



A Review on Types and Treatment Strategies of Severe Combined Immunodeficiency

Bhavani Dhomakonda ¹, Vankodoth Sireesha ^{1*}, Boddu Shirisha ¹, Gadila Sushma ¹, Mekala Sai Charitha ¹, T. Rama Rao ²

1. Department of Pharm D, CMR College of Pharmacy, Hyderabad, India.

2. Principal, Department of Pharmaceutical Sciences, CMR college of Pharmacy, Hyderabad, India.

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Abstract



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*Address for Correspondence:

V. Sireesha, Assistant Professor, CMR College of Pharmacy, Medchal, Hyderabad, India.

Severe Combined Immunodeficiency (SCID) is a rare and life-threatening congenital disorder affecting the immune system's functionality due to mutations in crucial genes involved in immune cell development. This review provides a comprehensive overview of SCID, covering its genetic basis, immune system components, clinical manifestations, diagnostic methods, and treatment strategies. The review emphasizes the importance of early detection through newborn screening, enabling prompt treatment and enhancing survival rates for individuals with SCID. SCID can be classified as Typical, Atypical which also includes Omenn Syndrome, atypical/leaky, variant. Gene mutations with various severe infections, diarrhea, lack of T cells, reduction in naive T cells, increase in T cells and absence of proliferative responses to mitogens, or T cells with a maternal ancestry are all characteristics of typical SCID. About a dozen genes, which together make up the rare genetic condition SCID, are chiefly responsible for its X-linked or autosomal recessive inheritance. Due to infrequent incidences, early detection and treatment may go unnoticed. CD3+ > 300 cells/L and a diminished, but discernible, proliferative response to PHA (>10-30% of the control) are characteristics of atypical SCID. Other names for it include "leaky SCID". When there is no known gene issue and there are still 300-1500 T cells per liter with reduced function, variant SCID is diagnosed. The treatment options available to treat SCID are bone marrow transplantation also known as hematopoietic stem cell transplant (HSCT), gene therapy, enzyme replacement therapy, gamma globulins etc. The most widely used treatment with a high success rate is bone marrow transplantation (BMT), which can enable the body to once again create those vital infection-fighting cells. Blood cell production occurs in the bone marrow. Most SCID children pass away before they are two without a BMT.

Keywords: Bubble boy disease, gene therapy, hematopoietic stem cell transplantation (HSCT), bone marrow transplantation (BMT), Enzyme replacement therapy (ERT).

Introduction:

Severe combined immunodeficiency disease (SCID) is one of the most serious primary immunodeficiency disorders, which is a group of rare disorders caused by mutations in different genes involved in the development and function of infection-fighting immune cells. The immune system begins its formation within the bone marrow. Stem cells possess the ability to transform into three distinct types of blood cells: red blood cells, white blood cells, and platelets. White blood cells play a critical role in defending the body against infections and foreign substances. Within the white blood cells, there exist different types, including lymphocytes. Lymphocytes are primarily categorized into two main groups: B-cells and T-cells. These cells play a fundamental role in combating infections, with T-cells identifying, attacking, and eliminating intruders, while B-cells produce antibodies that retain the memory of an infection and stand prepared in case the body encounters it again.¹ This disorder impacts both the

adaptive and innate immune system, often leading to life threatening complications within the initial two years of life. Inheritance follows an autosomal recessive pattern, where both copies of a specific gene, acquired from the mother and father, carry defects.

SCID, referred to as "bubble boy disease," this term originates from the widely known instance of David Vetter, born in 1971 with SCID X1. He spent a significant portion of his life in an enclosed plastic bubble, waiting for a bone marrow transplant. Sadly, he passed away at the age of 12 after undergoing the transplant.

