of, and no one ever expects their baby to have it.

Remember - you are not alone. There are other families whose children have SCID, and those families, along with SCID Compass, are here for you. Through its support groups and resources, SCID Compass can connect you to those families so you receive emotional and informational support from those who have traveled this path.

Let us share with you what SCID is and how you can move forward to best care for your baby.

# UNDERSTANDING SCID

**What is SCID?**
SCID is a condition in which a baby does not have an immune system that works properly. The immune system is made up of cells that fight infection and protect a baby from sickness. A child with SCID doesn't have that protection.

All babies with SCID share the problem of being born with either no T cells or too few T cells. The numbers of normal T cells in your baby are extremely low or are not made at all.

T cells are essential for the immune system to work properly. If your baby catches a cold or other infection, he or she might not be able to fight it off like most other people. The cold could get worse and be life threatening.


Doctors diagnosed your baby with SCID through newborn screening and additional testing. Newborn screening showed doctors that the T cells responsible for fighting infections were extremely low in your child.

SCID is rare. About 1 out of 58,000 children each year are diagnosed with SCID. That's about 76 cases of SCID diagnosed annually in the United States.

SCID can affect any infant, regardless of race, gender, ethnicity, or socioeconomic status. It is, however, more common in certain communities, such as the Navajo Nation and the Amish and Mennonite communities.

Though a child with SCID might appear healthy at birth, the child is extremely vulnerable to germs. If the child is exposed to viruses, bacteria, or fungi, he or she will likely grow ill while attempting to fight the infection without a complete immune system. Infections for children with SCID can be fatal.

# UNDERSTANDING SCID

**What causes SCID?**
A child born with severe combined immunodeficiency does not have an immune system that works properly. The immune system is made up of cells in the body that protect a person from sickness. A child with SCID doesn't have that protection.

Though a child with SCID might appear healthy at birth, the child is extremely vulnerable to germs. If a child is exposed to viruses, bacteria, or fungi, he or she will likely grow ill while attempting to fight the infection without a complete immune system. Infections are life-threatening for children with SCID.

Most cases of SCID are caused by mistakes in the genes that are passed down from parent to child. Genes are found in cells and serve as the instructions to make all the different parts of our body. For example, there are lots of genes involved in making a heart or a brain. Numerous genes are needed for a healthy immune system.

Part of the immune system is made up of T cells, B cells, and natural killer (NK) cells, which are all white blood cells. Each type of cell helps fight infection in a special way. But, without T cells, we could not survive. T cells are absolutely necessary for the immune system to fight infection. A dangerously low or absent number of T cells is the cause of SCID.

Several different genes are needed to make a T cell. A defect in any one of these genes can cause SCID. We sometimes name the type of SCID based on the gene that is damaged. For example, in ADA SCID the damaged gene is the ADA, or adenosine deaminase gene.

Sometimes, we categorize SCID based on the white blood count, specifically the number of T, B, and NK cells. For example, SCID with low numbers of T cells and B cells but normal numbers of NK cells is written or described as T-B-NK+ (or T cell negative, B cell negative, NK positive) SCID.

Regardless of which gene is damaged, or if NK cells or B cells are present or absent, all forms of SCID have extremely low or no normal T cells. The newborn screening test that is used to identify babies with SCID detects low or absent T cells. That is why this test can pick up all types of SCID, regardless of the gene that is damaged.

# UNDERSTANDING SCID

## TYPES OF SCID

There are more than 20 different types of SCID, and each is determined by the gene that is affected. The most common type is X-linked SCID, which generally affects only boys.The SCID type dictates the treatment approach, so it's important to know your child's exact diagnosis. Types of SCID include:

- X-linked SCID
- ADA SCID
- RAG-1 and RAG-2 deficiency SCID
- IL7R SCID
- DCLRE1C, or Artemis, SCID
- JAK3 deficiency SCID
- CD3 complex component deficiency SCID
- Coronin-1A deficiency SCID
- CD 45 deficiency SCID
- DNA ligase 4 deficiency SCID
- DNA-PKcs deficiency SCID
- LAT deficiency SCID
- Reticular dysgenesis SCID
- Cernunnos-XLF deficiency SCID

**Why is isolation important?**

Because your baby has no way to fight off germs, you and the doctors have to work together to keep the baby in an environment with as few germs as possible until treatment. One way to decrease the germs your baby is exposed to is to limit the number of people that can visit your baby. This is called isolation. Isolation may take place in your home or at the hospital. The goal is to prevent your baby from being exposed to germs that can make the baby sick.

Here are other considerations to help prevent infection during this critical period:

- Your baby should receive no live vaccines.
- Blood transfusions should be irradiated.
- The baby's mother should undergo a test for CMV before breastfeeding.
- You should adhere to isolation requirements and limit visitations.
- Follow strict hand-washing protocols.
- Your baby is extremely susceptible to any infection, so anyone who is sick should not visit the baby. For example, chickenpox can be fatal for a child with SCID.

# EXPLORING TREATMENT OPTIONS

A vital step in your family's journey with SCID is seeking treatment. Early diagnosis and treatment are critical to saving the lives of children diagnosed with SCID.

Babies who are treated within the first few months of life have a higher chance of successful recovery. If a child is diagnosed and treated early, before any serious infection, then the long-term survival rate is more than 90%. With early treatment, most children with SCID should be able to develop their own working immune system.

The best course of treatment for a child with SCID depends on several factors including the type of SCID, the child's health, and doctor recommendations. Most infants with SCID are treated with hematopoietic stem cell transplant (HSCT), also known as bone marrow transplant (BMT). Another promising but less common treatment option is gene therapy, which is currently in clinical trials. A third treatment is enzyme replacement therapy, which can only be used for children with ADA-SCID and is a temporary treatment until the child undergoes HSCT or gene therapy.

# TREATMENT OPTIONS

**HSCT: An Overview**
The current standard treatment for SCID is hematopoietic stem cell transplant (HSCT), also known as bone marrow transplant (BMT). In HSCT, doctors take healthy blood-forming cells from a donor and put them into your baby. The blood-forming cells reproduce and provide your child with an immune system.

HSCT is a multi-step medical process that requires a months-long stay at the hospital. At the hospital, a baby undergoes several tests and other procedures to get ready for HSCT. Importantly, doctors determine who is the best match to donate blood-forming cells for the baby's HSCT. The baby is also put on medicines to reduce the chance of infection and improve the success of the treatment.

When the baby receives the bone marrow cells, the procedure is similar to a blood transfusion and takes only a few hours. Following HSCT, doctors monitor the baby's immune system for months to determine if the HSCT was successful. With HSCT, there can be some complications and sometimes the HSCT needs to be repeated.

Your health plan might dictate which transplant center you can use for the HSCT or you might have a choice of where you would like the procedure to take place.

**Gene Therapy: An Overview**
Unlike HSCT, which can be used to treat all types of SCID, gene therapy is tailored to treat a specific gene and is performed only for specific types of SCID including X-linked SCID, ADA-SCID, and Artemis SCID. Also, gene therapy is still in clinical trials and is not yet a treatment approved by the U.S. Food and Drug Administration (FDA). In clinical trials, doctors are still experimenting with how best to perfect the treatment so that it can be approved for regular use.

In gene therapy, doctors take the baby's stem cells that have the incorrect copy of a gene out of the baby and put a corrected copy of the gene into those cells. They then put the cells back into the baby. The cells with the corrected gene make copies of themselves and create an immune system in the baby.

There are several clinical trials now taking place at children's hospitals throughout the United States and at the National Institutes of Health (NIH). Research clinical trials that are available at https://clinicaltrials.gov/. Families of children who choose gene therapy must enroll in a clinical trial.

# TREATMENT OPTIONS

**Pre-Treatment Conditioning: An Overview**
Conditioning describes a pre-treatment that may be given to a child before a hematopoietic stem cell transplant (HSCT) or gene therapy. Conditioning means that your child may receive chemotherapy and/or other drugs to prepare your child to receive the new stem cells. The goal is to increase the chance of your child having a successful outcome.

Conditioning can lower the risk of possible treatment complications and improve your child's short-term and long-term health outcomes. Conditioning may reduce the impact of these possible complications:

- **Graft/transplant rejection:** Your child's immune system, even if it doesn't work very well, might notice the new stem cells as different and kill them.
- **Failure of new stem cells to engraft:** The new stem cells might not find a place to land in your child's bone marrow and, therefore, may not give rise to the different types of immune cells needed for a full immune system.
- **New stem cells partially engraft:** The new stem cells may engraft and start working to make T cells with the help of the thymus, but fail to engraft in the bones, where B cells are made. If this happens, your child may still need lifelong immunoglobulin (Ig) replacement therapy, antibiotics, or other ongoing therapy to help the immune system.

**Enzyme Replacement Therapy: An Overview**
For children who have ADA-SCID, an enzyme replacement therapy, called PEG-ADA, is available. Children with ADA-SCID lack an important enzyme that helps their immune system function. In PEG-ADA therapy, children receive at least weekly intramuscular injections of a drug containing the missing enzyme, adenosine deaminase, or ADA. These injections allow the immune system to function.

PEG-ADA use is an important temporary step in the treatment of persons with ADA-SCID, even if they plan to get a more permanent treatment, like HSCT, soon. This is because even short-term PEG-ADA use can rapidly reduce the level of certain toxins that have built up in the body in the absence of the ADA enzyme. These toxins kill white blood cells, including T cells, and cause SCID.

Giving a baby PEG-ADA before HSCT increases the numbers of T cells in the baby, so that the baby will have less infections until definitive treatment is given.

# NAVIGATING A HOSPITAL STAY

**Hospital Tips**

Treatment for SCID often requires a hospital stay that could last for several months, or more. During this time, the baby must be kept in isolation. Isolation is necessary to reduce the spread of germs, and reduce the chance of infection.

There are ways that families can make the most of their time in the hospital and do their best to reduce stress. Below are some tips for life in the hospital.

- Take breaks from being in the room. Consider exercising, walking outside, meditation, or visiting with family members to relieve stress.
- Eat a balanced diet and get enough sleep.
- Keep a notebook to record the baby's condition, medical information, and any questions for medical staff.
- Express your personal feelings in a daily journal.
- Follow a daily routine with your baby. Activities could include feeding, playing, reading, and tummy time.
- Meet with the hospital social worker, or bone marrow transplant coordinator, to discuss topics like financial assistance, employment issues, and temporary housing.

# HOSPITAL STAY

**Support**

The physical isolation may also lead to emotional isolation because visitors are not allowed in the baby's room. Only primary caretakers, such as parents, are cleared for entrance into the baby's room. Consider taking the following steps to maintain your mental well-being.

- Seek out online support groups and information sessions through SCID Compass and meet other parents through SCID, Angels for Life, accessed at www.scidangelsforlife.org.
- Meet with a mental health professional trained in the area of trauma or seek assistance from a hospital social worker.
- Enlist the assistance of grandparents or family friends to help with drop-offs, pickups, and after-school activities for your other children at home.

In addition, letting family members and friends know that your child is diagnosed with SCID can be an overwhelming task. Parents of newly-diagnosed babies can direct their family and friends to the SCID Compass website for more information.

Below are some main points parents can convey to others about why the baby has to stay in isolation.

- SCID is a life-threatening medical condition in which a child has no immune system.
- While the child may not currently be sick, any kind of infection the child develops can be fatal.
- Only parents and hospital staff are allowed to interact with the baby to reduce the number of germs brought into the room.
- Treatment for the baby, which involves providing the baby with a new immune system, could take months. After treatment, when the child is producing his or her own immune system, family and friends may visit.

# HOSPITAL STAY

**Parents should also maintain a binder or other type of filing system for medical records. These records, including test results, information sheets, and copies of medical procedures, allow future healthcare workers, as well as school staff, easy access to information on the child's condition. Sections of a medical binder could include lab work, hospitalizations, specialists, pathology reports, X-rays, intravenous immunoglobulin orders, and emergency room visits.**

**Advocacy**

Parents and caregivers must advocate for their child and speak up if there are questions about the care their child is receiving. The following is a list of tips to remember when negotiating the many healthcare professionals that will come into contact with the child.

- Ask questions of doctors. Bring a notebook and pen to appointments to record notes, and to jot down questions that may arise later.
- Request to be in a unit of the hospital that provides the baby with the best isolation. The baby should be in a single room.
- Make sure that healthcare professionals entering the room follow practices consistent with what the doctor in charge has directed. That could include washing and disinfecting hands, and wearing a mask, gloves, and a gown.
- Be assertive. Most healthcare staff, including doctors, welcome questions and view the parents and caregivers as part of the child's healthcare team.

