## ALLERGY AND IMMUNOLOGY

# Allergy & Immunology

# Definition

Allergy & immunology is a medical specialty focused on the diagnosis, treatment, and management of allergies, asthma, and immune system disorders. Allergies are abnormal immune system reactions to substances that are typically harmless to most people, while immunological disorders involve problems with the body's immune system that can lead to increased susceptibility to infections or autoimmune diseases.

# Allergist / Immunologist Defined

Allergist / immunologists, often referred to as allergists, are specialists in the diagnosis and treatment of allergies, asthma and immune deficiency disorders.

Allergists in the United States have completed medical school, at least three years of residency in pediatrics or internal medicine, then at least two years of specialized training in allergy and immunology. To be board certified, they must pass an examination given by the American Board of Allergy and Immunology. To maintain board-certification, allergists must complete a rigorous maintenance of certification process that includes continuing medical education, practice assessment/quality improvement activities, and completion of a recertification exam at specified intervals.

# Allergist

An allergist (allergist/immunologist) is a doctor who diagnoses and treats allergies, asthma and immunologic conditions. In addition to medical school and residency, allergists have two to three years of special training in allergy and immunology. Allergists can help you manage your allergies or asthma and avoid serious reactions.

An allergist can use a small amount of allergen to see if you have a reaction to grasses, trees, foods, pet dander and more.

### What is an allergist?

An allergist (allergist/immunologist) is a doctor who specializes in certain conditions that affect your immune system. Your immune system is made up of special cells, organs and tissues that fight off disease. Types of immune system disorders an allergist treats include:

* [Allergies](https://my.clevelandclinic.org/health/diseases/8610-allergy-overview) and allergic disorders. You get allergies when your immune system overreacts to something you eat, breathe in (inhale) or touch.
* [Asthma](https://my.clevelandclinic.org/health/diseases/6424-asthma). Asthma is an inflammation of the airways in your lungs. Asthma attacks are usually brought on by triggers in the environment around you.
* [Primary immunodeficiency disorders](https://my.clevelandclinic.org/health/diseases/17964-primary-immunodeficiency). These are genetic disorders that keep your immune system from working properly. There are over 200 primary immunodeficiency disorders.

#### **What is a pediatric allergist?**

A pediatric allergist diagnoses and treats allergies, asthma and immune disorders in infants, children and teens.

### What is the difference between allergist and immunologist?

“Allergist” is usually short for an allergist/immunologist who focuses on treating allergies and asthma and who may also treat immune disorders. An immunologist is also an allergist/immunologist, but usually one who specializes in treating immune disorders or medical research on the immune system.

### What does an allergist do?

An allergist diagnoses and treats problems with your immune system. An allergist can:

* [Test for allergies](https://my.clevelandclinic.org/health/diagnostics/21495-allergy-testing) to foods, pollens (grass, trees, weeds), pet dander, mold and other triggers.
* Test your lung function and diagnose asthma.
* Prescribe medications or devices to prevent, treat or reduce the severity of allergic reactions and asthma attacks.
* Recommend lifestyle changes to help avoid asthma or allergy triggers.
* Give allergy shots or other forms of immunotherapy to help reduce allergic reactions.
* Diagnose immunodeficiency disorders.
* Recommend ways to avoid infection while living with an immune disorder.
* Administer intravenous immunoglobulin (IVIG) to treat certain immune disorders.
* Perform drug desensitization so you can safely take important medications.

### What conditions does an allergist treat?

Some conditions allergists commonly treat include:

* Allergic conjunctivitis.
* [Allergic rhinitis (hay fever)](https://my.clevelandclinic.org/health/diseases/8622-allergic-rhinitis-hay-fever).
* [Anaphylaxis](https://my.clevelandclinic.org/health/diseases/8619-anaphylaxis).
* [Angioedema](https://my.clevelandclinic.org/health/diseases/22632-angioedema).
* Asthma.
* [Drug allergies](https://my.clevelandclinic.org/health/diseases/8621-medication-allergies).
* [Eczema](https://my.clevelandclinic.org/health/diseases/9998-eczema).
* [Eosinophilic disorders](https://my.clevelandclinic.org/health/diseases/17710-eosinophilia).
* [Food allergies](https://my.clevelandclinic.org/health/diseases/9196-food-allergies).
* [Hives (urticaria)](https://my.clevelandclinic.org/health/diseases/8630-urticaria-hives-and-angioedema).
* Insect sting allergies.
* [Latex allergies](https://my.clevelandclinic.org/health/diseases/8623-latex-allergy).
* [Sinus infections](https://my.clevelandclinic.org/health/diseases/17701-sinusitis).

### Why do people see an allergist?

You might see an allergist to:

* Get tested for allergies or asthma.
* Receive treatment for allergies or asthma.
* Manage an immune system disorder.

### When should you see an allergist?

You should see an allergist, or ask your primary care physician if they recommend seeing an allergist, if:

* You have severe allergic reactions that include hives, face or tongue swelling or trouble breathing.
* You have allergies but need to find out what’s triggering them.
* You have allergies or asthma that you don’t feel are well controlled, even with medication or lifestyle changes.
* Allergies or asthma affect your quality of life or keep you from work or activities you enjoy.
* You wheeze, cough or feel short of breath frequently, especially after exercise or at night.
* You’re often sick or it takes you a long time to get over colds or other routine illnesses.

### How does an allergist test for allergies?

Depending on what kind of allergy they’re looking for, an allergist might use one or more types of tests, including:

* Skin prick/scratch tests. Skin prick tests use a small amount of allergen on an applicator. Your allergist scratches your skin lightly with the applicator and waits to see if it causes a reaction.
* [Blood tests](https://my.clevelandclinic.org/health/treatments/22345-allergy-blood-test). A lab tests a sample of your blood to see if you have signs of allergies to specific substances.
* Food challenge tests. During a food challenge test, your allergist gives you increasing amounts of a food that you might be allergic to. They monitor you for an allergic reaction.

In addition to allergy testing, your allergist appointment may also include:

* Lung function testing (spirometry, pulmonary function testing). This is a test to measure your lung function. It helps in the diagnosis and management of asthma.
* Instructions on how to use medical devices. Your provider might prescribe and demonstrate the use of epinephrine injectors for severe allergic reactions or inhalers and nebulizers for asthma.

### A note

Allergies, asthma and immune conditions can affect your daily life and cause serious reactions. An allergist can help you identify allergy or asthma triggers, prescribe treatments to help your symptoms and suggest lifestyle changes to avoid triggers. They can help you understand and manage your condition so it doesn’t disrupt your life.

**REFERENCES**

## <https://www.yalemedicine.org/clinical-keywords/allergy-&-immunology>

https://my.clevelandclinic.org/health/articles/24053-allergist

https://www.aaaai.org/tools-for-the-public/allergy,-asthma-immunology-glossary/allergist-immunologist-defined

## 

## Allergic Disorders and Hypersensitivity Reactions

## Type I Hypersensitivity (IgE-mediated Allergy / Atopic Disorders):

## Allergic rhinitis (hay fever)

## Atopic dermatitis (eczema)

## Allergic conjunctivitis

## Allergic asthma

## Food allergies

## Anaphylaxis

## Urticaria (hives)

## Angioedema (some forms)

## Latex allergy

## Venom allergy (e.g., bee sting allergy)

## Allergic bronchopulmonary aspergillosis

## Type II Hypersensitivity (Antibody-mediated):

## Autoimmune hemolytic anemia

## Goodpasture syndrome

## Hashimoto thyroiditis

## Hyperacute transplant rejection

## Type III Hypersensitivity (Immune complex-mediated):

## Serum sickness

## Rheumatoid arthritis

## Cryoglobulinemia

## Hypersensitivity pneumonitis

## Leukocytoclastic vasculitis

## Type IV Hypersensitivity (T-cell mediated / Delayed):

## Contact dermatitis (e.g., poison ivy)

## Stevens-Johnson syndrome / Toxic epidermal necrolysis (SJS/TEN)

## Drug rash with eosinophilia and systemic symptoms (DRESS)

## Chronic hypersensitivity pneumonitis

## Tuberculosis immune response

## Allograft rejection

## Primary Immunodeficiency Disorders

## Common Variable Immunodeficiency (CVID)

## X-linked Agammaglobulinemia (XLA)

## Selective Immunoglobulin A Deficiency

## Severe Combined Immunodeficiency (SCID)

## Chronic Granulomatous Disease (CGD)

## Hyper IgE Syndrome

## Wiskott-Aldrich Syndrome

## Complement Deficiencies

## Other Immune-Mediated and Autoimmune Disorders

## Autoimmune thyroid diseases (Hashimoto’s thyroiditis, Graves’ disease)

## Systemic lupus erythematosus (SLE)

## Sjögren’s syndrome

## Scleroderma (systemic sclerosis)

## Polymyositis / Dermatomyositis

## Vasculitides (e.g., Wegener’s granulomatosis, Churg-Strauss syndrome, Henoch-Schönlein purpura, Kawasaki disease)

## Primary biliary cirrhosis

## Primary sclerosing cholangitis

## Pemphigus and pemphigoid

## Polyendocrine autoimmune syndromes

## Respiratory and Pulmonary Allergic/Immunologic Diseases

## Asthma (non-allergic)

## Chronic cough related to allergy

## Bronchopulmonary eosinophilia

## Allergic fungal sinusitis

## Aspergilloma

## Food and Drug Allergies

## Food intolerance

## Drug allergy and hypersensitivity reactions (including anaphylaxis)

## Other Conditions Covered Under Allergy and Immunology

## Eosinophilic disorders (e.g., eosinophilic esophagitis)

## Recurrent fetal loss related to immune causes

## Hereditary angioedema and acquired C1-inhibitor deficiency

## Immunodeficiency secondary to infections (e.g., HIV)

## Screening and management of primary immunodeficiencies

## Lymphoproliferative disorders with immune dysregulation

## Paraneoplastic autoimmune syndromes

* Multiple sclerosis
* HAE
* Guillain barre syndrome
* rheumatoid arthritis
* Grave disease
* Coeliac disease
* motor neuron
* myasthenia gravis
* Autoimmune hepatitis
* Autoimmune pancreatitis
* Autoimmune encephalitis

### Allergic Rhinitis (hay fever)

**DEFINITION AND DESCRIPTION**

Allergic rhinitis (hay fever) is an allergic reaction to tiny particles in the air called allergens. When you breathe in allergens through your nose or mouth, your body reacts by releasing a natural chemical called histamine. Despite being called hay fever, hay doesn’t cause hay fever and most people don’t get a fever.

Symptoms of hay fever include sneezing, nasal congestion and irritation of your nose, throat, mouth and eyes. Allergic rhinitis isn’t the same as infectious rhinitis, otherwise known as the common cold. Hay fever isn’t contagious. Also, not all rhinitis is allergic. Many people suffer from nonallergic rhinitis resulting in similar symptoms. Inflammation causes rhinitis, not allergens or histamine release.

#### **What triggers allergic rhinitis?**

Several indoor and outdoor allergies cause hay fever. Common hay fever triggers include:

* Pollen from trees, weeds and plants.
* Mold spores.
* Pet dander.
* Dust mites.
* Cockroach droppings and saliva.

#### **When do people usually get hay fever?**

You can have hay fever any time of the year. Seasonal allergies occur in the spring, summer and early fall when trees and weeds bloom and pollen counts are higher. But pollen seasons can vary depending on your location, as well. Perennial allergies can happen year-round. They result from irritants that are always around, such as pet dander, cockroaches and dust mites.

## Symptoms and Causes

Symptoms of hay fever (allergic rhinitis) occur when your immune system overreacts to something in your environment.

**Symptoms of allergic rhinitis (hay fever)**

Hay fever symptoms can appear throughout the year. Outdoor allergies are worse in the spring, summer and early fall depending on where you live. In warm weather, weeds and flowers bloom, and pollen counts are higher. Indoor allergies, such as those from pets and dust mites, can get worse in winter because people spend more time indoors with their windows closed.

Symptoms of hay fever include:

* Nasal stuffiness (congestion), sneezing and runny nose.
* Itchy nose, throat and eyes.
* Red or watery eyes.
* Headaches, sinus pressure and dark circles under your eyes.
* More mucus in your nose and throat.
* Tiredness.
* Sore throat from mucus dripping down your throat (postnasal drip).
* Wheezing, coughing and trouble breathing.

### How do I know if it’s hay fever or a cold?

Symptoms of a cold and hay fever are similar, but there are some differences. Itchy, red and watery eyes are common with allergies, but not as common with a cold. A cold is more likely to cause muscle aches and pain or a fever.

Another way people can tell the difference is that allergic rhinitis usually has a trigger, like seasons changing or being around a new pet. Allergies often happen at the same time each year, like in spring and late summer, and they start quickly. On the other hand, a virus causes a cold and you catch viruses from other people. So, you may know it’s a cold if you’ve been around someone with a cold. A cold tends to go away within a week, whereas allergies will stick around until the allergen is out of the air.

### Causes of hay fever (allergic rhinitis)

Allergic rhinitis occurs when your body’s immune system reacts to an irritant in the air. The irritants (allergens) are so tiny that you can easily inhale them through your nose or mouth.

Allergens are harmless to most people. But if you have hay fever, your immune system thinks the allergen is intruding. Your immune system tries to protect your body by releasing natural chemicals into your bloodstream. The main chemical is called histamine. It causes mucous membranes in your nose, eyes and throat to become inflamed and itchy as they work to eject the allergen from your body.

Allergic rhinitis comes from many allergens, including:

* Dust mites that live in carpets, drapes, bedding and furniture.
* Pollen from trees, grass and weeds.
* Pet dander (tiny flakes of dead skin cells).
* Mold spores.
* Cockroaches (their saliva and waste).

Food allergies can also cause inflammation in your nose and throat. Food allergies can be life-threatening, so get medical help right away if you’re concerned that a certain food is consistently causing allergy symptoms.

#### **Risk factors for hay fever**

Allergies are inherited, which means you’re more likely to have hay fever if you have a parent or immediate family member with allergies. People who have asthma or eczema are also more likely to develop hay fever.

## Diagnosis and Tests

Your healthcare provider will examine you, ask about your symptoms and evaluate you for other conditions, such as a cold or asthma. They can also perform allergy tests.

A blood allergy test measures antibodies to an allergen in a sample of your blood. This blood test is called an immunoglobulin E (IgE) test. It can detect most types of allergies, including food allergies.

Your provider may also recommend a skin prick and/or intradermal test to determine what allergies are causing your symptoms. In a skin prick test, your provider places a small sample of different allergens on your skin (usually on your forearm or back). They scratch or prick your skin with a needle. If you’re allergic to a specific allergen, the area will become red, itchy and irritated in 15 to 30 minutes. Intradermal testing is similar, but your allergist places the allergen underneath your skin. Your skin reacts in the same way it does for a prick test.

## Management and Treatment

Several allergy medications can improve symptoms and help you live with hay fever. These treatments come in many forms, including liquids, pills, eye drops, nasal sprays and injections. Talk to your provider before taking any medication, especially if you’re pregnant or have other health concerns.

#### **Antihistamines**

Antihistamine medications are available with a prescription or over the counter (OTC). They work by blocking the histamine that your body releases during an allergic response. Antihistamines come as pills, liquids, eye drops, nasal sprays and inhalers. They include:

* Loratadine (Claritin®).
* Cetirizine (Zyrtec®).
* Fexofenadine (Allegra®).
* Levocetirizine (Xyzal®).

Antihistamines can cause drowsiness. Avoid alcohol when taking antihistamines, especially if you’re going to drive.

#### **Decongestants**

These medications relieve congestion in your nose and sinuses. You can take decongestants by mouth (in pill or liquid form) or use a nasal spray. They include:

* Afrin® nasal spray.
* Phenylephrine nasal spray (Neo-Synephrine®).
* Pseudoephedrine (Sudafed®).

Decongestants can increase blood pressure and cause headaches, trouble sleeping and irritability. Nasal decongestants can be addictive when you use them for longer than five days.

#### **Corticosteroid nasal sprays**

These sprays and inhalers reduce inflammation and relieve symptoms of hay fever. The most common nasal sprays are Flonase®, Nasacort® and Rhinocort®. Side effects include headaches, nasal irritation, nosebleeds and cough.

#### **Leukotriene inhibitors**

During an allergic reaction, your body releases leukotrienes, histamine and other chemicals that cause inflammation and hay fever symptoms. Available only with a prescription, these pills block leukotriene. The most common leukotriene inhibitor is montelukast (Singulair®). Some people experience changes in mood, vivid dreams, involuntary muscle movements and skin rash when taking this medication.

#### **Immunotherapy**

This treatment works by helping your body learn to tolerate allergens. Your provider gives you a series of injections (allergy shots or subcutaneous immunotherapy) with a small amount of the allergen. Every time you get a shot, your provider increases the amount of the allergen. Over time, your immune system develops immunity to the allergen and stops launching a reaction to it.

In certain circumstances, your provider might recommend immunotherapy in the form of a pill that you place under your tongue called oral immunotherapy. Currently, oral immunotherapy is only available for allergies to trees, grass and dust mites (in the U.S.).

### How many days does allergic rhinitis last?

It varies. Most people find relief from hay fever within a few days with medication, but they must take it continuously until the allergen is out of the air. Some people continue to have symptoms of hay fever for several weeks or months, especially if they aren’t taking or can’t take medication to help relieve symptoms.

## Outlook / Prognosis

Hay fever can make you feel miserable, but it generally doesn’t cause serious health problems. Most people with hay fever manage symptoms with lifestyle changes and over-the-counter medication.

People with airborne allergies have a higher risk of ear infections and sinus infections. Because hay fever can make it tough to get a good night’s sleep, you may feel tired during the day. If you have asthma, hay fever can make your asthma symptoms worse.

## Prevention

There’s no way to prevent hay fever, but lifestyle changes can help you live with allergies. You can relieve hay fever symptoms by avoiding irritants as much as possible. To reduce symptoms, you should:

* Avoid touching your face and rubbing your eyes or nose.
* Close windows in your home and car during the spring, summer and early fall when pollen counts are higher.
* Put covers on pillows, mattresses and box springs to protect against dust mites.
* Keep pets off couches and beds, and close doors to bedrooms you don’t want them to enter.
* Use filters in your vacuum cleaner and air conditioner to reduce the amount of allergens in the air.
* Wash your hands often, especially after playing with pets.
* Wear a hat and sunglasses to protect your eyes from pollen when you’re outside. Change your clothes as soon as you come indoors.

## Living With

Although hay fever usually doesn’t cause any serious health problems, you should see your provider to rule out other conditions, such as asthma or a sinus infection. Seek care if hay fever symptoms are:

* Getting in the way of your daily life.
* Making it hard for you to sleep.
* Not improving with allergy medication.

Your provider can help you identify the allergens that are causing a reaction and recommend treatments to help you feel better.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for AR includes other forms of rhinitis that are not allergic. Children, particularly those under the age of 2 years, should also be assessed for congenital causes of nasal obstruction, such as choanal atresia and immunodeficiencies.

* Vasomotor rhinitis - noninflammatory rhinitis that can be triggered by a change in temperature, odors, or humidity
* Infectious rhinitis - viral or bacterial infections, most commonly seen in the pediatric population
* Cerebrospinal fluid leak - clear rhinitis refractory to treatment
* Non-allergic rhinitis with eosinophilia syndrome (NARES) - infiltration of eosinophils in nasal tissue without allergic sensitization
* Chemical rhinitis - exposure to chemicals through occupation, household chemicals, sport/leisure exposure
* Rhinitis of pregnancy and hormonally-induced rhinitis
* Drug-induced rhinitis - e.g., NSAIDs, ACE inhibitors, nasal decongestants, cocaine
* Autoimmune, granulomatous, and vasculitic rhinitis - Granulomatosis with polyangiitis, sarcoidosis, etc.
* Nasal polyposis
* Nasopharyngeal neoplasm
* Sickle cell anemia - in a young child presenting with nasal polyposis and well-controlled asthma, sweat chloride testing is the appropriate next step in management to rule out cystic fibrosis.

**EPIDEMIOLOGY**

The prevalence of allergic rhinitis based on physician diagnosis is approximately 15%; however, the prevalence is estimated to be as high as 30% based on patients with nasal symptoms. AR is known to peak in the second to fourth decades of life and then gradually decline. The incidence of AR in the pediatric population is also quite high, making it one of the most common chronic pediatric disorders. According to data from the International Study for Asthma and Allergies in Childhood, 14.6% in the 13 to 14 year age group and 8.5% in the 6 to 7 year age group display symptoms of rhinoconjunctivitis linked to allergic rhinitis. Seasonal allergic rhinitis seems to be more common in the pediatric age group, whereas chronic rhinitis is more prevalent in adults.

A systematic review from 2018 estimated that 3.6% of adults had missed work, and 36% had impaired work performance due to allergic rhinitis. Economic evaluations have shown that indirect costs associated with lost work productivity account for the majority of the cost burden for AR.

Risk factors for developing AR include a family history of atopy, male sex, a presence of allergen-specific IgE, a serum IgE greater than 100 IU/mL before age 6, and higher socioeconomic status. Studies in young children have shown a higher risk of AR in those with an early introduction to foods or formula and/or heavy exposure to cigarette smoking in the first year of life. Although many recent studies have evaluated the link between pollution and the development of AR, no significant correlation yet exists. Interestingly, there are several factors identified that may have a protective effect on the development of AR. The role of breastfeeding in the development of AR is often debated, but it is still recommended due to its many other known benefits and no associated harms. There is no evidence that pet avoidance in childhood prevents AR; however, it is hypothesized that early pet exposure may induce immune tolerance. There is a growing interest in the "farm effect" on the development of allergies, and a meta-analysis of 8 studies showed a 40% lower risk in subjects who had lived on a farm during their first year of life.

REFERENCES

[Allergic Rhinitis - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK538186/#article-17370.s8)

[Allergic Rhinitis (Hay Fever): Symptoms & Treatment](https://my.clevelandclinic.org/health/diseases/8622-allergic-rhinitis-hay-fever)

**ATOPIC DERMATITIS**

**DEFINITION AND DESCRIPTION**

Atopic dermatitis (eczema) is a condition that causes dry, itchy and inflamed skin. It's common in young children but can occur at any age. Atopic dermatitis is long lasting (chronic) and tends to flare sometimes. It can be irritating but it's not contagious.

People with atopic dermatitis are at risk of developing food allergies, hay fever and asthma.

Moisturizing regularly and following other skin care habits can relieve itching and prevent new outbreaks (flares). Treatment may also include medicated ointments or creams.

**Symptoms**

Atopic dermatitis (eczema) symptoms can appear anywhere on the body and vary widely from person to person. They may include:

* Dry, cracked skin
* Itchiness (pruritus)
* Rash on swollen skin that varies in color depending on your skin color
* Small, raised bumps, on brown or Black skin
* Oozing and crusting
* Thickened skin
* Darkening of the skin around the eyes
* Raw, sensitive skin from scratching

Atopic dermatitis often begins before age 5 and may continue into the teen and adult years. For some people, it flares and then clears up for a time, even for several years.

### When to see a doctor

Talk with a health care provider if you or your child:

* Has symptoms of atopic dermatitis
* Is so uncomfortable that the condition is affecting sleep and daily activities
* Has a skin infection — look for new streaks, pus, yellow scabs
* Has symptoms even after trying self-care steps

**Seek immediate medical attention** if you or your child has a fever and the rash looks infected.

**Causes**

In some people, atopic dermatitis is related to a gene variation that affects the skin's ability to provide protection. With a weak barrier function, the skin is less able to retain moisture and protect against bacteria, irritants, allergens and environmental factors — such as tobacco smoke.

In other people, atopic dermatitis is caused by too much of the bacteria Staphylococcus aureus on the skin. This displaces helpful bacteria and disrupts the skin's barrier function.

A weak skin barrier function might also trigger an immune system response that causes the inflamed skin and other symptoms.

Atopic dermatitis (eczema) is one of several types of dermatitis. Other common types are contact dermatitis and seborrheic dermatitis (dandruff). Dermatitis isn't contagious.

**Risk factors**

The main risk factor for atopic dermatitis is having had eczema, allergies, hay fever or asthma in the past. Having family members with these conditions also increases your risk.

## Diagnosis and Tests

A healthcare provider will diagnose atopic dermatitis after reviewing your symptoms during a physical examination. They’ll look closely at your skin. They may ask you questions about your symptoms, like when they started and what it feels like. Your provider will also review your medical history and known family medical history.

In some cases, your provider may recommend a skin biopsy. This is a test to look at a sample of your skin more closely in a lab under a microscope.

## Management and Treatment

Your healthcare provider may recommend different options to treat your atopic dermatitis symptoms. This may include:

* Identifying and avoiding triggers and allergens
* Applying an over-the-counter, fragrance-free moisturizer (cream or ointment) to your skin at least twice daily
* Using topical prescription medication as directed by your provider
* Participating in allergen immunotherapy to reduce how many allergic reactions you have
* Undergoing light therapy (phototherapy)

#### **Atopic dermatitis medications**

Two medications that your provider may prescribe to treat atopic dermatitis include:

* Topical corticosteroids
* Topical calcineurin inhibitors

Topical medications are creams or ointments that you rub on your affected skin in the same way you apply a lotion. You should use these medications as directed. They may have side effects if you overuse them.

#### **How can I manage atopic dermatitis symptoms?**

To soothe mild, itchy, dry and cracked skin from atopic dermatitis, you can:

* Use over-the-counter anti-itch creams (hydrocortisone)
* Take allergy medication (antihistamine) as directed
* Keep your skin moisturized with products that don’t contain perfumes or dyes, particularly immediately after a bath or shower
* Trim your nails or wear gloves at night to prevent itching
* Wear comfortable clothing that isn’t tight or scratchy
* Use a humidifier to prevent dry air environments
* Take an oatmeal bath (use colloidal oatmeal as directed in your bath water) to lock the moisture into your skin

### How long does it take for atopic dermatitis to go away?

The timeline varies from person to person after you start treatment. For example, you may notice itch relief shortly after applying a prescription medication to your skin. The rash may start to fade within days to weeks.

Since there isn’t a cure for atopic dermatitis, the rash generally comes back after treatment. This is why it’s important to pay attention to your triggers and make sure you’re avoiding them, if possible.

If you have any questions about what you can expect, talk to your provider.

## Outlook / Prognosis

Atopic dermatitis symptoms may come and go throughout your life. But the condition doesn’t go away completely.

You may be able to reduce your symptoms by using a moisturizer at least twice daily. Even if you’re diligent in your skincare routine, you can still experience flare-ups. That’s why it’s important to know how to manage your symptoms when they come back. Your healthcare provider can help you do this.

**Complications**

Complications of atopic dermatitis (eczema) may include:

* **Asthma and hay fever.** Many people with atopic dermatitis develop asthma and hay fever. This can happen before or after developing atopic dermatitis.
* **Food allergies.** People with atopic dermatitis often develop food allergies. One of the main symptoms of this condition is hives (urticaria).
* **Chronic itchy, scaly skin.** A skin condition called neurodermatitis (lichen simplex chronicus) starts with a patch of itchy skin. You scratch the area, which provides only temporary relief. Scratching actually makes the skin itchier because it activates the nerve fibers in your skin. Over time, you may scratch out of habit. This condition can cause the affected skin to become discolored, thick and leathery.
* **Patches of skin that's darker or lighter than the surrounding area.** This complication after the rash has healed is called post-inflammatory hyperpigmentation or hypopigmentation. It's more common in people with brown or Black skin. It might take several months for the discoloration to fade.
* **Skin infections.** Repeated scratching that breaks the skin can cause open sores and cracks. These increase the risk of infection from bacteria and viruses. These skin infections can spread and become life-threatening.
* **Irritant hand dermatitis.** This especially affects people whose hands are often wet and exposed to harsh soaps, detergents and disinfectant at work.
* **Allergic contact dermatitis.** This condition is common in people with atopic dermatitis. Allergic contact dermatitis is an itchy rash caused by touching substances you're allergic to. The color of the rash varies depending on your skin color.
* **Sleep problems.** The itchiness of atopic dermatitis can interfere with sleep.
* **Mental health conditions.** Atopic dermatitis is associated with depression and anxiety. This may be related to the constant itching and sleep problems common among people with atopic dermatitis.

**Prevention**

Developing a basic skin care routine may help prevent eczema flares. The following tips may help reduce the drying effects of bathing:

* **Moisturize your skin at least twice a day.** Creams, ointments, shea butter and lotions seal in moisture. Choose a product or products that work well for you. Ideally, the best one for you will be safe, effective, affordable and unscented.  
  Using petroleum jelly on your baby's skin may help prevent development of atopic dermatitis.
* **Take a daily bath or shower.** Use warm, rather than hot, water and limit your bath or shower to about 10 minutes.
* **Use a gentle, non soap cleanser.** Choose a cleanser that's free of dyes, alcohols and fragrance. For young children, you usually need only warm water to get them clean — no soap or bubble bath needed. Soap can be especially irritating to the skin of young children. For people of any age, deodorant soaps and antibacterial soaps can remove too much of the skin's natural oils and dry the skin. Don't scrub the skin with a washcloth or loofah.
* **Pat dry.** After bathing, gently pat the skin with a soft towel. Apply moisturizer while your skin is still damp (within three minutes).

The triggers for atopic dermatitis vary widely from person to person. Try to identify and avoid irritants that trigger your eczema. In general, avoid anything that causes an itch because scratching often triggers a flare.

Common triggers for atopic dermatitis include:

* Rough wool fabric
* Dry skin
* Skin infection
* Heat and sweat
* Stress
* Cleaning products
* Dust mites and pet dander
* Mold
* Pollen
* Smoke from tobacco
* Cold and dry air
* Fragrances
* Other irritating chemicals

Infants and children may have flares triggered by eating certain foods, such as eggs and cow's milk. Talk with your child's health care provider about identifying potential food allergies.

Once you understand what triggers your eczema, talk with your health care provider about how to manage your symptoms and prevent flares.

**DIFFERENTIAL DIAGNOSIS**

* Allergic contact dermatitis
* Lichen simplex
* Lichen planus
* Psoriasis
* Scabies
* Tinea
* Seborrheic

**EPIDEMIOLOGY**

Atopic dermatitis is seen in approximately 10% to 30% of children and 2% to 10% of adults in developed countries. This prevalence has increased two to three-fold in recent decades. Atopic dermatitis has a higher incidence at higher latitudes, which may be related to decreased sun exposure and lower humidity levels. Atopic dermatitis is divided into three subsets based on the age of onset:

1. Early-onset atopic dermatitis (birth to 2 years old): most common type of atopic dermatitis, with approximately 60% of cases starting by age 1. Sixty percent of cases resolve by 12 years old
2. Late-onset atopic dermatitis: symptoms begin after the onset of puberty
3. Senile onset atopic dermatitis: an unusual subset with onset in patients older than 60 years old.

**RECOMMENDATION**

Strong recommendations were made for the use of the following:

* Moisturizers help to relieve patients' dry, cracked skin, decrease inflammation, and reduce the severity of and increase the time between flare-ups.
* Topical calcineurin inhibitors (pimecrolimus 1% cream and tacrolimus 0.03% or 0.1% ointment) reduce patients' inflammation and itching, as well as decrease their flare-ups.
* Topical corticosteroids are commonly used as the first-line treatment for patients with atopic dermatitis in all skin regions. They help to relieve itching, decrease inflammation, and can decrease infections.
* Phosphodiesterase-4 inhibitor (crisaborole ointment) can reduce patients' inflammation, help relieve itching, and decrease infections.
* Janus kinase inhibitor (ruxolitinib cream) can be used short term to ease the inflammation and itching of patients with mild to moderate atopic dermatitis.
* The guidelines provide conditional recommendations for the use of bathing and wet wrap therapy. Conditional recommendations apply to most patients, but the most appropriate action may differ depending on individual patient factors.
* Bathing, followed by moisturization, helps patients hydrate the skin. Bleach baths can help patients prevent infection and get rid of bacteria on their skin.
* Wet wrap therapy utilizes wet bandages to help hydrate and soothe patients' skin. This treatment provides a barrier against scratching, helps to decrease redness and inflammation, and can reduce the bacteria on patients' skin.

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### [AMERICAN ACADEMY OF DERMATOLOGY ISSUES UPDATED GUIDELINES FOR THE MANAGEMENT OF ATOPIC DERMATITIS IN ADULTS WITH TOPICAL THERAPIES](https://www.prnewswire.com/news-releases/american-academy-of-dermatology-issues-updated-guidelines-for-the-management-of-atopic-dermatitis-in-adults-with-topical-therapies-301720824.html)

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### Allergic conjunctivitis

**DEFINITION AND DESCRIPTION**

Allergic conjunctivitis is a type of pink eye that occurs when allergy-causing foreign substances (allergens) cause inflammation in your conjunctiva. The conjunctiva is a thin membrane that lines your eyelids and helps protect the whites of your eyes (sclera) and keep them moist.

In many people, the foreign substances are harmless. But if you have allergies, your immune system views them as harmful “invaders,” like bacteria or viruses. It then reacts to remove them from your body, causing allergic conjunctivitis symptoms.

Allergic conjunctivitis usually affects both eyes.

#### **Types of allergic conjunctivitis**

The two most common types of allergic conjunctivitis include:

* Seasonal allergic conjunctivitis (hay fever conjunctivitis). Seasonal allergic conjunctivitis typically occurs during the spring, summer and fall, when trees, grasses and weeds produce lots of pollen. Another name for seasonal allergic conjunctivitis is acute allergic conjunctivitis. “Acute” means it develops suddenly. This is the most common type of allergy.
* Perennial allergic conjunctivitis (year-round allergic conjunctivitis). Perennial allergic conjunctivitis may occur throughout the year. Common causes include pet dander and dust mites. Another name for perennial allergic conjunctivitis is chronic allergic conjunctivitis. “Chronic” means it continues or reoccurs often over a long time.

#### **How common is allergic conjunctivitis?**

Allergic conjunctivitis is common. It may affect up to 40% of people at some point in their lives.

## Symptoms and Causes

Allergic conjunctivitis symptoms commonly include:

* Itchy or burning eyes.
* Puffy or swollen eyes.
* Watery eyes.
* Red eyes.
* Stringy or watery, yellow-white eye discharge.
* Allergic shiners.

Some people may also have an itchy or runny nose and sneezing.

### Causes of allergic conjunctivitis

Common allergic conjunctivitis causes include:

* Pollen.
* Dust mites.
* Mold spores.
* Pet dander.
* Chemicals or fragrances in soaps, detergents, deodorants, moisturizers and cologne/perfume.

#### **Is allergic conjunctivitis contagious?**

No, unlike bacterial or viral conjunctivitis, allergic conjunctivitis isn’t contagious.

#### **Who does allergic conjunctivitis affect?**

Anyone can get allergic conjunctivitis. But you’re more likely to have or develop it if you have allergies or a biological family history of allergies. You may also be at greater risk of allergic conjunctivitis if you have pets or live in an area with high pollen counts.

## Diagnosis and Tests

A healthcare provider will review your health history and ask about your symptoms. Tell them if you have any allergies or if anything irritating has gotten in your eyes recently. They’ll look at your eyes for symptoms of conjunctivitis, including:

* Redness.
* Bumps on the inside of your eyelids (giant papillary conjunctivitis).

If they suspect you have allergic conjunctivitis, they may refer you to an allergist (immunologist). An allergist may order allergy tests to confirm their diagnosis, including:

* Skin prick (scratch) test. During this test, the allergist uses a thin needle to gently scratch your skin and introduce possible allergens. They’ll then measure any reactions on your skin.
* Blood test. The allergist will take a small blood sample from your arm and send it to a lab. The lab will add possible allergens and check if antibodies develop.

#### **How do I know if my conjunctivitis is allergic or bacterial?**

It can be difficult to tell what causes conjunctivitis. But itchy, watery eyes are generally more common with allergic conjunctivitis and are present in both eyes. Viral or bacterial conjunctivitis typically only involves one eye. Allergic conjunctivitis also lasts longer than bacterial or viral conjunctivitis. Your symptoms may go away and come back throughout the allergy seasons.

If you have conjunctivitis symptoms, it’s best not to guess. Contact a healthcare provider to get treatment.

## Management and Treatment

The only way to treat allergic conjunctivitis is to avoid the cause. First-line treatment typically involves avoiding touching your eyes, home remedies and over-the-counter (OTC) or prescription medications to help ease your symptoms.

Home remedies may include:

* Regularly flushing your eyes with water.
* Applying a cold compress to your eyes.

Over-the-counter or prescription medications may include:

* Artificial tears.
* Ketotifen eye solution.
* Bepotastine eye drops.
* Azelastine eye solution.
* Cetirizine eye solution.
* Antihistamines, including fexofenadine, loratadine or cetirizine.

In severe cases of allergic conjunctivitis that you can’t manage with home remedies or over-the-counter or prescription medications, a healthcare provider may recommend allergy immunotherapy (allergy shots or allergy drops). They’ll expose you to small amounts of allergens and gradually increase the dosage over several months. Gradual exposure creates a tolerance to the allergen. The next time you encounter the allergen, you won’t have symptoms, or they’ll be mild.

#### **Can Benadryl help allergic conjunctivitis?**

Yes, Benadryl® (diphenhydramine) can help treat allergic conjunctivitis symptoms. However, one of its side effects is sleepiness. It’s a good idea to take it before going to sleep.

Allergists recommend taking second-generation antihistamines rather than diphenhydramine. Second-generation antihistamines are more effective, have fewer side effects and have no association with dementia.

### How soon after treatment will I feel better?

In general:

* Antihistamines start to work about 30 minutes after you take them.
* Allergy eye drops start to work after about an hour.
* Allergy immunotherapy may start to work within several weeks. But it may take up to six months or longer to notice your symptoms decrease.

## Outlook / Prognosis

You can cure allergic conjunctivitis with allergy shots. You can also help reduce the symptoms by avoiding known allergens and taking medications.

#### **How long can allergic conjunctivitis last?**

It depends. Your body is unique, including your immune system. Your allergic conjunctivitis symptoms may last less than an hour. They can also last for days, weeks or even months. It depends on what you’re allergic to and the severity of your allergy.

## Prevention

Avoiding known allergens is the best way to prevent allergic conjunctivitis. You may also take antihistamines or other medications daily to help manage your symptoms.

Other tips to help avoid allergic conjunctivitis symptoms include:

* Frequently wash your hands.
* Regularly vacuuming rugs, carpets and other surfaces to help remove dust and pollen.
* Using a high-efficiency particulate (HEPA) air filter to remove airborne allergens from your home.
* Keeping your windows closed and using air conditioning during allergy seasons to reduce the amount of pollen entering your home.
* Don’t smoke or vape indoors.

## Living With

See a healthcare provider, allergist or eye care specialist if you regularly have allergic conjunctivitis symptoms that affect your day-to-day quality of life.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for allergic conjunctivitis can be broad and may include the following conditions:

* Viral conjunctivitis
* Bacterial conjunctivitis
* Molluscum conjunctivitis
* Giant fornix syndrome
* Adult chlamydial conjunctivitis
* Trachoma
* Neonatal conjunctivitis
* Non Allergic eosinophilic conjunctivitis
* Contact allergic blepharoconjunctivitis
* Mucous membrane pemphigoid
* Stevens-Johnson syndrome/toxic epidermal necrolysis (Lyell syndrome)
* Superior limbic keratoconjunctivitis
* Ligneous conjunctivitis
* Parinaud oculoglandular syndrome
* Factitious conjunctivitis

**EPIDEMIOLOGY**

**Simple Allergic Conjunctivitis**

Simple allergic conjunctivitis is a condition that often goes underappreciated. As a result, it is difficult to determine the exact number of affected individuals, as many patients do not seek medical care for their symptoms. However, it is estimated to affect approximately 10% to 30% of the general population. Onset occurs in individuals younger than 20, and the prevalence tends to decrease in older populations. While allergic conjunctivitis can manifest as an isolated finding, it is frequently associated with other allergic conditions such as allergic rhinitis, atopic dermatitis, and asthma.

