CONDITION

Adenosine deaminase severe combined immunodeficiency

Learn how ADA-SCID affects the immune system, how it is diagnosed, and how enzyme replacement, stem cell transplant, and gene therapy may be used.

WHAT IT IS
Rare inherited severe immune deficiency

BODY SYSTEM
Immune system

MAIN SYMPTOMS
Frequent severe infections, long-lasting diarrhea, poor growth, persistent oral thrush

WHAT CAUSES IT
Inherited ADA gene variants

HOW IT IS DIAGNOSED
ADA enzyme activity and genetic testing

MAIN TREATMENT
Stem cell transplant, enzyme replacement, gene therapy

CAN IT BE CURED?
Sometimes - definitive treatments may restore immunity

IS IT AN EMERGENCY?
Sometimes - severe trouble breathing

LONG-TERM OUTLOOK
Better with early treatment, poor if untreated

Overview

Adenosine deaminase severe combined immunodeficiency, or ADA-SCID, is a rare inherited disorder that severely weakens the immune system. It is one form of severe combined immunodeficiency, a group of conditions often called SCID.

The ADA gene provides instructions for making adenosine deaminase, an enzyme that helps cells break down certain natural substances. When the enzyme is missing or has very low activity, toxic substances build up inside cells. Immune cells called lymphocytes are especially sensitive to this buildup.

Lymphocytes include T cells, B cells, and natural killer cells. T cells coordinate immune

responses and attack infected cells. B cells make antibodies. Natural killer cells help control some viral infections and abnormal cells. In classic ADA-SCID, all three groups may be severely reduced or unable to work normally.

Most people with classic ADA-SCID develop signs during infancy. Without effective immune function, common viruses, bacteria, and fungi can cause persistent or serious infections. Some ADA variants allow a small amount of enzyme activity. These forms may appear later in childhood or adulthood and may cause a less severe but still important immune deficiency.

ADA is active throughout the body, not only in immune cells. Some affected people also develop hearing, neurological, liver, lung, skeletal, or developmental problems.

Early diagnosis matters because protective care and disease-specific treatment can begin before serious infections cause lasting harm. Newborn screening for SCID has made it possible to identify many affected infants before symptoms appear.

Symptoms

A newborn with ADA-SCID may appear healthy at first. Symptoms often develop as protection from antibodies transferred during pregnancy fades and the baby encounters more infections.

Possible signs include:

Some infants have very small tonsils or lymph nodes because they have too few lymphocytes. Others develop breathing problems, liver abnormalities, bone changes, hearing loss, delayed development, or changes in muscle control. These findings vary and are not present in everyone.

People with a later-onset form may have repeated sinus, ear, or lung infections rather than overwhelming infections in infancy. They may also have persistent viral infections, chronic lung problems, autoimmune disease, or a low lymphocyte count found during unrelated testing.

These symptoms can have many causes and do not by themselves establish ADA-SCID. However, repeated unusual infections, persistent thrush, chronic diarrhea, or poor growth in an infant should be evaluated promptly.

For a child with known or suspected SCID, contact the specialist team urgently about fever, a new cough, vomiting, diarrhea, unusual sleepiness, or possible exposure to an infection. Seek emergency care for severe trouble breathing, blue or gray skin, inability to wake, a seizure, or signs of severe dehydration.

- Frequent, severe, persistent, or unusual infections
- Pneumonia or repeated chest infections

- Long-lasting diarrhea
- Poor weight gain or slowed growth
- Persistent oral thrush, which causes white patches from a yeast infection
- Skin infections or widespread rashes
- Fevers that keep returning
- Infections that do not improve as expected with standard treatment

Causes and risk factors

ADA-SCID is caused by harmful changes, called pathogenic variants, in both copies of the ADA gene. It follows an autosomal recessive inheritance pattern.

A person usually has two copies of each gene, one inherited from each biological parent. Parents of a child with ADA-SCID usually carry one altered ADA copy and one working copy. Carriers generally do not have SCID.

When both parents carry an ADA variant, each pregnancy has:

These chances apply separately to each pregnancy. They may differ in unusual genetic situations, so a genetics professional can explain a family's specific results.

ADA-SCID is not caused by an infection, diet, medication, or anything a parent did during pregnancy. Having an affected relative increases the chance that someone carries an ADA variant. Parents who are biologically related are also more likely to carry the same rare recessive variant, although many affected children are born to unrelated parents with no known family history.

- A 25% chance of a child inheriting both altered copies and having ADA deficiency
- A 50% chance of a child being an unaffected carrier
- A 25% chance of a child inheriting neither altered copy

Diagnosis

In many places, newborn screening checks for low numbers of newly formed T cells by measuring T-cell receptor excision circles, known as TRECs. A low TREC result does not diagnose ADA-SCID. It signals that the baby needs urgent testing for SCID and other causes of low T cells.

Newborn screening may not identify every person with a partial or later-onset ADA deficiency. Symptoms, family history, and laboratory findings remain important.

Diagnostic testing may include:

Doctors also assess for active infections and check organ function before choosing treatment. Testing may include viral studies, cultures, chest imaging, hearing assessment, and liver, kidney, or lung evaluations.

A blood transfusion can affect some enzyme and immune test results because donor blood cells contain ADA. The laboratory and immunology team should know about any prior transfusions.

If ADA-SCID is confirmed, siblings may need prompt testing even if they appear well. Genetic counseling can help relatives understand carrier testing and reproductive options.

- A complete blood count and measurement of the absolute lymphocyte count
- Flow cytometry, which counts T cells, B cells, and natural killer cells
- Tests of how well lymphocytes respond to stimulation
- Measurement of ADA enzyme activity
- Measurement of toxic adenosine-related metabolites
- Genetic testing for variants in the ADA gene

Treatment and management

ADA-SCID should be managed by a center experienced in severe immune deficiencies, stem cell transplantation, and gene therapy. Treatment decisions depend on age, infections, organ health, donor availability, previous treatment, and access to specialized services.