# TIPS FOR SELF-CARE

**What is Normal**

Parents of children with SCID undergo tremendous stress. The isolation before, during, and after treatment at the hospital; the concern about germs; the day-to-day worry about the child's health and recovery – all of these factors can have lasting negative effects on parents. But you don't have to do it alone. Seek a therapist trained in trauma to help you manage the emotional pressure and learn your diagnosis based on symptoms.

Distress is very normal and expected when caring for a baby with SCID. There is never a bad time to seek help if you need additional support. Here are some emotions that a therapist can help you talk through.

- Feeling fearful and uncertain
- Feeling hyper-vigilant about your baby's health
- Feeling unable to relax or on edge
- Feeling exhausted and worn down
- Having difficulty focusing on other tasks
- Feeling a mix of different emotions that vary day by day or even moment to moment
- Feeling disconnected from family and friends
- Feeling tension with your significant other

**Signs of Concern**

The following may indicate a need for more immediate and/or more intensive help:

- Depressed mood, feeling down most of the time, nearly every day
- Loss of interest in things you previously enjoyed
- Feeling irritable or restless most of the time
- Feeling hopeless or helpless
- Feelings of excessive guilt, loneliness, or isolation
- Difficulty sleeping or eating
- Inability to complete daily tasks of self-care
- Thoughts of harming yourself or somebody else
- Disagreement with your significant other
- Upsetting interactions with family or friends

# TIPS FOR SELF-CARE

**Maintaining mental health**

- Ask your team for a referral to a pediatric psychologist or health psychologist. These specialists often have experience working with children and parents who are coping with traumatizing, prolonged, and/or life-threatening illness.
- Consider individual therapy, marriage counseling, and whole family therapy if you have children old enough to participate.
- If you are specifically experiencing symptoms of traumatic stress, including nightmares or unwanted memories, avoidance, heightened reactions, anxiety, or depressed mood, you may want to seek out a therapist with experience in treating individuals with post-traumatic stress disorder (PTSD).
- Call your insurance company and ask for covered mental health providers in your area. Make sure to ask about what benefits are offered and what services are covered or are not covered. Be aware that, in some situations, billing may be done through your child's insurance and medical diagnosis.
- Speak with your primary medical doctor (PMD) about therapy referrals. If appropriate, you may also choose to ask your PMD about medications to help with mood or anxiety. They may refer you to a psychiatrist, a physician who specializes in medical treatment of emotional and mental health concerns. It is very common for parents of children with serious health concerns to receive psychiatric help managing their distress.
- Social Support: Reach out to friends and family. Be honest about what you need and what you don't need, and don't feel like you need to return calls or message immediately.

**Genetic Counseling**

Families whose children have SCID may decide to meet with a genetic counselor. Genetic counselors can help families understand how inherited conditions, like SCID, affect their lives.

A genetic counselor can provide information about the type of SCID diagnosed in a child but they may also offer guidance to parents related to family planning options. Genetic counselors play a critical role in facilitating the decision-making process as parents consider building their family.

# COPING WITH POST-TREATMENT

HSCT recovery is a series of milestones that the baby reaches as the weeks pass. Doctors measure the production of different types of immune cells that help build a healthy immune system.

Some, but not all, patients may experience side effects or complications from a HSCT. These can include:

**Infection**
The child might have an infection going into the transplant, or develop one post-transplant. Conditioning the child with chemotherapy or other drugs will weaken the child's immune system further, making the child more prone to infection.

Doctors treat the child with preventative antibiotics before, during, and after the transplant. It can take the child several weeks to produce enough white blood cells to fight infection, so sometimes doctors give the child injections to jumpstart white blood cell production. Immunoglobulin, or Ig, antibody replacement therapy is also given during the transplant process to help prevent infection.

# POST-TREATMENT

**Conditioning Side Effects**
Before the child undergoes the HSCT, in some cases, the child receives medications, including chemotherapy, in a process known as conditioning. Sometimes the child develops complications from the conditioning. Some of these complications are short term, while others may be long term.

In the short term, the chemotherapy drugs can affect tissues, including those in the mouth, throat, and intestines. A child may experience sores in those areas, which lead to pain, drooling, nausea, vomiting, and diarrhea.

Because the chemotherapy can cause severe blistering in the mouth, the baby may refuse to eat. If a child doesn't feed through a bottle, then the child needs a feeding tube in the nasal passage or receives IV nutrition temporarily. The tube goes in the child's nose and the formula will be given to the child through the tube.

The chemotherapy drugs also can deplete all the cells in the bone marrow, making the child susceptible to infections. The child can become anemic and suffer from bleeding problems.

Possible long-term complications from chemotherapy drugs include harm to the vital organs such as the brain, lungs, kidney, and liver. Some of the time, the complications are reversible with medication. Other long-term complications include reduced fertility and an increased risk of cancer.

**Failure to Engraft**
After the transplant, doctors check the child's blood regularly to see if the donated immune system cells are growing and dividing. Sometimes, the new cells do not survive in the child and this complication is called failure to engraft. Doctors typically repeat the transplant, sometimes administering conditioning to the child beforehand to improve the possibility of a successful transplant on the second attempt.

**Graft Versus Host Disease**
After the transplant, the child may develop graft versus host disease, or GVHD. GVHD occurs when the immune system cells from the donor, or "the graft," attack the child, or "host." The reason for this is because the new T cells from the donor see the existing organs and tissues in the child as "foreign." The attacks occur on the skin, the gastrointestinal tract, the mucous membranes, and certain organs like the liver and lungs. This condition is treated with steroids and other drugs.

# RETURNING HOME

Once the doctor has approved your release to go home, it's both a happy and anxious time. Before leaving the hospital, make sure you know what care is required.

Leaving the hospital may be the most frightening part of the journey, as the care of your baby is now entirely in your hands. That's a prospect that some parents find daunting considering the fragile state of their child's health.

Have a plan in place should you have to make an emergency return to the hospital and be sure to keep all planned follow-up appointments with your provider. Providers monitor the health of your baby regularly after treatment to ensure that their immune system is healthy and that there are no side effects from treatment.

# RETURNING HOME

Before bringing your baby home, clean your house by disinfecting surfaces, dusting, and vacuuming. Your baby is still vulnerable to infection from bacteria, viruses, and fungi.

In addition to cleaning, another important way to keep your baby safe is to wash your hands. A thorough hand-washing for at least 20 seconds with warm water every time before you touch the baby is the best way you can prevent the spread of germs. You may also use hand sanitizer to clean your hands every time before you touch the baby.

Here are some additional tips for home while your child is still in the isolation stage of post-treatment:

### QUESTIONS FOR YOUR DOCTOR

Before leaving the hospital, make sure you know what care is required and ask questions.

- What medications are required, how much, and how frequently are they given?
- What are the side effects of the medication?
- What symptoms or signs are cause for concern?
- When should the doctor be contacted and what is the best option to do so during and after office hours?

Check in with your child's case manager or social worker before discharge, as this individual may have helpful tips and resources.

- Do not allow visitors to the home, beyond those who live there.
- Do not take the child with SCID out of the house to any enclosed public places like church, shopping, or daycare, until doctors allow the trips.
- Brothers and sisters should not be allowed to touch the child. If brothers or sisters attend daycare, or religious or academic school, the possibility of bringing germs into the home represents the greatest threat to the child.
- Keep anyone who is sick, even with a cold, away from the child.
- Alert the school where brothers and sisters attend that they have a sibling with no immune system and that parents must be contacted if there are any infectious outbreaks at school.
- Relocate pets, if possible.
- Keep the home clean by wiping surfaces with disinfectant.

# PLANNING FOR THE FUTURE

Caring for a child with SCID is a challenging experience. It may make you weary and stressed, but it can also make you more resilient. SCID is a journey and that journey requires you to take one day at a time, celebrate the joy of small accomplishments, and be present in the moment with your child.

Regular long-term follow-up for medical appointments and evaluations are essential for the health of your child. Your child may build a healthy, functioning immune system after treatment. Or your child's immune system may still be compromised afterwards, requiring regular immunoglobulin treatments.

Your child may also require interventions in education, beginning in the toddler years and continuing through the elementary and secondary levels of school. Efforts to coordinate services for your child as early as possible will help with their transition into a learning environment and provide them with a solid foundation for the rest of their education.

# PLANNING FOR THE FUTURE

**Early Intervention**
Because your child will spend a long time in the hospital and in isolation at home, he or she may be behind in developmental skills, such as speech and motor skills, or may have a cognitive disorder, such as attention deficit disorder (ADD). Also, some types of SCID can cause disabilities. For example, ADA-SCID is associated with hearing deficits. Ask your doctor if your child would benefit from early intervention services such as speech therapy, occupational therapy, and physical therapy.

In addition to private therapies, the school district where you live may provide early intervention programs for which your child may qualify. These programs - sometimes known as Child Find, Bright Beginnings, or Infant and Toddler Connection - offer resources to help a child who has experienced developmental delays for any reason.

**School**
When your child begins a public or private-based education program, they should be covered by a 504 Plan or an IEP (Individualized Education Program). Meet with school officials to determine which plan is appropriate for your child.

The IEP is a legal document that is developed for each public school child in the U.S. who needs special education. The IEP is created through a specific team of the child's parent(s) and district personnel who are knowledgeable about the child.

Not all children require specialized education, in which case a 504 Plan may be appropriate. A 504 Plan requires the school to provide special accommodations to keep your child healthy. Accommodations might include contacting you if there is an outbreak of sickness like flu or chickenpox at the school, or removing penalties for days missed for medical reasons. An appropriate label for a child with SCID who requires either plan might be "Other Health Impaired."

**Genetic Counseling**
Families whose children have SCID may decide to meet with a genetic counselor. Genetic counselors can help families understand how inherited conditions, like SCID, affect their lives.

A genetic counselor can provide information about the type of SCID diagnosed in a child but they may also offer guidance to parents related to family planning options. Genetic counselors play a critical role in facilitating the decision-making process as parents consider building their family.

# Family Planning Guide

SCID compass

An educational program of the Immune Deficiency Foundation

# Family Planning: Thinking About the Future

There are different ways to think about your family after having a child with Severe Combined Immunodeficiency (SCID). Whether you decide to grow your family or not, the best decision is ***your decision***. Use this resource to help you think through the different family planning options and special considerations after having your child with SCID.

***"Don't let other people who don't know what's going on in your lives and in your medical lives, hinder your thought process on whether or not to have children."***
***-Mother of 3***

Navigating your child's journey with SCID can be overwhelming and stressful with a number of life-changing decisions and experiences. While your child's journey with SCID is life-long, you may be ready to think about the next step for your family.

Remember, your decision to have children is an intimate and personal choice and it's important to recognize that thinking about your future may look different now. No matter what you ultimately choose - it is the right choice for you and your family.

## KEY CONSIDERATIONS

To help you have an informed discussion with your healthcare team and family about having additional children, it's important to know and understand your child's type of SCID and whether you or your partner are carriers for this genetic condition.

- **What type of SCID does my child have?** *(X-Linked, ADA, RAG 1 or 2, IL7R, etc.)*
- **Am I carrier?**
- **Is my partner a carrier?**

## Different Family Planning Options

There are different ways to think about your family now. You may be in the early phases of thinking about how to grow your family after having your child with SCID, or you may be considering not to have any more children. Regardless of what you decide, it's important to consult your healthcare team about any steps that you will need to take based on your unique health and your family's health. Below are options that you might choose after considering and assessing your benefits and risks.

### Complete Family

The decision to not have any more children is an option that may be best for your family.

**Consider:**

- Discussing your contraception options with your healthcare provider
- Building a support system of SCID families

### Natural Conception

**Consider:**

- Talking to a genetic counselor about prenatal genetic testing options
- Following up on your baby's newborn screening results shortly after birth

### In Vitro Fertilization

**Consider:**

- Contacting your insurance provider to learn what services are covered
- Searching for a fertility clinic that meets your unique needs

### Adoption

**Consider:**

- Thinking about what type of adoption fits your family's needs and preferences
- Being prepared to wait for varying amounts of time during the process

**Consider:**

- Discussing with your child's healthcare provider about recommended health precautions (e.g., isolation) for your SCID child
- Focusing on your mental health and seeking support when needed
- Thinking about the financial costs associated with each option

Ultimately, what you decide will be based on your family's own personal values and priorities. Here's a list of questions that can help you think through what will be best for your family. Use the space provided to jot down your thoughts, take notes, or to use it as a guide when you speak with your partner or your healthcare provider.