**Vernal Keratoconjunctivitis**

VKC is more commonly observed in males, with a male-to-female ratio ranging between 2 to 1 and 3 to 1. Most cases occur in patients between the ages of 5 and 10 years, often with a history of atopy or asthma. Around 95% of patients experience remission by late adolescence, while the remaining individuals may develop atopic keratoconjunctivitis.

VKC is rarely seen in temperate climates and is more prevalent in warm, dry regions such as the Middle East, sub-Saharan Africa, and the Mediterranean region. In temperate regions, 90% of patients present with atopy, asthma, and eczema, and two-thirds have a history of atopy.

The peak onset of VKC occurs in late spring and summer, although mild perennial symptoms may persist.

**Atopic Keratoconjunctivitis**

AKC is not usually observed before adolescence and reaches its peak prevalence between 30 and 50. It is a rare bilateral disease more commonly seen in individuals with a history of atopic dermatitis and asthma. Most cases of AKC are seen in patients with atopic dermatitis.

Like VKC, there is a male-to-female predominance, with a ratio between 2 to 1 and 3 to 1. Approximately 5% of these patients have a history of childhood VKC. AKC is a chronic condition with a relatively low expectation of resolution and can have low visual morbidity.

AKC tends to be more perennial, often worsening in the winter season, and individuals with AKC are sensitive to a wide range of airborne environmental pathogens.

**Giant Papillary Conjunctivitis**

GPC is commonly observed in teenagers and young adults, likely due to a temporal association with contact lens use. It is most commonly seen in individuals who use soft contact lenses, with approximately 5% of that population affected. GPC typically develops 1 to 2 years after initiating soft contact lens use, although the onset can vary significantly with other ocular foreign bodies.

The condition can be triggered by various stimuli affecting the tarsal conjunctiva. GPC is also referred to as contact lens-induced papillary conjunctivitis (CLPC). Protein deposits and cellular debris can accumulate on contact lenses, ocular prosthesis, sutures, and scleral buckles. Additionally, deposition on irregular corneal surfaces or filtering blebs can contribute to GPC.

The phenomenon known as mucus fishing syndrome, characterized by a chronic papillary reaction due to repeated mucus removal, can occur in various anterior segment disorders. GPC can also coexist with AKC and VKC

**RECOMMENDATION**

All patients with allergic conjunctivitis should receive education about general allergic eye care practices. They should be discouraged from rubbing their eyes, which causes mast cell degranulation and worsening symptoms. Applying artificial tears and cool compresses frequently can help alleviate discomfort.

Patients should avoid known allergen exposures and remove contact lenses if possible. Mild acute forms, over-the-counter antihistamines, antihistamines, and vasoconstrictor combination drops can be used for short periods. However, patients should be warned about the potential for mild rebound conjunctival injection if they use vasoconstrictor drops for extended periods.

A combination of antihistamine and mast cell stabilizing drops is often recommended for seasonal and perennial allergic conjunctivitis. Topical nonsteroidal anti-inflammatory drops can provide some relief but are ineffective as antihistamines or mast cell stabilizing drops.

In refractory cases, short bursts of corticosteroid drops (less than 2 weeks) can be used but should be done under the supervision of a specialist with appropriate follow-up. Systemic antihistamines and steroids are limited in treating refractory cases, especially when patients have systemic symptoms rather than isolated ocular symptoms.

The treatment of allergic conjunctivitis generally follows a step ladder approach based on the severity of symptoms. For mild symptoms, artificial eye drops are usually sufficient. Mast cell stabilizers such as sodium cromoglycate, nedocromil sodium, and lodoxamide are prescribed for a few weeks, and their maximal effect is seen after continuous use, making them suitable for long-term management.

Antihistamines such as emedastine, epinastine, bepotastine, and levocabastine are commonly used for acute exacerbations and are as effective as mast cell stabilizers. For severe and recurrent cases, a combination of antihistamines and vasoconstrictors, such as antazoline and xylometazoline, may be prescribed to provide more comprehensive relief.

NSAIDS are effective in reducing inflammation and providing symptomatic relief.

Topical steroids help relieve acute exacerbation, but their use should be limited to a short duration under the guidance of a specialist.

When symptoms are severe, oral antihistamines such as diphenhydramine and loratadine may be needed. Loratadine is preferred over diphenhydramine as it has less sedative action, making it a better option for daily use.

**Vernal and Atopic Keratoconjunctivitis**

The management of VKC and AKC follows similar principles of treatment. However, AKC generally requires more intensive and prolonged treatment than VKC.

Patients with VKC and AKC should be educated about general allergic eye care, which includes using artificial tears and cool compresses, minimizing allergen exposure, and avoiding rubbing their eyes.

Initial pharmacotherapy for both VKC and AKC typically involves a topical combination of antihistamine and mast cell stabilizing drops, similar to the treatment used for seasonal and perennial allergic conjunctivitis.

In refractory VKC or AKC cases, patients should be referred to a specialist who can prescribe topical corticosteroids. If the patient continues to be refractory to treatment or cannot be weaned from topical steroid therapy, topical or systemic calcineurin inhibitors can be considered an alternative therapeutic option.

**General Treatment**

The primary goal in managing allergic conjunctivitis, including VKC and AKC, is to avoid exposure to the allergen that triggers the allergic response. In some cases, eye patching may be required, and consulting with a cornea specialist can help determine the appropriate approach.

Cold compresses can provide relief from inflammation and discomfort. Maintaining good lid hygiene is also essential to prevent and treat staphylococcal blepharitis.

For patients with dry and fissured skin around the eyes, using a moisturizing cream such as E45 can help keep the skin hydrated and improve comfort.

A bandage contact lens may be recommended as part of the treatment plan for persistent epithelial defects. The bandage contact lens can protect the cornea and promote the healing of the defect.

**Medical Management**

**Mast cell stabilizers**

Sodium cromoglicate, nedocromil sodium, and lodoxamide are essential medications in managing acute exacerbations of allergic conjunctivitis, including VKC and AKC. They play a role in controlling symptoms and reducing the reliance on steroids, making them essential components of many treatment regimens. However, these medications are often not as effective when used in isolation and are typically combined with other treatments.

In cases of VKC and AKC, treatment may be required for several weeks to achieve significant improvement, and long-term therapy is necessary to maintain symptom control. However, it is essential to note that lodoxamide is not FDA-approved for long-term use.

**Topical antihistamines**

Emedastine, epinastine, levocabastine, and bepotastine are all equally effective antihistamine drugs that can relieve allergic conjunctivitis symptoms, including VKC and AKC. They act as mast cell stabilizers.

Antihistamines are an excellent choice to alleviate symptoms and relieve acute exacerbations of allergic conjunctivitis quickly. However, medications such as mast cell stabilizers, such as sodium cromoglicate, nedocromil sodium, and lodoxamide, may be required for long-term treatment to control inflammation and reduce dependence on steroids.

A combination of medications, including VKC and AKC, can effectively relieve symptoms when managing allergic conjunctivitis. In some instances, vasoconstrictors like xylometazoline and antazoline can be combined with antihistamines to provide additional comfort.

Combining antihistamines with mast cell stabilizers, such as ketotifen and olopatadine, has proven particularly effective in rapidly relieving symptoms.[[42]](https://www.ncbi.nlm.nih.gov/books/NBK448118/#) These medications work together to prevent the release of inflammatory substances from mast cells, further reducing allergic responses.

**Nonsteroidal anti-inflammatory drugs**

Nonsteroidal anti-inflammatory drugs (NSAIDs) like ketorolac, diclofenac, nepafenac, and bromfenac can relieve and improve comfort by blocking non-histamine mediators involved in the inflammatory response. For some patients, combining an NSAID with a mast cell stabilizer has proven to be an effective drug therapy for managing allergic conjunctivitis.

**Topical steroids**

Topical steroids are essential in managing severe acute exacerbations, inflammation, and keratopathy. Various commonly used steroids are 0.1% fluorometholone, 0.2% and 0.5% loteprednol, 1% rimexolone, and 1% prednisolone.

To effectively manage the inflammation and associated corneal pathology, a short and intense course of therapy with an hourly regimen may be required, followed by a careful tapering schedule. This approach helps reduce conjunctival inflammation, leading to an improvement in corneal health.

It is crucial to closely monitor patients receiving topical steroids to prevent adverse effects, particularly the elevation of intraocular pressure (IOP) and the development of steroid-induced glaucoma.

Some clinicians prefer to use steroid eye ointments, such as beclomethasone or hydrocortisone 0.5%, to manage AKC. However, strict IOP control and monitoring should be implemented during ointment treatment.

**Topical antibiotics**

In cases of severe keratopathy associated with allergic conjunctivitis, an antibiotic and steroid combination is often necessary to manage the condition effectively and prevent the development of bacterial keratitis. This combination therapy helps address both the inflammatory component and the risk of secondary bacterial infection.

**Mucolytic agents**

Acetylcysteine is useful in VKC and AKC for dissolving mucus filaments, deposits, and early plaque development.

**Immunomodulators**

Ciclosporin (0.05%-2%) may be needed 2 to 6 times daily in cases with a suboptimal response to steroids when steroids are ineffective, poorly tolerated, or when there is an inadequate response. These act as steroid-sparing agents in patients with severe diseases. Immunomodulators take approximately 6 weeks to act, and there can be rebound inflammation if the drug is stopped in between. The side effects are blurred vision and irritation.

**Calcineurin inhibitors**

Tacrolimus 0.03% eye ointment is an effective alternative to cyclosporine in resolving conjunctival inflammation in cases with refractory allergic conjunctivitis. It is usually instilled at bedtime in the conjunctival fornices.

**Supratarsal steroids**

Supratarsal steroids are required in patients with the severe palpebral form of the disease who are unresponsive to topical steroids or are non-compliant. The conjunctiva is everted, and injection is given in the supratarsal conjunctiva. An injection of 0.1 ml betamethasone 4 mg/mL, dexamethasone 4 mg/mL, or triamcinolone can be provided.

**Systemic Medications**

**Oral antihistamines**

Oral antihistaminics can be given to resolve symptoms, but effectiveness is guaranteed. The oral drugs induce sleep and help reduce itching and eye rubbing. Some medications, such as loratadine, can cause slight drowsiness.

**Antibiotics**

Doxycycline 50 to 100 mg once daily for 6 weeks and Azithromycin 500 mg once daily for 3 days can be given to reduce blepharitis aggravated inflammation, especially in AKC.

**Oral immunosuppressants**

Oral steroids, ciclosporin, tacrolimus, and azathioprine are useful in low doses for refractory allergic conjunctivitis. A short trial of high-dose steroids may be required to achieve control of the severe disease. Monoclonal antibodies are helpful in refractory cases. Aspirin has also been tried in patients with VKC but should be used cautiously due to the risk of Reye syndrome in children. Other measures used are allergen desensitization and plasmapheresis in patients with high IgE levels.

**Topical drugs**

After contact lens removal, instilling mast cell stabilizers can relieve itching. In some instances, long-term use of mast cell stabilizers may be necessary to manage and control allergic conjunctivitis symptoms effectively.

Additionally, NSAIDs and combined antihistamines and mast cell stabilizers can also be beneficial in managing allergic conjunctivitis symptoms.

If acute exacerbations or when the condition is resistant to other treatments, topical steroids may be necessary for their potent anti-inflammatory effects.

**Surgical Measures**

Glue with bandage contact lenses is required in patients with small corneal perforations. Superficial keratectomy is needed in cases with shield ulcers for debridement and removal of plaques and helps in epithelization. The topical drugs should be continued to prevent recurrences. Phototherapeutic keratectomy by using an excimer laser is another alternative. Amniotic membrane grafting is required in persistent epithelial defects. The other options are lamellar keratoplasty or patch graft. Botox-induced ptosis is another management option for persistent epithelial defects.

**Giant papillary conjunctivitis**

The first step in managing giant papillary conjunctivitis is to remove the mechanical irritant, which is most commonly a contact lens. Patients should discontinue lens wear for a few weeks and replace the lens to avoid reexposure to allergens. General allergic eye care should be practiced, such as avoiding eye rubbing, using artificial tears and cool compresses, and allergen avoidance.

Initial pharmacotherapy is similar to other ocular types of allergies, with options like topical antihistamines or a combination of an antihistamine and mast cell stabilizing drops used to alleviate symptoms.

In more severe and refractory cases, topical corticosteroid drops can be prescribed under the supervision of a specialist, similar to the treatment approach for vernal and atopic keratoconjunctivitis. However, calcineurin inhibitors do not play a role in treating GPC. Removing these devices may be necessary for patients with sutures or scleral buckles to reduce mechanical irritation. Regular assessment of prosthetic eye condition and fitting process is crucial.

Filtering blebs requires surgical intervention, such as excision or nonpenetrating glaucoma drainage surgery, followed by a glaucoma drainage device implantation. To prevent contact lens papillary conjunctivitis (CLPC), patients should regularly clean their contact lenses and consider switching to preservative-free solutions. Transitioning to monthly and daily disposable contact lenses is recommended.

Rigid lenses carry a lower risk of CLPC because they are easier to clean. Contact lenses should be stopped and substituted with spectacles, or rare cases may require refractive surgery. Protein removal tablets can be used to clean contact lens protein. For ocular prostheses, washing and cleaning with detergent and a protective coating are essential to maintain hygiene and comfort.

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### Allergic asthma

**Definition and description**

Allergic or allergy-induced asthma is a condition where your airways tighten when you breathe in an allergen. Most often, these allergens are in the air — like dust mites, pollen, animal dander or mold spores.

When you have allergies, your body creates a response to something it thinks is a threat — the allergen. Your immune system fires up all of its defenses to try and fight off this danger. Your immune system releases various chemicals that cause inflammation, or swelling, and squeezing of your airways upon exposure to an allergen.

#### **How common is allergic asthma?**

Allergic asthma is the most common type of asthma. In the United States, about 25 million people have asthma. Out of that group, approximately 60% have allergies.

## Symptoms and Causes

If you have allergic asthma, you may have many of the same symptoms you’d experience with other types of asthma. These symptoms can include:

* Feeling short of breath.
* Coughing frequently, especially at night.
* Wheezing (a whistling noise during breathing).
* Experiencing chest tightness (feeling like something is pressing on your chest).

Allergen exposure can also trigger other symptoms, including:

* A stuffy nose.
* Nasal drainage
* Itchy or watery eyes.
* A rash or hives.

### What does allergy-induced asthma feel like?

Allergy-induced asthma symptoms can range from mild respiratory symptoms to severe asthma attacks. During an asthma attack, your airways will tighten, making it difficult to breathe. You may also feel chest pressure, wheeze and cough. The symptoms of an allergic asthma attack are the same as an asthma attack caused by something else. The difference between the two is the cause of the asthma attack.

### What allergens trigger allergic asthma?

Allergens can be all around you — in your indoor and outdoor environments. When you have allergic asthma, inhaling these allergens can set off (trigger) your symptoms. It’s important to know what can trigger your asthma so that you can manage your condition.

Possible allergens that can trigger allergic asthma include:

* Pets or animals: Allergies to pets or animals can come from their fur, pee, saliva or from pet dander, which are flakes of skin.
* Pollen: Pollen is a powdery substance from trees, grass, weeds and ragweed. Tree pollen and grass pollen are most abundant in the spring. Weeds and ragweed release their pollen in the fall.
* Mold: Molds are typically found in places that hold moisture (like basements). Outdoors, mold is found during warm or humid days, after mulching or after rainfall. Mold produces spores that get into the air and can trigger your asthma.
* Dust mites: Dust mites are microscopic organisms that feed on human skin. They live on soft surfaces of your home, including carpets, soft furniture, pillows and mattresses. Both the mites themselves and their feces are allergens.
* Cockroaches: You can find these pests in many homes and older buildings. The feces, saliva and other body parts of the cockroaches can trigger asthma.

Food allergies may trigger allergic asthma in some people. Food allergies are rarely the cause of allergic asthma alone.

#### **Who is at risk for allergic asthma?**

You’re more at risk of having allergy-induced asthma if you have allergies or a family history of allergies.

### How serious is allergic asthma?

Allergy-induced asthma can be serious and cause complications. Some of the most common complications of allergic asthma include:

* Sleep disruptions.
* Missing school and work.
* Inability to exercise.
* Inability to take part in social activities that are outdoors or involve lots of walking.
* Higher rates of hospitalization and illness.

## Diagnosis and Tests

Your healthcare provider will order tests to determine if you have allergic asthma. The two most common tests are spirometry and bronchoprovocation testing:

* Spirometry: This breathing test involves taking a deep breath in and then exhaling into a tube. This tube connects to a computer that’ll collect information about how well the air moves when you breathe in and out. Spirometry can also be done with a bronchodilator (e.g. inhaler medication). Bronchodilator tests look at how well your airways relax before and after taking an inhaler medication.
* Bronchoprovocation testing (methacholine): Methacholine testing is similar to spirometry testing, but in this case, your provider uses a medication called methacholine to see if your airways constrict or tighten after taking it.

If your provider determines you have asthma, they’ll recommend either a blood test or skin test to help determine if environmental allergens are potential triggers for your asthma.

During a skin test, a provider puts small drops of liquid containing various allergens on your skin. Then, they gently scratch your skin to allow allergens to enter the top layer. If you’re allergic to the substance, your skin will react by swelling or you may develop tiny, raised bumps.

In certain cases, a blood test can identify allergic triggers. Allergy blood tests can miss a small percentage of allergies compared to skin testing.

## Management and Treatment

Your healthcare provider will work with you to treat both your allergies and your asthma. Some treatments work for asthma, while others treat just allergies, and some treatments can help manage both conditions. Treatment can involve avoiding the allergen or making lifestyle changes, and medications.

#### **Avoiding the allergen**

Your provider will help you figure out what’s triggering your asthma and find ways to either avoid or manage these allergens. Often, these triggers are in your environment. Once you know what they are, you can manage your interactions with them. This might mean hiring someone to cut your grass if you know that pollen is a trigger for your asthma, or avoiding places with a lot of animals if dander is a trigger for you.

Depending on what triggers your asthma, other steps you can take include:

* Cleaning your house frequently. This could include frequent mopping and dusting and washing your bedding and pillows in hot water every week.
* Using dust and allergen-proof sheets and pillows on your bed.
* Keeping house and car windows closed during peak pollen season. You can also avoid being outside when pollen counts are highest or wear glasses, face masks or other protective equipment when outdoors.
* Using high-quality filters in your home air conditioning units or running an air purifier.
* Developing an action plan. It’s important to have a plan in place that helps you know when to take certain medications, what to do if the medications aren’t working and who to call in those situations. The plan should include what to do during an asthma attack.

#### **Medical treatment**

Medications for allergy-induced asthma may include:

* Leukotriene modifiers: This is the name for a group of medications that treat both allergies and asthma. Montelukast (Singulair®) is one of the most common leukotriene modifiers.
* Allergy shots: Also called immunotherapy, allergy shots can reduce how your immune system reacts to an allergen. It involves getting regular injections (shots) of the allergen to build up your tolerance over time.
* Rescue inhalers: These offer fast relief for asthma symptoms by opening up your airways so you can breathe better.
* Antihistamines: This type of medication reduces mild to moderate allergy symptoms like itching skin or watery eyes. Your provider may suggest taking an antihistamine as part of your treatment plan.
* Corticosteroids: Both oral and inhaled corticosteroids can help prevent allergy-induced asthma symptoms by reducing inflammation in your airways.
* Biologics: These are small proteins that your provider injects to help treat the underlying cause of asthma. This treatment is for moderate or severe allergic asthma.

## Outlook / Prognosis

There isn’t a cure for allergic asthma. However, symptoms can get better or worse depending on your environment and exposures.

## Prevention

While asthma itself can’t be prevented, you can reduce your risk of an allergic asthma attack by understanding and avoiding triggers and ensuring you’re using the best medical treatment to manage your asthma.

## Living With

Contact your healthcare provider if you have asthma symptoms due to allergens so they can work on a treatment plan with you. Symptoms may include:

* Coughing or wheezing.
* Shortness of breath or breathing difficulties.
* Allergy symptoms like stuffy nose, itchy and watery eyes or skin rash.

**Epidemiology of Allergic Asthma**

* Global Prevalence:
  + Asthma affects approximately 262 million people worldwide as of 2019, causing about 455,000 deaths annually.
  + Allergic asthma is the most common asthma phenotype, particularly prevalent in children and adolescents.
  + The overall prevalence of current asthma symptoms is roughly 9.1% in children, 11.0% in adolescents, and 6.6% in adults globally, with higher rates in high-income countries.
  + In adults, clinical asthma prevalence averages around 4.5% globally, with regional variation (highest in Western Pacific region at ~6.2%).
* Age and Demographics:
  + Allergic asthma often begins in childhood or adolescence but can persist or develop in adulthood.
  + Childhood asthma prevalence is higher in males, while adult asthma is more common in females.
  + Non-Hispanic Black children in the U.S. have nearly twice the asthma prevalence compared to non-Hispanic White children.
  + Adult asthma rates in the U.S. have increased by approximately 14.3% since 2021, with about 29 million Americans affected in early 2025.
* Geographic and Socioeconomic Factors:
  + Asthma prevalence is generally higher in high-income countries and urban areas, with lower rates in low- to middle-income countries.
  + Urbanization, air pollution, and environmental changes contribute to rising allergic asthma rates worldwide.
  + Climate change has extended pollen seasons and increased exposure to allergens, exacerbating allergic asthma.
* Trends and Projections:
  + The global burden of asthma is expected to increase, with projections estimating 275 million asthma cases by 2050, driven largely by population growth.
  + Environmental factors such as air quality deterioration and longer allergy seasons are key drivers of the increasing prevalence and severity of allergic asthma.
* Burden and Impact:
  + Asthma is a leading chronic disease in children and adults, causing significant morbidity, healthcare utilization, and economic burden.
  + In 2020, asthma accounted for nearly 1 million emergency department visits and over 90,000 hospital discharges in the U.S..
  + Despite advances in treatment, a substantial proportion of patients have uncontrolled asthma, increasing the risk of exacerbations and mortality.

**DIFFERENTIAL DIAGNOSIS**

The first step in dealing with an asthma patient is to make sure it is asthma. Although many cases of recurrent cough and wheezing in children and adults are due to asthma, other conditions are often misdiagnosed as asthma. In adults, the differential diagnosis of asthma includes

* Chronic obstructive pulmonary disease (COPD),
* Congestive heart failure,
* Gastroesophageal reflux disease,
* Mechanical obstruction of the airways (e.g., tumors, foreign bodies), and
* Vocal cord dysfunction.

Infrequent causes of wheezing include

* Pulmonary embolism,
* Pulmonary infiltrates with eosinophilia, and
* Some medications (e.g., angiotensin-converting enzyme (ACE) inhibitors)

In children, chronic cough is a problem, which needs differentiation between asthma and not asthma. Chronic productive cough with purulent sputum is a reason for concern in children and is not usually a symptom of asthma. Nevertheless, respiratory infection presenting purulent sputum can exacerbate asthma in children previously diagnosed with asthma. The younger the child, the greater the need to exclude underlying disease at an early stage

Wheezing in children can be an allergic (i.e., asthma) or non-allergic response

Non-allergic wheezing in children occurs during acute infections, including viral bronchiolitis. Coughing and wheezing in bronchiolitis is difficult to distinguish from asthma. The differential diagnosis of children with frequent respiratory infection and wheezing should include

* Foreign body aspiration causing airway obstruction,
* Pneumonia/bronchiolitis,
* Cystic fibrosis,
* Bronchopulmonary dysplasia (in premature infants),
* Primary ciliary dyskinesia syndrome, and,
* Immune deficiency.

| **Infants and Children** | **Adults** |
| --- | --- |
| Upper airway diseases   * Allergic rhinitis and sinusitis   Obstructions involving large airways   * Foreign body in trachea or bronchus * Vocal cord dysfunction * Vascular rings or laryngeal webs * Laryngotracheomalacia, tracheal stenosis, or bronchostenosis * Enlarged lymph nodes or tumor   Obstructions involving small airways   * Viral bronchiolitis or obliterative bronchiolitis * Cystic fibrosis * Bronchopulmonary dysplasia   Other causes   * Congenital heart diseases * Recurrent cough not due to asthma * Aspiration from swallowing mechanism * Dysfunction or gastroesophageal reflux | * Chronic obstructive pulmonary disease (COPD) * Hyperventilation syndrome and panic attacks * Congestive heart failure * Pulmonary embolism * Laryngeal dysfunction * Mechanical obstruction of the airways (benign and malignant tumors) * Pulmonary infiltration with eosinophilia * Diffuse parenchymal lung diseases * Cough secondary to drugs (ACE inhibitors) * Vocal cord dysfunction |

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### Food allergies

**DEFINITION AND DESCRIPTION**

Food allergies are reactions your body has to a food that it mistakenly thinks is harmful. In trying to protect you, it can cause hives, swelling, an upset stomach and difficulty breathing.  
  
Food allergies can cause anaphylaxis, which can cause swelling in your airways or a severe drop in blood pressure. Call an emergency room immediately if you have face, mouth or throat swelling, difficulty breathing or swallowing, or feel faint.

#### **Types of food allergies**

Most commonly, “food allergies” refer to allergies to peanuts, tree nuts and other allergens that can cause immediate and often severe reactions. You might hear your provider call these “true allergies” or IgE-mediated allergies (for the IgE antibodies that cause them). Oral allergy syndrome is also a type of IgE-mediated allergy, but it causes a local reaction on your lips or in your mouth and rarely leads to anaphylaxis.

Non-IgE-mediated food reactions include:

* Food protein-induced enterocolitis syndrome (FPIES)
* Eosinophilic esophagitis
* Eosinophilic gastritis
* Food protein-induced proctitis

#### **Most common food allergies**

The nine most common food allergies include:

* Peanuts
* Tree nuts (like almonds, walnuts, pistachios, hazelnuts, pecans, cashews and Brazil nuts)
* Milk
* Eggs
* Fish
* Shellfish
* Soy
* Wheat
* Sesame

These account for about 90% of all food allergies. But you can be allergic to any food.

## Symptoms of food allergy

Symptoms of food allergies include:

* Hives or skin rash
* Itchy skin
* Swelling of your face, lips, mouth or tongue
* Itchy mouth and throat
* Hoarse voice
* Difficulty swallowing
* Wheezing
* Shortness of breath or difficulty breathing
* Coughing
* Abdominal pain
* Vomiting
* Diarrhea
* Lightheadedness or loss of consciousness (fainting)
* Runny nose
* Sneezing

Symptoms of food allergies can be severe, even if you’ve only had a mild reaction in the past. Go to the ER at the first sign of severe symptoms.

#### **When would symptoms start if you have a food allergy?**

Usually, you experience food allergy symptoms within two hours of eating.

### Causes of food allergies

When you have a food allergy, your immune system mistakenly identifies a food protein as something harmful (as if it were a virus or bacteria). When you eat something you’re allergic to, it activates mechanisms meant to protect you and flush the allergen out of your system. This causes your symptoms, which can sometimes be life-threatening.

#### **Risk factors of food allergies**

You might be at higher risk for food allergies if:

* You have other allergies, like pollen or dust.
* You have eczema or asthma. The tendency for people to have eczema, asthma and/or allergies together is called atopy.
* Someone else in your immediate family has allergies, asthma or eczema.

### Complications of food allergies

The most serious complication of food allergies is anaphylaxis, or swelling in multiple body systems that can cause uncontrolled vomiting, difficulty breathing and a severe drop in blood pressure (anaphylactic shock). Severe anaphylaxis can be fatal.

## Diagnosis and Tests

Healthcare providers diagnose food allergies by asking about your symptoms and performing allergy testing. It’s a good idea to be prepared to tell your provider:

* The food that’s causing your symptoms (if you know).
* Whether the food is cooked or uncooked.
* How much of the food you’ve eaten when you have symptoms.
* What symptoms you experience and how severe they are.
* How long it takes between eating the food and symptoms starting.
* Any other factors that would have contributed to your symptoms. (Were you sick with viral illness at the time? Were you exposed to other allergens — like pollen — on the same day?)
* Whether you’ve treated the symptoms at home and whether the treatments helped.
* Whether the symptoms always happen after exposure to the food, or only sometimes.
* How long it’s been since you last had the symptoms.
* Whether you have other known allergies (to food, pollen, dust, pets, etc.).
* Whether you have eczema or asthma.
* Whether anyone else in your family has allergies, asthma or eczema.

#### **What kind of testing do I need for a food allergy?**

Tests might include:

* Allergy skin test. A provider pricks your skin with a tiny amount of allergen to see if you develop a reaction.
* Allergy blood test. A provider tests your blood for antibodies to your suspected allergens.
* Food challenge test. Under the supervision of your provider, you’ll eat small amounts of your suspected allergen to see if you have a reaction.

## Management and Treatment

The best way to manage food allergies is to avoid your allergen. But there are a few treatment options that might reduce your risk of having an allergic reaction, including injections and oral and sublingual immunotherapy programs. You should also keep emergency medications, like epinephrine, on hand in case you accidentally eat something containing the food you’re allergic to.

#### **Omalizumab injections**

Your provider gives you omalizumab (Xolair®) injections once or twice a month (or your provider can train you to do it yourself). It can reduce your risk of having a reaction if you’re accidentally exposed to a food you’re allergic to.

#### **Oral immunotherapy**

Oral immunotherapy (OIT) is a program that can help you or your child build a tolerance to a food allergen. Your provider gives you increasing doses of your allergen over several months. The goal is to get to a point where you won’t have a reaction if you’re accidentally exposed to small amounts of the food you’re allergic to (called “bite-proof”). Some people can freely eat food they were once allergic to after OIT.

#### **Sublingual immunotherapy**

Sublingual immunotherapy (SLIT) works similarly to OIT in that you’re exposed to a small amount of your allergen every day to develop tolerance to it. Instead of eating the food you’re allergic to, you put a liquid or tablet under your tongue and let it dissolve. SLIT must be supervised by a healthcare provider for safety.

#### **Emergency medications**

If you’re accidentally exposed to your allergen and have an allergic reaction, your provider might give you or recommend you take:

* Your provider will recommend you carry an epinephrine auto-injector (EpiPen® or Auvi-Q®) to use at the first signs of a severe allergic reaction.
* Corticosteroids. Steroids reduce inflammation.
* Antihistamines can help stop or slow down allergic reactions. But providers don’t prescribe them to prevent reactions from food allergies.

## Outlook / Prognosis

If you or your child have a food allergy, you’ll likely need to develop a habit of reading labels and avoiding foods that could contain the allergen. An allergist can talk to you about what treatment options are available and what to do if you have a reaction. They may recommend repeating allergy tests periodically to see if your child would have outgrown the allergy (or if you or your child have developed a tolerance through treatment).

Allergic reactions are unpredictable, so they can become more severe with each additional exposure. And there’s no way to test for how severe your reaction to a food might be without eating it. So, even if you’ve only had a minor reaction to a food in the past, you still need to be cautious in the future.

### Can food allergies go away?

Sometimes. Many kids outgrow milk and egg allergies by age 6. But they rarely (less than 20% of the time) outgrow peanut, tree nut, shellfish or fish allergies.

## Prevention

While there’s no specific way to prevent food allergies, some strategies to reduce your child’s risk include:

* If you’re breastfeeding, make peanuts and other common allergens a part of your regular diet (as long as you’re not allergic to them yourself).
* Ask your baby’s healthcare provider when and how to introduce new foods. They may recommend introducing allergens to your child earlier or under the supervision of a provider, depending on your child’s other health conditions.
* After you’ve safely introduced your child to potential allergens, continue feeding them a variety of foods that they aren’t allergic to, including nuts, milk and eggs. This might reduce their risk of developing an allergy later on.

## Living With

To help prevent accidental exposure to a food you or your child is allergic to:

* Check the ingredient labels on pre-made foods. In the U.S., the label must state if a product contains any of the nine most common food allergens. Words to look for include “may contain” or “made on shared equipment.”
* Double-check labels when you buy food, when you put it away and before you eat it.
* Start talking to your child early about taking precautions about what they eat and not sharing food if they don’t know if it’s safe to eat.
* Be cautious at restaurants. Ask about whether the food contains your allergen but remember that they might not be able to make any guarantees.
* Let anyone who’s around your child know about their allergy and what foods are safe for them to eat.
* Talk to your child’s school or daycare about their allergy. Understand what plans they have in place to avoid accidental exposure.
* Carefully plan vacations and other times away from home. Bring safe foods with you or figure out in advance where you can go to eat.
* Ask your healthcare provider if you have any questions about what you can and can’t eat.

To be prepared in case of an allergic reaction:

* Always carry an epinephrine auto-injector with you. Ask your provider to show you exactly how to use it.
* Make sure your child’s school or daycare has an allergy action plan (Food Allergy & Anaphylaxis Emergency Care Plan) from your child’s provider on file. This details what to do if your child has an allergic reaction.
* Provide your child’s school or daycare with an epinephrine pen and any other medications your child might need.

### When should I see a doctor?

If you think you or your child have a food allergy, talk to a healthcare provider. They can refer you to a specialist and guide you on next steps.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of food allergies includes both immune-mediated and nonallergic disorders that present with a range of symptoms similar to food allergies. Eosinophilic gastrointestinal disorders, such as eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis, are chronic, immune-mediated conditions characterized by eosinophilic infiltration of the gastrointestinal tract. These disorders are associated with Th2 cell activity and are often triggered by food allergens. Eosinophilic esophagitis, the most common of these disorders, typically presents in school-age children to midlife and is frequently observed in individuals with a personal or family history of atopic conditions, including asthma, eczema, rhinitis, and IgE-mediated food allergies. Patients commonly experience dysphagia, vomiting, and reflux-like symptoms.

Mast cell activation syndrome is an immune-mediated condition characterized by the inappropriate activation of mast cells, leading to the release of mediators such as histamine and tryptase. This release causes a variety of symptoms across multiple organ systems. The symptoms can resemble those of food allergies, including gastrointestinal distress, rashes, and anaphylaxis.

Patients with celiac disease experience an autoimmune reaction to gluten. Symptoms often include abdominal pain after gluten ingestion, chronic diarrhea, weight loss, fatigue, and anemia. Celiac disease is typically diagnosed through serological testing or a small bowel biopsy. Clinicians must also differentiate allergic reactions from non-food causes, such as medications or insect stings, which can produce symptoms coinciding with food ingestion.

Non Allergic conditions that present with symptoms similar to those of food allergies include lactose intolerance, fructose malabsorption, gastroesophageal reflux disease (GERD), irritable bowel syndrome, histamine intolerance, and panic or anxiety-related reactions. For instance, lactose intolerance may cause bloating and diarrhea after consuming dairy products, while GERD-induced regurgitation may be mistaken for food allergy-related vomiting. Infants with symptoms such as vomiting, lethargy, and poor weight gain may have inborn errors of metabolism, such as galactosemia. Panic attacks can lead to throat tightness, dizziness, and hyperventilation, further complicating the differential diagnosis.

Histamine intolerance, a less common condition, can mimic the symptoms of food allergy reactions. Affected individuals may experience headache, flushing, and urticaria after consuming histamine-rich foods such as aged cheeses, processed meats, fermented products, and alcohol. Additionally, the ingestion of foods containing additives or spices can lead to irritant or vasomotor responses that resemble food allergy symptoms, including flushing, nasal congestion, headache, and a burning sensation in the mouth.

Other nonallergic conditions that can cause urticaria include infections, such as viral illnesses or reactions to enterotoxins produced by *Staphylococcus aureus*. Foodborne gastroenteritis from pathogens such as *Salmonella* or norovirus may be mistaken for food allergies, as symptoms such as vomiting and diarrhea can follow ingestion of contaminated food. Because both immune-mediated and nonallergic conditions can mimic food allergies, thorough history-taking and diagnostic evaluation are essential. Important differential diagnoses include eosinophilic gastrointestinal disorders, mast cell activation syndrome, celiac disease, food intolerances, infections, and anxiety-related symptoms.

**EPIDEMIOLOGY**

Healthcare experts increasingly recognize food allergies as a growing global public health concern, with rising prevalence in both high-income and resource-limited countries. An estimated 250 million people worldwide are affected by one or more food allergies. In the United States, approximately 8% of children and up to 10% of adults are affected by this condition. Notably, around 40% of affected children have multiple food allergies. The most common allergenic foods include cow milk, eggs, peanuts, tree nuts, soy, wheat, fish, shellfish, and sesame.

Although cow’s milk and egg allergies are among the most commonly reported food allergies worldwide, geographic variations exist, likely determined by cultural feeding patterns. Many children eventually outgrow allergies to milk, eggs, or soy; however, allergies to peanuts, tree nuts, and shellfish are more likely to persist into adulthood.Additionally, individuals with a history of allergies to bee venom, medications, or latex have an elevated risk of developing food allergies later in life.

Prevalence of food allergies varies widely and is influenced by factors such as geography, dietary habits, environmental exposures, access to healthcare, and the diagnostic criteria applied. Higher rates are observed in Westernized countries, particularly in urban areas, where food allergies affect up to 10% of infants. In contrast, prevalence tends to be lower in rural and resource-limited regions. These regional differences may be attributed to variations in early-life microbial exposure, air pollution, ingestion of microplastics, and contact with natural environments, including exposure to tree pollen, insects, and animals.

Racial and ethnic differences in food allergies are also observed within countries. For instance, Black children in the United States have higher rates of peanut and shellfish allergies compared to White children.The impact of food allergies extends beyond the individual, contributing to increased emergency department visits, hospital admissions, healthcare costs, and significant psychosocial stress for affected individuals and families. The incidence of food-induced anaphylaxis has also risen, particularly among children and adolescents. Understanding these epidemiological patterns is crucial for clinicians to guide screening, patient education, and preventive strategies tailored to the needs of diverse populations.

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### Anaphylaxis

**DEFINITION AND DESCRIPTION**

Anaphylaxis (pronounced “an-ah-fi-LAK-sis”) is a severe allergic reaction. It can be life-threatening if you don’t get treatment right away. Food allergies are one of the main causes of anaphylaxis. Other causes include stinging insects, medications and latex.

The only treatment for anaphylaxis is epinephrine, which comes as a shot you inject into your thigh. Even with treatment, a person experiencing anaphylaxis needs to go to the nearest emergency room. With prompt treatment, most people make a full recovery.

#### **What happens during anaphylaxis?**

When you’re allergic to something, your immune system overreacts by releasing chemicals like histamine. Symptoms of anaphylaxis include swelling, wheezing, shortness of breath and difficulty swallowing. An anaphylactic reaction may affect several areas of your body at once.

Call your emergency services number and go to the nearest emergency room if you, or someone around you, are experiencing anaphylaxis, even if you’ve already administered epinephrine.