While definitive treatment is being planned, the care team works to prevent and control infections. Management may include antimicrobial medicines, antibody replacement with immunoglobulin, nutritional support, and reduced exposure to infectious illnesses.

Live vaccines are generally avoided until an immune specialist confirms that immune recovery is adequate. Examples include rotavirus and the measles, mumps, and rubella vaccine. Inactivated vaccines cannot cause the infection, but they may not produce reliable protection before immune recovery. The specialist team should provide an individual vaccine plan.

If blood products are needed, special handling such as irradiation and screening for cytomegalovirus may be required. Families should tell emergency and hospital staff that the patient has or may have SCID.

The main disease-specific treatment approaches are described below.

Hematopoietic stem cell transplantation

A hematopoietic stem cell transplant replaces the blood-forming system with healthy donor stem cells. It is also called a bone marrow or blood stem cell transplant. The goal is to establish donor cells that can produce working immune cells.

A well-matched family donor may provide favorable results, but other donor sources can be considered. The team weighs the urgency of treatment against donor match, infection status, and transplant risks. Some patients receive conditioning chemotherapy to help donor cells establish themselves.

Important transplant risks include serious infection, organ injury, infertility, failure of the transplanted cells to grow, and graft-versus-host disease. Graft-versus-host disease occurs when donor immune cells attack the recipient's tissues.

ADA enzyme replacement

Enzyme replacement supplies a modified form of the missing ADA enzyme. In the United States, elapegademase-lvlr is an approved enzyme replacement for ADA-SCID.

Enzyme replacement can lower toxic metabolites and improve lymphocyte numbers. It may be used as a bridge while transplant or gene therapy is arranged. It may also be considered when another definitive treatment is not available or appropriate.

The response can be incomplete or decrease over time, so regular immune and metabolic testing is necessary. Enzyme replacement does not correct the underlying gene variant.

Gene therapy

Gene therapy uses the patient's own blood-forming stem cells. The cells are collected, modified in a laboratory to carry a working ADA gene, and returned after conditioning treatment. Because the cells come from the patient, graft-versus-host disease is not expected.

An ADA-SCID gene therapy has regulatory authorization in the European Union, and lentiviral gene therapy has produced encouraging results in clinical studies. Availability and approval status differ by country and treatment center.

Gene therapy still has risks, including those related to stem cell collection, conditioning, infection, and unintended effects of inserting genetic material into cells. Long-term monitoring is required.

Complications

The main complications of untreated or poorly controlled ADA-SCID are persistent infections, organ damage, and poor growth. Lung infections may lead to chronic breathing problems. Severe diarrhea can cause dehydration and malnutrition.

Some infections that are mild in people with healthy immune systems can become serious in someone with SCID. Cytomegalovirus, respiratory viruses, chickenpox, and certain fungal infections are particular concerns.

ADA deficiency may also affect hearing, development, behavior, movement, bones, liver function, and lung tissue. Restoring immune function does not always reverse damage that occurred before treatment.

Treatment can also cause complications. Stem cell transplant and gene therapy may require chemotherapy, which can temporarily lower blood counts and affect organs or fertility. Transplant can cause graft-versus-host disease. Enzyme replacement may not provide complete or lasting immune recovery. These risks are why treatment and long-term monitoring take place through specialized teams.

Follow up

Follow-up continues even after immune function improves. The schedule is more frequent during enzyme replacement, after transplant, or after gene therapy and may become less frequent once health is stable.

Monitoring commonly includes blood counts, lymphocyte numbers, immune-cell function, antibody levels, ADA activity, and toxic metabolite levels. Doctors also watch for infections, autoimmune problems, treatment effects, and changes in kidney or liver function.

Immunoglobulin replacement and preventive antimicrobial medicines may continue until testing shows that the immune system can provide adequate protection. Vaccines are restarted only under specialist guidance. The team may check vaccine responses with antibody testing.

Routine follow-up may also include assessment of growth, nutrition, hearing, development, school progress, lung health, and emotional well-being. People who received gene therapy or a stem cell transplant may need lifelong monitoring for delayed treatment effects.

Families should keep an emergency plan and current medication list. New healthcare professionals should be told about the immune deficiency, previous treatments, and any special blood-product requirements.

A genetics professional can discuss testing for relatives and options for future pregnancies. If a family has a known ADA variant, prenatal testing or testing of a newborn sibling can often be

arranged quickly.

Sources

- Hershfield MS. "Adenosine Deaminase Deficiency." GeneReviews . University of Washington, Seattle. Updated March 16, 2017.
- Flinn AM, Gennery AR. "Adenosine deaminase deficiency: a review." Orphanet Journal of Rare Diseases . 2018;13:65.
- Kohn DB, Booth C, Shaw KL, et al. "Autologous ex vivo lentiviral gene therapy for adenosine deaminase deficiency." New England Journal of Medicine . 2021;384:2002-2013.
- U.S. Food and Drug Administration. Revcovi (elapegademase-lvlr) Injection: Prescribing Information . Leadiant Biosciences.
- European Medicines Agency. Strimvelis: European Public Assessment Report and Product Information . European Medicines Agency.
- American College of Medical Genetics and Genomics. Newborn Screening ACT Sheet: Severe Combined Immunodeficiency and Conditions Associated With T-Cell Lymphopenia . ACMG.
- Immune Deficiency Foundation. Patient & Family Handbook for Primary Immunodeficiency Diseases: Severe Combined Immunodeficiency and Combined Immunodeficiency . Immune Deficiency Foundation.