**What do you believe are your family's greatest strengths? Consider specific qualities or characteristics that make your partner unique, your child unique, and your family as a unit unique.**

**What are your top priorities for your family's overall health and well-being? Consider your interpersonal relationships, financial well-being, and your physical and mental health.**

**When you think about these priorities, what worries or concerns do you have as it relates to your family planning goals?**

**What do you envision your family to look like in five years? Think about what steps you can take and what supports you need to get there.**



This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $2.97 million with 0% financed with nongovernmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS, or the U.S. Government.

# Fact Sheets

SCID compass

An educational program of the Immune Deficiency Foundation

# Severe Combined Immunodeficiency (SCID): What Parents Need to Know

Your baby had a newborn screening result that means he or she could have a condition called SCID. Your baby needs more tests as soon as possible to confirm if he or she has SCID.

**Talk to your baby's doctor right away about getting more testing.**

## What is SCID?

SCID stands for *Severe Combined Immunodeficiency*. Babies who have SCID have little or no immune system and can get seriously sick from common illnesses like a cold or flu. SCID is a genetic condition, meaning it is passed from parents to children through genes.

## Is SCID Treatable?

**SCID is treatable.** If doctors find SCID early, they are better able to treat babies with SCID. Talk to your doctor about more tests as soon as possible.

## What does this newborn screening result mean?

Your baby had routine newborn screening tests done to check for serious medical conditions. Your baby's test result showed low levels of immune cells which are used to fight infections. ***Screening tests are a first step and are not a diagnosis.*** A result that is not normal on the newborn screening test does not always mean that your baby will have SCID. The screening test also picks up other conditions associated with the immune system, but these are often not as severe as SCID. But it is very important to do the next test for your baby.

## How do I find out if my baby has SCID?

Your baby will need another test to tell for sure if he or she has SCID or a different condition that may be causing a lack of immune system. If these tests confirm that your baby does have SCID, your baby's doctor will likely connect you with a doctor who specializes in SCID. Babies with SCID need special care to stay as healthy as possible.

## How do I keep my baby safe right now?

Because your baby may have little or no immune system, the most important thing to do right now is to keep your baby from getting sick.

To keep your baby from getting sick:

- Keep your baby away from other people, especially anyone who may be sick.
- Wash your hands before touching or being near your baby.
- Talk to your doctor about whether it is safe to breastfeed. Mothers sometimes carry a virus called CMV in their breast milk. Boiled water instead of bottled water should be used with formula. Bottled water may still contain some bacteria which could be harmful to your baby.
- Talk to your doctor about whether your baby should get certain vaccines. Do not have your baby or other people in the household get a live vaccine. Live vaccines carry a live, weakened part of a virus. A child with little or no immune system can get sick from a live vaccine. The COVID-19 vaccines are not live vaccines.

## Where do I go for more information?

Visit scidcompass.org

Email scidcompass@primaryimmune.org

More scidangelsforlife.com



This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $2.97 million with 0% financed with nongovernmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS, or the U.S. Government.

RESEARCH SUMMARY:

# Educational and Support Needs for Families living with SCID

We asked families who have a child with SCID to tell us what educational and support resources are most needed.

## WE HEARD FROM 76 PARENTS IN AN ONLINE SURVEY

**87%** mothers

**13%** fathers

**45%** of children were diagnosed through newborn screening

## BIGGEST INFORMATION NEEDS

- Understanding all available treatment options
- Understanding what to expect across SCID lifespan
- Knowing what to expect during treatment and hospital stay
- Knowing how to keep child healthy after treatment
- Knowing where to access specialists
- Understanding child's specific type of SCID

## BIGGEST EMOTIONAL SUPPORT NEEDS

- Dealing with uncertainty about child's future
- Opportunity to talk with other families
- Managing emotions as a parent/caregiver
- Having access to professional organizations knowledgeable about SCID
- Understanding the importance of self-care

## THE SCID JOURNEY

*We also conducted interviews with parents and learned that most families go through 5 stages during the SCID Journey.*

**1 DIAGNOSIS**
Newbord screening (NBS) test is positive and diagnosis is confirmed.

**2 PRE-TREATMENT**
Care teams decide on treatment and seek donor match.

**3 TREATMENT**
Donor is found, chemo drugs are administered, treatment is provided.

**4 POST TREATMENT**
Families wait for treatment to take effect. Babies live in hospital for 2-6 months.

**5 THE NEW NORMAL**
Families return home, seek support and community.

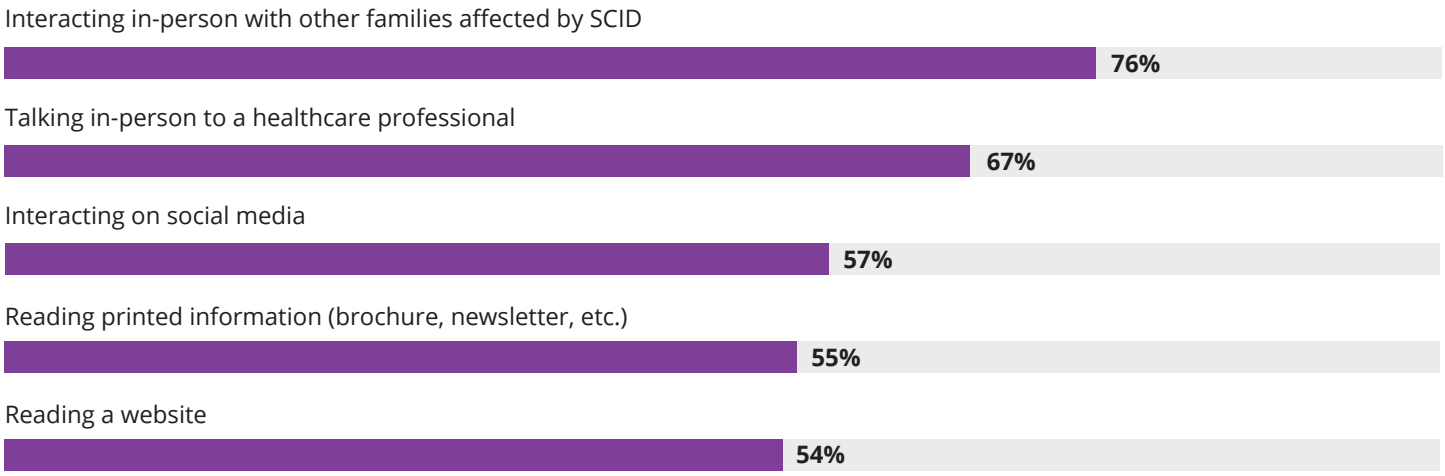
## WHERE ARE PARENTS CURRENTLY LOOKING FOR INFORMATION ABOUT SCID?

1. SCID Angels For Life Foundation
2. Immune Deficiency Foundation
3. NIH National Institutes of Health — Turning Discovery Into Health
4. facebook

## PARENTS' PRIORITIES FOR SCID EDUCATIONAL RESOURCES

- Treatment options by type of SCID
- Personal success stories and reassurance
- Guide for preparing home for baby after treatment
- Connections with other families
- Stories about how to survive isolation
- A SCID journey map for parents
- How to advocate for your child
- How to explain isolation to family and friends who want to visit

## PREFERRED FORMAT FOR EDUCATIONAL RESOURCES




## WHAT DOES THIS MEAN FOR FAMILIES?

We learned that parents have different education and support needs across the SCID journey. We learned that parents want specific information to inform treatment decisions, isolation, and preparation of their homes, but also that parents want connections with other families and support resources.

The SCID Compass website was developed in 2019 to meet the needs described by SCID families. Please visit https://primaryimmune.org/scid-compass to learn more about the SCID journey, review information about treatment options, and find support groups.

Raspa M, Lynch M, Squiers L, Gwaltney A, Porter K, Peay H, Huston A, Fitzek B and Boyle JG (2020) Information and Emotional Support Needs of Families Whose Infant Was Diagnosed With SCID Through Newborn Screening. *Front. Immunol*. 11:885. doi: 10.3389/fimmu.2020.00885

HRSA Acknowledgement/Disclaimer: This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $4 million with 0% financed with nongovernmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS or the U.S. Government.

Immune Deficiency Foundation

SCID Compass — An educational program of the Immune Deficiency Foundation

**Contact Information:**

SCIDCompass@primaryimmune.org

Immune Deficiency Foundation
110 West Road
Suite 300
Towson, MD 21204
Phone: 800-296-4433

Severe Combined Immunodeficiency (SCID):

# What Healthcare Providers Need to Know

## What is SCID?

Severe Combined Immunodeficiency (SCID) is a group of genetic disorders characterized by the absence or dysfunction of T lymphocytes and B lymphocytes. Newborns with SCID are at risk for severe, life-threatening bacterial, viral, and fungal infections. Without timely diagnosis and adequate treatment, patients with SCID do not survive infancy. SCID is a rare disease, with an estimated prevalence of 1 in 58,000 births.

## What causes SCID?

SCID may be inherited in an X-linked recessive or autosomal recessive manner. The most common form of SCID is associated with a mutation in the IL2RG gene on the X chromosome and occurs almost exclusively in males. Another common type of SCID is caused by mutations in the gene that encodes adenosine deaminase (ADA). Other forms of SCID are caused by mutations in genes that code for the alpha chain of the IL-7R receptor, the Janus kinase 3 enzyme, RAG1 and RAG2, as well as other, less common mutations. Certain types of SCID are more common among specific groups, such as the Amish communities and Navajo Native American populations. Regardless of the genetic cause, all patients with SCID have a lack of T and functional B cells.

## How is SCID identified?

SCID is identified using an assay to detect T-cell receptor excision circles (TRECs) which can be measured in dried blood spots obtained from newborns by heel prick. Newborns with SCID will usually have low or undetectable number of TRECs. The TRECs assay is also used to identify other, non-SCID conditions which are also characterized by T-cell deficiencies. As of December 2018, all states in the US have implemented newborn screening for SCID.

## How to handle an abnormal newborn screen for SCID?

- Let the family know about the NBS result. Emphasize that a diagnostic test is needed to confirm whether the infant has SCID. Explain that the baby is at an increased risk of being diagnosed with an immune deficiency. As a precaution, the family should keep the baby in isolation.
- Consult with a pediatric immunologist who can provide more information on confirmatory testing.
- Do not give the baby vaccines before approval from an immunologist.
- Many mothers can carry cytomegalovirus (CMV) in their breastmilk. Tell mothers to stop breastfeeding until they consult with an immunologist and get tested for CMV.
- Recommend parents to use boiled water instead of bottled water with formula to ensure the baby does not get exposed to trace amounts of bacteria. Feeding bottles, including nipples, should also be boiled. Ready-to-feed formula, which does not require preparation or mixing, can also be used. Leftover formula should be discarded.
- If a SCID diagnosis is confirmed, refer the family to a pediatric immunologist with experience in treating SCID and to genetic counseling.
- Provide information about social or mental health services to the family.

## How is SCID treated?

- Most infants with SCID are treated with hematopoietic stem cell transplantation (HSCT). The ideal donor is a sibling with identical human leukocyte antigens (HLA). If an HLA-identical sibling is not available, an unrelated donor or a parent could be used. Gene therapy has also been successful in treating some types of SCID, including ADA-deficient SCID, X-linked SCID, and Artemis SCID. Most gene therapies for SCID are currently in clinical trials. Treatments with enzyme and immunoglobulin replacement therapies are available for some forms of SCID, but they do not fully restore immune function.
- Until SCID patients undergo HSCT or gene therapy, isolation should be practiced, and supportive care with antibiotics and antifungals may be given to prevent infections. Because these preventive measures can only be used temporarily, children with SCID must undergo HSCT or gene therapy to restore the normal immune function. SCID patients who are diagnosed early and are infection free before HSCT or gene therapy, have a survival rate of about 95%.