#### **Stages of anaphylaxis**

Anaphylaxis tends to happen suddenly and quickly. There often isn’t a warning period, but there can be mild signs like hives or flushed skin. Some healthcare providers break the stages of anaphylaxis into four categories:

* Stage one: Mild anaphylaxis is the first stage and can cause symptoms like skin rash or redness, itching or hives.
* Stage two: Moderate anaphylaxis happens when a person has more widespread and extensive symptoms like skin rash and hives that are spreading or mild swelling in their lips or tongue.
* Stage three: Severe anaphylaxis happens next and involves a person displaying signs of difficulty breathing, extensive swelling, weak pulse or dizziness. A person in stage three anaphylaxis is experiencing a condition called anaphylactic shock.
* Stage four: Life-threatening anaphylaxis is the last stage and involves a person losing consciousness, being unable to breathe and having inadequate blood flow to vital organs. A person in this stage needs immediate medical attention to avoid death.

#### **Anaphylactic shock**

A person who has an anaphylactic reaction can go into anaphylactic shock when their blood pressure drops dangerously low. Bronchial tissues, which help carry air, may begin to swell and cause wheezing, shortness of breath and even loss of consciousness. Anaphylactic shock requires immediate treatment to save the person’s life.

#### **How common is anaphylaxis?**

Estimates vary, but the most recent data suggests that people in the U.S. have a 0.05% and 2% lifetime chance of experiencing anaphylaxis.

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### Symptoms of anaphylaxis

Anaphylaxis usually begins with skin symptoms of hives or itching. Within a few minutes, you may start experiencing more severe symptoms, including:

* Swelling in your throat, lips and tongue.
* Shortness of breath.
* Hives.
* Difficulty swallowing.
* Red rash.
* Abdominal (belly) pain.
* Chest tightness.
* Cramps.
* Diarrhea.
* Feeling of doom or dread.
* Vomiting.
* Wheezing.

#### **Severe signs of anaphylaxis**

If you notice symptoms, get medical help right away or use your allergy medication. Without treatment, more severe, life-threatening anaphylaxis symptoms may occur:

* Light-headedness or confusion due to a drop in blood pressure,
* Increased heart rate.
* Sudden weakness.
* Unconsciousness.
* Cardiac arrest.

Usually, symptoms start within five to 30 minutes of coming into contact with the allergen. For example, getting stung by a bee or eating a food you’re allergic to such as peanuts. But symptoms can sometimes start more than an hour later.

#### **Biphasic anaphylaxis**

Biphasic anaphylaxis is when you have a second wave of symptoms after the first symptoms go away. This second wave can be hours or even days after the first wave. About 20% of people who have anaphylaxis get biphasic anaphylaxis.

### Causes of anaphylaxis

Food allergies are one of the main causes of anaphylaxis. Foods that can cause this severe anaphylactic reaction include:

* Cow’s milk.
* Eggs.
* Peanuts.
* Shellfish (shrimp and lobster).
* Soy.
* Tree nuts (like walnuts, hazelnuts, Brazil nuts and cashews).
* Wheat.
* Seeds (like sesame seeds and sunflower seeds).

Other allergens (substances that cause allergies) that can lead to anaphylaxis include:

* Certain medications and substances, including penicillin, nonsteroidal anti-inflammatory drugs (NSAIDs) and dye used for CT scans.
* Latex, found in items such as disposable gloves, catheters and adhesive tapes.
* Insect stings from bees, wasps, hornets and yellow jackets.

### Risk Factor for anaphylaxis

People who have asthma and who have previously had a severe allergic reaction are most at risk for anaphylaxis.

Allergic reactions can be unpredictable. Even if you don’t experience severe symptoms the first time, the second allergic reaction could be life-threatening. That’s why it’s important to always have epinephrine with you.

#### **Does pollen cause anaphylaxis?**

Pollen and other allergens that you breathe in rarely cause anaphylaxis. They can cause allergy symptoms, but the chances of pollen or other environmental allergies causing anaphylaxis are very low.

### Complications of anaphylaxis

Severe anaphylaxis is potentially life-threatening, especially in people with underlying medical conditions like heart disease or lung disease (especially asthma). It’s a medical emergency that should be taken seriously to minimize the risk of serious complications.

## Diagnosis and Tests

If you’ve had an allergic reaction, or suspected allergic reaction, to food or insect stings (even a mild one), talk to a healthcare provider. A provider can often diagnose anaphylaxis based on your symptoms. They should refer you to an allergist, who can perform additional tests, determine triggers and teach you how to avoid those triggers.

Taking this important step can protect your health and even save your life. It applies to anyone who’s had any type of allergic reaction.

An allergist may recommend performing a skin test or a blood test to confirm an allergy and identify the specific allergic trigger. A skin test places a small amount of the allergen on your skin to see if it causes a reaction. A blood allergy test involves your provider taking a blood sample from a vein in your arm.

## Management and Treatment

If you’ve had allergic reactions to food or a stinging insect, your provider will prescribe an epinephrine auto injector injection (EpiPen® or a generic version of EpiPen). It’s an injectable medication, about the size of a larger marker, that you always keep with you. Some people have multiple EpiPens in case they need two injections to control their symptoms or as a backup.

If you experience an anaphylactic reaction, you inject yourself with the medication into the large muscle of your upper outer thigh. Epinephrine works quickly to reverse symptoms.

After injecting yourself, immediately get medical help. If symptoms don’t improve after five to 15 minutes, give yourself a second injection if you have one available. Although very effective, the effect of epinephrine is short-lived. Therefore, it’s important that you immediately seek medical care after having an anaphylactic reaction, even if the injection helps your symptoms.

### How can I tell if someone is having an anaphylactic reaction?

Look for these signs, usually involving their nose, mouth, skin or digestive system:

* Hives or swelling of their eyes, lips or tongue.
* Difficulty breathing.
* Signs of low blood pressure, such as a weak pulse, confusion or loss of consciousness.
* Stomach symptoms, such as vomiting, diarrhea and cramping.

### What should I do if someone goes into anaphylactic shock without an EpiPen?

If you’re nearby when someone is having an anaphylactic reaction, call 911 or get medical help immediately. The person may need CPR as well.

Other ways to help:

* Lay the person flat, unless they’re having trouble breathing. In that case, help them sit up to make it easier to breathe.
* If the person is unconscious, put them on their side. Open up their airway by lifting their chin.

#### **What other anaphylaxis treatments might be necessary in emergencies?**

If the person can’t breathe, emergency healthcare providers may need to:

* Place a tube through their nose or mouth into their airway.
* Perform emergency surgery, called a tracheostomy, to place the tube directly into their trachea (windpipe).

Providers may need to give other treatments for shock, including:

* IV fluids.
* IV medication to help strengthen their heart and circulatory system.
* Antihistamines and steroids to reduce symptoms after the person is stable.

### Can Benadryl stop anaphylaxis?

Benadryl® and other antihistamines can treat symptoms of mild, non-anaphylactic allergic reactions like hay fever. It’s not a substitute for epinephrine when treating anaphylaxis.

## Outlook / Prognosis

When people don’t get treatment in time, anaphylaxis may lead to unconsciousness and even death. But if you get prompt treatment with epinephrine, the prognosis is good. You’ll likely make a full recovery.

### How long does anaphylactic shock last?

The exact time varies between individuals, but you can expect it to peak within five to 30 minutes. But symptoms can continue for several hours, even with treatment.

It’s important that you not wait to see if anaphylaxis goes away. Time is crucial when someone is experiencing anaphylaxis and a slight delay could cost them their life.

### Does anaphylaxis go away?

Unfortunately, allergies that cause anaphylaxis last a lifetime. You can usually manage anaphylactic reactions with prompt use of epinephrine. But if you’ve had a severe allergic reaction, you can anticipate having that allergy for life.

## Prevention

You can’t prevent anaphylaxis, but certain steps can minimize your risk of accidental exposure to an allergen.

Some tips to avoid triggers include:

* Food: Read food labels carefully. Ask restaurants what ingredients are in their dishes and how they prepare them. (Sometimes, restaurants may prepare an allergen-free dish in the same pot or pan as an ingredient you’re allergic to.) If you have a child with an allergy, inform your child’s school or other caretakers of their allergies.
* Medications: Let healthcare providers know if you’re allergic to any medications and if you’ve had allergic reactions in the past. They can make sure to prescribe a safe alternative for you and avoid anything you may be allergic to. If there are no alternatives, they can potentially try drug desensitization.
* Insect stings: Don’t walk barefoot in the grass. It’s also smart not to drink from open cans, as insects can lurk around openings. Try to avoid wearing bright, flowery clothing or perfumes, hairsprays and lotions that could attract insects. Allergists may be able to use venom immunotherapy to treat people with allergies to insect stings.

If you have severe allergies, make sure you carry an epinephrine injection wherever you go. You should know what triggers your allergies and let your friends and family members know where you keep your injection.

#### **Drug desensitization**

Sometimes, you need to take medication that you’re allergic to. There may be no safe alternative. Drug desensitization helps your body temporarily accept the medicine. An allergy specialist gives you small doses of a drug in gradual amounts until you receive a full dose. You continue to take the medicine regularly. Doing so keeps you in this temporary non-allergic state. Once you stop taking the medication, you’ll be allergic to it again.

#### **Venom immunotherapy**

Venom immunotherapy is a highly effective method of eliminating, or greatly reducing, anaphylactic reactions to stinging insects. An allergist injects small doses of the venom under your skin. You get a series of these shots, which decrease your sensitivity to the allergen.

#### **Oral immunotherapy for food allergies**

This newer therapy can decrease food sensitivities in people with severe allergies. An allergist with special expertise in food desensitization performs oral immunotherapy. The provider starts by giving you a small dose of the allergen, then slowly increases it over a period of several months. Food oral immunotherapy doesn’t “cure” food allergies, but it can decrease the occurrence or severity of accidental ingestion of foods that cause anaphylaxis. People who have oral immunotherapy should still carry their epinephrine injector with them.

## Living With

If you know you have severe allergies to food or other things, prepare ahead of time:

* Carry your injector: Have your epinephrine injection kit with you at all times.
* Have ID: Wear jewelry or carry a card that identifies your allergy. This ID can save your life in emergencies.
* Don’t wait to inject: Use your epinephrine injection promptly if you come into contact with your allergen. Don’t wait to see if your reaction worsens.
* Tell your providers: If you have drug allergies, tell your healthcare provider before any test or treatment. That includes dental care.
* Educate loved ones: Tell family and friends about the allergy and your triggers. Make sure they know how to recognize anaphylaxis symptoms. Also explain how to use the injector, so they can help you in case of a reaction.

### When should I use my epinephrine injector?

If you think you’re having an anaphylactic reaction, don’t wait to use your injector. Do not take an antihistamine instead to see if that helps. Use your injector immediately.

Your life depends on taking quick action. You also need to call 911 or get to a hospital. Even after you inject yourself, you need medical evaluation and treatment.

If you’re not sure you’re having an anaphylactic reaction, it’s better to inject yourself. The risk of an unnecessary injection is less than the risk of not getting the medicine in time.

If you accidentally inject yourself with an epinephrine autoinjector, you may experience an increase in your blood pressure and heartbeat. Call your provider or get medical help if that happens.

#### **What do I need to do after an epinephrine injection?**

Call 911 or find a way to get to the hospital. You need to get to the nearest emergency room if you have an anaphylactic reaction.

### When should I see an allergist?

An allergist is a healthcare provider specially trained to diagnose and treat people with allergies. If you experience or think you’ve experienced an allergic/anaphylactic reaction, you should see an allergist. They can confirm if a reaction was due to an allergen and identify triggers. They can also help educate you on potential treatment options and avoidance of triggers. And they’ll provide you with a plan to manage an anaphylactic reaction in case of an accidental exposure.

### If my child has allergies, what should I do?

If your child has allergies, you should take these steps to keep them safe:

* Educate them about the allergy.
* Make sure they carry their injector with them and know how to use it.
* Inform staff at your child’s school of the allergy and share the treatment plan with them.
* Educate any adults who care for your child about the allergy and how to use the injector.

## Epidemiology

Recent publications show a global incidence of anaphylaxis between 50 and 112 episodes per 100 000 person-years while the estimated lifetime prevalence is 0.3–5.1%, variations depending on the definitions used, study methodology, and geographical areas. According to a recent systematic review, in children, the incidence of anaphylaxis ranged from 1 to 761 per 100 000 person-years. Worrying data indicate that recurrence of reactions occurs in 26.5–54.0% of anaphylaxis patients during a follow-up time of 1.5 years–25 years. Despite an increasing time trend for hospitalizations due to anaphylaxis, mortality remains low, estimated at 0.05–0.51 per million people/year for drugs, at 0.03–0.32 for food and at 0.09–0.13 for venom induced anaphylaxis, with no evidence in most regions of a change in incidence of fatal anaphylaxis.

**Differential diagnosis of anaphylaxis**.

Acute asthma symptoms, acute generalized urticaria, or myocardial infarction symptoms can also occur during an anaphylactic episode.

Histamine poisoning from fish, eg, tuna that has been stored at an elevated temperature; usually, more than one person eating the fish is affected.

Pollen-food allergy syndrome is elicited by fruits and vegetables containing various plant proteins that cross-react with airborne allergens. Typical symptoms include oral allergy symptoms (itching, tingling and angioedema of the lips, tongue, palate, throat, and ears) after eating raw, but not cooked, fruits and vegetables.

Distributive shock may be due to anaphylaxis or to spinal cord injury.

In mastocytosis and clonal mast cell disorders, there is an increased risk of anaphylaxis; also, anaphylaxis may be the first manifestation of the disease.

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### HIVES (URTICARIA)

**DEFINITION AND DESCRIPTION**

Hives are raised red bumps (welts) or splotches on the skin. They’re a type of swelling on the surface of your skin and happen when your body has an allergic reaction. Allergic reactions happen when your immune system comes in contact with an allergen. Allergens are proteins that are harmless to many people but cause an allergic reaction in sensitive people.

Hives are often very itchy, but you might also feel burning or stinging. They can be as small as a fingertip or as big as a dinner plate. The medical name for hives is urticaria.

Sometimes, the welts from hives join together to form larger areas called plaques. Hives tend to fade within 24 hours, although they may be noticeable for several days or longer.

#### **Types of hives**

Acute urticaria refers to hives that don’t last very long (less than six weeks). Chronic urticaria refers to hives that happen at least twice a week for more than six weeks.

Chronic, spontaneous urticaria is the name for chronic hives that don’t have an obvious cause. An older name for this condition is chronic idiopathic urticaria.

There’s also a condition called physical urticaria, or inducible urticaria. These hives might pop up when you’re in the cold, heat or sun. Some people react to vibrations or pressure, exercising or sweating. Physical hives usually appear within an hour after exposure. This type of hive can also be chronic.

### What’s the difference between hives and a rash?

A rash is a skin condition that involves something out of the ordinary, like spots, swelling, itchiness or redness. Hives are an example of a rash, but not all rashes are hives.

### Who is affected by hives?

Anyone can get hives. If you’re someone who reacts to many types of allergens, you may get hives frequently. Other people who don’t react to allergens may get hives once or a few times in their lives.

There seems to be a relationship between acute hives and conditions like asthma, allergic rhinitis and atopic dermatitis, especially in children. You might also be affected by hives during periods of extreme stress.

#### **How common are hives?**

Around 20% of the population will get hives at least one time. About 1% to 3% of the population has chronic hives.

## Symptoms

Hives look different depending on the person and the situation. They can show up anywhere on your body. Signs of acute hives include:

* Raise welts or bumps on your skin. The bumps may look reddish on lighter-colored skin.
* Hives blanch (the center of the hive becomes pale when pressed).
* Itchy skin.
* Swelling under your skin causes puffiness (angioedema).
* Also appearing with painful swelling of your lips, eyes and inside your throat.

### Symptoms of chronic hives

In many respects, chronic hives and acute hives may look alike: they can be itchy, swollen raised welts that turn lighter in the center and with pressure. However, chronic hives can:

* Shift sizes and shapes.
* Appear, disappear and then reappear at least every few days for long periods of time, even months or years.
* It Happens along with heat, exercise or stress.

### Causes of hives

#### **Causes of acute hives**

Acute hives are often an allergic reaction to something you put into your body, like food, drink or medication, or something that you touch. The skin has immune cells called mast cells. When these cells go into action, they release chemicals, including one called histamine. Histamine is the reason that hives form.

You can also get hives for a variety of other reasons. Some of these include having an infection, stress or physical pressure on your skin. It’s not uncommon for healthcare providers to be unable to determine exactly what caused your hives.

#### **Causes of chronic hives**

Unlike acute hives, chronic hives aren’t usually caused by allergies. They may be caused by infections from bacteria or viruses, or as a result of other medical conditions like lupus. Your provider may not discover an exact cause. In these cases, chronic hives are said to be idiopathic or spontaneous.

Chronic hives do last for long periods of time but usually aren’t permanent. They can be uncomfortable, but they aren’t life-threatening.

### Are hives contagious?

Unlike some other skin conditions, hives aren’t contagious. But if you develop hives because your skin is exposed to secretions from a plant like poison ivy, you can spread the allergenic plant product to others until you wash it off your skin.

## Diagnosis and Tests

Your healthcare provider can diagnose hives and angioedema by looking at your skin. Allergy tests can help identify what’s triggering a reaction, but this is true primarily for acute hives. Knowing the cause can help you avoid allergens and the hives that come with them. Allergy tests to diagnose hives include:

* Skin tests: During this test, healthcare providers test different allergens on your skin. If your skin turns red or swells, it means you’re allergic to that substance. This type of allergy test is also called a skin prick or scratch test. Skin testing usually isn’t done for chronic hives.
* Blood tests: A blood test checks for specific antibodies in your blood. Your body makes antibodies to fight off allergens. If your body makes too many antibodies, you can develop hives and swelling.

## Management and Treatment

Most of the time, hives go away without treatment. Your healthcare provider might recommend medications and at-home care to help you feel better and lower your chances of having hives again. Treatments include:

* Allergy medications: Medicines called antihistamines block histamine’s effects. They can be taken orally (swallow a pill) or topically (put on the affected skin). Antihistamines relieve itching from hives and make allergic reactions go away or become less severe. Some antihistamines react quickly, such as diphenhydramine (Benadryl®). Depending on how severe the hives are, your healthcare provider may recommend daily allergy medications, like loratadine (Claritin®), fexofenadine (Allegra®), cetirizine (Zyrtec®) or levocetirizine (Xyzal®).

Allergy shots: For hard-to-treat chronic hives, your healthcare provider may discuss monthly injections of drugs that block allergic reactions. People with severe allergies make too much IgE. These injections block your immune system from making IgE.

* At-home treatments: To relieve hives, you can take a cool bath or shower, wear loose-fitting clothing and apply cold compresses. An over-the-counter (OTC) hydrocortisone or antihistamine cream can relieve itching and swelling.
* Oral steroids: Corticosteroids, such as prednisone, can relieve hive symptoms that don’t respond to antihistamines or topical steroids.
* Epinephrine: Severe acute allergic reactions can lead to a life-threatening condition called anaphylaxis. Symptoms include hives, swelling of your face, mouth or throat, shortness of breath, wheezing, vomiting and low blood pressure. Anaphylaxis is life-threatening and anyone having this kind of reaction needs an immediate epinephrine injection (EpiPen®) to open a swollen airway.

#### **Complications of hives**

Anyone who has a severe acute allergic reaction could have life-threatening swelling of the airways — your throat and lungs. This condition is known as anaphylaxis. It can potentially close off the airways, resulting in death.

Anaphylaxis is often triggered by a severe allergic reaction to a certain food, like peanuts and tree nuts, or to a bee sting. If you have anaphylaxis, you need an immediate shot of epinephrine, such as injectable epinephrine (EpiPen® or AUVI-Q®).

Epinephrine opens airways, raises blood pressure and reduces hives and swelling. If you take epinephrine outside of a medical setting, you should go to the emergency room to be monitored. Symptoms of anaphylaxis can return as the epinephrine wears off.

## Outlook / Prognosis

For most people, hives don’t cause serious problems. Children often outgrow allergies that cause hives.

For some people, allergic reactions like angioedema can cause anaphylaxis — severe swelling of the airways and lungs. If you have this life-threatening condition, you should carry and know when and how to use injectable epinephrine (EpiPen®).

## Prevention

#### **Acute hives**

Your healthcare provider can use the results of allergy tests to help you figure out which substances bring on acute hives. Once you know your triggers, you can avoid them. You may want to:

* Cut certain food products out of your diet.
* Reduce exposure to airborne allergens.
* Switch to detergents and soaps without scents or dyes.
* Avoid extreme changes in temperature.
* Relax and take a break when you’re stressed or overworked.
* Wear loose-fitting, lightweight clothing.

Some of these tips can also help with chronic hives.

#### **Chronic hives**

It may not be possible to prevent chronic hives. Your provider may not be able to find exactly what causes them. They may also be a part of a bigger medical condition that affects your immune system.

## Living With Hives

Hives can get better without treatment. Call your healthcare provider if you have:

* Hives or swelling that lasts more than a week.
* Infected-looking bumps (red, swollen or pus-filled).
* Recurring hives (they come back every few months).
* Severe itching that might even keep you from sleeping.
* Signs of anaphylaxis, including wheezing, shortness of breath or vomiting.
* Swollen lips or face.

## Epidemiology

Acute urticaria (hives) affects 15–20% of the general population at some time during their lifetime. Chronic urticaria affects 2–3% of individuals over their lifetime.

Incidence rates for acute urticaria are similar for men and women; chronic urticaria occurs more frequently in women (60%).

Urticaria can occur in any age group, although chronic urticaria is more common in the fourth and fifth decades.

## Differential Diagnoses

* Urticarial Vasculitis
* Hereditary Angioedema
* Mastocytosis
* Erythema Multiforme
* Atopic Dermatitis
* Allergic Contact Dermatitis
* Irritant Contact Dermatitis
* Scabies
* Drug Eruption

**RECOMMENDATION**

First, the recommended treatment algorithm was streamlined, and it now features 3 steps instead of 4. The recommendations for the use of first-line treatment (antihistamine), second-line treatment (omalizumab), and third-line treatment (cyclosporine) now include guidance on updosing and duration . For omalizumab, for example, the recommendation is to start treatment with 300 mg every 4 weeks, based on well-designed robust double-blind placebo-controlled studies demonstrating its efficacy in CSU.

In patients with insufficient response, updosing should be considered; it can be done by shortening the interval and/or increasing the dosage. Several studies have shown that this can be of benefit in individual cases, especially in patients with a high body mass index. The maximum recommended dose of omalizumab is 600 mg every 14 days, and up to 6 months should be allowed for patients to respond to omalizumab. The recommendation to use higher than standard doses of omalizumab, if needed, is based on real-life experience with CSU and clinical trials in asthma, in which the safety of higher doses was shown to have a spectrum and frequency of adverse events similar to those observed with 300 mg every 4 weeks. The risk-benefit profile of high-dose omalizumab is superior to that of cyclosporine, which should be considered for the treatment of patients who do not respond to higher than standard doses of omalizumab. Treatment of urticaria with cyclosporine has shown positive outcomes in case studies and clinical studies, including double blind placebo-controlled studies.

Even long-term low-dose treatment with cyclosporine has been shown to be safe and successful in a small group of patients. It should be noted, however, that there are potential risks associated with cyclosporine, including the risk of hypertension, epilepsy in those predisposed, hirsutism, gum hypertrophy, and renal failure. It is also advised that blood pressure and renal function (blood urea nitrogen and creatinine levels) be monitored every 6 weeks while the patient is receiving cyclosporine.

Second, the latest update of the international urticaria guideline asks physicians to use an “as much as needed and as little as possible” approach, by stepping up and stepping down the treatment of CU, based on levels of disease control assessed with the UCT. In patients who are treated with a standard-dosed second-generation antihistamine and whose CU cannot be completely controlled (ie, those with a UCT score of 16), a higher dose (up to 4-fold higher) should be used. In patients with complete disease control, step-down should be considered to reduce the treatment burden and assess patients for spontaneous remission.

Step-down protocols should bring on board individual patient needs and, in general, be implemented with prudence and patience. For example, patients should not step down a higher than standard–dosed antihistamine before completing at least 3 consecutive months of complete control, and the daily dose should not be reduced by more than 1 tablet per month. When control is lost during treatment step-down (ie, when patients develop breakthrough signs and symptoms following dose reduction), the antihistamine should be used at the last dose that previously provided complete control.

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### Angioedema

**Definition and description**

ALTERNATIVE NAMES

Angioneurotic edema; Welts; Allergic reaction - angioedema; Hives - angioedema

Angioedema is a reaction to a trigger that causes swelling in the tissue below the inner layer of your skin called the dermis or the layer below a mucous membrane. Angioedema often happens at the same time as hives (urticaria) and for similar reasons. Both angioedema and hives happen when liquid from small blood vessels escapes and fills up tissues, causing swelling.

Usually, angioedema comes on quickly and lasts about a day or two. It most often affects your lips and eyes. However, angioedema can be serious, even fatal, when it affects your airways.

### Types of angioedema

There are several types of angioedema. Some organizations may classify angioedema into different types, and the types may vary. In general, though, angioedema types include:

* Acute allergic angioedema
* Non-allergic drug reaction
* Idiopathic angioedema
* Hereditary angioedema
* Acquired C1 inhibitor deficiency
* Vibratory angioedema

#### **Acute allergic angioedema**

You might be most familiar with this type of angioedema. It occurs as an allergic reaction to something you’ve come into contact with. This could be something you’ve eaten (a food or beverage), or taken (as in medications) or touched (as in items made with natural rubber latex). In addition, this type of angioedema can occur if an insect or spider bites you.

Acute allergic angioedema happens quickly, usually within minutes to about one to two hours after you’ve made contact with the allergen. You almost always have hives along with the swelling.

#### **Non-allergic drug reaction**

This type of angioedema doesn’t necessarily happen as soon as you take the medication. The most common group of medications that cause this non-allergic reaction is angiotensin-converting enzyme inhibitors, often called ACE inhibitors or ACEIs. These medications relax your blood vessels, treat heart failure and may lower blood pressure. Nonsteroidal anti-inflammatory medications, like ibuprofen and naproxen, can also cause angioedema.

#### **Idiopathic angioedema**

Idiopathic angioedema is angioedema that has no known cause. The swelling is located in your face, hands, trunk, arms and legs. Some people also have immune system conditions and emotional issues.

#### **Hereditary angioedema**

Hereditary angioedema (also called HAE) is something you get genetically from your parents. You can inherit HAE if only one parent carries the gene or has the condition. Some people have spontaneous genetic mutations that cause them to have this type of angioedema. An estimated 1 out of 50,000 people have hereditary angioedema. There are three types of this kind of angioedema, all of them related in some way to the C1 protein and/or C1 esterase inhibitor levels in your blood.

#### **Acquired C1 inhibitor deficiency**

Acquired C1 inhibitor deficiency results in angioedema, but it’s not inherited. Acquired means that you weren’t born with this deficiency but you developed it during your lifetime. This type of angioedema, like others, may affect your voice box (larynx) and result in asphyxiation (suffocation). Having B-cell lymphoma may cause acquired C1 inhibitor deficiency.

#### **Vibratory angioedema**

In this condition, the swelling is due to repeated vibrations. These can happen while you’re riding a motorcycle, running, jogging, vigorous massage or during other activities. Vibratory angioedema is a form of a similar and rare condition called chronic inducible urticaria, in which hives happen because of outside forces like cold, heat, water, pressure or vibrations. These itchy hives happen repeatedly and last for about six weeks.

## Symptoms

Signs and symptoms of angioedema include:

* Puffy or swollen face, especially your eyes and mouth, including lips and tongue.
* Digestive problems when your intestines are swollen. These problems include abdominal pain, diarrhea or nausea and vomiting.
* Swollen hands, feet or genitals.
* Dizziness or fainting due to blood pressure changes.
* Swelling in your mouth, throat or airway that may make it harder to breathe and talk. When this happens, it’s a medical emergency. Get help right away.

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### Causes of angioedema

The causes of angioedema depend on what type of angioedema you have. Allergies are probably the main cause of the swelling of angioedema. There are many types of allergies that can cause it, including:

* Food allergies: The main culprits are milk, egg, nuts and shellfish.
* Medication allergies: Some of the drugs that cause these allergies include antibiotics like penicillin and sulfa drugs, nonsteroidal anti-inflammatory drugs (NSAIDS) and contrast media used in imaging tests. You might also get hives with this type of allergy.
* Venom: This is released by stinging insects and, rarely, brown recluse spider bites.
* Natural rubber latex: Latex is used to make gloves, balloons, condoms and catheters (tubes used in medicine). Your healthcare provider has probably asked you if you’re allergic to latex.

Other causes of angioedema include inherited and acquired problems with the C1 inhibitor protein, drug reactions that aren’t standard allergy reactions (there’s no itchiness and no hives) and vibrational movements.

### Is angioedema contagious?

No. You can’t catch angioedema or give it to someone else.

## Diagnosis and Tests

It may be difficult to tell what kind of angioedema you have. Your provider will begin with a physical examination, though in many cases the swelling will be easy to see. They’ll ask you questions about:

* When the swelling started.
* What you may have eaten, taken or touched that could have caused the reaction.
* What medications and supplements you're taking.
* Whether or not you’ve had this type of reaction before.
* Other family members who may have had swelling.

In addition to the questions, your provider may order blood or skin tests for allergies or blood tests to find out if you have angioedema related to the C1 inhibitor protein.

## Management and Treatment

Treating angioedema depends on what kind of angioedema you have. For severe allergic reactions, you’ll often have injectable epinephrine to carry. You should administer this while calling 911.

For allergic angioedema, your provider may suggest antihistamines or steroids. You may get them either in oral (pill or liquid) or intravenous (in the vein) form.

If you have a non-allergic drug reaction, your provider will help you find a medication to replace the one that’s causing you to swell.

Home remedies include things like using ice to reduce swelling or taking cool showers. These may work best on things like swelling in one place or all over your lip or a cool wet cloth over your swollen eyes.

If you have hereditary, idiopathic or acquired C1 inhibitor deficiency angioedema, you’ll probably be referred to a specialist. Some medications that treat or prevent hereditary angioedema include:

* C1 esterase inhibitor (recombinant) (Ruconest®).
* C1 inhibitor (human) (Berinert®, Cinryze®, Haegarda®).
* Ecallantide (Kalbitor®).
* Icatibant (Firazyr®).
* Lanadelumab (Takhzyro®).
* Berotralstat (Orladeyo®).

## Outlook / Prognosis

Most episodes of angioedema won’t last very long. They will probably resolve themselves. For severe episodes, you must have treatment to open the airways.

### Is angioedema fatal?

For some people, allergic angioedema can cause anaphylaxis — severe swelling of the airways and lungs. People with this life-threatening condition should carry injectable epinephrine (EpiPen®, Auvi-Q®, Adrenaclick® and other brand names) to treat severe allergic reactions. Angioedema that affects the airways, no matter what the cause, is always a medical emergency and you should seek treatment immediately. Sometimes a tracheostomy, an opening in the windpipe/trachea, is performed to help people breathe.

## Prevention

If you have allergy-related angioedema, you can prevent occurrences by avoiding the food, medication or other triggers that cause allergic reactions. If you have non-allergic angioedema as a drug reaction to taking ACEIs, you’ll need to work with your healthcare provider to find another medication.

## Living With

If you have episodes of angioedema, you should avoid allergy triggers. If your healthcare provider suggests medications to prevent further episodes, you should take them as directed. If you need to carry injectable epinephrine, make sure you have the injectors with you at all times. Let your family and friends know how to use them.

### When to see a doctor

You should call 911 if you have a severe allergic reaction and the swelling affects your airways.

In less severe cases, contact your healthcare provider if you have repeated instances of angioedema. You may be able to work out preventive measures. Other treatment options include oral antihistamines and steroid medications. Some providers have used omalizumab (Xolair®), a monoclonal antibody, in difficult-to-treat idiopathic angioedema.

**DIFFERENTIAL DIAGNOSIS**

* Acute contact dermatitis
* Drug rash with eosinophilia and systemic symptoms
* Dermatomyositis
* Morbus Morbihan
* Superior vena cava syndrome
* Hypothyroidism
* Subcutaneous emphysema
* Orofacial granulomatosis
* Hypocomplementemic urticarial vasculitis syndrome
* Clarkson's disease
* Gleich's syndrome
* A cluster headache
* Idiopathic edema

Angioedema is one of the differential diagnoses in sudden onset of diffuse isolated edema.

C1 inhibitor hereditary angioedema can be misdiagnosed as familial Mediterranean fever

**EPIDEMIOLOGY**

A retrospective study showed angioedema was the second most common disorder after asthma for hospitalization in New York State. African Americans made up 42% of these angioedema admissions. Hereditary angioedema is a rare autosomal dominant condition and affects 1/50,000 individuals. A Swedish study showed hereditary angioedema affected females more severely compared to males

## Guidelines Summary

*For adult patients with weals*

* Check that symptomatic episodes have not followed ingestion of a nonsteroidal anti-inflammatory drug such as aspirin or ibuprofen.
* Give a once-daily dose of a long-acting, nonsedating antihistamine (*prn* if symptoms are infrequent).
* If necessary, double the dose of antihistamine (usually given at night), and/or add a second antihistamine.
* Consider further increase in dose of antihistamine up to 4 times the recommended dose.
* Consider adding one or more second-line drugs.
* Consider short-term oral corticosteroid rescue treatment.

*For adult patients with angioedema with weals*

In addition to the instructions above for adult patients with weals, the following steps should be considered:

* If the patient is taking an ACE inhibitor, this drug should be stopped.
* Even if the patient is not taking an ACE inhibitor, these drugs should be avoided in the future.
* Consider addition of tranexamic acid for higher-dose antihistamine-resistant angioedema.
* An adrenaline autoinjector is rarely required and should only be considered if there is a history of significant angioedema affecting the upper airway (rare in angioedema with urticaria).

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**LATEX ALLERGY**

**DEFINITION AND DESCRIPTION**

Latex allergy is a reaction to certain proteins found in natural rubber latex, a product made from the rubber tree. If you have a latex allergy, your body mistakes latex for a harmful substance.

Latex allergy may cause itchy skin and hives or even anaphylaxis. Anaphylaxis is a possibly life-threatening condition that can cause throat swelling and serious difficulty breathing. A healthcare professional can find out if you have a latex allergy or if you're at risk of developing a latex allergy.

Understanding latex allergy and knowing common sources of latex can help you prevent allergic reactions.

**CAUSES OF LATEX ALLERGY**

In a latex allergy, the immune system identifies latex as a harmful substance and triggers certain antibodies to fight it off. The next time there is a latex exposure, these antibodies tell the immune system to release histamine and other chemicals into the bloodstream. This process produces a range of allergy symptoms. The more times someone is exposed to latex, the more strongly their immune system is likely to respond. This is called sensitization.

Latex allergy can happen in these ways:

* **Direct contact.** The most common cause of latex allergy involves touching latex-containing products, including latex gloves, condoms and balloons.
* **Inhalation.** Latex products, especially gloves, release latex particles. You can breathe in these particles when they become airborne. The amount of airborne latex from gloves differs greatly depending on the brand of glove used.

It's possible to have other skin reactions when using latex. They include:

* **Allergic contact dermatitis.** This reaction results from the chemical additives used during manufacturing. The main symptom is a skin rash with formation of blisters 24 to 48 hours after exposure, similar to poison ivy.
* **Irritant contact dermatitis.** Not an allergy, this skin irritation is caused by wearing rubber gloves or exposure to the powder inside them. Symptoms include dry, itchy, irritated areas, usually on the hands.

Not all latex products are made from natural sources. Products containing synthetic materials, such as latex paint, are unlikely to cause a reaction.

**Risk factors**

Certain people are at greater risk of developing a latex allergy:

* **People with spina bifida.** The risk of latex allergy is highest in people with spina bifida — a birth defect that affects the development of the spine. People with this disorder often are exposed to latex products through early and frequent healthcare. People with spina bifida should always avoid latex products.
* **People who undergo multiple surgeries or medical procedures.** Repeated exposure to latex gloves and medical products increases your risk of developing latex allergy.
* **Healthcare workers.** If you work in healthcare, you're at increased risk of developing a latex allergy.
* **Rubber industry workers.** Repeated exposure to latex may increase sensitivity.
* **People with a personal or family history of allergies.** You're at increased risk of latex allergy if you have other allergies — such as hay fever or a food allergy — or they're common in your family.

### Connection between food allergy and latex allergy

Certain fruits contain the same allergens found in latex. They include:

* Avocado.
* Banana.
* Chestnut.
* Kiwi.
* Passion fruit.

If you're allergic to latex, you have a greater chance of also being allergic to these foods.

**SYMPTOMS**

If you're allergic to latex, you're likely to have symptoms after touching latex rubber products, such as gloves or balloons. You also can have symptoms if you breathe in latex particles that are released into the air when someone removes latex gloves.

Latex allergy symptoms range from mild to serious. A reaction depends on how sensitive you are to latex and the amount of latex you touch or inhale. Your reaction can become worse with each additional latex exposure.

### Mild symptoms

Mild latex allergy symptoms include:

* Itching.
* Skin redness.
* Hives or rash.

### More-serious symptoms

These include:

* Sneezing.
* Runny nose.
* Itchy, watery eyes.
* Scratchy throat.
* Difficulty breathing.
* Wheezing.
* Cough.

### Life-threatening symptoms: Anaphylaxis

The most serious allergic reaction to latex is anaphylaxis, which can be deadly. An anaphylactic (an-uh-fuh-LAK-tik) reaction develops immediately after latex exposure in highly sensitive people. However, it rarely happens the first time someone is exposed.

Symptoms of anaphylaxis include:

* Difficulty breathing.
* Hives or swelling.
* Nausea and vomiting.
* Wheezing.
* Drop in blood pressure.
* Dizziness.
* Loss of consciousness.
* Confusion.
* Rapid or weak pulse.

**DIAGNOSIS AND TESTS**

Diagnosis is sometimes a challenge. A healthcare professional typically examines the skin and asks questions about symptoms, medical history and if there have been reactions to latex in the past.

A skin test can help find out if someone's skin reacts to the latex protein. A medical professional uses a tiny needle to place a small amount of latex below the surface of the skin on the forearm or back. If someone is allergic to latex, a raised bump will form. Only an allergist or other healthcare professional experienced in skin testing should perform this test.

Blood tests also may be done to check for latex sensitivity.

**Treatment**

Although medicines are available to ease the symptoms of latex allergy, there is no cure. The only way to prevent a latex allergic reaction is to avoid products that contain latex.

Despite your best efforts to avoid latex, you may come into contact with it. If you've had a severe allergic reaction to latex, you may need to always carry injectable epinephrine with you. If you have an anaphylactic reaction, you will need to go to the emergency room for an immediate injection of adrenaline, also known as epinephrine.

For less severe reactions, a care professional may prescribe antihistamines or corticosteroids. These may be taken after exposure to latex to control the reaction and help relieve discomfort.

## Outlook / Prognosis

Most people manage a latex allergy with the help of an allergist. By making lifestyle changes and avoiding latex products and certain foods, you can minimize your risk of reaction. Talk to your healthcare provider about steps you can take to avoid latex and stay safe.

## Prevention

The best way to prevent latex allergy is to avoid latex. That means checking product labels on everything from the clothing and shoes you wear to household items like rubber bands and bandages. If tests show you have a latex allergy, ask your provider for a complete list of potential sources.