According to a research study utilizing data from newborn screening across 11 U.S. states, the incidence of SCID was determined to be approximately 1 in 58,000 live births, with a confidence interval of 1 in 46,000 to 1 in 80,000. Previous estimations had placed the incidence of SCID at about 1 in 100,000 births. However, recent assessments based on newborn screening indicate a higher incidence, potentially reaching 1 in

58,000 live births, although these numbers can fluctuate based on the ethnic composition of the population being studied.²

SCID arises primarily from genetic mutations, constituting a range of genetically diverse conditions that share a common clinical feature: a high susceptibility to severe infections. The severe malfunction of T cells can hinder the normal functioning of B cells, crucial for antibody production, as B cells rely

on signals from T cells. While the number of reported genetic defects linked to SCID can vary, researchers suggest around 12 to 15 distinct gene defects could underlie the typical forms of SCID. As a result, some cases of SCID may manifest primarily with T cell dysfunction. Natural killer (NK) cells, which mature independently from T and B cells, offer a level of protection in individuals with compromised T and B cell function. Evaluating the presence of NK cells is essential for gauging the severity and prognosis of SCID.³

Table 1: Immunological Comparison of a Functional Immune System and Severe Combined Immunodeficiency (SCID)

Normal Immune System	Severe Combined Immunodeficiency
↓	↓
cells & B cells present	No functional T cells or B cells
↓	↓
Can fight infections	Cannot fight infections
↓	↓
↓ Healthy immune response	↓ Decreased immune response
↓	↓
↓ Normal infection resistance	↑ High risk of severe infections

SCID often becomes evident in a child's first year with recurring and severe infections unresponsive to typical treatments. Babies displaying Infections persisting despite two months of antibiotics, Infections needing IV antibiotics, Chronic ear infections (eight or more), Persistent mouth or throat thrush, Frequent pneumonia or bronchitis should be evaluated for SCID or related immunodeficiencies.⁴

SCID can lead to severe, life-threatening infections by various pathogens, multi organ failure, opportunistic malignancies, and a range of critical health issues, including respiratory, cardiac, and renal problems, sometimes resulting in premature death. Metabolic imbalances and neurological complications like seizures are also possible.⁵ The SCID newborn screening, pioneered at NIH, assesses T-cell receptor excision circles (TRECs), which are indicative of T-cell development. SCID infants, lacking T cells, will often show a deficiency of TRECs, suggesting SCID. To confirm SCID, doctors analyze T and B cell quantities, types, and their functional capacity. Research, funded by organizations like NIAID, highlights that early SCID diagnosis through newborn screening results in rapid treatment and improved survival rates.⁵ In treating SCID infants, the approach involves not only curative methods but also practical strategies to reduce infection-related mortality.

Types of SCID:

SCID is classified into two types: Typical SCID, Atypical/leaky SCID.

A. Typical SCID: -

The European Society for Immunodeficiencies (ESID) claims that patients with typical SCID have one or more of the following characteristics: (a) mutation(s) in a gene associated with a typical SCID phenotype; or (b) presentation with severe or opportunistic infections, persistent diarrhea, and failure to thrive, in the presence of low (300/L) or absent CD3+ or CD4+ or CD8+ T cells, reduced naïve CD4+ (CD3+CD4+CD45RA+) and/or CD8+.

X-linked SCID, adenosine deaminase deficiency SCID, RAG-1/RAG-2 deficiency, and IL7R are among the most prevalent kinds of typical SCID.⁶

a) X linked SCID:

A genetic immune system condition known as X-linked SCID nearly exclusively affects men. Because they lack the immune cells required to defend themselves against certain bacteria, viruses, and fungi, children with X-linked SCID are more likely to have recurring and chronic illnesses.

Infants with X-linked SCID may experience poor development, persistent diarrhea, thrush, skin rashes, and potentially fatal infections if their condition is left untreated. Newborn screening can quickly identify X-linked SCID, allowing for effective therapy.⁷

Due to recurring infections by opportunistic bacteria, the majority of newborns with the condition pass away within a year. Cellular signaling has been shown to have several faults. A receptor -chain, which is a component of the IL-2 high-affinity receptor and several other IL receptors (IL-2, IL-4, IL-7, IL-9, and IL-15), cannot be

synthesized in individuals with X-linked SCID. The activation of these receptors is essential for the production of various antibodies, TCR rearrangements, and the generation of natural killer (NK) cells. The most prevalent kind of immunodeficiency, X-linked SCID, affects 1 in 50,000–100,000 newborns. Variants in more than 20 different genes have been linked to this category of illnesses. One in 60,000 infants have SCID out of which 25% to 30% are thought to be X-linked SCIDs.⁸