## Where to go for more information?

### Research

- HRSA Newborn Screening Information Center
- Immune Deficiency Foundation: SCID Overview
- Immune Deficiency Foundation:  TRECs and Newborn Screening
- SCID Compass: Low T Cell Counts and TRECs Screening
- NIH: Genetic and Rare Disease Information Center

### Clinical Care

- PIDTC: Participating Clinical Centers
- Rotavirus Vaccine Guidance
- ACMG SCID ACT Sheet

### Parent Support

- SCID Angels for Life Foundation
- SCID Compass: Informational Materials, Family Networking, and Advocacy Resources for Parents of Children Born with SCID
- SCID Compass: Parent Support Groups

### Contact

scidcompass.org
scidcompass@primaryimmune.com

SCID compass
An educational program of the Immune Deficiency Foundation



This project is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $2.97 million with 0% financed with nongovernmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS or the U.S. Government.

# Patient & Family Handbook

SCID compass

An educational program of the Immune Deficiency Foundation

*Chapter 8*

# Classic Severe Combined Immunodeficiency

*Rebecca Buckley, MD, Duke University School of Medicine, Durham, North Carolina, USA*

*Jennifer Heimall, MD, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA*

## Overview

Severe Combined Immunodeficiency (SCID, pronounced "skid") is a serious primary immunodeficiency disease (PI) in which there is combined absence of T lymphocyte and B lymphocyte function. SCID is fatal without a stem cell transplant or corrective gene therapy. There are at least 13 different genetic defects that can cause SCID. These defects lead to extreme susceptibility to very serious infections. This condition is generally considered to be one of the most serious forms of PI. Fortunately, effective treatments, such as hematopoietic stem cell transplantation (bone marrow transplant), exist that can treat the disorder, and the future holds the promise of gene therapy for some types.

## Definition

SCID is a rare and fatal syndrome of diverse genetic causes in which there is combined absence of T lymphocyte and B lymphocyte function and in many cases also natural killer (NK) lymphocyte function. These defects lead to extreme susceptibility to serious infections. There are currently at least thirteen different genes that, when mutated (changed), cause SCID. Although they vary with respect to the genetic type that causes the immunodeficiency, some of their laboratory findings and their pattern of inheritance, these infants all have an absence of T cells and severe deficiencies in both T cell and B cell function. Recently, leaky or atypical (hypomorphic) SCID was described. In these patients, there are low numbers of T cells with reduced but not absent function. While these patients can be diagnosed in infancy, particularly if SCID newborn screening is available, many are diagnosed later in life.

## Deficiency of the Common Gamma Chain of the T Cell Receptor

The most common form of SCID, affecting nearly 30% of all cases, is due to a mutation in a gene on the X chromosome that encodes a component (or chain) called IL2RG shared by the T cell growth factor receptor and other growth factor receptors. This component is referred to as the common gamma chain (γc). Changes in this gene result in very low T lymphocyte and NK lymphocyte numbers, but the B lymphocyte count is normal or high (a so-called T-, B+, NK- phenotype). Despite the presence of B lymphocytes, there is no B lymphocyte function, since the B cells have abnormal receptors for growth factors on their cell surfaces. (See The Immune System and Primary Immunodeficiency Diseases Chapter.) This deficiency is inherited as an X-linked recessive trait. (See Inheritance Chapter.) Only males have this type of SCID, but females may carry the gene and have a 1 in 2 chance (50%) of passing it on to each son as well as a 1 in 2 chance of passing the carrier state on to each daughter.

## Deficiency of Recombinase Activating Gene 1 and 2

With the advent of newborn screening, improved access to genetic testing and recognition of leaky SCID as a clinical entity, there has been increased diagnosis of SCID caused by autosomal recessive mutations in Recombinase Activating Gene 1 and 2 (RAG1 and RAG2). RAG1 and RAG2 are enzymes critical to development of T and B cells, but not NK cells. Babies with this type of SCID will present with low or absent T and B cells, but typically have normal or high NK cells. RAG1 and RAG2 mutations are seen in 40% of those with leaky SCID and about 19% of those with SCID overall. Both boys and girls can be affected.

## Adenosine Deaminase Deficiency

Another common type of SCID is caused by mutations in a gene that encodes an enzyme called adenosine deaminase (ADA). ADA is essential for the metabolic function of a variety of body cells but especially T cells. The absence of this enzyme leads to an accumulation of toxic metabolic by-products within lymphocytes that cause the cells to die. ADA deficiency is the second most common cause of SCID, accounting for about 15% of cases. Babies with this type of SCID can have the lowest total lymphocyte counts of all because T, B, and NK lymphocyte counts are all very low. This form of SCID is inherited as an autosomal recessive trait. (See Inheritance Chapter.) Both boys and girls can be affected.

## Deficiency of the Alpha Chain of the IL-7 Receptor

Another form of SCID is due to mutations in a gene on chromosome 5 that encodes another growth factor receptor component, the alpha chain of the IL-7 receptor (IL-7Rα). Infants with this type of SCID have B and NK cells, but no T cells. However, the B cells don't work because of the lack of T cells. The B cells and NK cells are intrinsically normal; however, so after T cell reconstitution through transplantation, the function of all cell lineages is normal. IL-7Rα deficiency accounts for less than 10% of SCID cases. It is inherited as an autosomal recessive trait. (See Inheritance Chapter.) Both boys and girls can be affected.

## Deficiency of Janus Kinase 3

Another type of SCID is caused by a mutation in a gene on chromosome 19 that encodes an enzyme found in lymphocytes called Janus kinase 3 (Jak3). This enzyme is necessary for function of the above-mentioned common gamma chain (γc). Infants with this type look very similar to those with X-linked SCID, so they are T-, B+, NK-. However, since this form of SCID is inherited as an autosomal recessive trait, both boys and girls can be affected. (See Inheritance Chapter.) Jak3 deficiency accounts for less than 10% of cases of SCID.

## Deficiencies of CD3 Chains

Three other forms of SCID are due to mutations in the genes that encode three of the individual protein chains that make up another component of the T cell receptor complex, CD3. These SCID-causing gene mutations result in deficiencies of CD3Aσ, ε or ζ chains (CD3 delta, epsilon or zeta). These deficiencies are also inherited as autosomal recessive traits and account for less than 5% of individuals with SCID. Both boys and girls can be affected.

## Deficiency of Artemis and Other Radiosensitive Forms of SCID

There are a group of other autosomal recessively inherited forms of SCID associated with a lack of T and B cells, but presence of NK cells as well as sensitivity to ionizing radiation. These are due to mutations in genes necessary for DNA repair, including DCLRE1C (encoding the ARTEMIS protein), PRKEDC, NHEJ1, and LIG4. In addition to radio sensitivity and absence of T and B cells, individuals with PRKEDC, NHEJ1, and LIG4 commonly exhibit microcephaly, when the brain does not develop properly resulting in a smaller than normal head. The radiosensitive forms of SCID comprise less than 5% of those with SCID, but they require special consideration in selection of conditioning agents to minimize the risk of late effects.

## Other Causes of SCID

There are several other genetic defects associated with autosomal recessive inheritance of SCID, including mutations in the genes that encode CD45, Coronin 1A, and LAT. In a recent study, in about 6-10% of individuals with SCID, there was not an identifiable genetic defect to explain their clinical and laboratory features.

## Clinical Presentation

The presentation of SCID is changing rapidly in the U.S. because of the introduction of nationwide newborn screening for SCID using the detection of T cell receptor excision circles (TREC) to identify infants at risk before the onset of infections. This allows for earlier intervention and improved survival. Infants with SCID have no outward physical findings to distinguish them from normal newborns and are usually clinically well until the onset of infections. For those not detected by newborn screening, an excessive number of infections is the most common presenting symptom of infants with typical SCID. These infections are not usually the same sorts of infections that normal children have, such as frequent colds. The infections of the infant with SCID can be much more serious and even life threatening, and they may include pneumonia, severe viral respiratory

infections, meningitis, and/or bloodstream infections. The widespread use of antibiotics, even for minimal infections, has changed the pattern of presentation of SCID, so the doctor seeing the infant must have a high index of suspicion in order to detect this condition.

Infants with SCID are susceptible to routine infections seen in healthy babies, but they are also at increased risk for infections caused by organisms or live vaccines which are usually not harmful in children with normal immunity. Among the most dangerous is an organism called *Pneumocystis jiroveci* that can cause a rapidly fatal pneumonia (PJP) if not diagnosed and treated promptly. Another very dangerous organism is the chickenpox virus (varicella). Although chickenpox is annoying and causes much discomfort in healthy children, it usually is limited to the skin and mucous membranes and resolves in a matter of days. In the infant with SCID, chickenpox can be fatal because it doesn't resolve and can then infect the lungs, liver, and brain. Cytomegalovirus (CMV), which nearly all of us carry in our salivary glands, may cause fatal pneumonia in infants with SCID. Other dangerous viruses for infants with SCID are the cold sore virus (Herpes simplex), adenovirus, respiratory syncytial virus, rhinovirus, parainfluenza 3, Epstein-Barr virus (EBV or the infectious mononucleosis virus), polioviruses, the measles virus (rubeola), and rotavirus.

Since vaccines that infants receive for chickenpox, measles and rotavirus are live virus vaccines, infants with SCID can contract infections from those viruses through these immunizations. If the newborn screen for SCID is abnormal or it is known that someone in the family has had SCID in the past, or currently has SCID, these vaccines should not be given to new babies born into the family until SCID has been ruled out in those babies. This is especially a problem for the rotavirus vaccine, which is routinely given when babies are 6 to 8 weeks old, and the baby with SCID may not have had any infections by that time, so would not be diagnosed except by newborn screening.

Fungal (yeast) infections may be very difficult to treat. As an example, candida infections of the mouth (thrush) are common in most babies but usually disappear spontaneously or with oral medication. In contrast, for the child with SCID, oral thrush may improve, but it either doesn't go completely away or recurs as soon as the medication is stopped. The diaper area may also be involved. Occasionally, candida pneumonia, abscesses, esophageal infection or even meningitis may develop in infants with SCID.

Persistent diarrhea resulting in failure to thrive is a common problem in children with SCID. It can lead to severe weight loss and malnutrition. Diarrhea may be caused by the same bacteria, viruses or parasites that affect normal children. However, in the case of SCID, the organisms are very difficult to get rid of once they become established.

The skin may be involved in children with SCID. The skin may become chronically infected with the same fungus (candida) that infects the mouth and causes thrush. Infants with SCID may also have a rash that is mistakenly diagnosed as eczema, but it is actually caused by a reaction of the mother's T cells (that entered the SCID baby's circulation before birth) against the baby's tissues. This reaction is called graft-versus-host disease (GVHD) due to maternal engraftment.

In individuals with leaky SCID, the clinical presentation may be later in life, if they are not diagnosed due to an abnormal newborn screen. In these individuals, the symptoms can be highly variable signs and symptoms of combined immunodeficiency, with autoimmunity and invasive granulomatous lesions being common as the individual ages.

## Diagnosis

The diagnosis of SCID currently and in the future is most likely going to be made after an abnormal newborn screen and while the newborn is clinically well. If newborn screening is not available, SCID is usually first suspected because of the above clinical features. In some instances, there has been a previous child with SCID in the family, and this positive family history may prompt the diagnosis even before the child develops any symptoms. One of the easiest ways to diagnose this condition is to count the peripheral blood lymphocytes in the child (or those in the cord blood). This is done by two tests; the complete blood count and the manual differential (or a count of the percentage of each *different* type of white cell in the blood), from which the doctor can calculate the absolute lymphocyte count (or total number of lymphocytes in the blood). There are usually more than 4,000 lymphocytes (per cubic millimeter) in normal infant blood in the first few months of life, 70% of which are T cells. Since infants with SCID have no T cells, they usually have many fewer lymphocytes than this. The average for all types of SCID is around 1,500 lymphocytes (per cubic millimeter). If a low lymphocyte count is found, this should be confirmed by repeating the test once

more. If the count is still low, then tests that count T cells and measure T cell function should be done promptly to confirm or exclude the diagnosis.

The different types of lymphocytes can be identified with special stains and counted in a technique called flow cytometry. In this way, the number of total T lymphocytes (including new T cells that have markers indicating they are made in the baby's thymus), helper T lymphocytes, killer T lymphocytes, B lymphocytes and NK lymphocytes can be counted. Since there are other conditions that can result in lower than normal numbers of the different types of lymphocytes, the most important tests are those that detect new T cells that have just come out of the baby's thymus and tests of T cell function. The most definitive test to examine the function of the lymphocytes is to place blood lymphocytes in culture tubes, treat them with various stimulants and then, incubate them for several days. Normal T lymphocytes react to these stimulants by undergoing cell division. In contrast, lymphocytes from individuals with SCID do not react to these stimuli.