You should also:

* Tell providers, caregivers, teachers and friends that you’re allergic.
* Avoid areas where latex may be in the air, such as a hospital room where providers use latex gloves.
* Talk to your healthcare provider about wearing a medical alert bracelet. In a medical emergency, the bracelet lets others know you’re allergic to latex.
* Before a medical procedure or dental work, tell your providers about your allergy. Ask them to use latex-free gloves and equipment.
* If your provider diagnoses you with an IgE-mediated latex allergy, you should carry injectable epinephrine with you. Show caregivers, friends and family members how to give you an injection if you’re having a reaction and can’t inject yourself.
* When ordering from a restaurant, if you have a severe latex allergy, ask the person who prepares your food to wear latex-free gloves.

#### **What products contain latex?**

Products that might contain latex include:

* Balloons.
* Cleaning and medical gloves.
* Parts of clothing and shoes, like raincoats and rain boots, shoe soles and elastic waistbands in underwear.
* Household items, including rubber bands, carpet backing, toys and bandages.
* Personal care items like sanitary napkins, condoms and diaphragms.
* Pacifiers and nipples for baby bottles.
* Some types of makeup, face paint and masks used for costumes.

#### **What foods should I avoid if I have a latex allergy?**

Some foods can cause an allergic reaction in people with a latex allergy. Foods more likely to cause a reaction in people with latex allergy include:

* Chestnuts.
* Certain fruits, including apples, bananas, avocados, peaches, kiwis, nectarines, melons, figs, papayas and tomatoes.
* Some vegetables, including potatoes, celery and carrots.

## Living With

If you have a latex allergy, you need to be vigilant about avoiding anything that you know may cause an allergic reaction. Household items, medical equipment and clothing can contain latex. Read labels carefully. Let healthcare providers, who may examine or treat you with products that contain latex, know about your allergy.

### When to see a doctor

See a healthcare provider if you think you have a latex allergy. They can help you understand what kind of allergy you have and what kind of precautions to take.

**DIFFERENTIAL DIAGNOSIS**

Irritant contact dermatitis can present similarly to a latex allergy and can be mistaken for an allergic reaction when it is, in fact, a nonimmunologic reaction. This type of reaction is due to friction or contact with chemicals resulting in irritated skin. Individuals with these reactions do not have a true latex allergy and may not develop a response to latex. These patients will need a protective barrier for their skin and do not necessarily need to avoid latex exposure.

**EPIDEMIOLOGY**

There have been varying reports of the prevalence of latex allergy among the general population. Latex allergy affects 1 to 2 percent of the population, and one study showed that latex sensitization is more likely in healthcare workers exposed to latex compared to the general population. Clinical manifestation, however, was approximately the same in both healthcare workers and the general population.

In developing countries, there are more cases of latex allergy, as more latex products are in use.Latex results in the most common cause of contact urticaria in occupational health as well as the second most common cause of intraoperative anaphylaxis, second to muscle relaxants.

Epidemiologic studies have shown that a specific patient population such as those with spina bifida are at increased risk of developing a latex allergy with the prevalence of spina bifida hypersensitivity ranging from 20% to 65%. The hypersensitivity is likely related to latex exposure from numerous corrective surgeries and procedures.

Patients with repeated catheterization due to urological abnormalities are also at increased risk.

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**INSECT VENOM ALLERGY**

**DEFINITION AND DESCRIPTION**

Similar to medication, cat hair, pollen or food, insect bites can also trigger an allergy.  
In Switzerland and the rest of Central Europe, the most common causes are bees, wasps or hornets.  
Allergies to bumblebee, horsefly, mosquito and ant stings are much rarer.  
When insects inject (inject) their venom under the human skin via a sting, it acts as a substance in the blood of the person affected, which is recognized as foreign by the human immune system and combated.  
This defense reaction (immune reaction) can be so strong that it produces allergic symptoms, i.e. an allergy.  
In the case of allergies, it is therefore not the poison but the excessive reaction of the immune system that triggers the symptoms of the disease.  
This reaction of your body does not manifest itself the first time you are bitten by an insect to whose venom you are allergic: Only on the second contact with the insect venom (and on all subsequent contacts) does your immune system react because it now recognizes and fights the allergen.  
You may have had previous contact with this venom, for example as a small child, without knowing or remembering it.  
You could therefore be surprised by an unrecognized allergy.

### Frequency and age

Allergies to insect venom are not all that rare; however, the vast majority only experience a strong local reaction after an insect bite: the body only reacts at the site of the bite, i.e. on the surface of the skin and underneath.  
In rarer cases, the sting triggers a systemic reaction that affects the body as a whole and can have a severe impact.  
The so-called systemic reaction after insect bites occurs in around 1.2 to 3.5 percent of the population.  
  
In most cases, however, other factors are involved in addition to the allergic reaction, such as existing cardiovascular disease or severe exhaustion.

## Causes and risk factors

When insect toxins enter your bloodstream, they are foreign bodies (antigens) for your organism.  
Defence cells in the blood (antibodies) recognize these intruders and try to fight them.  
In this case, they are antibodies of the IgE type (immunoglobulin E).  
Their defense mechanism consists of binding to the antigens and thus restricting their activity.  
Insect venoms and other antigens that trigger allergies are also called allergens.  
If the IgE antibodies recognize the allergen in a second or subsequent sting of the same insect species, the body is prepared (sensitized) and can react immediately to the insect sting.  
People with allergic reactions do this to an excessive extent: their immune system reacts too strongly to a substance that is harmless to others.  
When antigens (allergens) and antibodies come into contact, certain substances are released in the tissue.  
These are hormones or messenger substances that are distributed throughout the body via the blood.  
They trigger the allergic symptoms.  
An important messenger substance here is histamine.  
The venom of bees and wasps contains a number of different allergens, some of which are the same.  
The venom of hornets largely corresponds to that of wasps; the composition of the venom of bees is similar to that of bumblebees.  
There is also a certain, albeit smaller, cross-reactivity between bee and wasp venom.  
There are therefore people who are only allergic to bee or wasp venom and others who are allergic to both venoms.

## Symptoms: Insect venom allergy

Sometimes it only takes a few minutes for the first symptoms to appear on the skin after an insect bite.  
Non-local reactions (which go beyond the skin) can still occur after 30 minutes.  
Not every reaction is necessarily an allergic one: there are people who suffer from a severely swollen arm after an insect bite but do not have an insect venom allergy.  
Only a medical diagnosis by means of a blood test (determination of specific IgE against bee and wasp venom) can clarify the situation.

### The symptoms of an insect venom allergy can be divided into different degrees of severity

* Local reaction (local reaction): The insect venom causes redness or swelling of the skin in the area of the bite.  
  Other common symptoms are itching and burning.  
  The area of swelling is less than ten centimeters in diameter and subsides after 24 hours at the latest.  
  This reaction, which is externally limited to the skin, can also be accompanied by unpleasant sensations (e.g. dizziness, headache, general malaise).
* Severe local reaction (increased local reaction): The swelling is usually larger than ten centimeters, painful and persists for more than a day.  
  As a rule of thumb: Swelling that exceeds the palm of the stung person’s hand is considered excessive.  
  If you suffer from this degree of severity of an insect venom allergy, you may also feel a chill or feel ill.
* Systemic reaction (general reaction): In addition to the accompanying symptoms mentioned above, symptoms similar to hay fever may occur (watery eyes, swollen nasal mucosa).  
  However, serious and sometimes life-threatening symptoms are also possible: for example, shortness of breath, dizziness, nausea, diarrhea and cardiovascular problems.
* Allergic shock (anaphylactic shock): This is the most severe possible reaction to insect venom – it can be fatal.  
  If you initially feel a tingling or burning sensation on your tongue or in your throat after an insect bite (or sting), this may be the first sign of anaphylactic shock.  
  If it is not treated immediately, further reactions are possible: rapid heartbeat, vomiting, shortness of breath, excretion of urine and stool, unconsciousness.

### Anaphylactic shock: life-saving emergency aid

If you know that you are one of those people who are allergic to insect venom and have severe symptoms, you should carry an emergency kit with you.  
You can use it in an emergency without outside help and should have familiarized yourself with it before using it for the first time.  
Such a kit usually contains three different, fast-acting drugs, which are administered in liquid form or as a ready-to-use syringe (adrenaline):

* Antihistamine
* Cortisone
* Adrenaline (for injection)

## Diagnosis and test

When you visit us after an insect bite, we will first ask you questions about the specific incident:

* On what occasion were you stung?
* Have you seen the insect?
* What symptoms have occurred?
* How quickly did they appear?

Other questions relate to comparable experiences in your past:

* Have you ever been bitten by an insect?
* With what consequences?

We may also ask you questions about your lifestyle and dietary habits.  
Allergies sometimes take a severe course if their actual trigger (sting or bite) coincides with other factors.  
For example, with psychological stress, the consumption of certain foods or the intake of medication (e.g. beta-blockers, ACE inhibitors).  
This also needs to be clarified when diagnosing an insect venom allergy.  
To find out whether you actually have an insect venom allergy, we may arrange an allergy test.

* The best known is the skin test: In this procedure, insect venoms that are suspected of causing an allergy are highly diluted and brought into direct contact with the skin in small doses.  
  Allergic reactions then usually appear in the form of redness and swelling (wheals).  
  However, more severe symptoms can also occur, which is why the test should always be carried out under medical supervision.

This skin test can also show whether you are allergic not only to one specific venom, but to several.  
For example, if you have developed an allergy to bee venom after a bee sting, a second allergy to another insect venom could occur unnoticed.  
In such a case, medical professionals speak of a cross-reaction or cross-allergy.

* The CAP test (cellulose carrier polymer system) is a laboratory test to determine whether your blood contains certain antibodies (IgE antibodies) that are directed against a specific insect venom.
* Further laboratory tests can be carried out to, for example
  + Recognize differences between bee or wasp venom as a trigger
  + assess the possible protective effects of hyposensitization/immunotherapy with insect venom
  + recognize increased risk factors.

## prevention, early detection, prognosis

The best way to avoid the threatening symptoms of an insect venom allergy is to protect yourself from insects that are dangerous to you.

### The most important measures to avoid insect bites

* Do not walk barefoot outdoors.
* Wear long pants and clothing with long sleeves outdoors.
* Avoid brightly colored clothing because bees can mistake them for flowers.  
  (Wasps, on the other hand, are not interested in colors, but in smells).
* Do not rely on insect repellents; they usually do little or nothing to repel hymenoptera that trigger an insect venom allergy.
* Make sure that you do not drink from glasses or bottles that could contain bees, wasps or other insects that are dangerous to you.
* Please note that certain odors attract insects.  
  These include sweat, fragrances in creams, hairsprays or soap as well as various foods (meat, ham, fruit, sweets).

If you suffer from mastocytosis (a rare skin or blood disorder that sometimes also involves other organs), please make sure you inform us.  
Mastocytosis sufferers have an increased risk of suffering an anaphylactic shock after an insect bite.

### Insect venom allergy: prevention through hyposensitization

One method of prevention is to make your immune system less sensitive to the effects of insect bites or stings, to desensitize it.  
This is done by first administering very small and then slowly increasing amounts of highly diluted insect venom to your body.  
The aim is to get your body used to the venom.  
The aim of hyposensitization is to ensure that your body no longer reacts so violently if you are later exposed to a larger and undiluted dose of venom after a sting.  
This therapy is called desensitization, hyposensitization or specific immunotherapy.  
It usually lasts three to five years.  
Initiation begins with a day spent as an outpatient in hospital (so-called ultra-rush); after three injections in the allergy ward, injections are then required every four to six weeks at intervals of several weeks; these can be carried out by your family doctor or by us.  
Before we carry out hyposensitization on you, we must ensure that you actually have an allergy and that the triggering allergen (the insect venom) is known exactly.  
A further prerequisite is that you have had symptoms after previous contact with this venom (through a sting or bite) that are stressful for you.

### Course and prognosis of insect venom allergy

The acute situation: If you are stung by an insect to whose venom you are allergic, the course of your allergic reaction and the consequences depend above all on whether and how quickly treatment takes place.  
Untreated symptoms can be harmless but also life-threatening; they can last for minutes or even hours.  
The sooner the symptoms of an insect venom allergy appear after a sting, the more serious the complications tend to be – and the higher the likelihood of suffering an anaphylactic shock.  
On the other hand, if the symptoms are treated quickly, they often subside quickly and usually leave no noticeable consequences. The long-term situation: If you know that you suffer from an insect venom allergy, the aforementioned hyposensitization can lead to a favourable prognosis.  
After careful treatment, your chances are good that annoying or threatening insect sting symptoms will only be less severe in the future.  
They may even disappear completely.  
Without hyposensitization, an allergy to bees, wasps or other insects often lasts a lifetime.  
However, allergies can also become less severe with age.  
And they may only appear for the first time later in life.

## Insect venom allergy: effective treatment

If you are allergic to insect bites and have been stung, try to pull the stinger out of your skin as quickly but carefully as possible.  
If there is a venom gland attached to it, do not crush it, but lever it out from underneath with your fingernail, for example – otherwise more venom could get into your bloodstream.  
Beekeepers, who usually have experience with bee stings, flick the stinger out with their fingernail.  
At the same time, ask yourself a simple question: are the symptoms mild (and easily tolerated) or so severe that you need professional help?

## Differential Diagnoses

| **Condition** | **Distinguishing Features** |
| --- | --- |
| Large Local Reaction (Non-Allergic) | Extensive swelling and redness at sting site lasting >24 hours but without systemic symptoms; IgE-mediated allergy absent. |
| Anaphylaxis to Other Allergens | Systemic allergic reactions triggered by foods, medications, or other allergens; no history of insect sting. |
| Allergic Contact Dermatitis | Delayed hypersensitivity reaction causing localized eczema; no systemic symptoms typical of venom allergy. |
| Cellulitis / Bacterial Infection | Localized erythema, warmth, tenderness, fever; progressive infection rather than allergic reaction. |
| Folliculitis / Abscess | Pustular or nodular lesions at site of insect bite/sting; bacterial infection signs. |
| Other Insect Bites (Non-Hymenoptera) | Mosquito, flea, or tick bites causing localized reactions; usually no systemic allergic symptoms. |
| Idiopathic Anaphylaxis | Recurrent unexplained anaphylaxis without identifiable trigger, including insect venom. |
| Physical Urticaria / Dermographism | Urticaria induced by physical stimuli; no insect sting history. |
| Mastocytosis / Mast Cell Disorders | Patients prone to severe anaphylaxis; elevated baseline tryptase; systemic symptoms may mimic venom allergy. |
| Vasovagal Reactions | Syncope or hypotension after sting but without allergic features such as urticaria or bronchospasm. |

**RECOMMENDATIONS**

* If the person is unresponsive and not breathing normally, commence resuscitation
* Move the person to a safe place.
* In the case of a bee sting, remove the sting, by any means without compressing the venom sac e.g. scrape it out, as quickly as possible3.
* For small ticks (larvae and nymphs) use permethrin cream (available at pharmacies). For adult ticks, freeze with an ether containing spray- Avoid the use of freezing or permethrin cream for ticks close to the eyes, genitals or in ear canal
* For tick bite, if in a remote location, or freezing is not possible, consultation with healthcare professionals is recommended. If this is not possible, assess whether there is a history of anaphylaxis to tick bite. If there is a history of anaphylaxis to tick bite, the person should be carrying an adrenaline (epinephrine) auto-injector (eg Epipen™) and this should be used accordingly.
* If attempting removal of ticks in remote locations where there is no known anaphylaxis to tick bite, do not squeeze the body of the tick; use the most fine tipped forceps available to grasp the tick as close as possible to the skin.
* For all bites and stings, apply a cold compress to help reduce pain and swelling (except in the case of tick bites).
* Monitor the person for signs of severe allergic reaction (difficulty speaking, breathing difficulties, collapse, abdominal symptoms and generalized rash).
* Send for an ambulance if multiple stings to the face or tongue have occurred or there is a history of anaphylaxis to the sting or tick.

Rationale for freezing ticks and removal by health professional

The recently published CoSTR from ILCOR on the removal of ticks advised against freezing ticks because it did not result in removal of any ticks. In other countries, the rationale is that the greatest risk from tick bites is severe infections, such as Rickettsia infections, for which ticks are vectors.

References

[Guideline 9.4.3 – Envenomation from Tick Bites and Bee, Wasp and Ant Stings](https://www.anzcor.org/home/first-aid-for-bites-stings-and-poisoning/guideline-9-4-3-envenomation-from-tick-bites-and-bee-wasp-and-ant-stings/)

<https://www.usz.ch/en/disease/insect-venom-allergy/>

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# Allergic Bronchopulmonary Aspergillosis (ABPA)

## Definition and description

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic or hypersensitive reaction to a fungus known as Aspergillus fumigatus. This is a fungi found in the soil.

Although most of us are frequently exposed to Aspergillus, a reaction to it is rare in people with normal immune systems. However, in certain people, the immune system overreacts to the antigens of Aspergillus fumigatus found in the lungs. This may damage the airways and result in permanent lung damage.

ABPA most commonly affects people with asthma or cystic fibrosis. Many people with ABPA also suffer from allergic conditions such as atopic dermatitis (eczema), urticaria (hives), allergic rhinitis (hay fever) and sinusitis.

## **Symptoms** If you have asthma, the first noticeable symptoms of ABPA are usually progressive worsening of your asthma symptoms such as wheezing and shortness of breath.

Other symptoms of ABPA include:  
• Cough with brownish flecks or bloody mucous  
• Fever  
• General weakness or malaise

**Diagnosis**Diagnosis for ABPA is determined by health history, x-rays or CT scans, allergy skin testing and/or blood tests.

## Treatment & Management

The fungus that causes a reaction is difficult to avoid, so medication is typically prescribed to manage ABPA.

Asthma medications such as oral corticosteroids open the airways and make it easier to cough and clear out the fungus. The use of this medication depends upon the individual and the severity of ABPA. The prescription for some people is to take the medication when they have symptoms. Other people with more severe cases of the disease may require daily corticosteroid therapy.

In addition, an oral anti-fungal such as itraconazole may be recommended, although it is somewhat controversial regarding its effectiveness.

If you are diagnosed with ABPA, you should be followed closely by your physician in order to prevent or minimize damage to your lungs.

**EPIDEMIOLOGY**

Allergic bronchopulmonary aspergillosis (ABPA) likely affects between 1 and 15% of cystic fibrosis patients. One study calculated that 2.5% of adults who have asthma also have ABPA, which is approximately 4.8 million people worldwide. Of these 4.8 million people who have ABPA, an estimated 400,000 also have chronic pulmonary aspergillosis (CPA). Another 1.2 million people are estimated to have CPA after having tuberculosis, and over 70,000 people are estimated to have CPA as a complication of sarcoidosis.

Invasive aspergillosis is uncommon and occurs primarily in immunocompromised people. The first population-based incidence estimates for invasive aspergillosis were obtained from laboratory surveillance conducted in the San Francisco Bay Area during 1992-1993 and suggested a yearly rate of 1 to 2 cases of aspergillosis per 100,000 population. However, the epidemiology of invasive *Aspergillus* infections has likely shifted since this time due to the increasing number of solid organ and stem cell transplant recipients and newer immunosuppressive agents. The number of hospitalizations related to invasive aspergillosis in the United States increased an average of 3% per year during 2000-2013. Nearly 15,000 aspergillosis-associated hospitalizations occurred in the United States in 2014, at an estimated cost of $1.2 billion.

Prospective surveillance among transplant recipients performed during 2001-2006 found that invasive aspergillosis was the most common type of fungal infection among stem cell transplant recipients and was the second-most common type of fungal infection among solid organ transplant recipients. In a broad US healthcare network of intensive care unit autopsy studies, aspergillosis was one of the top four most common diagnoses that likely lead to death.

**Differential Diagnosis of allergic bronchopulmonary aspergillosis:**

ABPA mimics many diseases that involve both airway and lung parenchyma. Undiagnosed lung infiltrates, pneumonia, bronchiectasis make a long list of differential diagnoses. Following are few diseases which should be carefully ruled out while making a diagnosis of ABPA:

* Corticosteroid-dependent asthma without ABPA
* Severe asthma with fungal sensitivity (SAFS)
* Cystic fibrosis (CF)
* Bronchiectasis
* Chronic necrotizing aspergillosis
* Chronic eosinophilic pneumonia
* Chronic obstructive pulmonary disease (COPD)
* Churg–Strauss syndrome
* Bronchocentric granulomatosis
* Acute eosinophilic pneumonia (including drug-induced pneumonitis)
* Pulmonary tuberculosis
* Parasitic infections
* Hypersensitivity pneumonitis

**COMPLICATION**

Complications of allergic bronchopulmonary aspergillosis include

* Recurrent asthma exacerbations and steroid dependence
* Aspergilloma
* Invasive aspergillosis
* Chronic pulmonary aspergillosis
* Cavitation
* Local emphysema
* Chronic or recurrent lobar atelectasis
* Honeycomb fibrosis
* Complications related to bronchiectasis like hemoptysis, recurrent pulmonary infection

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**Goodpasture syndrome**

**Definition and description**

Goodpasture syndrome is a rare, life-threatening autoimmune disease that affects your kidneys and lungs. It happens when your immune system attacks collagen because it mistakes it as foreign. Collagen is a protein that helps make up your:

Skin.

Muscles.

Connective tissues, like tendons and ligaments.

Bones.

If you have Goodpasture syndrome, your body produces proteins (antibodies) that attach to collagen in certain parts of your lungs and kidneys. When this happens, it causes inflammation and destroys the tissues. Without treatment, Goodpasture syndrome can cause kidney inflammation (glomerulonephritis) that can lead to kidney failure. It can also cause severe bleeding in your lungs (pulmonary hemorrhage), which is the main cause of death from Goodpasture syndrome.

**Other names for Goodpasture syndrome include**:

Anti-glomerular basement membrane (anti-GBM) disease.

Goodpasture disease.

**How common is Goodpasture syndrome?**

Goodpasture syndrome is very rare. Healthcare experts report fewer than two new cases per 1 million people yearly.

**Symptoms**

Goodpasture syndrome is a pulmonary-renal condition. That means it affects your lungs (pulmonary) and kidneys (renal). Lung-related symptoms usually appear first. They include:

Shortness of breath (dyspnea).

Chest pain.

Cough.

Rattling lung sound when you breathe in.

Feeling very tired (fatigue).

Nosebleeds (epistaxis).

Coughing up blood.

Pale skin (pallor).

Kidney-related symptoms include:

Low red blood cell counts (anemia).

Blood in your pee (hematuria).

Peeing less than usual.

High blood pressure.

Nausea and vomiting.

**Causes Goodpasture syndrome**

Goodpasture syndrome causes your immune system’s antibodies to attack collagen in the glomerular basement membrane (GBM) of your kidneys. The GBM is part of your glomeruli. Glomeruli are tiny blood vessels in your kidneys that help filter your blood. Anti-GBM antibodies also attack collagen in your lungs’ air sacs. This destroys lung tissue, which leads to bleeding and difficulty breathing.

Healthcare providers and medical researchers aren’t exactly sure what causes your immune system to overreact to collagen. It may result from a combination of environmental factors and the genes you inherit from your biological parents. Studies of people with Goodpasture syndrome have shown a strong association with human leukocyte antigen (HLA) DR15. HLAs are proteins that help your immune system tell the difference between your tissues and invading substances.

Sometimes, Goodpasture syndrome can develop after an infection, like a cold or the flu. You may also be more likely to develop it if you:

Smoke.

Inhale (snort) cocaine.

Have exposure to metal dust and hydrocarbon chemicals, like methane or propane.

**Who does Goodpasture syndrome affect?**

Goodpasture syndrome affects people of all ages. But it more often affects those early in life (teens to 30s), then again in the 60s and 70s.

**Diagnosis and Tests**

A healthcare provider will ask about your symptoms and perform a physical exam. They’ll also order tests to help diagnose Goodpasture syndrome, including:

Blood tests. Providers use blood tests to measure your estimated glomerular filtration rate (eGFR). This measures how well your kidneys are working.

Pee test (urinalysis). This can determine if you have blood or high levels of protein (proteinuria) in your pee.

Imaging tests. A chest X-ray or CT scan will determine if you have lung damage.

Bronchoscopy. A provider will use a long, thin tube with a light and camera at the end (bronchoscope) to look for lung damage.

Kidney biopsy. A provider will remove a small sample of kidney tissue to help diagnose kidney disease.

**Management and Treatment**

Yes, with proper diagnosis, Goodpasture syndrome is treatable.

Goodpasture syndrome treatment can vary depending on its severity. Healthcare providers treat mild cases with medications, including:

Corticosteroids, like prednisone, to stop bleeding in your lungs.

Immunosuppressant drugs, like cyclophosphamide, to prevent your immune system from attacking your tissues.

Blood pressure medications (antihypertensives) to help lower your blood pressure and reduce kidney damage.

Providers also use plasmapheresis. During this procedure, they use a needle to remove blood from a vein in your body, usually your arm. They separate the liquid part of your blood (plasma) from the blood cells. The plasma contains the harmful anti-GBM antibodies. They replace your plasma with healthy plasma from blood donors and return it to your body.

**How soon after treatment will I feel better?**

You may need to take immunosuppressant drugs for six to 12 months. In most cases, you need plasmapheresis every day for several weeks.

**Outlook / Prognosis**

Without treatment, Goodpasture syndrome may cause life-threatening bleeding in your lungs. It can also lead to kidney failure. But with an early diagnosis, treatments are effective. Your immune system will only make the antibodies for a short period — a few weeks up to two years. Relapses or recurrences of the disease are very rare.

The most severe complication of Goodpasture syndrome is kidney failure. Kidney failure treatment requires dialysis or a kidney transplant.

**What is my life expectancy if I have Goodpasture syndrome?**

The five-year survival rate for people with Goodpasture syndrome is 80%.

**Prevention**

You may not be able to prevent Goodpasture syndrome. But you can lower your risk by avoiding:

Hydrocarbons, including methane, propane, gasoline, kerosene, tar and asphalt.

Metal dust.

Cocaine.

Hair-coloring products.

**Living With**

If you have Goodpasture syndrome, it’s a good idea to:

Quit smoking and avoid secondary smoke.

Engage in physical activity for at least 30 minutes each day.

Reduce stress.

**When should I see a healthcare provider?**

See a healthcare provider right away if you’re coughing up blood, having trouble breathing, peeing less than usual or having any other symptoms of Goodpasture syndrome. Early diagnosis can significantly improve your outlook. Without treatment, Goodpasture syndrome can cause permanent kidney damage or fatal lung problems.

**DIFFERENTIAL DIAGNOSIS**

All the pulmonary-renal syndromes that affect the lung and kidney should be considered in the differentials:

* Granulomatosis with polyangiitis (previously called Wegener granulomatosis)
* Microscopic polyangiitis
* Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
* Systemic lupus erythematosus

Some IgA-mediated disorders also present with pulmonary-renal syndromes:

* IgA nephropathy
* IgA vasculitis (Henoch-Schönlein purpura)

Other differential diagnoses include the following:

* Acute glomerulonephritis
* Community-acquired pneumonia with infection-related glomerulonephritis
* Cryoglobulinemia
* Endocarditis
* Drug-induced vasculitis
* Alport syndrome (rarely associated with pulmonary symptoms)

EPIDEMIOLOGY

Goodpasture syndrome is a rare disorder. The incidence of the anti-GBM disease is approximately 0.5 to 1.8 cases per million per year in Asian and European populations and is responsible for 1% to 5% of all kinds of glomerulonephritides, and it accounts for 10% to 15% of crescentic glomerulonephritis.Goodpasture syndrome is more common in White patients than Black. However, it may be more prevalent in certain ethnicities, such as the Maori people of New Zealand. The syndrome has a bimodal age distribution around the third and sixth decades of life. Of note, younger patients are more likely to have pulmonary involvement, and older patients are more likely to have less severe renal-limited disease.

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### Autoimmune hemolytic anemia

**Definition**

Autoimmune hemolytic anemia (AIHA) occurs when your immune system mistakes red blood cells as unwanted substances. As a result, your body produces antibodies that destroy red blood cells, which can lead to a low amount of red blood cells (known as anemia).

AIHA is highly manageable, but it can be fatal if left untreated. Immediate intervention is essential.

**Other Names for Hemolytic Anemia**

* Alloimmune hemolytic anemia
* Autoimmune hemolytic anemia (AIHA)
* Drug-induced hemolytic anemia
* Glucose-6-phosphate dehydrogenase (G6PD) deficiency
* Hereditary elliptocytosis
* Hereditary ovalocytosis
* Hereditary spherocytosis
* Immune hemolytic anemia

### What’s the difference between primary and secondary autoimmune hemolytic anemia?

If your AIHA develops without the obvious presence of an underlying condition, it’s called primary AIHA.

Secondary AIHA is when it’s linked to another condition, such as a viral illness, other autoimmune diseases, medication or underlying blood cancer (such as lymphoma).

### What are the types of autoimmune hemolytic anemia?

There are two main types of autoimmune hemolytic anemia: warm autoimmune hemolytic anemia and cold autoimmune hemolytic anemia. This classification depends on the type of antibodies involved in the disease.

#### **Warm autoimmune hemolytic anemia**

The most common type of AIHA, warm autoimmune hemolytic anemia, involves IgG antibodies, which bind red blood cells at normal body temperature. Generally, symptoms occur gradually over the course of several weeks. In some cases, however, they can develop within days.

#### **Cold autoimmune hemolytic anemia**

Affecting 10% to 20% of cases, cold autoimmune hemolytic anemia involves IgM autoantibodies. These bind red blood cells when your blood is at cooler temperatures compared to your body’s core temperature. There’s a wide variation in the temperature threshold at which a cold autoantibody will bind to red blood cells.

### Who does autoimmune hemolytic anemia affect?

AIHA can affect people of all ages and genders, though it most commonly occurs in females over the age of 40.

## Symptoms and Causes

AIHA can result in a wide range of symptoms, including:

* Fever.
* Tiredness.
* Weakness.
* Rapid heartbeat.
* Shortness of breath.
* Paleness.
* Jaundice (yellowing skin).
* Headaches.
* Muscle pain.
* Dark pee.
* Nausea and vomiting.
* Difficulty breathing.
* Diarrhea.
* A sore tongue.
* Heart palpitations.

Many symptoms are specific to the type of AIHA you have.

For example, warm autoimmune hemolytic anemia most commonly causes:

* Tiredness.
* Dizziness.
* Jaundice (yellowing skin).
* Heart palpitations.

Cold autoimmune hemolytic anemia symptoms often include:

* Tiredness.
* Dizziness.
* Cold hands and feet.
* Jaundice.
* Chest pain.
* Pain in the backs of your legs.
* Raynaud’s disease.
* Blue coloring in your hands and feet.
* Arrhythmia.
* Heart murmur.
* Heart failure.

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### Causes of autoimmune hemolytic anemia

In approximately half of all cases, autoimmune hemolytic anemia causes are unknown (idiopathic autoimmune hemolytic anemia). In other cases, there’s a link between AIHA and other disorders.

#### **What disorders can cause autoimmune hemolytic anemia?**

There are several autoimmune diseases associated with secondary AIHA. They include:

* Lupus.
* Rheumatoid arthritis.
* Sjogren’s syndrome.
* Thyroid disease.
* Ulcerative colitis.
* Hashimoto’s disease.

Sometimes, viruses can cause AIHA to develop, though the anemia goes away once the infection is treated. Common viruses that may be linked to AIHA include:

* Epstein-Barr virus.
* Measles.
* Mumps.
* Rubella.
* Atypical pneumonia.
* Varicella, the virus that causes chickenpox.
* HIV.
* Hepatitis.
* Cytomegalovirus.

Medications associated with AIHA include:

* Antibiotics.
* Nonsteroidal anti-inflammatory drugs (NSAIDs).
* Anti-cancer drugs.

## Diagnosis and Tests

Your healthcare provider will recommend a complete blood count (CBC) to look for warning signs of anemia. Specifically, this test measures:

* How many red blood cells, white blood cells and platelets you have.
* The size of your red blood cells.
* Hemoglobin, the protein in your blood that carries oxygen throughout your body.
* Hematocrit (how much space your red blood cells take up in your blood).

### What other tests help diagnose autoimmune hemolytic anemia?

If your healthcare provider suspects anemia, they might order additional tests. These assessments may include:

* Peripheral smear. Your healthcare provider examines a sample of your blood under a microscope to see if your blood cells are being destroyed.
* Reticulocyte count. This test measures how many young red blood cells are in your body. If your bone marrow is making a lot more cells to replace the destroyed ones, then your reticulocyte count will be high.
* Bilirubin test. Bilirubin increases when red blood cells are destroyed.
* Coombs’ test. Your healthcare provider will run this test to determine if your body is making antibodies against red blood cells.
* Haptoglobin test. Haptoglobin is a protein that eliminates debris produced by damaged red blood cells. If your body is using up a lot of haptoglobin, your levels will be low.
* Lactate dehydrogenase (LDH). Lactate dehydrogenase is an enzyme that’s present in red blood cells. When red blood cells are destroyed, the LDH level will rise.
* Cold agglutinin titer. If your healthcare provider suspects cold autoimmune hemolytic anemia, they may perform this test. It tells your healthcare provider the level of antibodies that attack red blood cells at cold temperatures.

## Management and Treatment

Autoimmune hemolytic anemia treatment usually involves addressing underlying conditions first. For example, if your AIHA is linked to lupus, then your healthcare provider will probably start by treating the lupus directly. If AIHA is caused by lymphoma, treating the lymphoma directly is important. If AIHA is associated with a certain drug, you’ll likely stop taking that medication. In addition, people with mild AIHA may not need treatment at all.

#### **Medications**

Corticosteroids help weaken your body’s immune response. That’s why they’re typically the first line of treatment for autoimmune hemolytic anemia. If corticosteroids don’t work, then your healthcare provider may prescribe immunosuppressants. The goal is to stop your immune system from attacking your bone marrow.

#### **Splenectomy**

When medications don’t work, you may need surgery to remove your spleen. Your spleen is responsible for eliminating abnormal red blood cells from your bloodstream, including those with antibodies. The spleen also houses antibody-producing cells. A splenectomy can help preserve red blood cells, reducing the risk of anemia.

#### **Blood transfusion**

In severe cases, people with AIHA may need a blood transfusion.

### Are warm and cold autoimmune hemolytic anemia treated differently?

Primary cold autoimmune hemolytic anemia is treated differently from warm autoimmune hemolytic anemia. Medications that work for warm autoimmune hemolytic anemia include corticosteroids or immunosuppressants. If that approach doesn’t work, then you may need a splenectomy. Blood transfusions are considered in the situation of severe anemia as supportive care while the disease is being treated.

Cold autoimmune hemolytic anemia doesn’t respond well to corticosteroids or splenectomy. In a mild case of cold autoimmune hemolytic anemia, keeping warm by using hand/feet warmers, gloves, socks or even moving to a warmer climate may be enough to keep the disease at bay. When treatment is needed, rituximab with or without other immunosuppressive agents is the first line of therapy.

## Outlook / Prognosis

Autoimmune hemolytic anemia can be so mild you don’t need treatment. But it can also be so advanced that you require surgery or a blood transfusion. If you’ve been diagnosed with AIHA, your healthcare provider can talk with you about the severity of your diagnosis and your treatment options.

### Can autoimmune hemolytic anemia be cured?

Yes. Most people with AIHA only need minimal treatment, if any. About 20% to 30% of people require medication, surgery or a blood transfusion.

It’s important to note that AIHA can be fatal if left untreated. That’s why immediate intervention is so important.

## Prevention

It’s not always possible to prevent autoimmune hemolytic anemia. But if you have a viral infection or use medications that are commonly linked to AIHA, then your healthcare provider can monitor your situation in an effort to reduce your risk of developing the condition.

## Living With

If you start showing anemia symptoms — such as fatigue, weakness, jaundice or shortness of breath — schedule an appointment with your healthcare provider right away.

**Epidemiology of Autoimmune Hemolytic Anemia (AIHA):**

* Incidence:
  + AIHA is a rare disorder with an estimated incidence of approximately 1 to 3 cases per 100,000 persons per year globally.
  + Some studies report an incidence rate around 1.77 to 1.8 per 100,000 person-years.
  + Incidence varies by subtype and population, with warm AIHA (wAIHA) being the most common form, accounting for about 60–70% of cases.
  + Cold agglutinin disease (CAD) accounts for about 13–15% of AIHA cases, and mixed-type AIHA is less than 10%.
* Prevalence:
  + Point prevalence estimates for AIHA range from 15 to 60 cases per million (1.5 to 6 per 100,000).
  + Warm AIHA prevalence is estimated at about 1 per 8,000 persons in some reports.
  + Cold agglutinin disease prevalence is estimated between 14 and 33 per million.
* Age Distribution:
  + AIHA can occur at any age but is most common in middle-aged and older adults, with a median age at diagnosis around 50 to 70 years.
  + Pediatric cases are less common but do occur, often with a higher proportion of secondary AIHA.
  + Warm AIHA median age is approximately 68.7 years in adults.
* Sex Distribution:
  + There is a female predominance, with females constituting about 60–69% of cases overall.
  + This female predominance is less evident in pediatric populations.
* Primary vs Secondary AIHA:
  + Approximately 50% of warm AIHA cases are secondary, commonly associated with autoimmune diseases (e.g., systemic lupus erythematosus), lymphoproliferative disorders, infections, or drug reactions.
  + Nearly all cold AIHA cases are secondary.
* Geographic Distribution:
  + Incidence and prevalence estimates are mostly from North America and Western Europe, with similar ranges reported.
  + AIHA is considered rare worldwide, with no strong racial predilection reported.

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### Hyperacute Graft Rejection

**Definition**

Hyperacute graft rejection is a severe and rapid form of rejection that occurs within minutes to hours after transplantation. It is also known as antibody-mediated graft rejection or humoral graft rejection. This type of rejection is caused by pre-existing antibodies in the recipient's blood that react to the donor's graft, leading to immediate and aggressive immune response.

### Causes of hyperacute graft rejection

The primary cause of hyperacute graft rejection is the presence of preformed antibodies against the donor's human leukocyte antigens (HLA) or other antigens, such as ABO blood group antigens. These antibodies can be formed due to previous exposure to the donor's antigens through blood transfusions, pregnancy, or previous transplants. When the graft is transplanted, the pre-formed antibodies bind to the donor's antigens, activating the complement system and initiating a cascade of events that lead to graft damage and rejection.

### Symptoms

Hyperacute graft rejection is characterized by:

* Rapid onset of graft dysfunction within minutes to hours after transplantation
* Severe inflammation and edema of the graft
* Thrombosis and vascular occlusion
* Graft necrosis and failure The symptoms of hyperacute graft rejection can vary depending on the type of transplant, but common symptoms include:
* Decreased urine output (in kidney transplants)
* Increased liver enzymes (in liver transplants)
* Shortness of breath (in lung transplants)
* Cardiac dysfunction (in heart transplants)

### Diagnosis and Treatment

Diagnosis of hyperacute graft rejection is based on clinical presentation, laboratory tests, and histopathological examination of the graft. Treatment options are limited, and the primary goal is to remove the graft and support the recipient's vital functions. In some cases, plasmapheresis may be used to remove the pre-formed antibodies from the recipient's blood.