Typical X linked SCID:

Most boys with typical X-SCID need medical attention between the ages of three and six months before universal newborn screening (NBS) for SCID due to recurrent infections, chronic illnesses, and infections with opportunistic organisms.

b) Adenosine Deaminase Deficiency or ADA SCID:

One of the more frequent causes of autosomal recessive SCID, ADA deficiency results from mutations in the ADA gene and accounts for roughly 10-15% of cases in outbred populations. ADA is a key enzyme of the purine salvage pathways. The hazardous metabolites adenosine, 2 deoxyadenosine, and deoxyadenosine triphosphate (dATP) build up when ADA function is absent or compromised. The hallmark of ADA-deficient SCID is severe lymphocytopenia affecting T- and B-lymphocytes as well as NK cells, but due to the enzyme's widespread presence, other symptoms such as skeletal abnormalities, sensorineural hearing loss, and deficits in neurodevelopment are also seen. In Europe, the prevalence of ADA deficiency is thought to range from 1: 375,000 to 1: 660,000 live births.⁹

c) Recombination activating genes (RAG-1 or RAG-2) SCID:

Rare hereditary T-B- severe combined immunodeficiency condition caused by null mutations in recombination activating gene (RAG) 1 and/or RAG2 with less than 1% of wild type V(D)J recombination activity is known as severe combined immunodeficiency due to total RAG1/2 deficiency. Patients appear with skin rashes, persistent diarrhea, failure to thrive, fever, and life-threatening, severe, recurrent infections caused by opportunistic fungal, viral, and bacterial microorganisms. Significant T- and B-cell lymphopenia, normal NK counts, low or absent serum immunoglobulin levels, and in some cases, eosinophilia is among the immunologic findings.

The form of T-B-NK+ SCID that is autosomal recessive is brought on by RAG1 or RAG2 deficiency. It represents about 4% of all SCID cases. Through a process known as V(D)J recombination, the tremendous diversity of distinct immunoglobulins, B cell receptors, and T cell receptors is produced. A wide variety of distinct antigen receptors are created by the random somatic recombination of genetic segments. The TCR and immunoglobulin heavy and light chain loci's DNA are cleaved by the RAG1 and RAG2 proteins to start V(D)J recombination. RAG1 or RAG2 mutations disrupt V(D)J recombination, which in turn affects the pre-TCR and

pre-BCR expression, a crucial step in the formation of T cells and B cells. Patients display a T-B-NK+ phenotype as a result. RAG1 and RAG2 mutant patients don't have more radio sensitivity.¹⁰

d) Interleukin 7r deficiency SCID:

Interleukin 7 receptor (IL7R) alpha chain deficiency is an autosomal recessive disorder that is caused by an IL7R gene mutation, and is the fourth most prevalent form of SCID. In this particular form of SCID, the faulty gene hinders the formation of the IL7 receptor chain, which obstructs the signaling necessary for T cell growth. Natural killer (NK) cell and B cell lineage development are not affected by this deficiency, which leads to normal to elevated levels of B lymphocytes and normal NK cell counts. This defect abnormally prevents T cell formation in the thymus.^{11,12}

B. Atypical SCID: -

CD3+ > 300 cells/L and a diminished, but discernible, proliferative response to PHA (>10-30% of the control) are characteristics of atypical SCID. Other names for it include "leaky SCID". When there is no known gene abnormality and there are still 300–1500 T cells per liter with reduced function, variant SCID is identified.⁶

a) Atypical X-SCID:

It can show up early in life or later with one of the following symptoms: recurrent upper and lower respiratory tract infections with bronchiectasis; Omenn syndrome, an immune dysregulation-related clinical phenotype; X-SCID combined immunodeficiency (often accompanied by recurrent infections, warts, and dermatitis); immune dysregulation and autoimmunity; or Epstein-Barr virus-related lymphoproliferative complications.⁷

b) CD3 complex component deficiency SCID:

Lack of the CD3 chain SCID also includes CD3D, CD3E, and CD247, often referred to as CD3Z. The mutations in the genes that encode three of the distinct protein chains that make up a component of the molecules on the surface of T cells are what cause these kinds of SCID. The T cell receptor complex, or CD3, is the name given to these molecules on the surface of T cells. T lymphocytes are harmed as a result of CD3 chain lack.¹³

c) CD45 deficiency SCID:

Another kind of SCID is brought on by mutations in the gene that produces CD45, a white blood cell surface protein required for T cell activity. The CD45 gene, which has 34 exons, is located on 1q31.3-q32.¹⁴ All hematopoietic cells and their progenitors express CD45, a type 1 glycoprotein, while RBCs and platelets do not. Tyrosine phosphatase CD45 is necessary for lymphocyte signaling⁴⁵. The encoded protein is crucial for controlling the kinases required for T and B cell antigen receptor signaling. The T-B + NK + SCID phenotype is caused by mutations in the CD45 gene and has an autosomal recessive inheritance pattern.¹⁵

d) Reticular dysgenesis:

Approximately 1-3% of SCID sufferers have reticular dysgenesis (RD), a rare autosomal recessive condition. Early in the process of hematopoiesis, the condition impairs stem cell development, which causes a variety of abnormalities in the T, B, NK, and other hematopoietic lineages. Low levels of leukocytes in blood smears from RD patients point to the presence of a remnant population of monocytes with the potential to develop into macrophages and osteoclasts. In RD patients, there are no Langerhans cells (LCs) in the epidermis. By encouraging stem cell differentiation, GM-CSF therapy can alleviate RD, but unless a BMT/HCT is scheduled, death occurs within three months as a result of overwhelming infections.¹⁶

Most patients' cases of reticular dysgenesis have been linked to mutations in the mitochondrial gene AK2. Infants are frequently victims of fatal infections. In some cases, a bone marrow transplant has been curative.¹⁷

e) Omenn syndrome:

Omenn syndrome is an autosomal recessive type of SCID marked by hepatosplenomegaly, erythroderma, desquamation, baldness, chronic diarrhea, and failure to grow. It is linked to mutations in the RAG1/RAG2 gene, which impair the recombinase genes' active core and normally prevent the creation of the recombinase protein. As a result, there are no B cells and aberrant T cells. Leaky SCIDs with Omenn syndrome have been linked to hypomorphic mutations in the recombinase genes RAG-1 and RAG-2, which hinder but do not completely prevent the recombination of variable, diversity, and joining (VDJ) portions of TCR and Ig genes. The unique inflammatory process known as Omenn syndrome.^{18,19}

f) Cernunnos- XLF deficiency SCID:

A rare kind of combined immunodeficiency known as cernuous-XLF deficiency is characterized by microcephaly, growth retardation, and T and B cell lymphopenia. NHEJ1 (also known as Cernuous) gene mutations (2q35) are the root cause of this illness. The core protein of the non-homologous end-joining (NHEJ) pathway, Cernunnos/XLF, is affected, which has an impact on the main method of DNA double-strand break repair.²⁰

g) Coronin 1a deficiency SCID:

A highly conserved actin regulatory protein called coronin 1A is present in both yeast and humans. It is expressed in different types of cells, including the brain, and it interacts with polymerized actin. Macrophages, NK, and neural cells have been found to express coronin 1A, which has been linked to T cell homeostasis in mice and humans. A patient with two null mutations who experienced T cell lymphopenia and subpar T cell responses was the first person with a human coronin 1A deficiency to be identified.^{21,22}

h) DCLRE1C OR Artemis SCID OR SCID A:

Artemis SCID, also called SCID A and Athabaskan-type SCID, can be brought on by mutations in the DCLRE1C

gene. DCLRE1C is a nuclease involved in non-homologous end-joining and hairpins, and genetic abnormalities in this enzyme lead to T-B-negative sclerodermal immunodeficiency (SCID). These mutations can also result in SCID when V(D)J recombination is flawed. Less severe disorders like Omenn syndrome, atypical SCID, or common variable immunodeficiency (CVID) can result from hypomorphic mutations in RAG1 or RAG2. Patients with DCLRE1C mutations have been associated with inflammatory bowel disease, atypical SCID, Omenn syndrome, Hyper IgM syndrome, and recurrent infections, candidiasis, immunological dysregulation, and cancers.^{23,24}

i) DNA ligase 4 deficiency SCID:

Ligase 4 syndrome, also known as DNA ligase IV deficiency (OMIM 606593) or LIG4 syndrome (ORPHA99812), is a rare autosomal recessive illness marked by microcephaly, unusual facial traits, vulnerability to ionizing radiation, and combined immunodeficiency. Developmental delays, skeletal malformations, skin disorders, and cancer susceptibility are additional characteristics that can exist. The DNA double strand break (DSB) repair mechanism, which is also involved in the generation of T and B lymphocyte receptors, is mediated by the ubiquitous non-homologous end-joining (NHEJ) pathway, which is caused by mutations in the gene encoding LIG4, which is responsible for this disease.²⁵

j) DNA-PKcs deficiency SCID:

Lack of DNA-PKcs SCID exhibits the typical signs of the disorder, which include infections, diarrhea, and slow growth especially in children. This type of SCID is an extremely rare condition.⁶

k) Janus kinase 3 (JAK3) deficiency SCID:

A protein essential for the growth and operation of the immune system is produced by the JAK3 gene. It is a component of the JAK/STAT pathway, which controls how B cells, natural killer cells, and T cells develop. However, more than 50 JAK3 gene mutations have been found in people with SCID, which can result in life-threatening infections and recurrent infections. These mutations stop the synthesis of functional JAK3 protein, which has an impact on lymphocyte formation and proliferation.

l) LAT deficiency SCID:

Insufficient LAT SCID refers to a condition in which a child's linker for activation of T cells (also known as LAT) gene has been altered. LAT is a molecule involved in the maturation of T cells. LAT aids in the thymus's ability to produce T lymphocytes.²⁶ T-cell growth and function depend on signaling via the T-cell receptor (TCR). As shown by LAT-deficient animals, who have no peripheral T cells at all, Linker for Activation of T Cells (LAT) is a transmembrane adaptor signaling protein that is a component of the TCR complex and needed for T-cell development.²⁶

Treatment of SCID

Hematopoietic stem cell transplantation or bone marrow transplantation:

For the treatment of SCID, hematopoietic stem cell transplantation (HSCT) is a successful strategy. The degree of HLA mismatch between the patient and the best-available donor and the patient's chances of receiving a transplant vary greatly depending on SCID subtypes and other factors.

According to retrospective analysis conducted in North America by Primary Immune Deficiency Treatment Consortium [PIDTC], patients transplanted at ages >3.5 months (old) had a considerably higher chance (52%) of having an active infection at the time of transplant than patients transplanted are ages <3.5 months (young) of age (22%). The time it takes to diagnose SCID has significantly decreased because to the increasing popularity of newborn screening (NBS) via T-cell receptor excision circle (TREC) measurement, making therapy accessible at a very young age. HSCT is advantageous for RAG1/2 SCID, ADA-SCID, Artemis SCID, Wiskott-Aldrich syndrome.² The following three circumstances, even in the absence of immunosuppressive conditioning medication, are likely to result in engraftment and restoration of at least T cell immunity in this patient population: (1) in the presence of an HLA-matched related donor, (2) in the presence of engrafted maternal cells, or (3) in the absence of NK cells. There are three other sources that can be used if an HLA-matched related donor is not available: a haplo compatible relative, an unrelated adult volunteer who matches your HLA, or an unrelated banked UCB unit. When children with SCID get a haplo compatible transplant, graft resistance is considered to be mostly influenced by NK cells. However, stem cells from HLA-matched siblings easily engraft without conditioning, independent of the SCID phenotype.²⁷

Regardless of the donor's HLA compatibility, the majority of infants with SCID shouldn't need conditioning to overcome graft resistance; 50% have NK-SCID, and of the remaining children, 30% to 40% are maternally engrafted, and 20% will have a matched sibling. Engraftment without immunosuppressive medication may still be possible for the remaining kids.