Since IgG from the mother passes into the baby's blood through the placenta, it will be present in the newborn's and young infant's blood at nearly normal levels. Therefore, IgG deficiency may not be present for several months until the transferred maternal IgG has been metabolized away. However, other immunoglobulin levels (IgA and IgM) are usually very low in SCID. IgE may be elevated, particularly in those with leaky SCID.

The diagnosis of SCID can also be made in utero (before the baby is born) if there has been a previously affected infant in the family and if the molecular defect has been identified. If genetic analysis had been completed on the previously affected infant, a diagnosis can be determined for the conceptus (an embryo or fetus with surrounding tissues). This can be done by molecular testing of cells from a chorionic villous sampling (CVS) or from an amniocentesis, where a small amount of fluid (that contains fetal cells) is removed from the uterine cavity. Even if the molecular abnormality has not been fully characterized in the family, there are tests that can rule out certain defects. For example, adenosine deaminase deficiency can be ruled in or out by enzyme analyses on the above-mentioned CVS or amnion cells. If there is documentation that the form of SCID is inherited as an X-linked recessive trait and the conceptus is a female, she would not be affected.

Early diagnosis, before the infant has had a chance to develop any infections, is extremely valuable since bone marrow transplants given in the first three and a half months of life have a 96% success rate prior to the onset of infection. As noted earlier, screening of all newborns to detect SCID soon after birth is possible through the use of TREC based newborn screening. As of 2018, all babies born in the U.S. are now being screened for this condition.

## Inheritance

All types of SCID are due to genetic defects. These defects can be inherited from the parents or can be due to new mutations that arise in the affected infant. As already noted, the defect can be inherited either as an X-linked (sex-linked) defect where the gene is inherited from the mother or as one of multiple types of autosomal recessive defects (see previous section on the causes SCID) where both parents carry a defective gene. See Inheritance Chapter to more fully understand how autosomal recessive and sex-linked recessive diseases are inherited, the risks for having other children with the disease, and how these patterns of inheritance affect other family members. Parents of children with SCID should seek genetic counseling so that they are aware of the risks for future pregnancies.

It should be emphasized that there is no right or wrong decision about having more children. The decision must be made in light of the special factors involved in the family structure; the basic philosophy of the parents; their religious beliefs and background; their perception of the impact of the illness upon their lives; and the lives of all the members of the family. There are countless factors that may be different for each family.

## General Treatment

Infants with this life-threatening condition need all the support and love that parents can provide. They may have to tolerate repeated hospitalizations that, in turn, may be associated with painful procedures. Parents need to call upon all of their inner resources to learn to handle the anxiety and stress of this devastating problem. They must have well-defined and useful coping mechanisms and support groups. The demands on the time and energies of the parents caring for someone with SCID can be overwhelming. If there are siblings, parents must remember that they need to share their love and care with them. Parents also need to spend energy in maintaining their own relationship with

each other. Family counseling may be necessary to keep relationships together, even with a successful therapeutic outcome for the child with SCID.

The infant with SCID needs to be isolated, especially from young children. If there are siblings who attend daycare, religious school, kindergarten, or grade school, the possibility of bringing infections, particularly those of viral origin, into the home represents the greatest danger. Cytomegalovirus (CMV), is currently the most common viral illness seen in newborns with SCID. This infection can lead to devastating long-term complications such as chronic lung disease and neurologic impairment, particularly blindness. It is for this reason that screening of mothers for serologic positivity to CMV is commonly done prior to allowing the child to breastfeed by many but not all immunology and transplant centers.

The infant with SCID should not be taken to public places, such as group child care settings, stores, doctors' offices, etc., where they are likely to be exposed to other young children who could be harboring infectious agents. Contact with relatives should also be limited, especially those with young children. Neither elaborate isolation procedures nor the wearing of masks or gowns by the parents is necessary at home. Frequent hand-washing is essential, however.

Although no special diets are helpful, nutrition is nevertheless very important. In some instances, the child with SCID cannot absorb food normally, which in turn can lead to poor nutrition. As a result, in some instances the child may need continuous intravenous feedings to maintain normal nutrition. Sick children generally have poor appetites, so maintaining good nutrition may not be possible in the usual fashion. (See General Care Chapter.)

Death from infection with *Pneumocystis jiroveci*, a widespread organism which rarely causes infection in normal individuals but causes pneumonia in individuals with SCID, used to be a common occurrence in this syndrome. This type of infection has become less common with early diagnosis and prophylactic treatment with trimethoprim-sulfamethoxazole. All infants with SCID should receive this preventive treatment until their T cell defect has been corrected.

**LIVE VIRUS VACCINES AND NON-IRRADIATED BLOOD OR PLATELET TRANSFUSIONS ARE DANGEROUS.** If you or your healthcare provider suspect that your child has a serious immunodeficiency, you should not allow rotavirus, chickenpox, mumps, measles, **live** virus polio, or BCG vaccinations to be given to your child until their immune status has been evaluated. As mentioned above, the child's siblings should not receive the rotavirus vaccine. If viruses in the other live virus vaccines are given to the child's siblings, they are not likely to be shed or transmitted from the sibling to the patient. The exception to this could be the chickenpox vaccine if the sibling develops a rash with blisters around the vaccine site.

If your infant with SCID needs to have a blood or platelet transfusion, your infant should always get irradiated (CMV-negative, leukocyte-depleted) blood or platelets. This precaution is necessary in order to prevent fatal GVHD from T cells in blood products and to prevent your infant from contracting an infection with CMV.

## Specific Therapy

Immunoglobulin (Ig) replacement therapy, given either intravenously or subcutaneously, should be given to infants with SCID when they are diagnosed and continued on an ongoing basis until they have been transplanted and demonstrate recovery of B cell function. Even after transplantation, individuals with SCID who do not develop B cell function will need to continue to receive this indefinitely. Although Ig replacement therapy will not restore the function of the deficient T cells, it does replace the missing antibodies resulting from the B cell defect and is, therefore, of benefit.

For individuals with SCID due to ADA deficiency, enzyme replacement therapy (elapegademase-lvlr) has been used with some success, particularly as a bridge or temporary treatment before transplant or gene therapy. The immune reconstitution effected by enzyme replacement therapy is not as good as with a transplant or gene therapy and is not a permanent cure; it requires regular injections for the rest of the child’s life.

Currently, the most successful therapy for SCID is immune reconstitution by hematopoietic stem cell transplantation (HSCT). HSCT for SCID is best performed at medical centers that have had experience with SCID and its optimal treatment, and where there are pediatric immunologists overseeing the transplant. In a HSCT, bone marrow cells, peripheral stem cells, or umbilical cord stem cells from a normal healthy donor are given to the individual with SCID to replace the defective lymphocytes of their immune system with the normal cells of the donor's immune system. The goal of

transplantation in SCID is to correct the immune dysfunction. This contrasts with transplantation in people with cancer, where the goal is to eradicate the cancer cells and drugs suppressing the immune system are used heavily in that type of transplant.

The ideal donor for an infant with SCID is a perfectly HLA-type matched normal brother or sister. Lacking that, techniques have been developed over the past four decades that permit good success with matched unrelated donors or half-matched related donors (such as a mother or a father). Several hundred marrow transplants have been performed in infants with SCID over the past 30 years, with an overall survival rate of 70% at 10 years from HSCT. However, the outcomes are better if the donor is a matched sibling (>94% success rate) and if the transplant can be performed soon after birth or less than three and a half months of life. There is controversy in the field regarding the use of pre-transplant chemotherapy based conditioning, and there does not appear to be an impact on survival with the use of conditioning. However, the use of conditioning does appear to be associated with improved immune function, particularly recovery of B cell function in certain genetic forms of SCID. The decisions regarding donor source and conditioning regimen choices should be discussed with the immunologist and the transplant team at the center to decide the best available treatment option for a particular person with SCID.

There does not appear to be any advantage to *in utero* marrow stem cell transplantation over transplantation performed immediately after birth.

Finally, another type of treatment that has been explored over the past three decades is gene therapy. There have been successful cases of gene therapy in both X-linked and ADA-deficient SCID leading to correction of the immunodeficiency. Unfortunately, in one of the clinical trials for X-linked SCID, there was a high rate of later development of blood born cancers in the treated individuals. This has led to the development of safer ways to administer gene therapy. Gene therapy for ADA SCID has been commercially available in Europe as Strimvelis since 2016. This gene therapy product has demonstrated similar efficacy to non-sibling donor HSCT. There are currently clinical trials underway to explore new gene therapy options for x-linked (IL2RG) and ARTEMIS forms of SCID. One cannot perform gene therapy, however, unless the abnormal gene is known; hence the importance of making a specific molecular diagnosis.

## Expectations

SCID is generally considered to be one of the most serious forms of PI. Without a successful HSCT, enzyme replacement therapy, and/or gene therapy, the individual with SCID is at constant risk for a severe or fatal infection. With a successful HSCT, the individual's own defective immune system is replaced with a normal immune system, and normal T lymphocyte function is restored. The first bone marrow transplantation for SCID was performed in 1968. That patient is alive and well today!

*Adapted from: Chapter 9 Severe Combined Immune Deficiency and Combined Immune Deficiency. IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition. 2013.*

# Guide to HSCT

SCID compass

An educational program of the Immune Deficiency Foundation

# Immune Deficiency Foundation Guide to Hematopoietic Stem Cell Transplantation

**This publication contains general medical information that cannot be applied safely to any individual case. Medical knowledge and practice can change rapidly. Therefore, this publication should not be used as a substitute for professional medical advice. In all cases, patients and caregivers should consult their healthcare providers. Each patient's condition and treatment are unique.**



*This publication has been made possible through the IDF SCID Initiative and the SCID, Angels for Life Foundation.*

## Acknowledgements

The Immune Deficiency Foundation would like to thank the organizations and individuals who helped make this publication possible and contributed to the development of the Immune Deficiency Foundation Guide to Hematopoietic Stem Cell Transplantation. A collaborative effort, this guide brought together a wide base of contributors including parents and healthcare professionals. Special thanks to:

**IDF Nurse Advisory Committee**

**IDF SCID Initiative**

**SCID, Angels for Life Foundation**

**Primary Immune Deficiency (PID) Treatment Consortium (PIDTC)**

**Barbara Ballard**
The SCID Group
*IDF Board of Trustees*

**Rebecca Buckley, MD**
Duke University School of Medicine
*IDF Medical Advisory Committee - Chair*

**Morton Cowan, MD**
University of California, San Francisco
*PIDTC*

**Carol Ann Demaret**
*IDF Board of Trustees*

**Mary Hintermeyer, APNP**
Children's Hospital of Wisconsin

**Yvette Shorten**
*IDF Board of Trustees*

**Heather Smith**
SCID, Angels for Life Foundation

**Kathleen Sullivan, MD, PhD**
Children's Hospital of Philadelphia
*IDF Medical Advisory Committee - Vice Chair*

**Jennifer Puck, MD**
University of California, San Francisco
*IDF Medical Advisory Committee*
*PIDTC*

**Amy Walsh**
*IDF Board of Trustees*

IDF Staff
Katherine Antilla, MAEd
John G. Boyle, MA
Brian Fitzek
Kara Moran


## Table of Contents

# Introduction

*Primary immunodeficiency diseases (PI) are a group of more than 350 rare conditions in which part of the body's immune system is missing or functions improperly. Some affect a single part of the immune system; others may affect one or more components of the system. Cells of the immune system normally arise from blood-forming "hematopoietic" stem cells (HSCs) in the bone marrow that is in the middle of every bone in the body; when this process is impaired, transplanting new HSCs from a healthy donor can be a potential cure. In some cases, replacing the immune system with one that functions normally is the best option in order to have a prolonged life with better quality. The procedure is commonly known in the medical world as hematopoietic stem cell transplant (HSCT), hematopoietic cell transplant (HCT) or bone marrow transplant (BMT). Unlike transplantation of a solid organ (such as a kidney or liver), HSCT does not involve surgery. It is similar to a blood transfusion. But instead of just blood, the transfusion contains hematopoietic cells, including the stem cells that both self-renew and mature, as needed, to give rise to white blood cells that fight infections, red blood cells that carry oxygen to the tissues, and platelets that help control bleeding. Traditionally, HSCs are obtained from the bone marrow. This process is called "bone marrow transplantation." HSCs may also be obtained from peripheral blood, or blood taken from the placenta at birth ("cord blood"), so that a more general term is HSCT.*

*This guide includes HSCT approaches that could potentially benefit patients with several types of PI. Subsequent chapters provide more details as to how a patient is prepared for a transplant, what the transplant experience is like, and what life can be like after a transplant.*

# 1 CHAPTER Primary Immunodeficiency Diseases That May Be Treated by Transplantation

Although many primary immunodeficiency diseases (PI) result in complications that have mild to moderate effects on the person's daily life, others are severe and require more definitive treatment, such as a hematopoietic stem cell transplantation (HSCT). This chapter describes the types of PI that may require HSCT as treatment, or for which HSCT is a consideration, depending on the assessment of an individual patient's risks and benefits.