### Prevention

Prevention of hyperacute graft rejection is crucial and involves:

* Screening for pre-formed antibodies against the donor's HLA and other antigens
* ABO blood group matching
* Cross-matching of the recipient's serum with the donor's lymphocytes
* Use of immunosuppressive agents to reduce the risk of rejection

**Epidemiology of Hyperacute Graft Rejection**

* Incidence:
  + Hyperacute graft rejection is a rare event, with a reported incidence of less than 1% of all transplants.
  + The frequency has been declining steadily due to advances in pretransplant screening for donor-specific antibodies (DSA) and improved crossmatching techniques.
  + Improved detection of preformed anti-donor antibodies, especially against ABO blood group and HLA antigens, has significantly reduced hyperacute rejection rates.
* Timing:
  + Occurs immediately or within minutes to hours after transplantation, often during or shortly after reperfusion of the graft.
* Risk Factors:
  + Presence of preformed antibodies due to previous sensitization from blood transfusions, pregnancies, or prior transplants.
  + ABO incompatibility between donor and recipient.
  + Insufficient or inadequate pretransplant immunological testing.
* Organ-Specific Data:
  + Most commonly reported in kidney and heart transplants, but can occur with other solid organ transplants.
  + The incidence of hyperacute rejection is now very low in centers with rigorous immunological screening.

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# Transplant rejection

Transplant rejection is a process in which a transplant recipient's immune system attacks the transplanted organ or tissue.

## Causes

Your body's immune system usually protects you from substances that may be harmful, such as germs, poisons, and sometimes, cancer cells.

These harmful substances have proteins called antigens coating their surfaces. As soon as these antigens enter the body, the immune system recognizes that they are not from that person's body and that they are "foreign," and attacks them.

When a person receives an organ from someone else during transplant surgery, that person's immune system may recognize that it is foreign. This is because the person's immune system detects that the antigens on the cells of the organ are different or not "matched." Mismatched organs, or organs that are not matched closely enough, can trigger a blood transfusion reaction or transplant rejection.

To help prevent this reaction, doctors type, or match both the organ donor and the person who is receiving the organ. The more similar the antigens are between the donor and recipient, the less likely that the organ will be rejected.

Tissue typing ensures that the organ or tissue is as similar as possible to the tissues of the recipient. The match is usually not perfect. No two people, except identical twins, have identical tissue antigens.

Doctors use medicines to suppress the recipient's immune system. The goal is to prevent the immune system from attacking the newly transplanted organ. If these medicines are not used, the body will almost always launch an immune response and destroy the foreign tissue.

There are some exceptions, though. Cornea transplants are rarely rejected because the cornea has no blood supply. Also, transplants from one identical twin to another are almost never rejected.

There are three types of rejection:

* **Hyperacute rejection** occurs a few minutes after the transplant when the antigens are completely unmatched. The tissue must be removed right away so the recipient does not die. This type of rejection is seen when a recipient is given the wrong type of blood. For example, when a person is given type A blood when he or she is type B.
* **Acute rejection** may occur any time from the first week after the transplant to 3 months afterward. All recipients have some amount of acute rejection.
* **Chronic rejection** can take place over many years. The body's constant immune response against the new organ slowly damages the transplanted tissues or organ.

## Symptoms

Symptoms may include:

* The organ's function may start to decrease
* General discomfort, uneasiness, or ill feeling
* Pain or swelling in the area of the organ (rare)
* Fever (rare)
* Flu-like symptoms, including chills, body aches, nausea, cough, and shortness of breath

The symptoms depend on the transplanted organ or tissue. For example, patients who reject a kidney may make less urine, and patients who reject a heart may have symptoms of heart failure.

## Exams and Tests

The health care provider will examine the area over and around the transplanted organ.

Signs that the organ is not working properly include:

* High blood sugar (pancreas transplant)
* Less urine released (kidney transplant)
* Shortness of breath and less ability to exercise (heart transplant or lung transplant)
* Yellow skin color and easy bleeding (liver transplant)

A biopsy of the transplanted organ can confirm that it is being rejected. A routine biopsy is often performed periodically to detect rejection early, before symptoms develop.

When organ rejection is suspected, one or more of the following tests may be done before the organ biopsy:

* Abdominal CT scan
* Chest x-ray
* Heart echocardiography
* Kidney arteriography
* Kidney ultrasound
* Lab tests of kidney or liver function

## Treatment

The goal of treatment is to improve the chances that the transplanted organ or tissue continues to work properly by suppressing your immune system response. Suppressing the immune response may prevent transplant rejection.

Medicines will likely be used to suppress the immune response. Dosage and choice of medicines depends on your condition. The dosage may be very high while the tissue is being rejected. After you no longer have signs of rejection, the dosage will likely be lowered.

## Outlook (Prognosis)

Medicines that suppress the immune system may stop the rejection. Most people need to take these medicines for the rest of their life.

Single episodes of acute rejection rarely lead to organ failure.

Chronic rejection is the leading cause of organ transplant failure. The organ slowly loses its function and symptoms start to appear. This type of rejection cannot be effectively treated with medicines. Some people may need another transplant.

## Possible Complications

Health problems that may result from transplant or transplant rejection include:

* Certain cancers (in some people who take strong immune-suppressing medicines for a long time)
* Infections (because the person's immune system is suppressed by taking immune-suppressing medicines)
* Loss of function in the transplanted organ/tissue
* Side effects of medicines, which may be severe

## When to Contact a Medical Professional

Contact your provider if the transplanted organ or tissue does not seem to be working properly, or if other symptoms occur. Also, contact your provider if you have side effects from medicines you are taking.

## Prevention

ABO blood typing and HLA (tissue antigen) typing before a transplant helps ensure a close match.

You will likely need to take medicine to suppress your immune system for the rest of your life to prevent the tissue from being rejected.

Being careful about taking your post-transplant medicines and being closely watched by your doctor may help prevent rejection.

## Alternative Names

Graft rejection; Tissue/organ rejection

**DIFFERENTIAL DIAGNOSIS**

Depending on the transplanted tissue or organ involved, various differential diagnoses that may present with similar clinical features following a graft procedure should be considered when evaluating acute transplantation rejection. For instance, following lung transplantation, conditions including reimplantation response and infection should be excluded, while acute tubular necrosis should be considered following renal transplants.Furthermore, cytologic examination of voided urine is the simple diagnostic method for differentiating allograft rejection and CMV infection. IgM anti-CMV antibodies can be detected and confirm the diagnosis of CMV infection. Adenovirus nephropathy may mimic allograft rejection and can be ruled out by polymerase chain reaction of the blood

**EPIDEMIOLOGY**

The risk of acute transplantation is highest in the first weeks following a transplantation procedure, with an estimated incidence of 50% to 70%.In renal transplantation, acute rejection rates have dramatically fallen, chiefly due to immunosuppressive (eg, calcineurin inhibitor) regimens. The long-term outcome has improved. Delayed graft function is a significant risk factor for acute rejection due to vulnerability or prolonged preservation times of allografts

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### Serum sickness

**DEFINITION AND DESCRIPTION**

Serum sickness is your immune system’s response to medication. The medicines cause hypersensitivity.

Serum sickness takes time to develop. It may take up to three weeks after your first exposure to a medicine. After the first exposure, you may develop symptoms just a few days after another exposure.

#### **Mechanism of serum sickness**

Healthcare providers classify immune reactions to a foreign substance (antigen) as hypersensitivity reactions. There are four types of hypersensitivity reactions. Serum sickness is type 3.

* Type 1. A type 1 hypersensitivity reaction is an immediate reaction that involves immunoglobulin E (IgE). IgE are antibodies that your immune system makes. They target specific types of allergens and attach to cells that contain histamine (mast cells). When IgE encounters the allergen, it causes the mast cells to release the histamine and other inflammatory mediators. Examples include a severe allergic reaction (anaphylaxis) and hay fever (allergic rhinitis).
* Type 2. A type 2 hypersensitivity reaction involves immunoglobulin G (IgG) or immunoglobulin M (IgM). IgG is the most common antibody and protects your body from infections. IgM is an antibody in your blood and lymph node fluid. It’s the first type of antibody your body makes to combat a new infection. An example is drug-induced hemolytic anemia.
* Type 3. IgM or IgG antibodies attach to the antigen to form an immune complex. The immune complex attaches to tissues or the walls of your blood vessels. You may have a localized reaction (symptoms around or that extend slightly beyond where you got a sting, bite or injection) or a systemic reaction (symptoms that spread to other organ systems in your body). Serum sickness is an example of a systemic type 3 reaction.
* Type 4. T lymphocytes (T-cells) cause type 4 hypersensitivity reactions, not antibodies. T-cells are a type of white blood cell. Examples include contact dermatitis from nickel or poison ivy.

## Symptoms

## Serum sickness symptoms may include:

* General feeling of illness, discomfort or fatigue (malaise).
* Skin rash.
* Hives.
* Itchy skin.
* Fever.
* Joint pain.
* Swollen lymph nodes.

### Causes serum sickness

Causes of serum sickness reactions may include:

* Antibiotics, including penicillin, sulfonamides and tetracyclines.
* Antivenoms (antivenins).
* Barbiturates.
* Buproprion.
* Medicines that contain proteins from animals or insects.
* Monoclonal antibodies.
* Stings or bites from bees, wasps, mosquitos and ticks.
* Streptokinase (a medicine that breaks up blood clots).
* Vaccines.

Many other antibiotics and other medications may cause serum sickness. Talk to a healthcare provider to get a complete list.

#### **What is the most common cause of serum sickness today?**

The most common causes of serum sickness reactions include:

* Antibiotics.
* Antitoxins.
* Antivenoms.
* Vaccines.
* Streptokinase.

#### **Can adults get serum sickness?**

Yes. Anyone can get serum sickness, including adults.

### Complications of serum sickness

Serum sickness complications may include:

* Kidney injury.
* Inflammation in your blood vessels (vasculitis).
* Nerve damage (neuropathy).
* A sudden drop in blood pressure in your body (shock).

Very rarely, serum sickness can cause glomerulonephritis (GN). GN is a type of kidney disease that damages the tiny blood vessels in your kidneys (glomeruli) that help filter your blood.

## Diagnosis and Tests

You may have serum sickness if you develop allergy-like symptoms several days or weeks after taking a medicine. A healthcare provider can make an official diagnosis. They’ll:

* Ask about your medical history.
* Ask if you’re taking any medications, including whether you’ve taken any medications or received any medications over the last several weeks.
* Perform a physical examination, including checking your lymph nodes for swelling or tenderness.

They’ll also order tests to confirm serum sickness.

#### **TESTS**

Healthcare providers usually diagnose serum sickness after reviewing your symptoms and performing a physical exam. But they may order the following tests to confirm the diagnosis and determine its severity:

* Blood test. They’ll use a tiny needle to withdraw a small amount of blood from a vein, usually in your arm, and study it in a lab.
* Skin biopsy. They’ll remove a small sample of your skin tissue and examine it in a lab. They’ll look for inflammation in your blood vessels along with different types of immunoglobulin.
* Urinalysis. You’ll urinate (pee) into a cup and they’ll examine your sample under a microscope. Your kidneys make pee and serum sickness can affect your kidneys. They’ll look for signs of kidney damage in your pee.

## Management and Treatment

Yes, serum sickness is curable. Symptoms usually go away on their own after a few days. But treatment may include the following:

* Stopping the medicine that causes serum sickness, if possible.
* Corticosteroids.
* Antihistamines.
* Nonsteroidal anti-inflammatory drugs (NSAIDs).

Following your healthcare provider’s recommended treatment is the best way to recover from serum sickness. Most people feel better a few days after symptoms start.

## Outlook / Prognosis

The outlook for serum sickness is good. Many people make a full recovery without treatment after a few days. But regular or long-term exposure to the medicine that causes serum sickness can cause serious problems, including kidney damage and even kidney failure.

Serum sickness usually doesn’t have long-term effects. Be sure to avoid any medicines that cause serum sickness to prevent kidney failure.

## Prevention

The best way to prevent serum sickness is to avoid medicines that cause symptoms.

## Living With

It’s a good idea to talk to a healthcare provider if you take a medicine or antiserum (plasma) and develop symptoms of serum sickness a few weeks later. They’ll conduct tests and, if necessary, give you a new medicine that doesn’t cause serum sickness.

## Differential Diagnoses

* Cryoglobulinemia
* Immediate Hypersensitivity Reactions
* Epstein-Barr Virus (EBV) Infectious Mononucleosis (Mono)
* Infective Endocarditis
* Kawasaki Disease
* Small-Vessel Vasculitis (Leukocytoclastic Vasculitis)
* Poststreptococcal Glomerulonephritis
* Sickle Cell Disease

## Epidemiology

The annual incidence of serum sickness is decreasing as the administration of foreign antigens in medical therapeutics is refined.The likelihood of developing serum sickness is dose-related. In one study, 10% of patients who received 10 mL of tetanus antitoxin developed serum sickness; the administration of 80 mL or more produced the disease in almost all patients.

The likelihood also varies by antigen type. Antirabies serum is associated with a higher likelihood (16.3%) of serum sickness than tetanus antitoxin (2.5%-5%).The reported rate of serum sickness–like reaction per course of cefaclor in United States children is 0.2%.

In one study, serum sickness was more common in patients older than 15 years who were given antirabies serum.Antibiotic-associated serum sickness–like disease, however, is more frequently described in children younger than 5 years.

In a prospective cohort study of 109 patients who received snake antivenom in Australia, serum sickness occurred in 29% of the patients.

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### LUPUS (Systemic Lupus Erythematosus)

### DEFINITION AND DESCRIPTION

Lupus is a condition that causes inflammation throughout your body. It’s an autoimmune disease, which means your immune system damages your body instead of protecting it. You may experience symptoms throughout your body depending on where your autoimmune system damages tissue, including in your:

* Skin.
* Blood.
* Joints.
* Kidneys.
* Brain.
* Heart.
* Lungs.

Visit a healthcare provider if you notice new pain, rashes or changes to your skin, hair or eyes.

#### **Types of lupus**

Healthcare providers sometimes call lupus systemic lupus erythematosus (SLE). It’s the most common type of lupus, and means you have lupus throughout your body. Other types include:

* Cutaneous lupus erythematosus: Lupus that only affects your skin.
* Drug-induced lupus: Some medications trigger lupus symptoms as a side effect. It’s usually temporary and might go away after you stop taking the medication that caused it.
* Neonatal lupus: Babies are sometimes born with lupus. Babies born to biological parents with lupus aren’t certain to have lupus, but they might have an increased risk.

## Symptoms

Lupus causes symptoms throughout your body, depending on which organs or systems it affects. Everyone experiences a different combination and severity of symptoms.

Lupus symptoms usually come and go in waves called flare-ups. During a flare-up, the symptoms can be severe enough to affect your daily routine. You might also have periods of remission when you have mild or no symptoms.

Symptoms usually develop slowly. You might notice one or two signs of lupus at first, and then more or different symptoms later on. The most common symptoms include:

* Joint pain, muscle pain or chest pain (especially when you’re taking a deep breath).
* Headaches.
* Rashes (it’s common to have a rash across your face that providers sometimes call a butterfly rash).
* Fever.
* Hair loss.
* Mouth sores.
* Fatigue (feeling tired all the time).
* Shortness of breath (dyspnea).
* Swollen glands.
* Swelling in your arms, legs or on your face.
* Confusion.
* Blood clots.

Lupus can sometimes cause other health conditions or issues, including:

* Photosensitivity (sensitivity to sunlight).
* Dry eye.
* Depression (or other mental health conditions).
* Seizures.
* Anemia.
* Raynaud’s syndrome.
* Osteoporosis.
* Heart disease.
* Kidney disease.

### Causes of lupus

Experts don’t know for certain what causes lupus. Studies have found that certain factors about your health or where you live may trigger lupus:

* Genetic factors: Having certain genetic mutations may make you more likely to have lupus.
* Hormones: Reactions to certain hormones in your body (especially estrogen) may make you more likely to develop lupus.
* Environmental factors: Aspects about where you live and how much pollution or sunlight you’re exposed to might affect your lupus risk.
* Your health history: Smoking, your stress level and having certain other health conditions (like other autoimmune diseases) might trigger lupus.

#### **Risk factors**

Anyone can develop lupus, but some groups of people have a higher risk:

* Women, especially women between the ages of 15 and 44.
* Black people.
* Hispanic people.
* Asian people.
* Native Americans, Alaska Natives and First Nations people.
* Pacific Islanders.
* People with a biological parent who has lupus.

## Diagnosis and Tests

A healthcare provider will diagnose lupus with a physical exam and some tests. They’ll examine your symptoms and talk to you about what you’re experiencing. Tell your provider when you first noticed symptoms or changes in your body. Your provider will ask about your medical history, including conditions you may have now and how you’re treating or managing them.

Lupus can be tricky to diagnose because it can affect so many parts of your body and cause lots of different symptoms. Even small changes or issues that seem unusual for you can be a key. Don’t be afraid to tell your provider about anything you’ve felt or sensed — you know your body better than anyone.

#### **Test**

There’s not one test that can confirm a lupus diagnosis. Diagnosing it is usually part of a differential diagnosis. This means your provider will probably use a few tests to determine what’s causing your symptoms before ruling out other conditions and diagnosing you with lupus. They might use:

* Blood tests to see how well your immune system is working and to check for infections or other issues like anemia or low blood cell counts.
* Urinalysis to check your pee for signs of infections or other health conditions.
* An antinuclear antibody (ANA) test looks for antibodies (protein markers that show a history of your body fighting off infections). People who have lupus usually have certain antibodies that show their immune system has been overly active.
* A biopsy of your skin or kidney tissue can show if your immune system has damaged them.

## Management and Treatment

Your healthcare provider will suggest treatments for lupus that manage your symptoms. The goal is minimizing damage to your organs and how much lupus affects your day-to-day life. Most people with lupus need a combination of medications to help them prevent flare-ups and lessen their symptom severity during one. You might need:

* Hydroxychloroquine: Hydroxychloroquine is a disease-modifying antirheumatic drug (DMARD) that can relieve lupus symptoms and slow down how they progress (change or get worse).
* Nonsteroidal anti-inflammatory drugs (NSAIDs): Over-the-counter (OTC) NSAIDs relieve pain and reduce inflammation. Your provider will tell you which type of NSAID will work best for you, and how often you should take it. Don’t take NSAIDs for more than 10 days in a row without talking to your provider.
* Corticosteroids: Corticosteroids are prescription medications that reduce inflammation. Prednisone is a common corticosteroid provider use to manage lupus. Your provider might prescribe you pills you take by mouth or inject a corticosteroid directly into one of your joints.
* Immunosuppressants: Immunosuppressants are medications that hold back your immune system and stop it from being as active. They can help prevent tissue damage and inflammation.

You might need other medications or treatments to manage specific lupus symptoms you have or other health conditions it’s causing. For example, you may need treatment for anemia, high blood pressure (hypertension) or osteoporosis if lupus causes those issues.

## Outlook / Prognosis

Lupus is a lifelong (chronic) condition. You should expect to manage lupus symptoms for the rest of your life.

Lupus can be unpredictable, and the way it impacts you can change over time. You’ll need to regularly visit your healthcare provider so they can track changes in your symptoms.

You’ll probably work with a team of providers as you learn to live with lupus. Your primary care provider will suggest specialists who can help with specific issues or symptoms. You’ll probably need to visit a rheumatologist — a healthcare provider who specializes in diagnosing and treating autoimmune diseases. Which specialists you need to visit depends on which symptoms you have and how they affect your body.

There’s currently no cure for lupus. Your healthcare provider will help you find a combination of treatments to manage your symptoms and hopefully put lupus into remission (long periods of time with no symptoms or flare-ups).

## Prevention

You can’t prevent lupus because experts aren’t sure what causes it. Talk to a healthcare provider about your risk if one of your biological parents has lupus.

### How can I prevent lupus flare-ups?

You might be able to prevent and reduce lupus flare-ups by avoiding activities that trigger your symptoms, including:

* Avoiding sun exposure: Spending too much time in the sun can trigger lupus symptoms in some people. Try to avoid going outside when the sun is brightest (usually between 10 a.m. and 4 p.m.). Wear long sleeves, a hat or sun-protective clothing. Use a sunscreen that’s at least SPF 50.
* Staying active: Joint pain can make it hard or painful to move. But moving and gently using your joints can be the best way to relieve symptoms like pain and stiffness. Walking, biking, swimming, yoga and tai chi are all great ways to move your body without putting too much stress on your joints. Ask your healthcare provider which types of activities are safest for you.
* Getting enough sleep and protecting your mental health: Living with lupus can be frustrating. Getting the right amount of sleep (seven to nine hours for adults) and reducing your stress can help prevent flare-ups for some people. A psychologist or other mental health professional can help you develop healthy coping mechanisms.

## Living With

Visit a healthcare provider as soon as you notice any new or changing symptoms. Even small shifts in what you’re feeling and experiencing can be important.

Talk to your provider if it feels like your treatments aren’t managing lupus symptoms as well as they used to. Tell your provider if you’re having flare-ups more often — or if the flare-ups cause more severe symptoms. They’ll help you adjust your treatments as needed.

Go to the emergency room or call 911 (or your local emergency services number) if you’re experiencing any of the following symptoms:

* You can’t breathe.
* You’re in severe pain.
* You think you’re experiencing heart attack symptoms

**Epidemiology of Systemic Lupus Erythematosus (SLE)**

* Global Prevalence:
  + The estimated global prevalence of SLE is approximately 43.7 per 100,000 persons (range 15.9 to 108.9 per 100,000), affecting about 3.41 million people worldwide.
  + Prevalence varies widely by region, with the highest rates reported in the United Arab Emirates (~167 per 100,000), Barbados (~163 per 100,000), Cuba, and Brazil, and the lowest in Argentina (~5 per 100,000).
  + Prevalence is generally higher in high-income countries and tropical Latin America.
* Global Incidence:
  + The global incidence is estimated at 5.14 per 100,000 person-years, corresponding to about 400,000 new cases annually worldwide.
  + Incidence varies regionally from as low as 1.18 per 100,000 person-years in Central Asia to 13.74 per 100,000 in Central Europe.
  + Poland, the USA, and Barbados have among the highest reported incidence rates.
* Sex Differences:
  + SLE predominantly affects women, especially those of reproductive age.
  + Female incidence is about 8.8 per 100,000 person-years, with prevalence around 79 per 100,000.
  + Male incidence and prevalence are much lower, approximately 1.5 per 100,000 person-years and 9.3 per 100,000, respectively.
* Age Distribution:
  + Most new cases occur in adults, with adult incidence about 1.4 times higher than in the general population.
  + Peak incidence is typically in women aged 15–45 years.
  + Pediatric cases are less common but recognized.
* Ethnic and Geographic Variations:
  + Higher prevalence and incidence are reported among individuals of Asian, Black, Hispanic, and Indigenous descent compared to White populations.
  + Environmental, genetic, socioeconomic, and healthcare access factors contribute to these disparities.
  + Data are limited or lacking for many low- and middle-income countries, particularly in Africa, parts of Asia, and Latin America.
* Trends:
  + Some studies suggest an increasing prevalence over time, possibly due to improved diagnosis and survival.
  + Mortality remains elevated, about 2–3 times higher than in the general population, with infections and cardiovascular disease being leading causes of death

## Differential Diagnoses of Systemic Lupus Erythematosus (SLE)

* Adult-onset Still Disease
* Behçet Syndrome
* Chronic Fatigue Syndrome
* HIV Infection
* Inflammatory Bowel Disease (IBD)
* Lyme Disease
* Mixed Connective Tissue Disease (MCTD)
* Psoriatic Arthritis
* Reactive Arthritis
* Rheumatoid Arthritis (RA)
* Sarcoidosis
* Systemic Sclerosis (Scleroderma)
* Drug-induced Lupus
* Fibromyalgia
* Viral Infections (e.g., Epstein-Barr Virus, Hepatitis C)
* Hemophagocytic Lymphohistiocytosis (HLH)
* Anti-GBM Antibody Disease (Goodpasture’s Syndrome)
* Antiphospholipid Antibody Syndrome
* Acute Poststreptococcal Glomerulonephritis
* Angioedema
* Other Autoimmune and Inflammatory Disorders

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### Hypersensitivity pneumonitis

**Definition and description**

Hypersensitivity pneumonitis (HP) is a type of allergy that causes inflammation in the small air sacs of your lungs (alveoli). Your symptoms can be immediate (acute) and go away quickly, or they may develop over time and become ongoing (chronic).

Chronic hypersensitivity pneumonitis is considered an interstitial lung disease. It can lead to lung scarring over time.

## Alternative Names

Extrinsic allergic alveolitis; Farmer's lung; Mushroom picker's disease; Humidifier or air-conditioner lung; Bird breeder's or bird fancier's lung

#### **What is the difference between hypersensitivity pneumonitis and other allergies?**

Hypersensitivity pneumonitis causes a different immune reaction in your body than pollen or pet allergies. Unlike common allergies that cause hay fever and asthma, repeated exposure to allergens that cause HP can lead to inflammation that can permanently damage your lungs.

### Who does hypersensitivity pneumonitis affect?

You’re at higher risk for hypersensitivity pneumonitis if you work in certain occupations or are around specific allergens. You’re more likely to develop HP if you:

* Work on a farm (for instance, with cattle or vegetables).
* Handle animals (veterinarians, bird or poultry handlers).
* Process and load grains or flour.
* Work in lumber mills or strip wood.
* Manufacture wallboard and paper.
* Are a metal worker.
* Are around bird droppings or feathers. This includes using feather-filled bedding.
* Breathe in allergens from humidifiers, heating and air conditioning systems or hot tubs, especially if they aren’t maintained well.
* Are between 50 and 70 years old.

#### **Is hypersensitivity pneumonitis serious?**

Hypersensitivity pneumonitis can be very serious. If you have repeated exposures to allergens that cause HP, the inflammation in your lungs can cause permanent damage.

### How does hypersensitivity pneumonitis affect my body?

If you have hypersensitivity pneumonitis, your body overreacts to particles (allergens) you’re breathing in, usually while on the job or in your home. The allergens are small enough to get all the way into the small air sacs in your lungs (alveoli) and cause inflammation.

When you first react to the allergen, your body makes chemicals to recognize it in the future. As you’re exposed to the allergen again and again, your body becomes more sensitized and responds with worsening reactions. Over time, this damages your alveoli and the small airways that lead to them. This causes symptoms like shortness of breath and coughing.

## Symptoms and Causes

Symptoms of hypersensitivity pneumonitis can be acute or chronic. Acute symptoms come on within a few hours of being around an allergen and last a few hours or days. Chronic symptoms can develop slowly and get worse over time.

#### **Symptoms of acute hypersensitivity pneumonitis**

* Shortness of breath (dyspnea).
* Dry cough.
* Chest tightness.
* Chills.
* Fatigue.
* Fever.
* Muscle aches.

#### **Symptoms of chronic hypersensitivity pneumonitis**

* Shortness of breath, especially with exertion or activity.
* Cough.
* Fatigue.
* Weight loss.
* Finger or toe clubbing.

### What does hypersensitivity pneumonitis feel like?

Acute hypersensitivity pneumonitis might feel like the flu. Chronic HP can develop gradually and may be harder to pinpoint. You might notice that you get short of breath easier than you used to or that you have a cough or fatigue that’s slowly gotten worse.

### Causes hypersensitivity pneumonitis

Breathing in substances (allergens) that create an immune reaction in your lungs causes hypersensitivity pneumonitis. Over time, this can damage your lungs and worsen your symptoms. There are over 300 known causes of hypersensitivity pneumonitis, including:

* Bacteria.
* Molds and fungi.
* Certain chemicals and metals.
* Animal and plant proteins.

#### **Examples of hypersensitivity pneumonitis**

Many allergens cause types of hypersensitivity pneumonitis that go by their own names. Examples of HP include:

| **Condition** | **Caused by** |
| --- | --- |
| Bird fancier’s lung. | Proteins in bird feathers or droppings. |
| Farmer’s lung. | Mold that grows on hay, straw and grain. |
| Hot tub lung. | Bacteria in water vapor from hot tubs. |
| Humidifier lung. | Fungi and bacteria in humidifiers and heating and air conditioning systems. |
| Cheese worker’s lung (or cheese washer’s lung). | Fungi on cheese. |
| Bagassosis. | Sugar cane mold dust. |
| Mushroom worker’s lung. | Dust from fungi. |

### Does COVID-19 cause hypersensitivity pneumonitis?

COVID-19 isn’t a known cause of hypersensitivity pneumonitis, but it can cause lung inflammation that sometimes looks like HP. There’s also evidence that it may make existing HP worse.

## Diagnosis and Tests

A healthcare provider diagnoses hypersensitivity pneumonitis based on your symptoms and personal history, physical exam and other tests. They may ask you about your work or living environment to understand if you could be exposed to allergens.

Your provider will listen to your lungs with a stethoscope and check your oxygen level with a device they put on your finger (pulse oximeter). You might also get lung function tests, blood tests or imaging.

### What tests will be done to diagnose hypersensitivity pneumonitis?

To help diagnose hypersensitivity pneumonitis, your provider might perform or order additional tests, including:

* Allergy blood tests. A provider takes a small sample of blood from your arm using a needle. A lab tests the sample to see if you have signs of a reaction to the allergens that cause HP (hypersensitivity pneumonitis panel).
* Imaging. Chest X-rays and CT scans give your provider images of your lungs so they can look for damage.
* Pulmonary function tests. Most lung function tests involve breathing into a tube attached to a machine to measure how well your lungs are working. Your provider may also do blood tests or exercise tests to check your lung function.
* Bronchoscopy. A healthcare provider uses a small, flexible tube passed through your nose or mouth to view the inside of your lungs and collect samples.

## Management and Treatment

To successfully treat hypersensitivity pneumonitis, you have to stay away from the cause.

Even with medication, HP won’t go away completely if you continue to breathe in the allergen. Chronic HP causes damage that may get worse even if you aren’t exposed to the allergen anymore.

Your provider may prescribe drugs to reduce inflammation, open your airways or increase your oxygen levels.

### Medications/treatments used for hypersensitivity pneumonitis

* Corticosteroids or immunosuppressive medications. These medications help reduce inflammation. Specific drugs could include prednisone, mycophenolate or azathioprine.
* Anti-fibrotic drugs (pirfenidone and nintedanib). These medications can slow lung scarring.
* Pulmonary rehabilitation. Breathing exercises and physical therapy can help make breathing easier.
* Oxygen therapy. If you have severe HP, you may need extra oxygen to make sure your blood or tissues are getting enough. It’s delivered through a mask on your face or a tube in your nose.
* Lung transplant. If your HP progresses to pulmonary fibrosis, you may need a lung transplant.

#### **How soon after treatment for hypersensitivity pneumonitis will I feel better?**

It can take several months for your lungs to heal from the inflammation HP causes. Some damage can be permanent.

### How do you get rid of hypersensitivity pneumonitis?

You usually can’t get rid of chronic hypersensitivity pneumonitis. Acute and subacute HP can go away on its own or with medication if you aren’t exposed to the allergen anymore.

## Outlook / Prognosis

What you can expect depends on how long you’ve had hypersensitivity pneumonitis and how severe it is.

Acute HP usually goes away within a few days as long as you don’t get exposed to the allergen again. Subacute cases of HP (caused by longer, low-level exposure to allergens over time) can last a few months and are usually treated with medication. Chronic HP usually doesn’t go away but medication may make your symptoms more manageable.

#### **Complications of hypersensitivity pneumonitis**

With continued exposure to an allergen that causes HP, you can have serious complications, including:

* Scarring in your lungs (pulmonary fibrosis).
* High blood pressure between your heart and lungs (pulmonary hypertension).

#### **Outlook for hypersensitivity pneumonitis**

The outlook for chronic hypersensitivity pneumonitis depends on the damage to your lungs. If you don’t have lung scarring, research suggests you can have significant improvement within a year of diagnosis. For those with lung scarring, HP is often fatal within a few years without a lung transplant.

### What is the life expectancy of someone with hypersensitivity pneumonitis?

Life expectancy of someone with hypersensitivity pneumonitis depends on the severity of damage to their lungs. A lung transplant can extend your life past these expected timelines.

* Someone with no scarring (fibrosis) has a life expectancy of greater than 15 years after diagnosis.
* Someone with fibrosis but no other lung damage, like cysts (honeycombing), has a life expectancy of around eight years after diagnosis.
* Someone with severe damage — fibrosis and honeycombing — has a life expectancy of around three years after diagnosis.

## Prevention

The damage chronic HP causes isn’t reversible. The best way to prevent hypersensitivity pneumonitis is by avoiding exposure to allergens that cause lung inflammation. If you have to be around potential allergens, ways you may be able to reduce your risk include:

* If you have a job that puts you at risk (like working with metal, birds or other animals, lumber, paper, grain and more), wear personal protective equipment (PPE) while working. This includes wearing a mask that filters small particles.
* Keep humidifiers, hot tubs and heating and cooling systems clean and in good condition.
* Avoid feather-filled bedding.
* Keep your pets’ living spaces (especially bird cages) clean. Wear a mask when you clean them.

## Living With

If you’ve been diagnosed with hypersensitivity pneumonitis, make a plan with your healthcare provider to reduce the risk of further damage to your lungs. Take all medications as directed by your provider. Ask if there are any physical or breathing exercises you can do at home to improve your lung function.

### When should I see my healthcare provider about hypersensitivity pneumonitis?

See a healthcare provider if you have symptoms of hypersensitivity pneumonitis. If you’ve been diagnosed with HP, see your provider for any new or worsening symptoms.

**DIFFERENTIAL DIAGNOSIS**

**Acute and Subacute HP**

The primary differential for acute HP is infections of the respiratory tract. Conditions such as metal fume fever and organic dust toxic syndrome can also present similarly. Detailed history, physical examination and radiologic examination should help differentiate the conditions.

Sarcoidosis can have a similar clinical and radiologic picture to sub-acute HP. Exposure history, the presence of serum precipitins, lymphocytosis on BAL support a diagnosis of HP. Pathological examination in sarcoidosis typically reveals well-formed non-caseating granulomas along the bronchovascular bundle, without inflammatory cell infiltrate.

Organizing pneumonia and smoking-related ILDs should be considered in the differential, but history, HRCT findings, and pathological examination will help in differentiating the conditions.

**Chronic HP**

Chronic HP can appear similar to UIP/IPF clinically, radiographically and pathologically. A detailed history may provide some insight into exposure history supporting HP. BAL lymphocytosis supports the diagnosis of HP. Radiographically the reticulation and honeycombing in chronic HP tend to be predominantly upper and mid zone as opposed to UIP. Additionally, patchy ground-glass opacities and areas of air trapping support chronic HP. Fibrosis predominantly involving the upper zone, peribronchiolar fibrosis, the presence of granulomas, and lymphocytic interstitial inflammation are pathological features that help differentiate chronic HP from UIP. UIP will have marked sub-pleural fibrosis and microscopic honeycombing with distortion of pulmonary parenchyma.

Fibrotic NSIP can have similar radiographic and pathologic appearance. Pathological presence of granulomas and giant cells provide supportive evidence for chronic HP. HP/NSIP overlap syndromes have also been reported.

**EPIDEMIOLOGY**

The incidence and prevalence are variable largely due to lack of internationally accepted diagnostic criteria, seasonal and geographical variability in antigen exposures and other host factors. Mild HP may also be misdiagnosed due to non-specific findings. The incidence of HP among Swedish farmers as reported in the Sweden population registry is approximately 20 per 100,000 person-years. Other European population registries report HP incidence at 1.5% to 12% of all interstitial lung diseases (ILD). Data from surveys of high-risk occupations report the prevalence of 1.3% to 12% and 8% to 10% for exposed farmers and pigeon-breeders respectively. Globally, bird-related HP is the most commonly reported form of HP. HP is reported more often in middle-aged men. HP occurs more frequently in certain occupational groups and hobbies due to the specific exposures

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**LEUKOCYTOCLASTIC VASCULITIS**

**DEFINITION AND DESCRIPTION**

Leukocytoclastic vasculitis (LCV) describes small blood vessel inflammation. It’s **also known as hypersensitivity vasculitis and hypersensitivity angiitis**. LCV may be caused by many other conditions or for unknown reasons.

The word “leukocytoclastic” comes from “leukocytoclasia,” a process where neutrophils (immune cells) break down and release debris. “Vasculitis” means inflammation of the blood vessels.

When people use the term “leukocytoclastic vasculitis,” they’re usually talking about small blood vessel inflammation in the skin due to infiltrating, dying neutrophils.

However, the term is misleading for the following reasons:

* Leukocytoclasia occurs when neutrophils are involved in any type of inflammation — not just vasculitis.
* Similarly, small vessel vasculitis doesn’t always involve neutrophils. It may include other immune cells like lymphocytes and granulomas.
* The condition can affect the small blood vessels of any organ. It’s not specific to skin.

“Cutaneous leukocytoclastic vasculitis” is thought to be a more accurate name. This term, along with acute leukocytoclastic vasculitis, is often used interchangeably with LCV.

Read on to learn about the symptoms, causes, and treatment of leukocytoclastic vasculitis.

## Leukocytoclastic vasculitis causes

LCV has many possible causes. Yet, it may also be idiopathic, which means the underlying cause is unknown.

In general, it’s thought that immune system issues are involved. Potential LCV causes include:

### Allergic reaction

In most cases with a known cause, LCV is caused by an [allergic reaction](https://www.healthline.com/health/allergies/allergic-reaction) to a drug. Usually, the condition develops 1 to 3 weeks after starting the medication.

LCV has been associated with many drugs, including:

* beta-lactams
* erythromycin
* clindamycin
* vancomycin
* sulfonamides
* furosemide
* allopurinol
* nonsteroidal anti-inflammatory drugs (NSAIDs)
* amiodarone
* beta-blockers
* TNF-alpha inhibitors
* selective serotonin reuptake inhibitors (SSRIs)
* metformin
* warfarin
* valproic acid

Sometimes, LCV might be caused by an allergy to a food or food additive.

### Infection

Infections are another frequent cause of LCV. Bacterial, viral, and parasitic infections are all possible triggers.

Commonly, it’s due to a streptococcal upper respiratory tract infection. Other causes include:

* *Mycobacterium*
* hepatitis B
* hepatitis C
* *Staphylococcus aureus*
* *Chlamydiatrachomatis*
* *Neisseria gonorrhoeae*
* HIV

### Autoimmune disorders

Various autoimmune diseases have been associated with LCV, which supports the theory that LCV is related to a problem with the immune system.

Autoimmune disorders connected to LCV include:

* rheumatoid arthritis
* lupus erythematosus
* Sjögren‘s disease
* Henoch-Schönlein purpura (most common in children)

LCV may be related to inflammatory bowel disease (IBD), including Crohn’s disease and ulcerative colitis.

In some cases, LCV is caused by drugs that treat IBD. The condition also typically develops years after an IBD diagnosis.

### Malignancy

A malignancy is characterized by abnormal cell growth. The cells divide uncontrollably and invade surrounding tissues.

Less commonly, LCV may be linked to malignancies such as:

* solid tumors
* lymphoma
* leukemia
* myeloproliferative disorders
* myelodysplastic disorders

## Is leukocytoclastic vasculitis cancer?

Leukocytoclastic vasculitis is an inflammation of blood vessels. It is not a form of cancer.

However, leukocytoclastic vasculitis is the form of vasculitis most frequently associated with cancer. Most commonly, it is associated with cancers that begin in the blood.