In large multicenter retrospective cohorts, the overall survival rate following HCT was between 65 and 70%, whereas more recent prospective cohorts reported survival rates of 85 to 90%.²

Gene therapy:

Gene treatments for SCID have been investigated in recent years. It entails the removal of the patient's own hematological stem cells with mutations, molecular repair of the mutations, and transplantation of the functioning cells back into the patient.²⁸

The child's blood or bone marrow is drawn out, and the aberrant hematopoietic stem cells which carry the mutant gene are sent to be fixed in a lab. The gene that causes SCID is replicated in a laboratory. These copies lack the mutation and are normal genes. The normal

gene is then inserted into a virus that is highly effective at penetrating hematopoietic stem cells while being inactive and unable to transmit infection. Doctors combine the patient's hematopoietic stem cells with the virus that has the healthy gene in a lab. The normal gene becomes a permanent component of the hematopoietic stem cell once the virus invades it, and it is replicated into additional cells during cell division. Hematopoietic stem cells that have been "corrected" may now produce healthy T cells. Then, frozen storage is used to keep these corrected hematopoietic stem cells.²⁸

Before receiving the corrected hematopoietic stem cells, the child may or may not undergo conditioning treatments like chemotherapy or other immunosuppressant medications. In order for the corrected hematopoietic stem cells to have adequate space in the bone marrow to develop and divide appropriately, this is occasionally necessary. The child receives a simple IV injection of the corrected hematopoietic stem cells once they have been removed from storage. The child's body will have a new, healthy immune system with normal T cells after the corrected hematopoietic stem cells are distributed throughout it during the course of two to three months.

Artemis SCID gene therapy is now available for infants diagnosed with X-linked SCID.²

Early attempts to use gene therapy to treat X-linked SCID were effective in restoring T-cell function in children, but two to five years later, around 25% of the children got leukemia. Modern gene therapy techniques employ modified vectors that seem efficient and secure. Young adults and older children with X-linked SCID are being effectively treated by NIAID researchers utilizing a unique gene therapy strategy.²⁹

Enzyme replacement therapy:

Revcovi is an enzyme replacement therapy (ERT) medication that can be used to treat both children and adults with ADA-SCID. People with ADA-SCID are deficient in a critical immune system-supporting enzyme. Children with ADA-SCID who participate in ERT get intramuscular injections of the medication Revcovi, which contains the deficient enzyme, at least once a week. The immune system is capable of functioning due to these injections. After a few classes, parents may administer the injection to their child at home without a doctor or nurse's assistance.²

Even if a person with ADA-SCID plans to receive a more permanent therapy, such as HSCT, shortly, using ERT is a crucial interim step in their care. This is due to the fact that even brief ERT treatment can quickly lower the level of certain toxins that have accumulated in the body without the ADA enzyme. These poisons cause SCID and harm white blood cells, including T cells.²

Other therapies:

Other treatment options for SCID are gamma globulin; Transfer factor; Treatment for infections such as antibacterial treatment, anti-fungal treatment, antiparasitic drugs, anti-viral, anti-inflammatory; Irradiated blood transfusions.³⁰

Conclusion:

Severe combined immunodeficiency (SCID) is a group of rare disorders caused by mutations in different genes involved in the development and function of infection-fighting immune cells. SCID is often called “bubble boy disease.” Infants with SCID appear healthy at birth but are highly susceptible to severe infections. Most often, SCID is inherited in an autosomal recessive pattern. A genetic test called full gene sequencing can be done to confirm a diagnosis of SCID. The most common form of SCID is X-linked. It affects the interleukin (IL)-2 receptor common gamma chain (a component of at least 6 cytokine receptors) and thus causes severe disease; phenotype is T- B+ NK-. Nearly every child with SCID is treated with a stem cell transplant, also known as a bone marrow transplant. Elapegademase (Revcovi, Elapegademase-lvlr) Elapegademase a recombinant adenosine deaminase based on bovine amino acid sequence and conjugated to PEG. It is indicated for treatment of ADA severe combined immune deficiency (ADA-SCID) in pediatric and adult patients. BCG vaccine is contraindicated in patients with SCID.

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