## Severe Combined Immune Deficiency (SCID)

Severe Combined Immune Deficiency (SCID), sometimes referred to as the "bubble boy disease," refers to the most severe group of primary immunodeficiency diseases, which place the affected child at a high risk for life-threatening infections. The term "combined" refers to the fact that both T lymphocytes (with many functions, including the direct killing of virus-infected cells) and B lymphocytes (antibody producing cells) are affected. Infants born with SCID can be identified shortly after birth through state newborn screening (NBS) programs. In some instances, there is a family history of SCID and, because of that history, the immune evaluation can be performed on an infant shortly after birth, or even prenatally.

Infants not picked up by NBS or family history can still be identified through a traditional immune evaluation. Patients should undergo evaluation if they experience recurrent, persistent or severe infections, or if they get infections with organisms that do not cause illness in healthy people.

Infants with SCID who completely lack T lymphocytes are not able to reject transplanted cells from a healthy donor; therefore, most SCID transplants can be performed without prior treatment (chemotherapy or conditioning) depending on the type of SCID and the tissue matching between the donor and recipient. SCID has many different genetic causes. In some cases, the exact genetic cause cannot be identified. Despite different genetic causes, however, the children are unable to fight infections. When SCID is diagnosed, the only curative option is to provide them with a functional immune system, most often through HSCT. In some forms of SCID, gene therapy and enzyme replacement therapy may represent valid alternatives. Studies have shown that when HSCT is performed in an infant with SCID soon after birth and before infectious complications occur, the outcomes are very good with survival rates approaching 95%. Babies with SCID must be isolated from exposure to infections and may be treated with immunoglobulin (Ig) replacement therapy and preventive antibiotics while awaiting transplant. Based on the circumstances and practices of the transplant center, some infants may be cared for at home pre-transplant with strict isolation guidelines in place; other infants, however, are admitted to the hospital until the transplant has occurred and immune function is restored.

## Combined Immunodeficiencies (CID)

These disorders, like SCID, are characterized by problems with both T cell and B cell immunity and can be caused by defects in any of a number of genes. They include: "Leaky SCID" in which the gene mutation is incomplete and some poorly functioning T cells are present; Omenn syndrome, a special form of Leaky SCID in which lymphocytes may reproduce in an unregulated manner and attack the infant's tissues; ZAP70 deficiency; bare lymphocyte syndrome; and others. Depending on the defect, CID may or may not be detected by newborn screening. While minimal lymphocyte function is preserved, it is not sufficient for effective responses to infections. HSCT can be curative for these disorders, but the residual host immunity is a barrier to successful transplantation. Therefore, chemotherapy to eliminate host lymphocytes prior to transplant is generally required.

## Hyper IgM Syndrome (HIGM)

Hyper IgM Syndrome (HIGM) can vary in severity because there are different genetic causes, and different environmental exposures for each patient. One form of HIGM is carried on the X chromosome (X-linked), and the mutation can be passed from unaffected mothers to their sons. (The chance of a carrier mother passing the mutation to male offspring is 50%.) People with HIGM cannot make protective IgG antibodies, despite levels of IgM antibodies that are often high (giving the disorder its name). HIGM requires Ig replacement therapy and preventive antibiotics. Some affected individuals develop low white blood cell counts and may need medication to stimulate production of their white blood cells. Some patients may develop chronic intestinal infections leading to liver and intestinal damage. HSCT from a well-matched donor can cure HIGM, but like all non-SCID primary immunodeficiency diseases, host lymphocytes must be eliminated with chemotherapy to allow engraftment of the new stem cells. Pre-transplant infections and other complications increase risks of HSCT. Therefore, risks and benefits of HSCT must be carefully weighed for each case.

## Chronic Granulomatous Disease (CGD)

Individuals with Chronic Granulomatous Disease (CGD) have white blood cells that can engulf bacteria and fungi, but the white blood cells then fail to kill them, leading to chronic and severe infections. Some patients have been managed with lifelong preventive antibiotics and, in some cases, injections of an immune system hormone or cytokine, gamma-interferon. This approach, however, does not cure the disease. Individuals with CGD may experience progressive infections that do not respond to treatment. HSCT is increasingly being used to treat CGD and can be curative, but it is not necessarily indicated for all patients, as some do well on medical management, depending on the severity of their condition. The risks and benefits of the all treatments and procedures must always be carefully weighed. There are ongoing trials of gene therapy for CGD.

## Wiskott Aldrich Syndrome (WAS)

Wiskott Aldrich Syndrome (WAS) affects several types of immune cells as well as platelets (the clotting particles in the blood). Individuals with WAS may experience bleeding or bruising as well as frequent infections, usually affecting the sinuses, ears, lungs and/or skin. Patients frequently have significant eczema as well. In many cases, they require Ig replacement therapy. They often require placement of ear tubes, sinus procedures and frequent antibiotics to manage their infections. They are at high risk for bleeding due to low platelet counts if they experience physical trauma. There is also an increased risk of malignancy. Many patients with WAS are candidates for HSCT, which can be curative. The decision to perform HSCT depends on many factors, including what type of donor is available. There are ongoing clinical trials of gene therapy for WAS.

## Immune Dysregulation-Polyendocrinopathy-Enteropathy-X linked Syndrome (IPEX)

Immune Dysregulation-Polyendocrinopathy-Enteropathy-X-Linked Syndrome (IPEX) is a PI in which immune cells are not regulated properly, resulting in an attack on the body's own tissue. Therefore, IPEX has symptoms of severe failure to thrive, severe eczema and endocrine disorders such as hypothyroidism, diabetes, growth hormone deficiency, and/or adrenal insufficiency. Individuals with IPEX often present with chronic diarrhea and eczema, and they may have been diagnosed with food allergies or inflammatory bowel disease and/or celiac disease in some cases. They may have infections and, unfortunately, they are typically not diagnosed until the disease process has done severe damage to the body, as their symptoms can mimic other diseases. HSCT is recommended for treatment to resolve their multiple problems and help with proper growth and nutrition.

## Common Variable Immune Deficiency (CVID)

Common Variable Immune Deficiency (CVID) is characterized by the inability to make sufficient immune proteins (antibodies) to fight infection. Most individuals with CVID do well on Ig replacement therapy alone. Some people with CVID, however, experience autoimmune complications involving the lung, central nervous system, blood components, intestines, and muscles, or develop lymphoma, a cancer of the lymphocytes. These complications can severely impair the patient's daily function or even be life threatening. In certain select cases, HSCT has been performed in patients with CVID. Due to the multiple systems affected and the general older age of the patient, however, HSCT is much riskier in this population. Up until the present, HSCT has only rarely been recommended for CVID.

## Other Primary Immunodeficiency Diseases

The aforementioned disorders are only some of the types of PI that may be treated by HSCT. There are many more rare diseases of the immune system that could benefit from HSCT. An immunologist is the best source of information as to the disease state and whether HSCT would be a good option. HSCT is not without risk or complications and should be undertaken only for severe disorders.

Most PIs can be successfully managed without HSCT. Typically, diseases such as CVID, X-linked Agammaglobulinemia (XLA or Bruton's disease) and most 22q11 deletion syndrome (incomplete DiGeorge Syndrome) are not candidates for transplant as affected individuals can achieve a good quality of life and normal life expectancy with treatments, such as Ig replacement therapy alone or no immune therapy. Rarely, there are patients with the complete DiGeorge syndrome who require a thymus transplant, not HSCT. Other PIs have significant health impairments besides the immune disorder that would not be helped by HSCT, and still others are due to immune system factors such as complement proteins that are not part of the hematopoietic system.

As will be explained in the next few chapters, HSCT is a very involved process with potential for serious complications. It should only be considered in a patient where alternative treatments are not effective or if the patient is at high risk for complications if not transplanted.

# 2 CHAPTER The Evaluation Process for Hematopoietic Stem Cell Transplantation

This chapter includes how patients are evaluated for hematopoietic stem cell Transplantation (HSCT), how donors are selected and the different types of HSCT.

## HCST Evaluation

Once it has been determined that an individual with primary immunodeficiency disease (PI) may need HSCT, that individual is usually referred to a transplant team for evaluation and care. The team will do a thorough evaluation to determine any underlying health issues that would affect the timing and type of transplant or cause the patient to have additional risks. The evaluation typically involves human leukocyte antigen (HLA) typing of the patient and his/her family members to find out if there is a possible family member who could serve as a donor. The patient/family will meet extensively with the transplant physician and other team members to discuss in detail important items such as donor selection, conditioning regimen (chemotherapy) if needed [patients with Severe Combined Immune Deficiency (SCID) might not need it, but all other PIs do need conditioning], and post-transplant monitoring. Risks and benefits of transplant are discussed at this time. The evaluation may include scans, X-rays, lung function test, echocardiogram (heart testing), hearing evaluation and blood tests. The patient and family will usually meet with a social worker to discuss the impact of the transplant on patient/family functioning, support systems and financial issues.

If the patient is going to receive pre-transplant conditioning, he/she will have a long-term catheter (tube) placed in a large vein typically in the neck. This is needed for the multiple medications (including chemotherapy), IV fluids, blood tests and the stem cells that the patient will receive while in the hospital.

## Finding a Donor Match

There are several types of donors who can be used for any patient undergoing HSCT. Finding the best matched donor is key to getting the patient's body to accept the transplant and to avoid having the transplant react against the patient. It can be a lengthy process to find and prepare a suitable donor, sometimes taking months. Poorly matched donor transplants can result in the patient's body rejecting the new cells. Poorly matched donors also greatly increase the risk of Graft versus Host Disease (GVHD) after transplant. In GVHD, the "new" immune system sees the patient's body organs and tissue as "foreign" and will attack it, causing damage. There are national and international donor registries that are searched for possible donors if there are no suitable donors within the family. In some cases, a partially matched family member can safely be a donor providing the donor T cells in the HSC collection can be eliminated either before or after the transplant. HLA typing: The most important evaluation in finding a donor is to HLA type all potential donors and the patient (recipient). There are 10 critical HLA genes that are evaluated for most HSCT. These genes are inherited by the patient, 5 from the mother and 5 from the father. Each sibling has a 25% chance of inheriting the same 10 genes from the parents and this is called a "genotypic" match, the best possible match for HSCT.

### *Donor Types:*

- **Identical Twin:** This is an identical twin of the patient and is the best possible match. Since all the tissues of identical twins match, there is no risk of GVHD occurring. An identical twin, however, is usually affected with the same PI as the patient, so would not be considered if also diagnosed with PI.

- **Sibling HLA matched donor:** This is a full brother or sister who matches the patient at the 10 major HLA genes. This is considered an optimal donor. Even though there is a perfect match for the major HLA genes, however, there could still be minor mismatches at other genes that differ, so GVHD is still possible.

- **Haploidentical family match:** This is a half-matched donor and is usually a parent but can be a sibling or even an aunt, uncle or cousin. Transplants from half-matched donors must have the donor T cells removed before or destroyed after the transplant to minimize the risk of severe GVHD. These donors are used when matched sibling donors or a very good matched unrelated donor are not available. Many patients with SCID have accepted T cell-depleted parental donor marrow or peripheral blood stem cells without any preconditioning and with excellent outcomes. The transplant physician will determine which patients are candidates for this type of transplant. For recipients of a haplocompatible HSCT, the risks for complications such as rejection of the cells or GVHD are higher. There may also be a delay in recovery of T cells so that infection risks may also be higher.

- **Unrelated HLA matched donor** (also referred to as matched unrelated donor or "MUD"): This is an unrelated adult donor (identified through the donor registries) whose HLA type closely matches the patient. This is considered a good donor choice, although the risk of rejection and the chance of GVHD is higher than with a related matched donor due to possible mismatches at non-HLA factors and the fact that these are not genotypic matches as in a matched sibling.