## Leukocytoclastic vasculitis symptoms

The most notable symptoms of LCV involve the skin. Usually, this includes a rash characterized by:

* palpable purpura (raised purple-red spots)
* pain and burning
* itchiness
* bullae (fluid-filled sacs)
* pustules
* nodules
* crusted ulcers
* livedo reticularis (mottled skin)

The following LCV symptoms are systemic, or more generalized:

* low grade fever
* unexplained weight loss
* muscle aches
* joint pain
* bloody urine or stool
* abdominal pain
* vomiting
* coughing
* weakness

These systemic symptoms affect about 30 percent of people with LCV. Rarely, LCV also causes kidney inflammation.

## Diagnosing the condition

To determine what’s causing your symptoms, a healthcare professional can use several tests, which may include:

* Physical exam. During a physical exam of your skin, a healthcare professional will check for pain, swelling, and inflammation.
* Chest X-ray. This test may be used to detect pulmonary vasculitis.
* Medical history. This helps your healthcare professional figure out if something specific triggered your symptoms.
* Blood tests. Blood tests can show signs of underlying conditions. The tests may include a complete blood count, a basic metabolic panel, and liver and kidney function.
* Urinalysis. A sample of your urine might be checked for signs of disease.
* Punch biopsy. A healthcare professional takes a small skin sample with a circular tool. The sample, which includes deeper skin layers, is examined in a lab.

While a healthcare professional can diagnose LCV through a physical examination, a punch biopsy is often used to confirm the diagnosis.

## Does leukocytoclastic vasculitis go away?

Leukocytoclastic vasculitis may be treated either with home remedies like ice packs and compression stockings, or with medications.

### Treatment options

Treatment begins with removing or treating the underlying cause of LCV. For example, if you developed LCV due to a drug, your healthcare professional will likely have you stop taking it.

It’s important to remember to speak with your healthcare professional before stopping any prescribed medications.

A mild case of LCV can be treated with home remedies, including:

* ice packs
* elevation
* antihistamines
* compression stockings
* rest

However, if your LCV is chronic (long lasting) or severe, you’ll need additional treatments, which may involve:

### NSAIDs

NSAIDs can help manage skin and joint pain. They’re available over the counter (OTC), so you don’t need a prescription.

NSAIDs may cause some side effects that can be serious, including:

* bleeding
* ulcers
* holes in the intestine or stomach

The risk of this occurring is greater:

* if NSAIDs are taken over a longer period of time
* in older adults
* in people in poor overall health
* in people who consume three or more alcoholic beverages a day

### Colchicine

Your healthcare professional may prescribe colchicine, which is made from the plant *Colchicum autumnale*. This oral drug works to manage neutrophils in the immune system.

While colchicine may help skin and joint symptoms, it doesn’t work for everyone. You might need to take it with other medical treatments.

In some cases, colchicine may cause side effects. Speak with a doctor if you experience severe or persistent:

* abdominal pain
* stomach cramps
* nausea
* vomiting
* diarrhea

If you experience any of the following symptoms, stop taking colchicine and immediately contact your doctor:

* pale or gray lips, palms, or tongue
* tiredness
* weakness
* pain in muscles
* muscle weakness
* tingling or numb fingers or toes
* fever
* chills
* sore throat
* unusual bleeding
* unusual bruising

### Dapsone

Dapsone is an anti-inflammatory drug used to treat chronic LCV. It helps reduce inflammation due to neutrophils.

Depending on your symptoms, your healthcare professional might prescribe dapsone along with:

* colchicine
* steroids
* antihistamines

Dapsone may cause some side effects. You should contact your doctor if you experience severe or persistent:

* vomiting
* upset stomach

You should also contact your doctor right away if you experience:

* yellowing of the eyes or skin (jaundice)
* rash
* fever
* sore throat
* unusual bruising

### Prescription steroids

Like NSAIDs, oral steroids are used to manage skin rashes and joint pain. Most people respond to a short course of steroids, such as prednisone or methylprednisolone.

If your internal organs are affected, or if you have severe skin lesions, your healthcare professional might recommend intravenous (IV) corticosteroids.

In most people, steroids won’t cause major side effects if they are taken at a low dose or only for a short period of time.

In some people, they may cause:

* mood changes
* problems sleeping
* increase in appetite

It is important to not stop taking steroids without first speaking with your doctor, as this can cause more side effects.

## When to see a doctor

Leukocytoclastic vasculitis can range from mild to severe. Therefore, it’s recommended that you see your healthcare professional if you notice any symptoms of LCV.

Seek medical attention if you have:

* painful, burning rashes
* raised purple-red spots
* fever
* unexplained weight loss
* trouble breathing
* weakness
* bloody urine or stool
* vomiting
* persisting joint or muscle pain

## Is leukocytoclastic vasculitis life threatening?

The outlook of leukocytoclastic vasculitis is good. Roughly 90 percent of cases of LCV will resolve. This may occur in weeks to months after the start of symptoms.

The remaining 10 percent of cases will have chronic disease that may last from 2 to 4 years on average.

The mortality rate of leukocytoclastic vasculitis is low, at roughly 2 percent But this is related to system involvement, when the disease impacts multiple areas in the body.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis includes:

* Thrombocytopenic purpura
* Benign pigmented purpura
* Schamberg disease
  + This is an idiopathic phenomenon, which results from erythrocyte extravasation into the dermis in the lower extremities due to capillary fragility or leaky blood vessels, venous stasis or exercise. Hyperpigmentation in the lower extremities is frequently present.

Skin biopsy can easily differentiate benign pigmented purpura from leukocytoclastic vasculitis given the lack of features of vasculitis such as fibrinoid necrosis and vessel wall disruption by the inflammatory infiltrates.

**EPIDEMIOLOGY**

The annual incidence of biopsy-proven leukocytoclastic vasculitis is approximately 45 per million individuals. The epidemiology of leukocytoclastic vasculitis varies with the underlying etiology. Leukocytoclastic vasculitis occurs in all ages and both genders; however, it typically presents in adults. However, HSP is usually seen in children and young adults with an incidence of up to 270 cases per million children per year with a slight male predominance.

## Recommendations for Leukocytoclastic Vasculitis (LCV)

* Mild, Limited Cutaneous LCV:
  + Supportive care including rest, leg elevation, and compression stockings.
  + Symptomatic relief with NSAIDs for pain and inflammation.
  + Topical corticosteroids may be used for itch relief.
  + Removal or treatment of any identified underlying cause or trigger (e.g., offending drug, infection) is essential
* Moderate to Severe or Chronic/Recurrent LCV:
  + Systemic corticosteroids (e.g., prednisone 0.5–1 mg/kg/day) are often used to control acute inflammation, especially in painful, ulcerative, or systemic cases. Steroids should be tapered gradually once remission is achieved.
  + Steroid-sparing agents are recommended for chronic or relapsing disease to minimize long-term corticosteroid exposure. Common options include:
    - Colchicine (0.6 mg twice daily), effective for skin and joint symptoms but may cause gastrointestinal side effects.
    - Dapsone (50–150 mg daily), useful for neutrophil-driven inflammation; requires G6PD deficiency screening and monitoring for anemia and methemoglobinemia.
    - Azathioprine (around 2 mg/kg/day), used especially in systemic involvement; requires TPMT activity screening and monitoring for hematologic and hepatic toxicity.
  + Other immunosuppressants such as methotrexate, mycophenolate mofetil, cyclophosphamide, or biologics like rituximab may be considered in refractory or severe cases but are less commonly used and guided by disease severity and comorbidities.
* Severe Systemic or Organ-Involved Disease:
  + High-dose systemic corticosteroids and immunosuppressive agents (e.g., cyclophosphamide) may be necessary.
  + Emerging therapies like avacopan (a complement inhibitor) are being used to reduce steroid burden in certain vasculitides but are not standard for isolated LCV[7](https://health.clevelandclinic.org/vasculitis-medications)

### Common medications for vasculitis

Almost all types of vasculitis get treated with a specific class of corticosteroids known as glucocorticoids. For certain types of vasculitis, another medication — typically a DMARD — may be used in tandem.

Here are six of the more commonly used medications. (There are other medications beyond those listed that your doctor may prescribe for vasculitis.)

The potential side effects that are included aren’t intended to be complete. It’s best to review your medication treatment plan carefully with your healthcare provider and pharmacist to understand possible risks specific to your situation.

#### **Prednisone**

Prednisone is a corticosteroid (glucocorticoid) that has proven effective in quickly treating inflammation from vasculitis.

Treatment details: Prednisone can be taken as a pill or injected as a shot, typically in the morning. The type and severity of your vasculitis will determine your initial dosage. Over time, dosage levels are usually reduced.

Potential side effects: Increased infection risk is the No. 1 concern with prednisone. Other potential side effects include:

* Increased blood sugar (diabetes).
* Increased blood pressure.
* Loss of bone density (osteoporosis).
* Easy bruising and poor healing.
* Mood swings.
* Insomnia.

Prednisone is also associated with increased appetite and weight gain. People taking prednisone may notice a change in appearance related to the redistribution of normal fat cells in the face and trunk. This usually improves as the dosage is lowered.

#### **Rituximab**

Rituximab is a DMARD approved for use in the treatment of two forms of vasculitis — granulomatosis with polyangiitis (GPA or Wegener’s) and microscopic polyangiitis (MPA).

Treatment details: Rituximab is delivered by vein in an infusion center or hospital. The process typically takes four to six hours, though it can run longer. The dosage and frequency of rituximab treatment varies based on several different factors.

Potential side effects: Reactions such as rashes and sores of the skin and mouth sometimes follow a rituximab infusion. There’s also a risk of a rare brain virus infection called progressive multifocal leukoencephalopathy (PML).

#### **Avacopan**

This relative newcomer to vasculitis treatment gained approval from the U.S. Food and Drug Administration (FDA) in 2021. Avacopan is used to treat GPA and MPA, two types of anti-neutrophil cytoplasmic antibody (ANCA) vasculitis.

Taking avacopan can help reduce the amount of steroids a patient requires.

Treatment details: Avacopan comes in a tablet and is typically taken twice daily with food. (The dosage may be reduced if you’re taking other medication.) The capsules shouldn’t be crushed, chewed or opened.

Potential side effects: The most common reactions to avacopan during trials included nausea, headache and elevated blood pressure. Liver damage has been reported in people taking avacopan, and monitoring is recommended. There’s also an elevated risk of serious infections.

#### **Cyclophosphamide**

When it comes to vasculitis treatment, cyclophosphamide is a tried-and-true DMARD used primarily for severe small- and medium-vessel vasculitis. The medication — known by the brand name Cytoxan® — can be taken orally or intravenously.

Cyclophosphamide is used much less commonly in the treatment of vasculitis than it was 10 years ago.

Treatment details: The medicine can be taken either orally daily or through an IV every two to four weeks. It’s important to hydrate after taking the medication to prevent it from sitting in your bladder.

Potential side effects: Cyclophosphamide can increase your risk of bladder cancer, which is why hydrating is so important to help flush it out of your bladder. The medication can also lower your blood counts, which your provider will probably test every week or two as a precaution.

Nausea and/or vomiting may sometimes occur after the medication is given intravenously. Cyclophosphamide can reduce fertility in women, too. And if you’re pregnant, cyclophosphamide increases the risk of birth defects.

#### **Methotrexate**

Methotrexate is a DMARD used to treat vasculitis, as well as other autoimmune conditions.

Treatment details: Methotrexate can be taken once a week as a tablet. Your doctor will base the dosage on your weight and other factors. The medication may be given as an injection just under the skin.

Potential side effects: Methotrexate can be associated with lowering blood counts, irritation of the lungs (pneumonitis) and liver damage. Your provider may order blood tests to monitor your blood counts and liver.

Nausea, vomiting, mouth sores, rash or diarrhea are also possible side effects. Avoid taking methotrexate if you’re pregnant or trying to get pregnant, as it’s been associated with miscarriages and birth defects.

#### **Azathioprine**

Doctors mainly use azathioprine as a “maintenance medication” in people with small- or medium-vessel vasculitis after the vasculitis has been managed. It’s taken as a pill.

Treatment details: Prior to beginning treatment, healthcare providers usually perform a blood test to check for a natural body enzyme (thiopurine methyltransferase, or TPMT) that breaks down the medication.

People who don’t make this enzyme can’t take azathioprine. If you make lower amounts of TPMT, the dosages will be smaller.

Those who make enough TPMT are given a dosage based on body weight.

Potential side effects: Nausea, vomiting, abdominal cramping or diarrhea are possible side effects. Taking the medication twice a day instead of all at once, or taking it with meals, often helps minimize these issues.

Azathioprine is also associated with lower blood counts and liver issues, which makes it important to have regular blood tests to watch for problems.

Rarely, allergic reactions to azathioprine require the medication to be stopped.

REFERENCE

<https://health.clevelandclinic.org/vasculitis-medications>

<https://www.ncbi.nlm.nih.gov/books/NBK482159/#article-24215.s10>

**CONTACT DERMATITIS**

**DEFINITION AND DESCRIPTION**

Contact dermatitis is an itchy rash caused by direct contact with a substance or an allergic reaction to it. The rash isn't contagious, but it can be very uncomfortable.

Many substances can cause this reaction, such as cosmetics, fragrances, jewelry and plants. The rash often shows up within days of exposure.

To treat contact dermatitis successfully, you need to identify and avoid the cause of your reaction. If you avoid the substance causing the reaction, the rash often clears up in 2 to 4 weeks. You can try soothing your skin with a cool, wet cloth and other self-care steps.

**Causes**

Contact dermatitis is caused by exposure to a substance that irritates your skin or triggers an allergic reaction. The substance could be one of thousands of known allergens and irritants. Often people have irritant and allergic reactions at the same time.

**Irritant contact dermatitis** is the most common type. This nonallergic skin reaction occurs when an irritant damages your skin's outer protective layer.

Some people react to strong irritants after a single exposure. Others may develop a rash after repeated exposures to even mild irritants, such as soap and water. And some people develop a tolerance to the substance over time.

Common irritants include:

* Solvents
* Rubber gloves
* Bleach and detergents
* Hair products
* Soap
* Airborne substances
* Plants
* Fertilizers and pesticides

**Allergic contact dermatitis** occurs when a substance to which you're sensitive (allergen) triggers an immune reaction in your skin. It often affects only the area that came into contact with the allergen. But it may be triggered by something that enters your body through foods, flavorings, medicine, or medical or dental procedures (systemic contact dermatitis).

People often become sensitized to allergens after many contacts with it over years. Once you develop an allergy to a substance, even a small amount of it can cause a reaction.

Common allergens include:

* Nickel, which is used in jewelry, buckles and many other items
* Medications, such as antibiotic creams
* Balsam of Peru, which is used in many products, such as perfumes, toothpastes, mouth rinses and flavorings
* Formaldehyde, which is in preservatives, cosmetics and other products
* Personal care products, such as body washes, hair dyes and cosmetics
* Plants such as poison ivy and mango, which contain a highly allergenic substance called urushiol
* Airborne allergens, such as ragweed pollen and spray insecticides
* Products that cause a reaction when you're in the sun (photoallergic contact dermatitis), such as some sunscreens and cosmetics

Children develop allergic contact dermatitis from the usual offenders and also from exposure to diapers, baby wipes, jewelry used in ear piercing, clothing with snaps or dyes, and so on.

**Risk factors**

The risk of contact dermatitis may be higher in people who have certain jobs and hobbies. Examples include:

* Agricultural workers
* Cleaners
* Construction workers
* Cooks and others who work with food
* Florists
* Hair stylists and cosmetologists
* Health care workers, including dental workers
* Machinists
* Mechanics
* Scuba divers or swimmers, due to the rubber in face masks or goggles

**SIGNS AND SYMPTOMS**

Contact dermatitis shows up on skin that has been directly exposed to the substance causing the reaction. For example, the rash may show up along a leg that brushed against poison ivy. The rash can develop within minutes to hours of exposure, and it can last 2 to 4 weeks.

Signs and symptoms of contact dermatitis vary widely and may include:

* An itchy rash
* Leathery patches that are darker than usual (hyperpigmented), typically on brown or Black skin
* Dry, cracked, scaly skin, typically on white skin
* Bumps and blisters, sometimes with oozing and crusting
* Swelling, burning or tenderness

### 

### DIAGNOSIS AND TEST

### Your health care provider may be able to diagnose contact dermatitis by talking to you about your signs and symptoms. You might be asked questions to help identify the cause of your condition and uncover clues about the trigger substance. And you'll likely undergo a skin exam to assess the rash.

### Your health care provider may suggest a patch test to identify the cause of your rash. In this test, small amounts of potential allergens are put on sticky patches. Then the patches are placed on your skin. They stay on your skin for 2 to 3 days. During this time, you'll need to keep your back dry. Then your health care provider checks for skin reactions under the patches and determines whether further testing is needed.

### This test can be useful if the cause of your rash isn't apparent or if your rash recurs often. But the redness indicating a reaction can be hard to see on brown or Black skin, which may lead to a missed diagnosis.

### Treatment

### If home care steps don't ease your signs and symptoms, your health care provider may prescribe medications. Examples include:

### Steroid creams or ointments. These are applied to the skin to help soothe the rash. You might apply prescription topical steroids, such as clobetasol 0.05% or triamcinolone 0.1%. Talk with your health care provider about how many times a day to apply it and for how many weeks.

### Pills. In severe cases, your health care provider may prescribe pills you take by mouth (oral medications) to reduce swelling, relieve itching or fight a bacterial infection.

### 

### Lifestyle and home remedies

### To help reduce itching and soothe inflamed skin, try these self-care approaches:

### Avoid the irritant or allergen. The key to this is identifying what's causing your rash and staying away from it. Your health care provider may give you a list of products that typically contain the substance that affects you. Also ask for a list of products that are free of the substance that affects you.

### Apply an anti-itch cream or ointment. Put on the itchy area 1% hydrocortisone cream or ointment (Cortizone 10, others). This is a nonprescription product that you can buy at a drugstore. Use it 1 to 2 times a day for a few days. Or try calamine lotion. Whatever product you use, try cooling it in the refrigerator before applying.

### Take an anti-itch drug. An oral antihistamine, such as diphenhydramine (Advil PM, Benadryl, others), which may also help you sleep better. A non-prescription antihistamine that won't make you so drowsy is loratadine (Alavert, Claritin, others).

### Apply cool, wet compresses. Place a cool, wet cloth over the rash for 15 to 30 minutes several times a day.

### Protect your skin. Avoid scratching. Trim your nails. If you can't keep from scratching an itchy area, cover it with a dressing. Leave blisters alone. While your skin heals, stay out of the sun or use other sun protection measures.

### Soak in a soothing cool bath. Soak the affected area in cool water for 20 minutes. Sprinkle the water on an oatmeal-based bath product (Aveeno).

### Protect your hands. Rinse and dry your hands well and gently after washing. Use moisturizers throughout the day — on top of any medicated cream you're using. And choose gloves based on what you're protecting your hands from. For example, plastic gloves lined with cotton are good if your hands are often wet.

### When to see a doctor

See your healthcare provider if:

* The rash is so itchy that you can't sleep or go about your day
* The rash is severe or widespread
* You're worried about how your rash looks
* The rash doesn't get better within three weeks
* The rash involves the eyes, mouth, face or genitals

**Seek immediate medical care** in the following situations:

* You think your skin is infected. Clues include fever and pus oozing from blisters.
* It's hard to breathe after inhaling burning weeds.
* Your eyes or nasal passages hurt after inhaling smoke from burning poison ivy.
* You think an ingested substance has damaged the lining of your mouth or digestive tract.

**Complications**

Contact dermatitis can lead to an infection if you repeatedly scratch the affected area, causing it to become wet and oozing. This creates a good place for bacteria or fungi to grow and may cause an infection.

**Prevention**

You can take the following steps to help prevent contact dermatitis:

* **Avoid irritants and allergens.** Try to identify and avoid the cause of your rash. For ear and body piercings, use jewelry made of hypoallergenic material, such as surgical steel or gold.
* **Wash your skin.** For poison ivy, poison oak or poison sumac, you might be able to remove most of the rash-causing substance if you wash your skin right away after coming into contact with it. Use a mild, fragrance-free soap and warm water. Rinse completely. Also wash any clothing or other items that may have come into contact with a plant allergen, such as poison ivy.
* **Wear protective clothing or gloves.** Face masks, goggles, gloves and other protective items can shield you from irritating substances, including household cleansers.
* **Apply an iron-on patch to cover metal fasteners next to your skin.** This can help you avoid a reaction to jean snaps, for example.
* **Apply a barrier cream or gel.** These products can provide a protective layer for your skin. For example, a nonprescription skin cream containing bentoquatam (Ivy Block) may prevent or lessen your skin's reaction to poison ivy.
* **Use moisturizer.** Regularly applying moisturizing lotions can help restore your skin's outermost layer and keep your skin supple.
* **Take care around pets.** Allergens from plants, such as poison ivy, can cling to pets and then be spread to people. Bathe your pet if you think it got into poison ivy or something similar.

**Epidemiology of Contact Dermatitis (CD)**

* Prevalence and Incidence:
  + Contact dermatitis affects an estimated 1.7% to 9.8% of the general population according to various studies.
  + Among patch-tested patients, the prevalence of contact allergy ranges between 15.0% and 20.1%.
  + Lifetime prevalence of contact dermatitis is estimated around 15% of adults.
  + In dermatology clinics, CD accounts for about 4% to 7% of all consultations annually.
  + The National Health and Nutrition Examination Survey (NHANES) in the U.S. estimated a prevalence of 13.6 cases per 1000 population (~1.36%).
  + Occupational contact dermatitis represents about 90% of occupational skin disorders in industrialized countries.
* Demographics:
  + CD can occur at any age and in both sexes but is more common in women, especially those engaged in household activities or certain occupations.
  + Female-to-male ratios range from approximately 1.3:1 to 1.8:1 in various studies.
  + The most affected age group is 45 to 65 years, with many cases reported in patients over 45 years old.
  + No significant racial predilection has been identified.
* Occupational Risk:
  + Occupation is the main risk factor for CD.
  + High-risk professions include hairdressers, wet workers, food handlers, healthcare workers, building and metal workers due to repeated allergen or irritant exposure.
  + About 21% to 41% of contact dermatitis cases are occupationally related.
* Common Allergens and Sites:
  + Frequent allergens include plants, topical drugs, antiseptics, detergents, and soaps.
  + The face and hands are the most commonly affected areas, with hands involved in about 19% of cases.
  + Seasonal variation shows increased cases in spring and summer, likely due to increased allergen exposure.

## Differential Diagnoses of Contact Dermatitis

1. Irritant Contact Dermatitis (ICD)
2. Atopic Dermatitis
3. Psoriasis (especially inverse psoriasis)
4. Seborrheic Dermatitis
5. Dyshidrotic Eczema
6. Scabies
7. Tinea (Dermatophytosis)
8. Drug Eruptions
9. Photodermatitis / Photoallergic Dermatitis
10. Lichen Planus / Lichenoid Eruptions
11. Cutaneous T-cell Lymphoma (Mycosis Fungoides)
12. Erysipelas / Cellulitis
13. Autoimmune Bullous Diseases
14. Dermatitis Herpetiformis
15. Contact Urticaria

**GUIDELINES**

Characteristics specific to contact dermatitis include:

* Glazed, parched, or scalded appearance
* Sharply circumscribed dermatitis
* Healing begins promptly on withdrawal of the offending agent

Industries and jobs that pose a high risk for development of occupational contact dermatitis are as follows:

1. Food service and food processing (cooks and caterers)
2. Cosmetology (beauticians and hairdressers)
3. Health care (personnel)
4. Agriculture, forestry, and fishing
5. Cleaning
6. Painting
7. Mechanics, metal working, and vehicle assembly
8. Electronics industry
9. Printing and/or lithography
10. Construction

First-line recommendations:

* **Trigger identification**: Identification and avoidance of contact with the offending agent(s) is the key to successful treatment. Review any recent abnormal exposures, new lotions, garments, foods, furniture, etc.
* **Topical corticosteroids**: Reduce inflammation and itching. Hydrocortisone 1% cream (FDA M017): Apply thinly to affected areas 1-2 times daily for up to 7 days.

Second-line recommendations:

* **Emollients**: Moisturizers to repair the skin barrier and reduce dryness. Examples: Petroleum jelly (FDA M016) or ceramide-based creams (same class as FDA K1 10757) as needed.
* Calamine lotion (FDA M016) and colloidal oatmeal baths (FDA M016) can also provide symptomatic relief

Prevention:

* **Reducing exposure**: If irritant is related to job or other necessary task, examples of methods of reducing exposure include using long handled cleaning tools (brush with a handle), vacuuming, or wet sweeping

Prescription medications:

* **Systemic corticosteroids**: For widespread or severe cases (e.g., prednisone).
* **Topical calcineurin inhibitors**: For sensitive areas like the face.

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**TOXIC EPIDERMAL NECROLYSIS ( TEN )**

**DEFINITION AND DESCRIPTION**

Toxic epidermal necrolysis (TEN) is a rare, life-threatening skin reaction, usually caused by a medication. It's a severe form of Stevens-Johnson syndrome (SJS). In people with SJS, TEN is diagnosed when more than 30% of the skin surface is affected and the moist linings of the body (mucous membranes) have extensive damage.

TEN is a life-threatening condition that affects people of all ages. TEN is usually treated in a hospital. While the skin heals, supportive care includes controlling pain, caring for wounds and making sure you're getting enough fluids. Recovery can take weeks to months.

If your condition was caused by a medication, you'll need to permanently avoid that drug and those related to it.

**Causes**

SJS/TEN is usually caused by a skin reaction to medicine. The symptoms are likely to start showing up one to four weeks after you start taking a new drug.

The most common drug triggers of SJS/TEN include antibiotics, epilepsy drugs, sulfa drugs and allopurinol (Aloprim, Zyloprim).

**Risk factors**

Factors that increase your risk of SJS/TEN include:

* **HIV infection.** Among people with HIV, the incidence of SJS/TEN is about 100 times greater than that among the general population.
* **A weakened immune system.** The immune system can be affected by an organ transplant, HIV/AIDS and autoimmune diseases.
* **Cancer.** People with cancer, especially blood cancers (hematologic malignancies), are at increased risk of SJS/TEN.
* **A history of SJS/TEN.** If you've had a medication-related form of this condition, you are at risk of a recurrence if you use that drug again.
* **A family history of SJS/TEN.** If a first-degree relative, such as a parent or sibling, has had SJS/TEN, you may be more susceptible to developing it too.
* **Genetic factors.** Having certain genetic variations puts you at increased risk of SJS/TEN, especially if you're also taking drugs for seizures, gout or mental illness.

**SIGNS AND SYMPTOMS**

Toxic epidermal necrolysis signs and symptoms include:

* Widespread skin pain
* A spreading rash covering more than 30% of the body
* Blisters and large areas of peeling skin
* Sores, swelling and crusting on the mucous membranes, including the mouth, eyes and vagina

## Diagnosis and test

### TEN is diagnosed when people with SJS develop severe disease that affects more than 30% of the body.

### Treatment

### If your doctor suspects that your TEN was caused by medicine you took, you'll need to stop taking that drug. Then you'll likely be moved to a hospital for treatment, possibly in its burn center or intensive care unit. Full recovery can take several months.

### Supportive care

### The main treatment for TEN is trying to make you as comfortable as possible while your skin heals. You'll receive this supportive care while in the hospital. It might include:

### Fluid replacement and nutrition. Because skin loss can result in loss of fluid from the body, it's vital to replace fluids and electrolytes. You might receive fluids and nutrients through a tube inserted in the nose and guided to the stomach (nasogastric tube).

### Wound care. Your health care team might gently cleanse the affected skin and apply special dressings infused with petroleum jelly (Vaseline) or medication. Your care team also monitors you for infection and gives you antibiotics if needed.

### Breathing help. You might need tests and procedures to evaluate your airway and help keep it clear. With advanced disease, you might need intubation or mechanical breathing assistance (ventilation).

### Pain control. You'll receive pain medicine to reduce your discomfort. For pain in your mouth, you might be given a mouthwash containing a numbing agent, such as lidocaine.

### Eye care. For mild eye symptoms, you might benefit from applying preservative-free artificial tears at least four times a day. Eye drops with corticosteroids might be used to control eye inflammation. Your care team might include an eye specialist (ophthalmologist).

### Medications

### Treatment of TEN also might include one or a combination of medications that affect the whole body (systemic drugs), such as cyclosporine (Neoral, Sandimmune), etanercept (Enbrel) and intravenous immunoglobulin (IVIG). Further study is needed to determine their benefit, if any.

### When to see a doctor

Early treatment is key for people with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). If you have symptoms, seek immediate medical attention. You'll likely need care from a skin specialist (dermatologist) and other experts in a hospital.

**Complications**

People at highest risk of TEN complications are those over age 70 and those who have liver cirrhosis or spreading (metastatic) cancer. Complications of TEN include:

* **Blood infection (sepsis).** Sepsis occurs when bacteria from an infection enter your bloodstream and spread throughout your body. Sepsis is a rapidly progressing, life-threatening condition that can cause shock and organ failure.
* **Lung involvement.** This can cause coughing, difficulty breathing and, with severe disease, acute respiratory failure.
* **Visual impairment.** TEN can cause eye problems, such as dry eye, ingrown eyelashes, corneal scarring and, rarely, blindness.
* **Permanent skin damage.** After recovering from TEN, your skin may have bumps, scars and discoloration. Lasting skin problems might cause your hair to fall out, and your fingernails and toenails might not grow normally.
* **Vaginal sores.** In women, TEN can cause sores in the tissues lining the vagina, leading to pain or, if left untreated, vaginal fusion.
* **Emotional distress.** This condition causes distress and can have long-term psychological impact.

**Prevention**

To prevent another episode of TEN, learn whether it was caused by a medicine. If so, never take that medicine or anything similar again. A recurrence could be worse and life-threatening. Also tell any future health care providers about your history of TEN, and wear a medic alert bracelet or necklace with information about your condition. Or carry an allergy passport.

## Epidemiology

In the United States, the annual frequency of TEN is reported to be 0.22-1.23 cases per 100,000 population. In the HIV-positive population, the incidence of TEN increases to 1 case per thousand per year.

Worldwide, the average annual incidence of TEN is 0.4-1.3 cases per million population.In 1992, the cumulative incidence of TEN and SJS in Germany was 1.9 cases per million population. A French survey of dermatologists and health care facilities reported an annual incidence of 1 case per million population.

### Race-, sex-, and age-related demographics

A genetic predilection toward carbamazepine-induced TEN has been observed in HLA-B\*1502–positive patients in mainland southeast Asian people from China to India. The US Food and Drug Administration recommends screening for the HLA-B\*1502 allele before initiating carbamazepine in patients of Asian ancestry.The HLA-B\*58:01 allele is associated with allopurinol-induced TEN in Han Chinese people. HLA-A\*66:01, HLA-B\*44:03, and HLA-C\*12:03 have been associated with cold medicine-TEN with severe ocular complications in patients who had taken cold medicines in the 1-14 days prior to onset of the disease. The HLA-B\*44:03 (odds ratio, 5.50) and HLA-C\*12:03 (OR, 8.79) alleles were associated with a less-robust tisk of cold medicine-TEN only in European patients.

Registration databases from Tawain, Thailand, Japan, Malaysia, Singapore, Hong Kong, the Philippines, and mainland China (Fujian) identified that from 1998-2017, greater than 50% of cases of SJS/TENS involved carbamazepine, allopurinol, phenytoin, lamotrigine, and sulfamethoxazole.

## Diagnostic Considerations

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are considered to be a single disease entity differing in severity. There is debate whether TEN and SJS are part of a spectrum of disorders including erythema multiforme major (EMM); however, it is widely accepted that SJS and TEN are distinct entities differing in etiology, clinical manifestations, histopathology, treatment, and prognosis.

EMM is characterized by typical target lesions (at least 3 concentric rings) with or without blister formation in a symmetric, predominantly acral distribution. In contrast, the skin lesions of SJS and TEN are predominately central (trunk and face), consisting of blisters that arise on erythematous or purpuric macules and involve 2 or more mucosal surfaces.

Histopathologic examination is necessary in differentiating these disorders from other severe bullous skin diseases, including the following

* Staphylococcal scalded skin syndrome
* Toxic shock syndrome
* Phototoxic skin reactions
* Drug reaction with eosinophilia
* Acute generalized exanthematous pustulosis
* Generalized pustular figurate erythema
* Paraneoplastic pemphigus

TEN and SJS are characterized by apoptotic keratinocyte cell death in the epidermis with dermal-epidermal separation that results in bullae formation.

Other problems to be considered in the differential diagnosis of TEN include the following:

* Cauterization burns
* Caustic agents
* Drug reaction with eosinophilia
* Generalized pustular figurate erythemasometimes seen with pustulosis and atypical targetoid erythema

**RECOMMENDATIONS**

## Recent Guideline and Treatment Recommendations for Stevens-Johnson Syndrome (SJS) / Toxic Epidermal

## 1. Supportive Care (Cornerstone of Management)

* Immediate withdrawal of the culprit drug is critical.
* Supportive care in an intensive care or burn unit setting is essential, focusing on:
  + Fluid and electrolyte management.
  + Temperature regulation.
  + Nutritional support.
  + Pain control.
  + Prevention of infections with meticulous wound care.
* Use of topical agents such as 0.5% silver nitrate spray on denuded skin areas has shown benefit in mucocutaneous healing.

## 2. Systemic Corticosteroids

* Frequently used despite lack of definitive trial evidence.
* High-dose corticosteroids or pulse therapy may reduce mortality and disease progression if started early.
* Risks include increased susceptibility to infections, especially in extensive epidermal detachment.
* Corticosteroids remain a mainstay but require careful patient selection and monitoring.

## 3. Immunomodulatory Therapies

* Cyclosporine A: Shows promise in reducing mortality and halting disease progression by inhibiting T-cell activation.
* Intravenous Immunoglobulin (IVIG): Used widely but evidence of benefit is mixed; may be considered in combination therapies.
* Tumor Necrosis Factor-alpha (TNF-α) inhibitors (e.g., etanercept):
  + Emerging evidence supports their use to modulate immune response.
  + A single dose of etanercept combined with topical silver nitrate demonstrated rapid skin and mucosal healing in a small series.
* Other biologics and targeted therapies are under investigation but not yet standard of care.

## 4. Prognostic Assessment

* Use of clinical scores such as CRISTEN or SCORTEN to predict mortality risk and guide treatment intensity is recommended.

## 5. Multidisciplinary Approach

* Management by a team including dermatologists, intensivists, ophthalmologists, and other specialists is crucial to address multisystem involvement and complications.

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# Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

**DEFINITION AND DESCRIPTION**

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a type of drug allergy which can occur as a reaction to a large variety of medications.

DRESS syndrome, also known as drug-induced hypersensitivity syndrome (DIHS) or drug hypersensitivity syndrome, is a severe reaction to certain drugs. Experts classify DRESS syndrome as a type 4 hypersensitivity reaction. It is a serious drug reaction affecting the skin and other organs, with a mortality rate of up to 10%.

The overall incidence of DRESS syndrome is uncommon, with estimates of risk ranging from 1 in every 1,000 to 1 in every 10,000 people after exposure to triggering drugs. It typically happens within 2–6 weeks of a person’s first exposure to the drug, causing characteristic yet variable features affecting the skin and multiple organs.

## Causes

DRESS syndrome is a delayed T-cell mediated hypersensitivity reaction in response to certain drugs. The damage occurs due to an overreaction from the immune system, which involves the activation of T-cells and the release of cytokines. There are many potential culprit drugs and common medications associated with DRESS syndrome include:

* anticonvulsants
* antiviral drugs
* antibiotics
* allopurinol (Zyloprim)
* mexiletine (Mexitil)
* mood stabilizers and antidepressants
* biologic agents

Evidence also suggests that other factors are likely to play a role. These may include:

* a genetic predisposition to DRESS syndrome
* an inability of the liver to metabolize certain drugs
* the reactivation of certain viruses, such as the Epstein-Barr virus (EBV) or human herpesvirus 6 (HHV6)

## Symptoms

Some people may refer to DRESS syndrome as an idiosyncratic multisystem reaction to a drug. This refers to the fact that the condition can have a variety of symptoms. Although people may experience different symptoms, the name DRESS derives from the characteristic high eosinophil count, known as eosinophilia, and the body-wide symptoms that usually manifest.

The symptoms can vary, but they typically develop over several days, with the typical onset being 2–6 weeks after starting the responsible medicine. Typical signs of DRESS syndrome include:

* fever
* skin rashes or eruption
* eosinophilia
* atypical lymphocytosis
* swollen lymph nodes
* inflammation of internal organs

## Diagnosis

Patients with DRESS can have a broad range of symptoms, which can include fever, rash, facial swelling, enlarged lymph nodes and kidney or liver injury. Most patients with DRESS will have an abnormal level of blood cells found in their blood tests, which are called eosinophils. Eosinophils are cells associated with allergic diseases, and, when they are present in large numbers, can cause organ damage. The rash can present in a variety of different ways, commonly as a red rash, and can be present anywhere on the skin, but will often start on the face and upper body. Although it is rare, other organs can also be inflamed due to DRESS.  
  
**Drugs**Although some drugs are more commonly associated with DRESS than others, almost any drug could cause DRESS. Antibiotics, allopurinol (a medication for gout) and medications used to treat seizures are the most common drugs involved with DRESS. Generally, symptoms of DRESS will begin about two to six weeks after the patient has started the medication, so immediate symptoms are not seen in DRESS. Medications which have been taken for more than three months are unlikely to be the cause of the DRESS reaction.

## Treatment

The most important step in treating DRESS is to stop the medication involved in the reaction, and sometimes, no further treatment is needed. Topical steroids can be given to treat the rash. Often, however, further treatment is needed to protect the organs from damage, such as with steroids, which can be given either intravenously or orally. Treatment with steroids can be needed for weeks or even months, and lab work is monitored carefully during this time. The average time to recovery is six to nine weeks. Long term, most patients do well, although some patients can go on to develop autoimmune diseases so additional monitoring should be considered.

## Recovery and prevention

While most people with DRESS syndrome fully recover, some may have a prolonged course. For these individuals, the disease may recur or lead to autoimmune complications.Gradually tapering corticosteroid medications may help prevent disease flare-ups and the development of autoimmune diseases.

People who experience a DRESS syndrome reaction should take note of the culprit drug and try to avoid it and other similar drugs. If a doctor has prescribed the medication, they should speak with the doctor about alternative treatments.

Although more research is still necessary, scientists are investigating the use of avoidability tools that may help reduce the occurrence of these reactions.

## Complications

Even after recovery, some individuals may suffer long-term consequences from DRESS syndrome, including permanent organ damage and the development of autoimmune conditions.

The majority of individuals who recovered from DRESS syndrome developed new diseases. Thyroid diseases, such as Hashimoto’s disease, Grave’s disease, and painless thyroiditis, are the most common long-term complications of DRESS syndrome.

Organ damage resulting from DRESS syndrome is also associated with long-term complications. Individuals with severe liver damage may need a liver transplant, while those with prior kidney disease may require long-term hemodialysis.

Infectious diseases are another common complication associated with DRESS syndrome. People who have received corticosteroid treatment may have a higher risk of infectious diseases such as herpes and pneumonia.

## Differential Diagnosis

DRESS must be distinguished from other severe cutaneous adverse reactions — namely, the Stevens–Johnson syndrome and its related disease, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis (AGEP) . The latency period of DRESS is generally longer than that of other severe cutaneous adverse reactions.

The Stevens–Johnson syndrome and toxic epidermal necrolysis have rapid evolution, with resolution typically occurring over the course of 3 to 4 weeks. Mucosal involvement in DRESS can arouse concern about one of these conditions, but oral mucosal disease in DRESS tends to be milder and less hemorrhagic.