- **Umbilical cord blood donor** (also referred to as cord blood transplant): Cord blood donations to banks, or "repositories," have expanded the options for many patients who need a transplant and lack an HLA matched donor. Use of cord blood can be limited due to the lower number of cells that are available, which can limit the size of the recipient for whom it can be used. GVHD is still a problem because of the fact that most unrelated cord bloods are HLA mismatched. However, despite some degree of HLA mismatch, cord blood may induce somewhat less GVHD than other types of donor cells. Also, the risk of rejection is much higher with cord blood transplants, and there is a delay in recovery of the red and white cells and platelets compared to other donor types. Finally, there is no opportunity to repeat the transplant from the same donor if the graft fails. Conditioning using high dose chemotherapy is most often used with cord blood transplants.

- **Autologous** (or "self") **transplant with gene-corrected cells, also known as gene therapy:** Correcting a patient's own hematopoietic stem cells (HSCs) would avoid problems with rejection and GVHD, and these advantages have spurred promising research in gene therapy. Almost all gene therapy is restricted to experimental clinical trials, and it is available for only a limited number of PIs. Immunologists are a good source on the most current information about gene therapy, which is beyond the scope of this discussion.

## *Donor Sources:*

- **Bone marrow:** This is liquid tissue found inside all bones that contains the HSCs which generate the cells in the blood including red cells, white cells and platelets. This marrow can be harvested and prepared to infuse into the selected recipient. Typically, the marrow is harvested through multiple needle sticks into the pelvic bones until an adequate volume of cells is harvested. The donor is anesthetized for the procedure.

- **Peripheral blood stem cells:** HSCs are normally found in the bone marrow, but they can be mobilized into the peripheral blood circulation for collection. For this, the donor is given injections of a medication for several days prior to the harvest that causes some of the HSCs in the bone marrow to temporarily go into the blood circulation. A special IV is placed in the donor's veins (usually veins in the arms or sometimes in the neck), and the blood is passed through a machine that removes those white cells containing the HSCs and returns the rest of the white cells plus the red cells, platelets and plasma back into the donor. This procedure is called leukapheresis and it is similar to donating platelets. This process usually takes 4 or more hours until enough stem cells are collected.

- **Umbilical cord blood:** Cord blood is a rich source of HSC and can be used for HSCT. The cord donor is usually non-related, although sibling's cord blood can be used if available. A search for an unrelated cord blood that has been stored for HSCT is usually done through a bone marrow registry. In the US this is the National Marrow Donor Program (NMDP). Your transplant physician can tell you more about this process.

# 3 CHAPTER The Transplant Process

## Pre-admission

Once a patient has been determined to be a suitable candidate for hematopoietic stem cell transplantation (HSCT) and an acceptable donor has been found, the transplant is scheduled. There are several elements to the pre-admission process for transplant:

- **Transplant consent:** The physician and other team members meet with the patient and family to discuss in detail all aspects of the transplant procedure. Depending on the type of primary immunodeficiency disease (PI), the patient may or may not require a conditioning regimen. The team discusses the risks, benefits and complications associated with transplant. The family should ask all the questions they feel are necessary to be sure they fully understand the proposed treatment including the short-term and long-term risks as well as the benefits. Other family members, the family physician and outside experts can be involved if desired. If the patient and family agree to the procedure, formal consent is obtained.
- **Conditioning regimen:** This refers to administration of chemotherapy and other medicines for several days before the transplant. The conditioning regimen helps to make "space" in the recipient's marrow for the new donor cells and to prevent rejection of these cells by the recipient's immune system. The chemotherapy agents used for conditioning may have short-term and long-term side effects. Many patients with Severe Combined Immune Deficiency (SCID) can accept donor cells without any preconditioning because they do not have any T cells to reject the transplant. In some SCID cases (depending on the type of SCID, donor, and donor match with the recipient), there may be a choice of conditioning or no conditioning. For patients who do not have SCID, conditioning treatments vary widely. The transplant physician will determine which patients are candidates for conditioning and will explain the possible outcomes depending on whether or not conditioning is used.
- **Transplant date:** The transplant team has many components to coordinate in order to accomplish the transplant. If a related donor is to be used, a time must be arranged for the hematopoietic stem cells (HSCs) to be harvested (also for the T cell depletion if this is a half-matched parental donor) prior to giving the cells to a recipient with SCID. If pre-transplant conditioning is given, the timing of the harvest has to coincide with the patient's completion of his/her conditioning. If an unrelated donor is to be used, arrangements must be made with the National Marrow Donor Program (NMDP) for collection and shipping of HSCs to the transplant center to arrive when the patient is prepared to receive the donor cells. Cord blood has to be analyzed to determine if it contains enough cells for the size of the patient. Finally, the patient must be kept as healthy as possible to undergo the transplant.
- **Insurance approval:** Since HSCT is expensive, the transplant center will need to work with the patient's insurance to obtain approval before the transplant can be scheduled. This is usually started during the referral process.

## Transplant Hospitalization

- **Admission:** If the patient requires pre-transplant chemotherapy, the patient will be admitted several days to a couple of weeks before the actual transplant to receive the conditioning regimen and to prepare for the transplant. The transplant itself is not a surgical procedure and occurs in the patient's room. It is similar to a blood transfusion. On the day of the transplant, the donor's cells arrive at the patient's room suspended in a liquid solution and are infused into the patient intravenously. The length of the infusion depends on the volume and source of cells and can take anywhere from less than 30 minutes in a baby to several hours in a young adult.
- **Inpatient stay:** After a conditioned transplant, the amount of time the patient will be in the hospital varies significantly from a few weeks to several months. Patients who are more subject to a prolonged hospital stay are those who experience transplant-related complications or infections. The type of donor and transplant also influence the length of hospitalization, e.g., recipients of unrelated donor cells including cord blood tend to have longer hospital stays.
- **Discharge:** Most patients who receive pre-transplant conditioning may require some type of home healthcare assistance once discharged. They will likely go home with an IV in place and may be receiving IV fluids and IV medications at home. They will need to take several oral medicines as well.

## Complications

### Failure to engraft:

- After a sufficient period of time has passed following the transplant, the patient's blood is tested for the presence of donor cells (also called "chimerism"). If there are no "donor cells" found after multiple tests, the donor cells have not "taken." This means the transplant has failed, and the patient will likely need to receive another transplant. This may be accomplished using more cells from the original donor. Sometimes the original donor cannot be used again, and a new donor must be found. The patient might require conditioning before a second transplant.

### Graft rejection:

- This means that the donor cells initially engrafted, but at some point, the patient's body "rejected" the cells. This typically occurs in patients with non-SCID PIs who received mild (called "reduced intensity") conditioning or in patients with SCID who received no conditioning. The recipient's original immune system may still be present enough to eliminate the new donor cells. In this case, the patient will likely require another transplant with a different conditioning regimen to prevent this from occurring again, but in rare cases the effect can be reversed with a "boost" of more cells from the original donor.

### Graft versus Host Disease (GVHD):

- Graft versus Host Disease (GVHD) occurs when the new immune system attacks the patients' organs and tissues as they appear "foreign" to the donor T cells. Prevention and treatment of GVHD involve additional medications to quiet down or suppress elements of the new immune system that may recognize and injure the tissues of the patient. GVHD can be mild or severe. It usually attacks the skin, the gastrointestinal tract, the mucous membranes and certain organs such as the liver and lungs.

### Acute and Chronic GVHD:

- Acute GVHD typically appears in the first 100 days after transplant. Chronic GVHD can appear any time after day 100 and may last for weeks, months or years. Common symptoms of both acute and chronic GVHD are inflamed skin (rashes), nausea, vomiting and diarrhea, and impairment of organ function, especially the lung and the liver. Treatment usually consists of topical steroid creams to the skin (for mild skin GVHD), and systemic medications such as steroids and other types of immunosuppressive agents for more severe symptoms. Acute and chronic GVHD can be mild or severe, and life threatening.

### Mucositis (ulcers):

- Conditioning chemotherapy drugs can affect all tissues, including the mouth, throat and intestines. The patient may experience ulcers (sores) in these areas leading to pain, drooling, nausea, vomiting, diarrhea and sometimes bleeding. This is temporary and improves within 2-4 weeks. The ulcers are managed with good oral hygiene and pain medications, as well as bowel rest, which can be further discussed with the provider. Depending on the severity of the pain, narcotics may be used. The severity of mucositis correlates with the intensity of the chemotherapy conditioning.

### Infections:

- Patients with PI are already at risk to develop infections and may have an ongoing infection at the time of transplant. A conditioning regimen for the transplant will remove their neutrophils (another type of white blood cell). This means the patient cannot fight infections. All patients are given preventive antibiotics during the transplant, but at times breakthrough infections can occur. It can take sometimes several weeks for the new donor cells to start producing enough neutrophils to help fight infection. Injections to stimulate neutrophil production are given, and neutrophil infusions are occasionally needed. Immunoglobulin (Ig) replacement therapy is given regularly during the transplant process to help control infection, and strict precautions are used to prevent infections. Monitoring for infections is of utmost importance.

### Bleeding:

- As mentioned above, the patient's own blood forming cells are destroyed during conditioning. Platelets work to help the blood clot. A low number of platelets can result in spontaneous bleeding. The patient's blood counts are closely monitored during transplant and platelet and red blood cell transfusions may be administered.

### Nausea, vomiting and diarrhea:

- Both the conditioning regimen and subsequent GVHD can cause these symptoms. Nutrition is important for patients to handle the stress of transplant and to heal their mucositis. Patients may be given medications to combat nausea and vomiting. They may receive tube feedings during the post-transplant period, or they may be given liquid nutrition through their veins. The latter is known as total parenteral nutrition (TPN).

**Organ toxicity:**

- The conditioning regimen can adversely affect the body's functioning, particularly the lungs, kidneys and liver. Tissue damage from the conditioning is variable depending on the intensity of the chemotherapy and most often, but not always, reversible with medication. Usually the damage to the organs is mild and temporary, but there can be long-term damage such as a liver condition called sinusoidal obstruction syndrome (SOS) or veno-occlusive disease (VOD).

**Psychological\Social Issues:**

- The hospital stay for a transplant can be long. The patient is kept in isolation due to the risk of infection, and patients may also be irritable and in pain. This can be difficult for the family to experience, and they may feel stressed with all the medical procedures. Also, it may be difficult for a parent/caregiver to get adequate sleep in the hospital room with the patient being evaluated frequently during the night by the nursing staff. The family may feel isolated from others as well and not always receive the social support they need. They may have competing demands on their time from others who are left at home. Families also have associated financial issues to handle. The longer the hospital stay, the more the pressures can build up. Social workers are available to help families with these issues. In addition, having supportive extended family and/or friends can help make this process easier to handle.
- Families can become very close with other patients and families during the hospital stay. While this can be helpful, awareness of events in the hospital, including other patients' adverse events or even death, can be traumatic and can make the transplant stay more difficult. Many hospitals have trained personnel to assist with stress, grief and depression. These emotions are common among families of children with severe illness, and medical personnel will be able to provide support. Support from other families with PI can be found through the Immune Deficiency Foundation (IDF): 800-296-4433.

## Discharge from the Hospital

**Discharge readiness:** Discharge readiness of patients who have received a transplant generally requires resolution of any serious complications or side effects, absence of fevers and active infections. Patients are usually showing some signs of the new immune system producing blood cells prior to discharge. They are able to tolerate some type of feeding. They may still require an occasional blood transfusion.

- The patient and family are prepared for discharge by the hospital staff. The patient/family are trained in daily care including hygiene, administering medications and monitoring for complications.
- If the patient is going home with a central line in place, the family and/or patient is trained in care of the central line (most patients will be discharged with the central line in place).
- A discharge planner will help coordinate delivery of supplies and ensure that medications are ready at the pharmacy before discharge.
- If the family does not live locally, they may initially be discharged to a nearby housing facility managed by a medical facility or nonprofit organization.

# 4 CHAPTER Life After Transplant

## First Years after Transplant

### Home Healthcare Company

While primary caregivers are generally expected to oversee patient care post-transplant, in some cases, a home healthcare company may be involved to help the family care for patients upon discharge from the hospital. A nurse or other home healthcare provider will meet the patient/family at home to provide a smooth transition, supervising and training family members on use of the equipment, IV fluids and IV medications. Other care such as tube feedings or dressing changes will also be addressed. Rarely is the home healthcare provider in the home to provide direct care to the patient. The home healthcare provider may check the patient's blood pressure and temperature as well as check on his/her general well-being and recovery. The intention is for the family to take over as much of the care as possible.