Marked dermal edema in DRESS can result in the formation of tense secondary bullae and erosions that are negative for Nikolsky’s sign, in contrast to the full-thickness epidermal separation with application of lateral tension seen in the Stevens–Johnson syndrome and toxic epidermal necrolysis, which is consistent with a positive Nikolsky’s sign.

AGEP manifests within hours to days after drug exposure and typically resolves over the course of 1 to 2 weeks. In contrast to DRESS, AGEP is characterized by flexural accentuation of the rash, which consists of generalized pustules without predilection for hair follicles. A prospective evaluation of patients with DRESS showed that 6.8% had features of the Stevens–Johnson syndrome, toxic epidermal necrolysis, or AGEP, with the reactions in 2.5% of cases considered to be caused by one of these conditions in addition to DRESS (overlapping severe cutaneous adverse reactions).

Use of the RegiSCAR validation criteria may help to distinguish these conditions.Common morbilliform drug eruptions typically manifest 1 to 2 weeks after drug exposure (sooner with drug reexposure) and are not usually associated with elevated aminotransferase levels, eosinophilia, or prolonged recovery times. DRESS must also be distinguished from hemophagocytic lymphohistiocytosis, angioimmunoblastic T-cell lymphoma, and acute graft-versus-host disease

### Affected populations

While DReSS does occur in children, it is predominantly seen in adults with a mean age of onset between 40 and 60 years old. Female patients tend to be significantly younger than their male counterparts, and while several studies have found a slight female predominance in DReSS, many more have not replicated this finding. There is significant association between ethnic background and DReSS, with an abundance of research showing HLA alleles being a strong risk factor with exposure to certain drugs. Specific ethnicities at risk include Han-Chinese, Korean, Thai and Europeans with allopurinol exposure, the Chinese with dapsone, and European, Chinese, Korean and Japanese groups with carbamazepine.

Incidence rates of DReSS range from 3.89 per 10,000 inpatients in Spain, to 0.9 per 100,000 people in a West Indian population. Prevalence estimates include 2.18 per 100,000 in the US and 9.63 cases per 100,000 inpatients in Thailand.

## Treatment Recommendations for DRESS Syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms)

## 1. Immediate Actions

* Prompt discontinuation of the suspected culprit drug(s) is essential and the first step in management.

## 2. Corticosteroids – Mainstay of Treatment

* Systemic corticosteroids are the cornerstone therapy for all patients with confirmed DRESS.
* Typical initial dosing is prednisone or equivalent at approximately 1 mg/kg/day, adjusted according to disease severity.
* In mild cases, very high potency topical corticosteroids may suffice.
* For moderate disease, both systemic corticosteroids and very high potency topical steroids are recommended.
* For severe cases, systemic corticosteroids should be initiated promptly.
* Corticosteroids should be tapered slowly over 6 weeks to 3–6 months to reduce the risk of relapse, which occurs in about 10–15% of cases.

## 3. Additional Immunomodulatory Therapies

* In corticosteroid-refractory or severe cases, adjunctive therapies may be considered:
  + Cyclosporine has shown clinical benefit.
  + Intravenous immunoglobulins (IVIG) may be used, often combined with corticosteroids or cyclosporine.
  + Targeted biologics, such as anti–IL-5 or anti–IL-5 receptor antibodies, are emerging options for refractory disease.
  + Other immunosuppressants like cyclophosphamide or mycophenolate are less commonly used but may be considered in select cases.

## 4. Antiviral Therapy

* Reactivation of human herpesviruses (especially CMV) can complicate DRESS.
* Antiviral agents (e.g., ganciclovir, valganciclovir) may be considered in patients with high viral loads or life-threatening viral complications.

## 5. Supportive Care and Monitoring

* Supportive care tailored to organ involvement is essential.
* Regular follow-up, especially during the first 6 months, is recommended to monitor for relapse, organ damage, and late complications.

## 6. Allergy Workup

* Patch testing can be considered cautiously to identify the culprit drug.
* Skin prick tests are generally not recommended due to safety concerns.

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### Common variable immunodeficiency (CVID)

**DEFINITION AND DESCRIPTION**

Common variable immunodeficiency (CVID) is a group of genetic disorders that affect your immune system. People with CVID have low levels of antibodies (proteins that fight infections) in their blood.

When you don’t have enough antibodies, you can get sick more often and more severely than other people. People with CVID have frequent respiratory, ear and sinus infections. Vaccines are also ineffective because your immune system can’t respond to them by making antibodies.

#### **How serious is CVID?**

In addition to frequent infections — which are sometimes hard to treat — CVID increases your risk of developing other life-threatening conditions. This includes severe lung disease and certain cancers.

### Symptoms of common variable immunodeficiency (CVID)

The most common sign of CVID is frequent infections — most commonly, sinusitis, pneumonia, bronchitis, ear infections and shingles.

Other symptoms of CVID can include:

* Chronic rhinitis (runny nose or nasal congestion).
* Enlarged lymph nodes.
* Gastrointestinal (GI) symptoms. This includes abdominal pain, nausea, vomiting and diarrhea.
* Unintended weight loss.
* Joint pain.
* Finger clubbing.

### Causes of CVID

Genetic variations (changes in your DNA, the instructions that make your body work) cause CVID. No single change causes CVID — many different gene changes are associated with it and experts think it takes more than one change to cause CVID. The most commonly found mutations are in the *TNFRSF13B* gene.

These changes mean that your B-cells — a type of immune cell — don’t work properly. They don’t develop into plasma and memory B-cells, which make antibodies (also called immunoglobulins). Specifically, people with CVID have low levels of IgG, IgA and IgM antibodies.

Low levels of antibodies mean your body can’t fight off infections as easily. And since your body’s way of making antibodies doesn’t work, vaccines aren’t effective at helping your body create immunity to diseases.

The gene variations that lead to CVID are inherited in about 10% of cases. Experts don’t know what causes them in the other 90% of people with CVID. They think epigenetic changes (changes in the way your body interprets DNA, caused by environmental or lifestyle factors) could contribute to developing CVID. But researchers need more studies to understand this theory better.

### Complications of CVID

Damage from infections and CVID’s effects on your immune system can lead to additional diseases and conditions. These include:

* Autoimmune disorders.
* Cancers. Lymphoma and cancers that affect your GI tract are the most common cancers in people with CVID.
* Chronic lung diseases.
* Enlarged spleen (splenomegaly).
* Granulomas.

People with CVID are also at a higher risk of developing depression.

#### **CVID and autoimmune disorders**

People with CVID are at a higher risk for developing autoimmune disorders, including:

* Antiphospholipid syndrome.
* Autoimmune hemolytic anemia.
* Autoimmune hepatitis.
* Celiac-like diseases.
* Hashimoto’s Disease.
* Immune thrombocytopenia purpura (ITP).
* Inflammatory bowel disease (IBD).
* Rheumatoid arthritis.
* Vasculitis.

#### **CVID and chronic lung diseases**

Damage from infections and inflammation in your lungs can lead to chronic lung and airway diseases. People with CVID are at risk for developing:

* Asthma.
* Bronchiectasis.
* COPD (chronic obstructive pulmonary disease).
* Emphysema.
* Granulomatous–lymphocytic interstitial lung disease (GLILD). GLILD is a condition that damages your lungs and causes nodules of immune cells to form.

## Diagnosis and Tests

Healthcare providers diagnose CVID with blood tests. They’ll measure the amount of IgG, IgA and IgM antibodies in your blood. If test results show a low level of antibodies, your provider might order genetic testing to look for DNA changes.

Providers also look at your health history and might perform other tests or imaging to rule out other conditions.

## Management and Treatment

CVID can be managed with replacement immunoglobulin therapy (RIgG). This provides your body with antibodies that it can’t make on its own. This can either be:

* Intravenous immunoglobulin therapy (IVIg). Your provider gives you antibodies directly into a vein every three to four weeks.
* Subcutaneous immunoglobulin therapy (SCIg). Your provider gives you antibodies under your skin (subcutaneous injections) every one to four weeks.

Replacement therapy isn’t a cure for CVID — you’ll need to be on this treatment for the rest of your life. Your provider may also give you antibiotics to prevent bacterial infections or to treat them at the first sign of infection.

## Outlook / Prognosis

If you have CVID, you’ll need treatment for the rest of your life to protect yourself from infectious diseases. You’ll need to work closely with a healthcare provider to treat any illnesses as soon as possible. You may have regular screening for cancer, lung diseases or other complications.

You should avoid getting vaccinations unless your provider recommends them. Live vaccinations can be dangerous for people with CVID.

There’s no cure for CVID. But immunoglobulin replacement treatments (IVIg and SCIg) have increased survival rates in the past few decades. They’ll reduce your risk of getting a life-threatening infection.

Studies suggest that most people with CVID (over 75%) are alive 25 years after diagnosis. About half live 45 years or more after their diagnosis. The most common cause of death is lung disease.

## Living With

The best way to take care of yourself with CVID is to prioritize your care. Keep appointments with your provider, and make sure you can recognize signs of an infection or other diseases. Ask your provider what to do if you have symptoms of an infection.

People with CVID are at a higher risk for depression. Talk to a provider if you have symptoms of depression, or if you just don’t feel like yourself. Addressing your mental health is as important as managing any other aspect of your well-being.

### When to see a doctor

Talk to a healthcare provider if you:

* Get sick from a live vaccine.
* Get sick frequently with bacterial infections.
* Have other long-lasting symptoms, like lung or GI issues.

They can tell you whether they need to look into it more.

**DIFFERENTIAL DIAGNOSIS**

The basis for differential diagnosis is on the main laboratory characteristic of CVID: hypogammaglobulinemia.

Hypogammaglobulinemia can be primary or secondary. The primary causes are more common in children.

* Secondary hypogammaglobulinemia can be due to decreased production (drugs, disorders that cause bone marrow suppression, Goodpasture syndrome, malignancy) or increased loss (protein-losing disorders such as enteropathies, nephrotic syndrome, burns).
* Primary hypogammaglobulinemia can be due to deficiency in IgG1 and IgG2, hyper-immunoglobulin M syndromes, and other combined immunodeficiencies.

**EPIDEMIOLOGY**

CVID affects approximately 1 of 25000 individuals, with a higher prevalence in northern Europe.It is typically most diagnosed after puberty, being the majority between 20 and 45 years of age.It does not show any predilection for race or gender.

**RECOMMENDATION**

Generally, after treating an active infection, therapy begins with adequate hydration. Subsequently, a slow infusion load of intravenous immune globulin (IVIG) must be administered until tolerance is appropriate, followed by maintenance doses.

In patients prone to reactions, diphenhydramine and acetaminophen (and sometimes hydrocortisone) can be premedicated. The subcutaneous route is an optional alternative in maintenance therapy (normally, weekly, or every other week). The initial dose for IVIG is 300 to 600 mg/kg every three to four weeks.

The monitoring of IgG levels should take place every six months. Therefore, dosing adjustments may occur according to the patient's weight and IgG production.

**Adverse Reactions:**

Intravenous immune globulin adverse reactions can be seen in 20 to 50% of patients, most likely during the first infusion, but they depend on the dose, infusion rate, organ dysfunction, prothrombotic stimuli, and brand.

Subcutaneous immune globulin systemic adverse reactions are much lower than the first ones. Local reactions, such as pain and swelling are the most frequent ones.

* Inflammatory reactions can occur during IVIG administration. The management is generally symptomatic.
* Anaphylaxis is rare but may be life-threatening. The treatment basis is on common protocols (securing the airway, administration of epinephrine, oxygen, salbutamol, antihistamine agents, and glucocorticoids).
* Thromboembolic risk events (such as myocardial infarction, stroke, and venous thromboembolism) can be diminished by adequate hydration, avoiding prolonged immobilization, spacing larger doses, slowing infusions.
* Headache is common and treatable with normal painkillers.
* Acute kidney injury risk can be minimized with adequate hydration and avoiding concentrated or sucrose-containing products in those with existing renal disease.
* Hemolytic anemia can occur due to passive antibodies in the IVIG product. Reactions can vary from a positive direct Coombs test, mild extravascular hemolysis, and infrequently, intravascular hemolysis.
* Neutropenia can occur but is normally mild and transient.

**2. Infections and antimicrobials**

Generally, active bacterial infections are treated with longer courses of antibiotics (sometimes 2 or 3 times longer).

Sputum examination or bronchoalveolar lavage is mandatory in all patients with sinopulmonary infections before antibiotic treatment.

Prophylactic antimicrobials are not a routine recommendation. However, exacerbation of sinopulmonary infections could be less frequent with the administration of 250 mg of azithromycin three times weekly in susceptible individuals who receive replacement therapy.

High-risk immunodeficient patients should be considered during seasonal influenza. Prophylactic treatment may include antiviral therapy.

**3.**  **Autoimmune disorders**

Glucocorticoids are the first-line treatment for immune thrombocytopenia and autoimmune hemolytic anemia. Higher doses are deliverable in patients that are currently on immune globulin replacement therapy. In glucocorticoid-refractory cases, rituximab should be considered, maintaining immune globulin replacement therapy; however, in severe refractory cases, splenectomy is the last option.

Treatment for rheumatologic diseases is the same as for patients who are not immunocompromised, along with the addition of immunoglobulin replacement.

**4. Malignancies**

Treatment for malignancies has as its basis for general population protocols.

Unfortunately, there are no standardized monitoring protocols for cancer risk in these patients, therefore current recommendations of screening procedures must be age-appropriate, according to each country’s guidelines. However, all patients must be tested for Helicobacter pylori infection and pernicious anemia laboratory features, because of their relation to gastric malignancy.

**5. Vaccinations**

Recommendations for vaccination is based on the antibody deficiency severity:

* Routine schedule for inactivated or subunit vaccines in mild deficiency:
  + DTaP (diphtheria, tetanus toxoid, acellular pertussis vaccine)
  + HAV (Hepatitis A virus)
  + HBV (hepatitis B virus)
  + HIB (Haemophilus influenzae type B)
  + HPV (human papillomavirus)
  + Influenza
  + Meningococcal
  + Pneumococcal
  + Polio (intramuscular)
  + Anthrax
  + JE (Japanese encephalitis)
  + Typhoid (intramuscular).
  + Rabies
* Routine schedule for inactivated or subunit vaccines in severe deficiency:
  + HPV
  + Influenza
  + Anthrax
  + Rabies
* Recommended administration of live-attenuated vaccines in mild deficiency (likely benefit but possible harm):
  + MMR (measles-mumps-rubella)
  + Rotavirus
  + Varicella
  + Herpes Zoster
  + Smallpox (for pre-exposure)
  + BCG (Bacille Calmette-Guerin)
* Live-attenuated vaccines are not recommended in severe deficiency.

**6. Other recommendations**

* Pulmonary diseases should be treated individually since there are no specific indications in CVID patients.
* Patients should not be given blood or blood components without testing for *Cytomegalovirus*.
* Regular dental care is mandatory. Prophylactic antibiotics are crucial before invasive dental procedures.
* Mental health following is crucial because patients are sometimes disintegrated from normal life activities.
* Audition care is essential given the fact that sensorineural loss frequently occurs probably because of recurrent bacterial otitis media, viral infections, periodic use of ototoxic antibiotics, and central nervous system infections.
* The patient's parents must receive genetic counseling about the possibility of future children with the same disease.

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**Chronic cough related to allergy**

**DEFINITION AND DESCRIPTION**

An allergy cough happens when you breathe in a substance (allergen) that your immune system recognizes as dangerous, though it's not. Tree and grass pollen, pet dander, dust mites, or mold are just a few allergens that can cause an allergy cough.

The cough is typically dry and non-productive, meaning it doesn't bring up mucus. It is sometimes described as having a "barking" or "hacking" sound. An allergy cough will last until it’s treated or you remove the allergen that triggered it.

## Symptoms

An allergy cough can feel like a persistent tickle or irritation at the back of the throat. It's usually accompanied by other allergy symptoms, including:

* Runny nose
* Nasal congestion
* Sneezing
* Fatigue
* Sinus headache

Generally speaking, an allergy-related cough does not bring up mucus or phlegm.

Cough.

In some people, the cough can become chronic and last for several weeks.

Allergy coughs can sometimes be hard to tell from conditions like asthma or an upper respiratory tract infection. An allergy can also set off asthma, which can cause a cough and trouble breathing. You may experience:

* Chest tightness
* Shortness of breath (dyspnea)
* Wheezing caused by the narrowing of your airways

With infections like the flu or COVID-19, you are more likely to have other symptoms along with a cough, such as fever, chill, and body or muscle aches. You could also have symptoms like loss of taste or smell as well as nausea, vomiting, and diarrhea if you have COVID.

## Causes

An allergy cough is caused by your immune system's overreaction to a substance (allergen). The cough is not caused by an infection like it is when you have a cold or the flu. Rather, it's a common symptom of seasonal allergies and hay fever.

Some allergens that can cause allergy symptoms, including allergy cough, include:

* Pollen (trees, grass) and certain food allergies (fruit, nuts) related to these pollen allergies
* Dust mites that live in bedding, carpets, and furniture of most homes
* Pet dander due to dead skin cells of pets (more often cats than dogs)
* Mold, including aspergillus (an indoor allergen that can lead to health issues)

When you're exposed to an allergen, your immune system makes immunoglobulin E (IgE). This substance sets off a chain reaction that starts with immune cells (mast cells and basophils) breaking open and releasing the chemical histamine into the bloodstream.

Histamine is the main cause of allergy symptoms. It causes tiny blood vessels to widen and leak fluid into the tissues nearby. When this happens in the nose and sinuses, it can lead to congestion and a runny nose.

An allergy-related cough happens when that mucus drains from your nose and down the back of your throat (postnasal drip). The drainage can make your throat itch or tickle, which triggers coughing.

### Allergy Medications That Cause Coughs

Some medications used to treat allergies can also cause a cough. One example is a certain type of antihistamine, a drug that works by keeping histamine from attaching to cells and triggering inflammation.

Antihistamines can have a drying effect and can leave the throat feeling scratchy, which can make you cough. This cough is generally mild and will go away when you stop treatment.

### Antihistamines and Allergy Cough

Older antihistamines like Benadryl (diphenhydramine) may be better at treating a cough but they are more likely to make you drowsy.Newer antihistamines like Claritin (loratidine) and Zyrtec (cetirizine) don't cause drowsiness but may not be as helpful with allergy cough symptoms. Research continues into how specific medications might be effective in treating cough.

## Treatment of Allergy Cough

Healthcare providers usually suggest starting with oral antihistamines to help with allergy symptoms. They are considered a "first-line" treatment. You may also find some relief with certain natural remedies, though research is limited.

### Over-the-Counter Options

If you need allergy symptom relief during the day, second-generation antihistamines are usually preferred because they are less likely to cause drowsiness.

Other over-the-counter (OTC) options can also help you treat an allergy cough at home:

* **Expectorants** like Mucinex (guaifenesin) to loosen phlegm
* **Decongestants** like Sudafed (pseudoephedrine) to open the nasal passages
* **Nasal steroid sprays** like Nasacort AQ (triamcinolone) to relieve inflammation and ease breathing
* **Cough lozenges**, especially ones with eucalyptus in them
* **Saline nasal sprays or irrigation** **systems** to clear the nasal passages

### Treating a Nighttime Allergy Cough

If your allergy cough is keeping you up at night, try taking a first-generation antihistamine like Benadryl before you go to bed. In this case, the side effect of drowsiness works in your favor.

### Natural Allergy Cough Treatments

Here are a few natural treatments for dry coughs that may help with allergy coughs. Many are available as teas, which can be warm and soothing:

* Honey
* Turmeric
* Marjoram
* Garlic
* Marshmallow root
* Licorice root
* Ginger
* Thyme

Be sure to talk with your healthcare provider about over-the-counter products, supplements, and natural treatments you use to relieve allergy cough symptoms.

### Environmental Factors

At-home remedies can include lifestyle changes and simple interventions, such as:

* Using a humidifier or vaporizer to help moisturize the air, loosen mucus, and ease throat irritation
* Running an air purifier to reduce allergen exposure
* Routinely changing your heat and air conditioning (AC) filters. A 2022 study of 189 dust samples from homes, schools, and hotels suggests that clean AC filters can limit dust mites (a cause of allergy symptoms in many people).
* Limiting fireplace and gas stove exposures. Indoor gas stove use can contribute to allergy symptoms and other breathing problems, but more research is needed to better understand the connection.

## When to See a doctor

A cough from allergies is not usually a serious threat to your health, but that doesn’t mean it’s easy to deal with. Allergy symptoms can interfere with your daily life and may even keep you from getting enough sleep.

If you're avoiding allergens and using OTC treatments but it doesn't help, see your healthcare provider or an allergist, a specialist that can test for allergen sensitivity.

Two tests that are commonly used to diagnose allergies include:

* **Skin prick test:** This involves putting tiny amounts of suspected allergens under your skin to see if a reaction occurs.
* **Blood tests**: IgE-specific blood tests (also known as RAST testing) can detect antibodies associated with certain allergens.

An allergist can also determine if your cough is related to allergic rhinitis (hay fever) or asthma and help you find the right treatment(s) to ease your symptoms. You might even be able to get long-term relief with a treatment like allergy shots.

**Differential Diagnosis of Chronic Cough Related to Allergy**

Chronic cough related to allergy is most commonly due to conditions involving airway inflammation and hypersensitivity. The differential diagnosis includes:

Common Allergy-Related Causes of Chronic Cough

* Asthma and Cough-Variant Asthma (CVA):
  + Classic allergic airway disease causing cough with or without wheezing.
  + Often associated with airway hyperresponsiveness and eosinophilic inflammation.
* Non-Asthmatic Eosinophilic Bronchitis (EB):
  + Eosinophilic airway inflammation causes chronic cough without airway obstruction or hyperresponsiveness.
  + Distinguished from asthma by normal spirometry and absence of bronchial hyperreactivity.
* Upper Airway Cough Syndrome (UACS) / Postnasal Drip Syndrome:
  + Allergic rhinitis or sinusitis causes nasal secretions to drip into the throat, triggering cough reflex.
  + Commonly associated with allergic rhinitis.
* Allergic Rhinitis:
  + Nasal congestion, sneezing, and postnasal drip contributing to coughing.

Other Important Differential Diagnoses to Consider (Non-Allergic and Overlapping)

* Gastroesophageal Reflux Disease (GERD):
  + Acid reflux irritating the larynx and airways, causing cough.
* Laryngopharyngeal Reflux (LPR):
  + Reflux reaching the upper airway, causing hoarseness and cough.
* Vocal Cord Dysfunction (VCD):
  + Paradoxical vocal cord movement causing cough and dyspnea, often misdiagnosed as asthma.
* Infections:
  + Chronic or occult sinusitis, pertussis, or other respiratory infections.
* Medication-Induced Cough:
  + Angiotensin-converting enzyme (ACE) inhibitors commonly cause chronic cough.

Clinical Clues and Features

* Asthma/CVA: Female predominance; cough worsened by irritants; associated wheezing or dyspnea.
* Eosinophilic Bronchitis: Less severe cough than asthma; absence of wheezing; eosinophilia in sputum.
* UACS: Voice hoarseness, throat clearing, nasal symptoms.
* GERD: Heartburn, regurgitation, cough worse after meals or lying down.
* VCD: Hoarseness, throat tightness, cough triggered by irritants.

**Epidemiology of Chronic Cough Related to Allergy**

* Prevalence of Chronic Cough:
  + Chronic cough, defined as cough lasting more than 8 weeks, has a global prevalence estimated between 1% and 10% in the adult population, depending on the study and region
  + For example, a large U.S. managed care study found an overall chronic cough prevalence of about 1.04%, with higher rates in females (1.21%) and older adults aged 65–85 years (2.2%)
  + Other population studies report prevalence rates such as 2.6% in South Korea, 4.3% in Japan, 4% in Denmark, and up to 15.8% in older adults in Canada.
  + A meta-analysis estimated a global chronic cough prevalence of approximately 9.6%

Allergy as a Contributing Factor:

* + Allergic conditions such as allergic rhinitis, asthma, and eosinophilic bronchitis are common causes or contributors to chronic cough.
  + In one study, comorbidities among chronic cough patients included asthma (14–36%), chronic rhinosinusitis (up to 40%), and gastroesophageal reflux disease (16–24%), with asthma and upper airway cough syndrome (often allergy-related) being significant contributors.
  + Allergic airway inflammation leads to cough hypersensitivity and persistent symptoms.

Demographic and Risk Factors:

* + Chronic cough prevalence is higher in females and older adults (especially over 65 years).
  + Ethnic differences exist; for instance, higher prevalence in Blacks compared to Whites in the U.S., possibly due to higher rates of asthma and obesity.
  + Smoking is a strong risk factor, increasing chronic cough prevalence markedly.
  + Environmental allergen exposure and atopic predisposition contribute to allergy-related chronic cough.

## Recent Guideline Recommendations on Chronic Cough Related to Allergy

## 1. Allergic Rhinitis and Upper Airway Cough Syndrome (UACS)

* Saline Nasal Irrigation: Strongly recommended to improve nasal secretions and reduce cough symptoms in patients with allergic rhinitis causing UACS.
* Intranasal Corticosteroids (INCS): Recommended for moderate to severe allergic rhinitis; effective in reducing cough related to nasal inflammation.
* Oral or Intranasal Antihistamines: Routine empirical use of antihistamines for chronic cough is not recommended. However, antihistamines may be used specifically for allergic rhinitis symptoms but not solely for cough suppression.
* Combination Therapy: For patients with more severe symptoms (Visual Analog Scale ≥5), INCS combined with intranasal antihistamines (e.g., azelastine) may be used.

## 2. Cough Variant Asthma (CVA)

* Inhaled Corticosteroids (ICS): Empirical trial of ICS is suggested for chronic cough patients with normal chest radiographs and no suspicion of other causes. ICS reduces airway inflammation and improves cough, especially in patients with elevated biomarkers of type 2 inflammation (e.g., FeNO ≥25 ppb).
* Leukotriene Receptor Antagonists (LTRA): A short-term trial (2–4 weeks) may be considered in CVA patients, either alone or combined with ICS/long-acting beta-agonists (LABA).

## 3. Gastroesophageal Reflux Disease (GERD)-Related Cough

* Empirical use of proton pump inhibitors (PPIs) is not recommended for chronic cough unless typical GERD symptoms (heartburn, acid regurgitation) are present.
* Lifestyle and dietary modifications are advised for suspected GERD-related cough.
* Referral to specialists is recommended if alarming symptoms or poor response to initial management occur.

## 4. Other Recommendations

* Cough Suppressants: May be considered for persistent cough but have low-quality evidence.
* Neuromodulating Agents: Gabapentin or pregabalin can be used for refractory chronic cough with close monitoring for adverse effects.

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**SELECTIVE IMMUNOGLOBULIN A DEFICIENCY**

**Definition and description**

Selective IgA deficiency is the lack of a disease-fighting antibody in the immune system called immunoglobulin A (IgA). People with this condition usually have typical levels of other immunoglobulins (im-u-no-GLOB-u-lins).

An immunoglobulin is an antibody produced by immune system cells to fight bacteria, parasites and other agents that cause illness. IgA antibodies circulate in the blood and are found in tears, saliva, breast milk, and fluids released from the lining of the airways, lungs and digestive system.

Most people with selective IgA deficiency have no symptoms. But some people who have selective IgA deficiency have frequent illness of the airways, lungs and digestive system.

Selective IgA deficiency may increase the risk of other conditions related to the immune system, such as allergies, asthma, rheumatoid arthritis, inflammatory bowel diseases and others.

There is no treatment specifically for selective IgA deficiency. Treatments focus on addressing the frequent, repeat or long-lasting conditions that develop with this immune system disorder.

**Causes**

Selective IgA deficiency happens when immune system cells don't produce any or produce very few IgA antibodies. The exact reason cells don't produce these antibodies isn't known.

Certain medicines used to treat seizures, epilepsy or rheumatoid arthritis may cause selective IgA deficiency in some people. The deficiency may continue after the medicine is no longer taken.

**Risk factors**

A family history of selective IgA deficiency increases the risk of the condition. Certain variations of genes appear to be linked to selective IgA deficiency, but no gene is known to directly cause the condition.

**Symptoms**

Most people with selective IgA deficiency have no symptoms. Some people have illnesses more often than is typical. They also may have a particular illness that returns often. Having frequent illnesses doesn't necessarily mean a person has selective IgA deficiency.

People with selective IgA deficiency may have frequent or repeat episodes of the following:

## Ear infections, particularly in young children.

## Colds.

## Sinus infections.

## Lung illnesses, such as bronchitis or pneumonia.

## Giardiasis, a parasitic illness of the digestive system that causes diarrhea.

## Children with frequent illnesses may not eat well or may not gain weight typical for their age.

## 

## Diagnosis

## A diagnosis of selective IgA deficiency is based on a blood test that measures levels of immunoglobulins in the blood. IgA deficiency can be complete or partial.

## Your healthcare professional may order an immunoglobulin blood test because you have had frequent or repeat illnesses. The test also may be a part of a series of lab tests to diagnose or rule out other conditions.

## Treatment

## Antibiotic treatments are prescribed as needed to treat bacterial disease. If you have had a long-term illness, such as chronic bronchitis, you may receive antibiotics as a preventive treatment. This therapy is called antibiotic prophylaxis (pro-fuh-LAK-sis).

## Complications

People with selective IgA deficiency are at increased risk of other long-term conditions. These include:

* Allergies and asthma.
* Rheumatoid arthritis.
* Celiac disease.
* Inflammatory bowel disease.
* Common variable immunodeficiency, which is a lack of two or more types of immunoglobulins.

### Risk of reaction to blood products

People with selective IgA deficiency are at risk of reactions to blood transfusions or blood products. Because a person's body doesn't make IgA, the immune system may see it as a foreign substance in a blood transfusion or other treatment with blood products.

A reaction may cause high fever, chills, sweating and other symptoms. Rarely, people with selective IgA deficiency have a life-threatening allergic reaction, called anaphylaxis (an-uh-fuh-LAK-sis).

Healthcare professionals recommend wearing a medical bracelet. A bracelet can show that you have selective IgA deficiency and should receive modified blood or blood products.

## Diagnostic Considerations

Primary immunodeficiencies include agammaglobulinemia, hypoglobulinemia, selective deficiency of IgG subclasses with or without immunoglobulin A deficiency (IgAD), X-linked agammaglobulinemia, autosomal recessive agammaglobulinemia, impaired polysaccharide responsiveness, B-cell disorders, T-cell disorders, combined B- and T-cell disorders, common variable immunodeficiency (CVID), severe combined variable immunodeficiency, transient hypogammaglobulinemia of infancy, and Wiskott-Aldrich syndrome.

Acquired immunodeficiencies include drug-induced hypogammaglobulinemia (most commonly, long-term therapy with anticonvulsants and steroids), AIDS, and postinfectious hypogammaglobulinemia.

Recurrent sinopulmonary infections include cystic fibrosis, immotile cilia syndrome, endobronchial obstruction, and recurrent aspiration.

## Differential Diagnoses

* Ataxia-Telangiectasia
* Severe Combined Immunodeficiency (SCID)
* IgG subclass deficiency and/or specific polysaccharide antibody deficiency
* Pediatric Severe Combined Immunodeficiency
* Wiskott-Aldrich Syndrome

## Epidemiology

### Frequency

At a minimum, an estimated 250,000 individuals have immunoglobulin A deficiency (IgAD) in the United States.In African Americans, the prevalence of IgAD is 1 case per 6000 persons. IgA levels are estimated to be abnormally low in 1:500 subjects, with the incidence as high as 1:100 atopic individuals. Complete absence of IgA is less frequent.

Factors associated with the prevalence of IgAD include a family history of IgAD and the country of origin. Family studies using IgAD blood donors as probands show that first-degree relatives have a 7.5% prevalence rate of IgAD, which is 38-fold higher than that of unrelated donors.The serological prevalence of IgAD varies 100-fold among populations. Prevalences, in decreasing order, are as follows:

* Iran - 1 in 651 persons
* Arabian peninsula - 1 in 143 persons
* Spain - 1 in 163 persons
* Eastern Nigeria - 1 in 252 persons
* Finland - 1 in 396 persons
* Czech Republic - 1 in 408 persons
* Basque regions of Spain and France - 1 in 521 persons
* Canada - 1 in 531 persons
* Iceland - 1 in 533 persons
* England - 1 in 875 persons
* Brazil - 1 in 965 persons
* France - 1 in 3040 persons

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**CHRONIC GRANULOMATOUS DISEASE**

**DEFINITION AND DESCRIPTION**

Chronic granulomatous (gran-u-LOM-uh-tus) disease (CGD) is a genetic condition in which infection-fighting white blood cells don't work properly. These white blood cells are called phagocytes. When phagocytes don't work as they should, they can't protect the body from bacterial and fungal infections.

People with CGD may develop infections in their lungs, skin, lymph nodes, liver, stomach and intestines, or other areas. They also may develop clusters of white blood cells in infected areas. CGD is inherited, meaning it runs in families. Most people are diagnosed with CGD during childhood, but some people may not be diagnosed until adulthood.

**Causes**

A change in one of five genes can cause CGD. People with CGD inherit the changed gene from a parent. These genes produce proteins that form an enzyme. This enzyme helps your immune system work properly. The enzyme is active in white blood cells, called phagocytes, that protect you from infections by destroying fungi and bacteria. The enzyme also is active in immune cells that help your body heal.

When there are changes to one of these genes, the protective proteins are not produced. Or they're produced, but they don't work properly.

Some people with CGD don't have one of these changed genes. In these cases, medical professionals don't know what causes the condition.

**Risk factors**

Boys are more likely to have CGD.

**SYMPTOMS**

People with chronic granulomatous disease get a serious bacterial or fungal infection every few years. An infection in the lungs, including pneumonia, is common. People with CGD may develop a serious type of fungal pneumonia after being exposed to dead leaves, mulch or hay.

It's also common for people with CGD to experience infections of the skin, liver, stomach and intestines, brain, and eyes. Symptoms that may happen with infections include:

* Fever.
* Chest pain when inhaling or exhaling.
* Swollen and sore lymph glands.
* An ongoing runny nose.
* Skin irritation that may include a rash, swelling or redness.
* Swelling and redness in the mouth.
* Trouble swallowing.
* Gastrointestinal problems that may include:
  + Vomiting.
  + Diarrhea.
  + Stomach pain.
  + Bloody stool.
  + A painful pocket of pus near the anus, called an abscess.

### When to see a doctor

If you think you or your child has a type of fungal pneumonia from being around dead leaves, mulch or hay, get medical care right away. If you or your child often has infections and the symptoms listed above, talk to a healthcare professional.

## Diagnosis and tests

To diagnose CGD, a healthcare professional will review a family and medical history and do a physical exam. There are several tests used to diagnose CGD, including:

* **Neutrophil function tests.** A healthcare professional may do a dihydrorhodamine 123 (DHR) test or other tests to see how well a type of white blood cell, called a neutrophil, is functioning. This test is commonly used to diagnose CGD.
* **Genetic testing.** A genetic test can confirm the presence of a specific genetic alteration that results in chronic granulomatous disease.
* **Prenatal testing.** A healthcare professional may do prenatal testing to diagnose CGD if one of your children already has been diagnosed with CGD.

**Treatment**

Treatment for CGD is aimed at helping avoid infections and manage the condition. Treatments may include:

* **Infection management.** A healthcare professional will work to prevent bacterial and fungal infections before they start. Treatment may include a trimethoprim and sulfamethoxazole combination (Bactrim, Sulfatrim Pediatric) or itraconazole (Sporanox, Tolsura). Additional antibiotics or antifungal medicines may be necessary should infection happen.
* **Interferon-gamma.** Someone with CGD may occasionally have interferon-gamma injections, which may help boost cells in the immune system to fight infections.
* **Stem cell transplantation.** For some people, a stem cell transplant can provide a cure for CGD. Deciding to treat with stem cell transplantation depends on a number of factors, including prognosis, donor availability and personal preference.

### Potential future treatments

Gene therapy is currently being explored for CGD treatment, but further research is necessary.

Researchers also are investigating repairing defective genes to treat CGD.

## Outlook / Prognosis

The outlook is generally very good. Healthcare providers can usually manage symptoms of CGD and prevent serious infections. Treatment may continue indefinitely to keep infections and inflammation from becoming severe.

With ongoing treatment and support, many people with CGD live active and fulfilling lives. Prompt treatment is necessary so that your provider can treat infections before they become severe or life-threatening.

## Prevention

You can’t prevent CGD. People with a family history of the disease who want to have children should seek genetic counseling to learn about the risk of having a child with CGD.

## Living With

Contact your healthcare provider if you or your child experiences symptoms of CGD. One of the first signs of CGD is frequent bacterial and fungal infections.

**Epidemiology**

CGD occurs in 1 in every 200,000 live births in the United States. Due to the X-chromosome-linked gene mutation, approximately 80% of patients with CGD are males. The incidence rates are nearly identical across ethnic and racial groups, and approximately one-third of the X-linked mutations occur in de-novo. In cultures where consanguineous marriage is common, the autosomal recessive subtype of the disease is more common than the X-linked recessive forms, and the overall incidence rates are higher. Children with the X-linked variant of CGD tend to have an earlier onset and suffer a more severe disorder than the autosomal recessive form.

## Differential Diagnoses

* Acne Conglobata
* Acneiform Eruptions
* Acute Complications of Sarcoidosis
* Aphthous Stomatitis
* Cancers of the Oral Mucosa
* Cheilitis Glandularis
* Chronic Mucocutaneous Candidiasis
* Common Variable Immunodeficiency
* Complement Receptor Deficiency
* Cutaneous Candidiasis
* Cutaneous Manifestations of HIV
* Dermatologic Manifestations of Coccidioidomycosis
* Dermatologic Manifestations of Job Syndrome
* Eosinophilic Pustular Folliculitis
* Folliculitis
* Food or milk allergy
* Gram-Negative Folliculitis
* Gram-Negative Toe Web Infection
* Impetigo
* Intertrigo
* Iron Deficiency Anemia
* Mucosal Candidiasis
* Paronychia
* Pediatric HIV Infection
* Pediatric Pyloric Stenosis
* Pediatric Wiskott-Aldrich Syndrome
* Perifolliculitis Capitis Abscedens et Suffodiens
* Seborrheic Dermatitis

R**ECOMMENDATIONS**

Acute Infectious Episodes

Patients with CGD are more susceptible to se-vere bacterial and fungal infections. Symptoms typically begin in infancy, with the average age

of diagnosis being around 2.5 to 3 years. However, some individuals may not be diagnosed until their teenage years or even adulthood (20). Major

sites of infection are lungs (66%), skin/subcutis (53%), lymph nodes (50%), gastrointestinal tract(48%), liver (32%), kidney/urinary tract (22%), septicaemia (20%), ears (14%), bone (13%), eyes(11%), joints (7%) and brain (7%)(21).

Invasive Aspergillosis (IA)

CGD patients face the highest lifetime risk of developing invasive aspergillosis. The lungs are the most frequently affected site, followed by infections in the skin, lymph nodes, liver, and gastro-intestinal tract.

Even with antifungal prophylaxis, aspergillus infections remain the leading cause of death in patients with CGD. Itraconazole prophylaxis has been proven to significantly lower the risk of invasive fungal infections in patients with CGD . Posaconazole, a newer mold-active azole

with a broader spectrum of activity and increased tolerability, seems to be a favorable alternative .