### Outpatient Clinic Visits

Patients will require frequent visits to the transplant clinic. This can be as often as daily or once per week but becomes less frequent as the patient becomes more stable. Clinic visits can be lengthy at times as the patient will have blood tests performed, exams by healthcare providers, and, in some cases, transfusions of blood products or immunoglobulin (Ig) replacement therapy. If a patient lives a distance away, the family may need to stay in the area at a hotel or a nearby approved housing facility.

### Illnesses after Discharge

The new immune system is not fully functional for many months; therefore, the patient remains at risk from infections for quite some time after transplant, although the risk typically decreases over time. Illnesses need to be assessed by the healthcare team when they occur. Often, the patient will need to make an unanticipated clinic visit or be hospitalized.

### Healthcare Team

The bone marrow transplant specialist is the primary healthcare provider for patients following transplant and makes the majority of the decisions about the patient's plan of care. In some centers, immunologists participate in post-transplant management, helping to assess the function of the new immune system after transplant and sharing long-term follow-up.

### Dealing with Complications after Transplant

Patients can experience complications after being sent home from the hospital. Often these are similar to what inpatients experience. Some of these complications can become chronic issues that require care and attention for months, even years after transplant.

Most patients will receive Ig replacement therapy during the transplant and for up to a year or longer afterwards. Unfortunately, some patients, in particular with SCID, may not achieve good antibody production after the transplant and still require Ig replacement therapy indefinitely. Families may be disappointed that the hematopoietic stem cell transplantation (HSCT) did not totally resolve the immune deficiency. Nevertheless, if the T cells are engrafted and functional, the patient is protected from the most serious infections.

### Long-Term Outlook

Most people with primary immunodeficiency diseases (PI) do well after transplant. Because their disease is not a cancerous condition, some people with PI can undergo a transplant with less intense chemotherapy, which decreases the risk of complications. Some patients will end up with "mixed chimerism," meaning that they have some donor and some of their own cells coexisting. In many cases, the new donor cells provide just enough immune function to keep the patient healthy.

People with PI who have had a HSCT and are stable can generally expect to live full and healthy lives. Once they get past the first year or two, many require only an annual or every-other-year visit to their transplant doctors and immunologist. It has recently been emphasized by PI specialists, however, that long-term follow-up is needed to monitor patients for the side effects of conditioning, such as sterility or effects on growth and organ function. Also, the immune function of the patient may wane or unanticipated problems may arise.

### Coping with Stress after Transplant

Patients and families will have different experiences as they move through the transplant process. Each patient will vary in his/her response to illness and treatment based on his/her age, development, environment, physical and mental health, family support, and social and financial resources. A key aspect is that family members should feel free to discuss their stressors with each other and outsiders as needed, and everyone involved should have an outlet for stress. Parents/caregivers should feel comfortable to ask their healthcare team for help at any time.

# Questions to Ask

The following are suggested questions for a parent/caregiver (or adult patient) to ask their healthcare care team when considering a hematopoietic stem cell transplantation (HSCT).

- What should go into picking a transplant center/doctor?
- A transplant center is near us, but they do not specialize in my child's/my particular type of PI. The doctors at the center say they can perform the procedure. Should I stay local, which would be easier/less expensive, or travel to a place that specializes in transplants for this type of PI?
- How important is it to choose a transplant center with experience in my/my child's type of PI?
- Centers differ in the amount of conditioning recommended (sometimes none at all for SCID, all the way to full ablation). How does the use of conditioning depend on the disease, the specific gene, or the preferred practice of a given center?
- What if any options other than HSCT or allogeneic transplant are there? Medical management, gene therapy or enzyme replacement therapy? If so, how do these treatments compare with allogeneic transplant for my/my child's condition?
- We cannot find an unrelated donor match. I understand our other options include haploidentical and umbilical cord blood transplants. What are the risks and benefits of each?
- What special considerations regarding transplant apply to my/my child's specific condition?
- What kind of insurance coverage should I have if a transplant is recommended?
- What precautions should be taken prior to admission for transplant?
- How long will my child/myself be in isolation*?
- What isolation precautions are required before, during, and after transplant?
- What are my responsibilities, as caregiver, to keep isolation precautions in place?
- What are the isolation guidelines and expectations of members of the medical team, and visitors when entering my child's hospital room?
- If things go well during transplant, what is the average amount of time in the hospital and recovery time?
- Which doctor or group of doctors will be in charge of my child's care during transplant?
- What is expected of a primary caregiver while the patient is in the hospital and after he/she goes home?
- Which doctor or group of doctors will be in charge of my child's care after discharge?
- I understand that transplants for PI can be curative. If a patient with PI undergoes a transplant and it is considered a success, will he or she be considered "fully cured?" Will there be any reoccurrence like within other diseases?
- Can my child receive live vaccines?
- In which PI category has there been the most progress in terms of gene therapy?

**To learn more about isolation, watch this video about one family's journey through isolation:* ***http://bit.ly/SCIDisolation.***

# Resources - Immune Deficiency Foundation

The Immune Deficiency Foundation (IDF), founded in 1980, is the national non-profit patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases (PI) through advocacy, education and research. IDF has a wealth of resources and groundbreaking information developed by a legion of dedicated professionals – healthcare, insurance, education and lifestyle advocates. Because of the generosity of donors and sponsors, most IDF services and resources are provided at no cost. For complete information on all IDF has to offer, please visit **www.primaryimmune.org**, or call **800-296-4433**.

***IDF Website – Information Gateway for the PI Community***

Features the latest information about diagnosis, treatment, programs, services and much more. Create an account to receive the latest updates: **www.primaryimmune.org/my-account**.

***Education Meetings – Local & National Educational Meetings for all Ages***

Education meetings, retreats and conferences held across the country. For regularly updated information on all events, visit **www.primaryimmune.org/events-calendar**.

***Educational Publications – Heralded as Best Patient Resources for PI in the World***

IDF publications developed by world renowned immunologists and healthcare professionals. To download or order copies, visit **www.primaryimmune.org/idf-publications**.

***Ask IDF – Individualized Assistance for all Living with PI***

IDF offers help with the unique aspects of living with PI. Individuals and caregivers can use Ask IDF to answer their questions, receive peer support, help them locate a specialist in their area and assist them with insurance issues. Go to: **www.primaryimmune.org/ask-idf**.

***Join the PI Community – Learn and Share with Others***

- **IDF Friends**, **www.idffriends.org**, is an exclusive community page for people living with PI.
- **IDF Get Connected Groups** – Individuals and families can meet others living with PI in their local area. To find an upcoming group in your area, visit **www.primaryimmune.org/events-calendar**. No groups in your area? Contact IDF to learn about starting your own group: **volunteer@primaryimmune.org.**
- **IDF Advocacy Center** - Monitor public policy issues that are critical to patients at national and state levels. Learn more at **www.primaryimmune.org/idf-advocacy-center**.

***United States Immunodeficiency Network (USIDNET)* – Patient Registry and Research Consortium***

USIDNET, a program of the Immune Deficiency Foundation (IDF) funded in part by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH), is a research consortium established to advance scientific research in the field of PI. The current focus of this initiative is on the patient-consented registry, and education and mentoring for young investigators. Learn more at: **www.usidnet.org**.

***Valuable Tools – Improving Health, Powering Research***

IDF ePHR, **www.idfephr.org,** is the electronic personal health record for people with PI to track their health and the opportunity to consent into PI CONNECT, the IDF Patient-Powered Research Network, **www.idfpiconnect.org**, which transforms research by bringing together patient data with clinical data in USIDNET.

** The United States Immunodeficiency Network (USIDNET) is funded by a cooperative agreement, U24AI086037, from the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH), awarded to the Immune Deficiency Foundation (IDF). NIAID supports basic and applied research to better understand, treat and ultimately prevent infectious, immunologic, and allergic diseases*

# Resources - Other Organizations and Programs

### *FILL – Following Infants with Low Lymphocytes*

www.usidnet.org/fill

FILL (Following Infants with Low Lymphocytes) is a program of the Clinical Immunology Society (CIS) and the United States Immunodeficiency Network* (USIDNET) sponsored by the Jeffrey Modell Foundation. Infants with low lymphocytes are being identified, often by newborn screening for Severe Combined Immune Deficiency (SCID). This research study will track their diagnoses and outcomes. For more information about how to include your child's information in the FILL program, contact USIDNET: contact@USIDNET.org.

### *International Patient Organization for Primary Immunodeficiencies*

www.ipopi.org

International Patient Organization for Primary Immunodeficiencies (IPOPI) is an international organization whose members are national patient organizations for primary immunodeficiencies. The website provides general information on primary immunodeficiency disease and resource contacts for patients and professionals worldwide.

### *National Institutes of Health: National Heart, Lung and Blood Institute*

www.nhlbi.nih.gov

The National Heart, Lung and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lung, and blood; blood resources; and sleep disorders.

### *National Institutes of Health: Laboratory of Immunology and Microbiology*

www.niaid.nih.gov/research/lab-clinical-immunology-and-microbiology

The research program of includes both clinical trials and basic bench research. The gene therapy program has a particular focus at the bench and in the clinic on development of gene transfer treatments for X-linked chronic granulomatous disease (CGD) and X-linked severe combined immune deficiency (X-SCID).

### *National Organization for Rare Disorders*

www.rarediseases.org 800-999-NORD

The National Organization for Rare Disorders (NORD) is a non-profit organization which provides information, programs and services for thousands of rare medical conditions, including primary immunodeficiencies.

### *Primary Immune Deficiency Treatment Consortium*

www.rarediseasesnetwork.org/cms/pidtc/

The Primary Immune Deficiency Treatment Consortium (PIDTC) consists of 45 centers in North America whose shared goal is to improve the outcome of patients with rare, life threatening, inherited disorders of the immune system. Basic scientists, immunologists, and transplant physicians from the participating centers have contributed much of the current knowledge of the cause and treatments of PID. The immediate focus of the consortium is to concentrate on severe immune disorders which can be cured by hematopoietic stem cell transplantation, enzyme replacement, and/or gene therapy by bringing together physician/scientists who evaluate and care for the majority of children with PID in North America. Helpful resources from PIDTC:

- What is a Blood and Marrow Transplantation (also known as a stem cell transplant)? www.rarediseasesnetwork.org/cms/pidtc/Learn-More/Therapies/BMT
- What are the complications of a Blood and Marrow Transplantation? www.rarediseasesnetwork.org/cms/pidtc/Learn-More/Therapies/BMT
- What is gene therapy? www.rarediseasesnetwork.org/cms/pidtc/Learn-More/Therapies/Gene-Therapy
- What is PEG-ADA enzyme replacement? www.rarediseasesnetwork.org/cms/pidtc/Learn-More/Therapies/PEG-ADA

### *SCID, Angels for Life Foundation*

www.SCIDAngelsforlife.com

The SCID, Angels for Life Foundation offers emotional support to affected families while also providing limited financial assistance to families currently going through treatment for Severe Combined Immune Deficiency (SCID).

### *The SCID Group*

www.scid.net

The SCID Group is designed to help families dealing with Severe Combined Immune Deficiency (SCID) find a support network of similar families. Go to www.scid.net, and select the "SCID Email Listserv Support Group" to sign up.

### *The Jeffrey Modell Foundation*

www.jmfworld.org

The Jeffrey Modell Foundation is dedicated to early and precise diagnosis, meaningful treatments, and ultimately cures of primary immunodeficiencies.

### *Wiskott-Aldrich Foundation*

www.wiskott.org

This site provides information about Wiskott-Aldrich Syndrome (WAS). The links on this site include information for patients and families, the latest research related to WAS and financial support.

### *Articles / Websites*

American Psychological Association: "When your child is diagnosed with chronic illness: how to cope"
www.apa.org/helpcenter/chronic-illness-child.aspx

American Academy of Child and Adolescent Psychiatry: "Helping children cope with chronic illness"
www.aacap.org/aacap/medical_students_and_residents/mentorship_matters/developmentor/Helping_Children_Cope_with_Chronic_Illness.aspx

Centers for Disease Control and Prevention: "Child Development Section" www.cdc.gov/ncbddd/childdevelopment/index.html

SCID compass

An educational program of the
Immune Deficiency Foundation