Mulch Pneumonitis

Mulch pneumonitis as a medical emergency occurs within one week of exposure to organic material such as mulch, hay, or leaves. Treatment for these patients includes high-dose corticosteroids and antifungal and antibacterial agents.

Liver Abscesses

These abscesses develop in roughly one-third of CGD patients and are often caused by Staphylococcus aureus. These abscesses are typically

multi-loculated and surrounded by a thickened pseudocapsule. In patients with CGD, surgical resection of liver abscesses, when combined

with antibiotic therapy, it is considered safe. It is also linked to lower recurrence rates and shorter hospital stays.

Treating CGD-related liver abscesses with corticosteroids (at a median dose of 1 mg/kg/day for about five months) alongside targeted antimicro-bial therapy has been shown to lead to better out-comes and fewer follow-up liver procedures compared to invasive approaches like interventional radiology or open surgery. Steroids may help by reducing systemic inflammation, improving local immune response in the liver, and enhancing the effectiveness of antibiotics by allowing better tissue penetration in a less inflamed environment.

Lung Abscesses

These abscesses are relatively less common but potentially severe. Treatment for the condition often involves lifelong antibiotics, antifun-

gals and INF-γ.

Mycobacterial Infections Caused by Bacillus Calmette–Guérin and

Mycobacterium tuberculosis

Mycobacterial infections are a significant concern for patients with CGD, particularly in regions where the BCG vaccine is commonly given, tuberculosis is widespread, or both. Long-term remission can be reached with a combination of three or four antibiotics, such as rifampicin, ethambutol, isoniazid, and/or streptomycin . BCG vaccination should be officially avoided in individuals diagnosed with or suspected of having CGD, as well as in their newborn siblings.This recommendation aligns with guidelines for children with other inborn errors of immunity (IEI) that affect T cells, phagocytes, or IFN-gamma immunity.

Suppurative or Necrotising Lymphadenitis

It can affect at least 50% of these patients. CGD Patients are predisposed to lymphadenitis after receiving BCG vaccination. In addition to anti-

microbial therapy, lymphadenitis often requires excisional surgery.

Osteomyelitis

Surgical debridement is not routinely advised as first-line treatment for osteomyelitis but may be considered in certain situations, such as when

infection persists or other complications arise .

Autoimmunity

About half of CGD patients experience not only frequent infections but also autoinflammation or immune system dysregulation such as

inflammatory bowel disease (IBD). For mild cases of IBD in CGD, treatments like sulfasalazine or other aminosalicylates are typically used

initially. Recently, monoclonal antibodies targeting pro-inflammatory cytokines, such as infliximab, anakinra, adalimumab, and ustekinumab, have been studied, though evidence is limited. Of these, ustekinumab has shown somewhat better outcomes. Despite known side effects,many patients continue to rely on corticosteroids to manage their IBD.Immunomodulators

for CGD-related inflammatory manifestations are under investigation, including pioglitazone, tamoxifen, and rapamycin .

Hemophagocytic Lymphohistiocytosis (HLH)

Children with CGD can develop HLH, a condition marked by excessive and harmful in-flammation often triggered by infections. When diagnosing HLH in children, it’s essential to consider underlying conditions like CGD, as HLH may sometimes point to its presence. However, managing HLH in children with CGD remains a challenge, and there is still no established best approach for treatment. Early recognition and proper management of infectious triggers and HLH are crucial to reducing mortality.Children with CGD often face challenges with growth, with growth delays being a common issue. In young children, difficulty thriving is often one of the first noticeable signs of the condition.Approximately 75% are below the population mean for height and weight at the time of diagnosis and 35% require nasogastric and/or parenteral nutritional supplementation. Growth often

improves in late adolescence, and many patients with CGD attain their expected growth potential by adulthood.

Trimethoprim-sulfamethoxazole (TMP-SMX) has been used routinely to prevent bacterial infections in patients with CGD. TMP-SMX prophylaxis has significantly increased the proportion of infection-free

patients from 5% to over 40% . It is effective for both X-linked and autosomal recessive CGD and is typically dosed at 5 mg/kg/day (based on the TMP component) up to one double-strength tablet daily.

Invasive fungal infections pose a significant mortality risk in CGD patients.

Aspergillus

species, particularly Aspergillus fumigatus and Aspergillus nidulans, account for over 35% of these deaths. Other notable pathogens include Paecilomyces,Rasamsonia Argillacea, and Candida species .Traditionally, itraconazole has been the preferred azole for preventing fungal infections in

CGD patients. However, due to the emergence of resistant organisms and occasional intolerance to medication, there has been an increase in the use

of voriconazole and posaconazole. These newer azoles offer broader antifungal coverage and, in some cases, better patient tolerability. This shift underscores the ongoing need to evaluate and optimize prophylactic strategies in CGD management. Itraconazole is typically dosed at 100

mg up to 200 mg daily based on age and weight. Due to resistant organisms and intolerance, the use of voriconazole and posaconazole has

been recommended.

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### Wiskott-Aldrich syndrome

**Definition and description**

Wiskott-Aldrich syndrome is a rare genetic condition that affects the function of your child’s immune system and cells. It causes symptoms that include:

* Eczema.
* Immune deficiency.
* Bleeding and bruising.

This condition can lead to life-threatening complications and a short life expectancy. But treatment options help prevent these risks.

### What is a WAS-related disorder?

Your healthcare provider may refer to Wiskott-Aldrich syndrome as a WAS-related disorder. A WAS-related disorder affects the immune system and results from a genetic change of the *WAS* gene. X-linked thrombocytopenia is WAS-related.

A healthcare provider may identify congenital neutropenia after serious bacterial infections. Congenital neutropenia is associated with another genetic change, not *WAS*.

## Symptoms and Causes

There are three main symptoms of Wiskott-Aldrich syndrome:

* Eczema: Eczema is a skin condition that causes itchy, dry patches of skin.
* Immune deficiency: White blood cells that help keep your body healthy don’t work as they should or don’t function at all. As a result, your immune system can attack itself and make you ill. This can cause frequent infections, rheumatoid arthritis, vasculitis, anemia, leukemia or lymphoma.
* Problems with bleeding (microthrombocytopenia): Your blood isn’t able to clot as it should, or stop excessive bleeding. This happens because you have fewer and smaller blood cells that are responsible for clotting (platelets). It can cause bruising, nosebleeds, bloody diarrhea, bleeding under the surface of your skin (purpura) and a skin rash with tiny red dots (petechiae).

Infants with loss of function Wiskott-Aldrich syndrome may present with:

* Eczema.
* Immune deficiency.
* Severe thrush.
* Pneumonia.

There may be severe bacterial infections or myelodysplastic syndrome for gain-of-function WAS (congenital neutropenia).

### Causes Wiskott-Aldrich syndrome

A genetic change (mutation) of the *WAS* gene causes Wiskott-Aldrich syndrome. *WAS* is located on the short arm of your X chromosome. This gene is responsible for producing the Wiskott-Aldrich syndrome protein. This protein exists in all of your blood cells.

The Wiskott-Aldrich syndrome protein tells your cells to attach to other cells and tissues in a process called adhesion. Adhesion helps your immune system defeat invaders like bacteria or viruses, which can make you sick.

If you have a genetic mutation on the *WAS* gene, your blood cells aren’t able to attach to other cells and tissues. This can affect how your immune system defends itself, which results in the symptoms of Wiskott-Aldrich syndrome.

In congenital neutropenia, the genetic mutation causes neutrophils and monocytes to stall in their movement. Your immune system then doesn’t release them to fight infection.

#### **Can you inherit Wiskott-Aldrich syndrome?**

Yes, you can inherit Wiskott-Aldrich syndrome. This condition has an X-linked recessive pattern of inheritance where you get the genetic change from both of your biological parents.

You inherit one sex chromosome from each of your biological parents. Males have one X and one Y sex chromosome, and females have two X chromosomes. The condition affects males because the mutation affects the function of their only X chromosome.

The condition does have a pattern of inheritance in biological families, but over 30% of all cases occur without a presence in your biological family history (de novo). These cases are the result of a new genetic mutation that happens during conception.

## Diagnosis and Tests

A healthcare provider usually diagnoses Wiskott-Aldrich syndrome during infancy or childhood after a physical exam and testing. Early signs of the condition are bloody diarrhea, unusual bleeding or bruising. A healthcare provider will offer tests to confirm a diagnosis that includes:

* A complete blood count (CBC).
* A genetic blood test.
* Peripheral blood smear.

The condition will become more apparent during childhood if your child didn’t receive a diagnosis during infancy.

Additional testing might be necessary during childhood if they show signs of a compromised immune system, like getting frequent infections. This happens because their body isn’t able to process bacteria, viruses or certain types of vaccines as expected.

A provider may offer a blood test to detect whether your child’s body can produce antibodies after a vaccine. Antibodies trigger an immune response that helps prevent a severe illness. Additionally, they’ll perform another blood test that evaluates your child’s white blood cells, including their T-cells and immunoglobulins, which help produce antibodies.

## Management and Treatment

Treatment for Wiskott-Aldrich syndrome could include:

* Antibiotics or antiviral medications to treat infections.
* Antibody (immunoglobulin) infusions to replace missing antibodies.
* Blood-platelet transfusions for bleeding complications.
* Topical medications and over-the-counter (OTC) moisturizers to treat eczema.

An illness or an infection can have a severe or life-threatening impact on your child’s health. Treatment to preserve your child’s life may include:

* Stem cell transplant.
* Gene therapy (investigational).

Your child’s healthcare provider will discuss treatment options to give your child the best outcome and improve their quality of life.

## Outlook / Prognosis

If your child has Wiskott-Aldrich syndrome, their healthcare provider will offer a treatment plan that prevents life-threatening complications caused by their malfunctioning immune system. They may recommend genetic counseling after a diagnosis. This can help you and your family learn more about Wiskott-Aldrich syndrome and the treatment options available.

Your child may have health complications from common illnesses throughout childhood like chickenpox. Since their immune system isn’t able to protect their body in the same way as others their own age, your child may need quick treatment from a healthcare provider. Treating illnesses and infections quickly can lead to a more positive outcome.

Their provider may not recommend giving your child live virus vaccines like the flu shot. This is because a live strain of the virus may cause an illness in your child. Your child may receive some vaccines, but they may be less effective. If your child does get sick from a virus, early treatment with antiviral medications is usually positive. Complications from common illnesses may occur.

Since your child is at a higher risk of developing certain types of cancers, they’ll need regular cancer screenings for leukemia or lymphoma throughout their life.

### Is there a cure for Wiskott-Aldrich syndrome?

A stem cell transplant (bone marrow transplant) can cure Wiskott-Aldrich syndrome. These types of transplants replace stem cells that make blood cells in your body. Since Wiskott-Aldrich syndrome produces abnormally functioning blood cells, a stem cell transplant can replace those cells with healthy ones that function as expected.

### Is Wiskott-Aldrich syndrome fatal?

Wiskott-Aldrich syndrome can be fatal. Children who don’t undergo stem cell transplant may have a life expectancy of 15 years. Symptoms from infections, bleeding in your child’s brain, severe infection or cancer may be life-threatening and can lead to early death.

Medical advancements and treatment options are available to improve your child’s overall life expectancy.

## Prevention

You can’t prevent Wiskott-Aldrich syndrome because it’s genetic. If you plan on having biological children and want to understand your risk of having a child with a genetic condition, talk with your healthcare provider about genetic testing.

## Living With

If your child diagnosed with Wiskott-Aldrich syndrome is sick, contact their healthcare provider. Your child may get frequent infections since their immune system isn’t fully functional. Their healthcare provider can offer treatment to help their illness or infection go away, or to prevent any life-threatening complications that could occur.

Visit your child’s provider if they have:

* Bloody diarrhea.
* Frequent nosebleeds.
* Large areas of bruising.
* Changes to their skin.
* Recurrent infections (such as severe chickenpox or thrush, bacterial infections).

## Differential Diagnoses

* Hypogammaglobulinemia
* Immune Thrombocytopenia (ITP)
* Pediatric Severe Combined Immunodeficiency
* Thrombotic Thrombocytopenic Purpura (TTP)
* X-linked Lymphoproliferative Syndrome

## 

## Epidemiology

### Frequency

The incidence of classic Wiskott-Aldrich syndrome (WAS) phenotype has been estimated at 1–10 in 1 million cases per live birth. Overall, WAS accounts for about 3% of all primary immunodeficiency disorders.

A study from Switzerland reported the incidence of WAS as 4.1 cases per 1 million live births. The same study also examined the prevalence of WAS in several national registries (ie, Italy, Japan, Switzerland, Sweden) and found that this condition occurred in 2 -- 8.8% of patients with primary immunodeficiencies, although this statistic is subject to ascertainment bias.A similar range has been documented in a national registry in Ireland, as well.

### Mortality and morbidity

Median survival has increased from 8 months (patients born before 1935) to longer than 6 years (patients born after 1964).In one case series, 94 surviving patients ranged in age from 1–35 years, with a median of 11 years; the average age of patients who died was 8 years.

The cause of death is largely infections or bleeding, but, in one series, 12% of patients developed malignancies, primarily B-cell lymphomas, and leukemia. In that series, the relative risk of malignancy was more than 100-fold that of normal and the risk increased with age.Another study showed similar results, with the reported cause of death among patients who did not receive hematopoietic stem cell transplant (HSCT) being infection (44%), bleeding (23%), or malignancy (26%).

## Medical Care

Patients with Wiskott-Aldrich syndrome (WAS) require vigilant general medical or pediatric care. Promptly and aggressively treat infections and bleeding. General treatment strategies include use of prophylactic antibiotics, immunoglobulin replacement therapy (IgRT), splenectomy in special cases, and early hematopoietic stem cell transplantation (HSCT) or gene therapy when matched donors are not available. Immunomodulatory agents such as rituximab may serve a role in associated autoimmunity.

* Patients with WAS mutations and lymphopenia are candidates for *Pneumocystis Jerovici* prophylaxis (Cotrimazole 20 mg/kg/day).
* Give immunoglobulin replacement therapy (IgRT): intravenous immunoglobulin (IVIG) (500 mg/kg) every 3–4 weeks or subcutaneous immunoglobulin (SQIG) 100 mg/kg every week for patients with classic WAS. Gamma Globulin replacement may be considered for patients with the milder variant of X-linked thrombocytopenia and for those with recurrent infection.
* Additional prophylactic antibiotic therapy such as azithromycin (10 mg/kg/day three times a week) may be considered if infections continue despite immunoglobulin infusions.
* Acyclovir may be considered for chronic herpes virus infection.
* Post-exposure to chickenpox may be treated with IVIG, which contains high anti-varicella antibody titers.
* Eczema may be severe. Manage the eczema aggressively, with careful attention to skin care, emollient use, and appropriate topical steroid therapy.
* Cutaneous infections are common and may require systemic antibiotics.

## Curative Treatment

## Hematopoietic Stem Cell Transplantation (HSCT)

* HSCT remains the only curative treatment for WAS.
* Best outcomes are seen with matched sibling donors (MSD) or matched unrelated donors (MUD).
* Alternative donor sources such as umbilical cord blood and haploidentical transplants have become viable due to advances in graft selection and conditioning regimens.
* Early HSCT, ideally before severe infections or malignancies develop, is associated with improved survival and immune reconstitution.

## Gene Therapy

* Gene therapy using autologous hematopoietic stem cells transduced with a lentiviral vector carrying the WAS gene is an emerging curative option.
* Currently available only in clinical trials, gene therapy shows promising results in correcting immune defects and thrombocytopenia.
* Regulatory orphan designation was granted but some products have been withdrawn from the EU orphan register as of 2025 pending further development.

Supportive and Symptomatic Care

## Infection Prevention and Management

* Prophylactic antibiotics are used to prevent bacterial infections.
* Prompt treatment of infections with appropriate antibiotics, antivirals, or antifungals is critical.
* Immunoglobulin replacement therapy (IVIG) is routinely administered to boost humoral immunity and reduce infection risk.

## Bleeding Management

* Platelet transfusions are used to control bleeding episodes and prevent hemorrhagic complications.
* Splenectomy may be considered in select cases to improve platelet counts but carries infection risks and is less commonly performed with availability of HSCT.

## Eczema and Inflammation

* Topical corticosteroids and skin care are used to manage eczema and reduce inflammation.

Monitoring and Long-Term Care

* Regular surveillance for hematolymphoid malignancies (leukemia, lymphoma) is essential due to increased cancer risk, especially in adolescents and young adults.
* Genetic counseling is recommended for affected families.
* Vaccination schedules should be individualized; live vaccines are generally contraindicated due to immunodeficiency.
* Education on infection prevention, including hand hygiene and avoiding exposure to sick contacts, is critical.

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### COMPLEMENT DEFICIENCY

**DEFINITION AND DESCRIPTION**

### Complement is the term used to describe a group of over 30 proteins that kill microorganisms and assist other cells of the immune system to fight infection. Complement proteins also play an important role in inflammation. Complement proteins are made mainly in the liver and then secreted into the blood. They are numbered C1 to C9, and there are other supporting proteins that are also considered to be complement proteins (e.g. C1 inhibitor, properdin, factor B, factor D, factor H and factor I). The proteins form part of a tightly regulated pathway that is designed to kill invading microbes whilst limiting damage to other body tissues. When the complement proteins encounter bacteria, a virus, an immune complex, damaged tissue or other substance not usually present in the body, the complement proteins become ‘activated’ and act in a coordinated way. This activation is often referred to as a cascade reaction and is likened to the falling of a row of dominoes because the process must occur in a specific order. Complement deficiency results when any of the proteins that make up the complement pathway are missing or do not work properly. Because each protein has a different role in the pathway, each complement deficiency has different symptoms and treatments. 2

### complement system

**Causes of complement deficiency**

Most complement deficiencies have a genetic cause. They are often inherited (passed down between generations) but can arise for the first time in an affected individual. People with genetic causes of complement deficiencies have DNA that does not enable a working form of the affected protein to be made. The way in which complement deficiencies are inherited is complex, so speak to your doctor if you have any questions. In some medical conditions, such as infection, blood cancers and autoimmune conditions, and some types of kidney problems, complement proteins can be ‘used up’ and their levels become low. These conditions are referred to as acquired complement deficiencies.

**signs and symptoms**

Cells of the immune system Complement system Innate immunity

• Marking pathogens for destruction (opsonization)

• Breaking them down (lysis)

• Inflammation

• Cell activation Disposal system

• Clearing of immune complexes and dying cells Adaptive immunity

• Enhancing antibody responses

• Promoting T-cell responses

• Eliminating self reactive B-cells

• Enhancing immunological memory The complement system acts on different cells of the immune system to ensure the effective elimination of infectious microorganisms.

The signs and symptoms depend on the type of complement deficiency, as changes in different complement proteins can have very different symptoms. Low levels of mannose-binding lectin (MBL) are common, and patients often do not have any symptoms. By itself, a low level of MBL does not cause a major immunodeficiency. See our separate booklet on MBL deficiency. C1 inhibitor deficiency includes the conditions hereditary angioedema (HAE) and acquired angioedema. C1 inhibitor is a protein that helps to regulate the complement pathway and regulates production of a chemical called bradykinin. People with reduced C1 inhibitor may have high levels of bradykinin, which can cause tissue swellings called angioedema. They may also get episodes of severe abdominal pain caused by swelling of the gut. The organisation HAE UK offers support and advice on the symptoms, management and treatment of C1 inhibitor deficiencies. People with defects in proteins in the early parts of the complement pathway (proteins C1–C4) may be more likely to develop autoimmune diseases, such as systemic lupus erythematosus (also called lupus, or SLE). They may also be susceptible to infections with encapsulated bacteria, such as pneumococcal and neisseria species, that can cause severe infections, including pneumonia and meningitis. Low but not absent C4 is very common and is not usually associated with any major health problems. Antibodies against C3 or C4 can occur and are called nephritic factors because they are associated with kidney disease. People with defects in proteins in the later parts of the complement pathway (proteins C5–C9) are also susceptible to infection with encapsulated bacteria (bacteria that are surrounded by a coating that helps protect them and evade immune responses). When complement factors B or D are reduced, this may predispose those affected to recurrent infection. Rarely, changes that lead to over-activity of factor B and factor D may cause a disorder called atypical haemolytic uraemic syndrome (aHUS), characterised by excessive destruction of red blood cells. Factor H and factor I genetic mutations can also cause this disorder. Sometimes people may have complement abnormalities detected on blood tests before they have any symptoms.

**Diagnosis**

Treatment Complement deficiencies are usually diagnosed by performing special blood tests in people who have symptoms of disease. Sometimes these blood tests have to be repeated to make sure the result is accurate. Complement proteins are often reduced due to infection or because the blood sample didn’t get to the lab quickly enough. The results may also be confirmed by genetic testing. Sometimes relatives of people affected are also tested for the condition.

**TREATMENT**

Treatment depends on the type of complement deficiency. C1 inhibitor deficiencies may be treated by a range of different medications, including C1 inhibitor replacement, Lanadelumab; tranexamic acid; hormones; and drugs such as icatibant that block the action of bradykinin. People with these conditions need to avoid particular drugs for blood pressure (ACE inhibitors). Medications that contain oestrogen, such as some contraceptives, can make the condition worse. The support group HAE UK has information on all the treatments available to patients affected by C1 deficiency. If patients have autoimmune conditions, such as SLE, they may need to be treated with steroids and other immunosuppressants. If patients are more susceptible to bacterial infections, they might need to take daily antibiotics and be vaccinated to improve their protection against specific infections. They should seek medical advice early if they are unwell. This is because, if they get an infection, it can progress rapidly, with fewer signs than in people with normal complement function. Immunisation Patients with complement deficiencies can usually have all vaccines without any problems. Vaccination is an important part of protecting patients with certain complement deficiencies. If you have a complement deficiency, you should check with your doctor before taking live vaccines, such as the MMR vaccine or the yellow fever vaccine, especially if you are on immunosuppressive drugs. If you are travelling abroad, you should seek advice about any vaccinations needed a few months before you travel

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for these recurrent infections broadly includes B cell immunodeficiency, combined immunodeficiency, acquired immunodeficiencies, and asplenia with a predisposition for encapsulated organisms. The list of differential diagnoses is:

* Asplenia
* Common variable deficiency
* Hypogammaglobulinemia
* Human immunodeficiency virus
* Chronic granulomatous disease
* Chediak-Higashi syndrome
* Leukocyte adhesion deficiency
* Cyclic neutropenia
* SLE
* Immunoglobulin A deficiency
* Immunoglobulin G deficiency
* Immunoglobulin D deficiency
* Immunoglobulin M deficiency
* Meningococcemia

**EPIDEMIOLOGY**

Complement deficiencies are rare worldwide; high-risk populations are screened to estimate prevalence. The mannan-binding lectin (MBL) of the lectin-based pathway is the most prevalent form of complement deficiency in 5% of the White population, and it may be clinically silent. Apart from the MBL pathway, complement deficiencies are prevalent in 0.03% of the population. Deficiency of C2 protein is the second most common form after MBL deficiency and is also clinically silent. C3 is a crucial player in the complement system as this protein is the last step of the early pathway, a precursor to C3a, the anaphylatoxin, and a facilitator of chemotaxis for neutrophils and macrophages. Among all patients with primary immunodeficiency diseases, approximately 5% have complement deficiency. The most common type of primary immunodeficiency is antibody deficiency, which occurs in approximately 65% of cases.

In the cases of meningococcal infection, the prevalence rate is nearly 30%. Patients with C1q deficiency are observed to have a 93% chance of having SLE in the future. Similarly, C1rs deficiency is found to have a 57% association with SLE, and C4 deficiency is associated with a 75% association with SLE.

Properdin and C2 deficiencies have been more commonly observed in the White population, C6 deficiencies have been observed to have a predisposition in Africans, and deficiencies in C8 and C9 are more commonly seen in Asian populations. Specifically, 2 distinct C8 deficiency states have been studied: C8 alpha-gamma deficiency, seen mostly in Afro-Caribbeans, Hispanics, and Japanese, and C8beta, mainly in Whites.

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### Multiple sclerosis

**Definition and description**

Multiple sclerosis (MS) is an autoimmune condition that affects your brain and spinal cord (central nervous system).

With MS, your immune system mistakenly attacks myelin cells. These are the protective covers (sheaths) that surround your brain and spinal cord nerves. Myelin sheath damage interrupts messages (signals) that your nerves send throughout your body to perform functions like vision, sensation and movement.

Myelin damage can occur in your brain, spinal cord and nerves that supply your eyes. There’s no cure for MS, but treatment is available to help minimize ongoing damage and help you manage symptoms.

#### **Types of multiple sclerosis**

There are four types of multiple sclerosis. You can think of the types as a way for your provider to describe your symptoms, instead of being four different conditions:

* Clinically isolated syndrome (CIS). This is when you have the first episode of symptoms suggestive of MS, but don’t meet the criteria for having MS, healthcare providers often categorize it as CIS. Inflammation and myelin damage cause your symptoms. CIS may develop into multiple sclerosis.
* Relapsing-remitting multiple sclerosis (RRMS). This is the most common way that multiple sclerosis begins — an estimated 85% of people diagnosed with MS have this type. MS causes flare-ups (relapses or attacks) of new or old symptoms. Periods of remission follow (when symptoms stabilize or go away).
* Secondary progressive multiple sclerosis (SPMS). In many cases, RRMS eventually progresses to SPMS. In the secondary progressive stage of multiple sclerosis, nerve damage accumulates and symptoms gradually worsen. You may still experience some relapses or flares, but periods of remission (when symptoms stabilize or go away) are less likely to happen.
* Primary progressive multiple sclerosis (PPMS). In some cases, MS symptoms may start off slowly and gradually worsen over time from the very beginning, without any periods of clear relapses or remission.

Three rare MS variants include:

* Tumefactive multiple sclerosis. A characterization of this variant of MS is the formation of large areas of demyelination in your brain, which may appear similar to tumors. Often, a sample of brain tissue is needed to differentiate this from other issues, like brain cancers.
* Balo’s concentric sclerosis. A characteristic of this variant of MS is lesions with the appearance of concentric rings (in the shape of a target) of myelin damage appearing on an MRI, which gives this condition its name.
* Marburg variant multiple sclerosis. This is a very rare and aggressive form of MS characterized by rapid progression, which may result in death when left untreated.

## Symptoms and Causes

Multiple sclerosis symptoms affect your brain, spinal cord and eyes.

Early signs and symptoms of MS include:

* Changes to your vision (optic neuritis, double vision, vision loss)
* Muscle weakness (usually affecting one side of your face or body, or below your waist)
* Numbness or abnormal sensations (usually affecting one side of your face or body, or below your waist)

### Symptoms of multiple sclerosis

Common symptoms of MS include:

* Fatigue
* Clumsiness
* Dizziness
* Difficulty with bladder regulation
* Loss of balance and coordination
* Difficulty with cognitive function (thinking, memory, concentration, learning and judgment)
* Mood changes
* Muscle stiffness and muscle spasms (tremors)

These symptoms vary from person to person and may fluctuate in severity from one day to the next. You may have a few of these symptoms, but it’s unlikely you’ll experience all of them at once.

#### **Do you ever feel normal with MS?**

This can be challenging to predict because everyone perceives “normal” in their own way. With MS, you may have periods of remission where your symptoms go away, and you feel more like yourself. You might even forget you have MS until symptoms flare up (return) again. This feeling of normalcy, and the degree of normalcy, can vary by type and stage.

### Causes of MS

Demyelination, or the destruction of myelin, causes multiple sclerosis. Myelin is a protective cover (sheath) around nerve cells (neurons) in your brain and spinal cord. It moves messages (signals) between your brain and the rest of your body to control functions like vision, sensation and movement.

Your immune system’s job is to protect your body from things that can harm it, like bacteria or viruses. With MS, your immune system becomes overactive and mistakes healthy myelin (and sometimes, the nerve cells below the myelin) as a threat to your body. Your immune system’s attack on the healthy myelin damages it. This is demyelination.

On an imaging test (an MRI), your provider can find evidence of myelin damage. They may refer to it as a scar, lesion or plaque. Messages don’t pass between nerve cells easily where there is myelin damage, which leads to the development of MS symptoms.

Experts aren’t sure why some people develop MS. Research suggests the following may contribute to an elevated risk of developing MS:

* Smoking
* Toxin exposure, like secondhand smoke and pesticides
* Low levels of vitamin D
* Exposure to a virus (Epstein-Barr virus or mononucleosis)
* Obesity during childhood
* Genetic predisposition (someone in your biological family has the condition or carries genes, which can lead to you being more susceptible to developing the disease)

#### **Risk factors for multiple sclerosis**

You may be more at risk of MS if you:

* Are between the ages 20 and 40
* Are of Northern European descent
* Are female

MS can affect anyone. Rarer cases can affect children.

### Complications of multiple sclerosis

Worsening or progressive symptoms of MS may lead to complications such as:

* Difficulty walking without assistance
* Loss of bowel or bladder control
* Memory loss
* Sexual dysfunction
* Depression and anxiety

## Diagnosis and Tests

There isn’t a single diagnostic tool available to pinpoint the condition. Instead, a provider will diagnose MS after a physical exam, a neurological exam and testing.

During an exam, your provider will learn more about your symptoms and medical history. Testing may include blood work, MRIs of your brain and spinal cord, and an analysis of your spinal fluid.

It can take time before you receive an official MS diagnosis. You may need to make several trips to see your provider before you know for sure. This happens because MS symptoms can look like or happen with several other common conditions. While the delay in an official diagnosis can be frustrating, getting the right diagnosis helps your provider accurately treat your symptoms.

#### **TESTS**

Diagnostic testing helps your provider rule out conditions with similar symptoms to MS. Testing may include:

* Blood tests and urine tests
* Magnetic resonance imaging test (MRI)
* Optical coherence tomography (OCT) test
* Lumbar puncture
* Evoked potential (EP) test

#### **Who diagnoses MS?**

If your primary care provider suspects you may have MS, they may refer you to see a neurologist. A neurologist is a doctor who specializes in treating conditions that affect the nervous system, which includes your brain and spinal cord.

## Management and Treatment

There isn’t currently a cure for MS.

Multiple sclerosis treatment focuses on minimizing further damage, managing symptoms and preventing complications. Your treatment plan may include:

* Medications
* Physical, occupational or speech therapy
* Mental health counseling

Other types of symptom management vary based on how the condition affects you. Management may include:

* Wearing glasses or taking medications for vision symptoms
* Deep brain stimulation for muscle spasms (tremors)
* Using assistive mobility devices like a cane, walker or wheelchair
* Antiseizure medications or antispasmodic medications (gabapentin or nortriptyline) for pain
* Medications like donepezil for cognitive symptoms
* Alternative therapies like acupuncture and yoga

Your healthcare provider may recommend plasma exchange (plasmapheresis) if your body doesn’t respond well to certain medications during an MS attack. This is more effective in minimizing damage from an ongoing attack as opposed to preventing additional attacks in the long term.

Your provider can also discuss if any clinical trials are available to participate in. Clinical trials are tests of new medications or uses of existing medications on humans to find new treatment options for MS and other conditions.

#### **Multiple sclerosis medications**

Medications for multiple sclerosis can reduce relapses (periods when symptoms worsen or new symptoms develop) and the development of new lesions/scars, and slow the disease’s progression. Common types of medications for MS include:

* Disease-modifying therapies (DMTs). DMTs reduce how often you have relapses, slow down MS progression, and prevent new lesions from forming on your brain and spinal cord. Several medications have U.S. Food and Drug Administration (FDA) approval for long-term MS treatment.
* Relapse management medications. For severe symptom attacks, corticosteroids (like methylprednisolone) quickly reduce inflammation by suppressing your immune system. These medications can speed up your recovery time after an attack. They also slow damage to the myelin sheath surrounding your nerve cells. Your provider may give you this medication into a vein in your arm through an IV (intravenously). Other short-term treatments for severe attacks include IV immunoglobulin therapy or plasma exchange.

DMTs for MS

Common disease-modifying therapies (DMTs) for MS and their administration types include:

* Injections into your skin: Beta interferon, glatiramer acetate or ofatumumab
* Infusions into a vein (IV): Alemtuzumab, natalizumab, rituximab, ocrelizumab or ublituximab
* Oral medications (taken by mouth): Cladribine, dimethyl fumarate, diroximel fumarate, monomethyl fumarate, fingolimod, siponimod, ponesimod, ozanimod or teriflunomide
* Stem cell transplant

## Outlook / Prognosis

Multiple sclerosis is a lifelong condition without a cure. However, available treatment options are very effective in helping manage symptoms and minimizing the frequency of flare-ups. Regardless of treatment, MS can lead to disability and make it difficult to do routine things without assistance over time. Your care team is available to help you throughout your MS journey, to take steps to prevent complications and improve your quality of life.

You can expect to have a normal life expectancy with MS. Older studies have shown that MS can take up to 10 years off of your life expectancy, but advances in treatment options have significantly improved this outlook. Only in very rare cases is MS fatal.

## Prevention

There isn’t a known way to prevent MS.

#### **How can I lower my risk of multiple sclerosis symptom flare-ups?**

Disease-modifying therapies are the most effective way to reduce the number of flare-ups (also called relapses or attacks) you experience.

Leading a healthy lifestyle is also important. The choices you make can help slow disease progression. Your provider may recommend the following to stay healthy:

* Eating nutritious meals
* Getting enough sleep
* Participating in physical activities regularly
* Not using tobacco products

Coping with a chronic condition can be emotionally challenging. MS can sometimes affect your mood and memory. Working with a neuropsychologist or a mental health provider is an essential part of managing the condition long term.

## Living With

Yes. MS can be a challenging condition to diagnose and manage, but your care team will help you every step of the way. Despite having a condition without a cure, you can still lead a fulfilling and active life with MS. Support is available to help you maximize your function both physically and mentally, from medications to therapy. There are even support groups you can join to help you connect with people who share a similar experience.

### When to see a doctor

You should contact a healthcare provider if you experience the following:

* Feeling overly sensitive to heat
* Feeling unsteady or off balance
* Difficulty remembering things
* Numbness or tingling, especially in your arms or legs
* Sudden vision changes
* Weakness in your arms or legs

Let your healthcare provider know if you have MS and experience new or worsening symptoms.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of multiple sclerosis is extensive and can be categorized into 7 categories, as listed below.

* Other demyelinating or inflammatory CNS syndromes:
  + Optic neuritis
  + Marburg disease
  + Acute disseminated encephalomyelitis
  + Devic neuromyelitis optical
  + Susac syndrome
  + Primary cerebral vasculitis and partial transverse myelitis
  + Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), a rare form of encephalomyelitis typically affecting the spinal cord, cerebellum, and brainstem
* General inflammatory and autoimmune syndromes:
  + Systemic lupus erythematosus
  + Wegener granulomatosis
  + Sarcoidosis
  + Antiphospholipid antibody syndrome
  + Behcet syndrome
  + Sjögren syndrome
* Infectious etiologies:
  + Lyme disease
  + Syphilis
  + HIV
  + Herpes viruses
* Vascular etiologies
  + Migraine headaches
  + Dural arteriovenous fistula
  + Small vessel ischemia
  + Ischemic optic neuropathy (arteritic and nonarteritic)
  + Vascular malformations and emboli
* Metabolic causes:
  + Vitamin deficiencies
  + Thyroid disease
  + Hereditary ataxias
  + Adult-onset leukodystrophy, such as adult-onset adrenoleukodystrophy
* Uncommon genetic etiologies:
  + Mitochondrial cytopathy
  + Fabry disease
  + Alexander disease
  + Hereditary spastic paraplegia
* Neoplastic causes include primary CNS malignancies, such as gliomas and meningiomas, or metastasis

**EPIDEMIOLOGY**

Multiple sclerosis is the most common immune-mediated inflammatory demyelinating disease of the CNS. This condition affects approximately 400,000 individuals in the United States and 2.5 million individuals worldwide. The disease is 3-fold more common in females than in males. Although onset typically occurs in individuals between the ages of 20 and 40, multiple sclerosis can present at any age, with the mean age of onset being 25 to 29 for relapsing-remitting multiple sclerosis and 39 to 41 for primary progressive multiple sclerosis. Almost 10% of the cases are present before the age of 18. The overall prevalence is cited as 1 in 1000 for populations of European ancestry.

Less is known about the prevalence of multiple sclerosis in non-European populations, with most data indicating lower prevalence in individuals of East Asian and African descent. However, recent studies have observed a higher prevalence in African-American populations, similar to those with European ancestry. Multiple sclerosis demonstrates a prevalence gradient based on latitude, with higher prevalence in northern latitudes of Europe and North America. Additionally, observations have noted variable genetic susceptibility factors among different human subpopulations, apart from latitude, suggesting poorly understood genetic factors interacting with environmental influences.

Several studies have highlighted that populations migrating to regions with higher multiple sclerosis prevalence during childhood also adopt a higher risk of acquiring multiple sclerosis. However, other studies have raised doubts about this observation. Neither genetic nor external risk factors can solely account for the epidemiological patterns seen in multiple sclerosis. Notably, multiple sclerosis stands as the leading cause of permanent disability among young adults. One study reported an incidence rate of pediatric-acquired multiple sclerosis at 0.51 per 100,000 person-years

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**SJOGREN SYNDROME**

Sjogren's (SHOW-grins) syndrome is a disorder of your immune system identified by its two most common symptoms — dry eyes and a dry mouth.

The condition often accompanies other immune system disorders, such as rheumatoid arthritis and lupus. In Sjogren's syndrome, the mucous membranes and moisture-secreting glands of your eyes and mouth are usually affected first — resulting in decreased tears and saliva.

Although you can develop Sjogren's syndrome at any age, most people are older than 40 at the time of diagnosis. The condition is much more common in women. Treatment focuses on relieving symptoms.

**Causes**

Sjogren's syndrome is an autoimmune disorder. Your immune system mistakenly attacks your body's own cells and tissues.

Scientists aren't certain why some people develop Sjogren's syndrome. Certain genes put people at higher risk of the disorder, but it appears that a triggering mechanism — such as infection with a particular virus or strain of bacteria — is also necessary.

In Sjogren's syndrome, your immune system first targets the glands that make tears and saliva. But it can also damage other parts of your body, such as:

* Joints
* Thyroid
* Kidneys
* Liver
* Lungs
* Skin
* Nerves

**Risk factors**

Sjogren's syndrome typically occurs in people with one or more known risk factors, including:

* Age. Sjogren's syndrome is usually diagnosed in people older than 40.
* Sex. Women are much more likely to have Sjogren's syndrome.
* Rheumatic disease. It's common for people who have Sjogren's syndrome to also have a rheumatic disease — such as rheumatoid arthritis or lupus.

The two main symptoms of Sjogren's syndrome are:

## Dry eyes. Your eyes might burn, itch or feel gritty — as if there's sand in them.

## Dry mouth. Your mouth might feel like it's full of cotton, making it difficult to swallow or speak.

## Some people with Sjogren's syndrome also have one or more of the following:

## Joint pain, swelling and stiffness

## Swollen salivary glands — particularly the set located behind your jaw and in front of your ears

## Skin rashes or dry skin

## Vaginal dryness

## Persistent dry cough

## Prolonged fatigue

## Diagnosis and tests

## Sjogren's syndrome can be difficult to diagnose because the signs and symptoms vary from person to person and can be similar to those caused by other diseases. Side effects of a number of medications also mimic some signs and symptoms of Sjogren's syndrome.

## Tests can help rule out other conditions and help pinpoint a diagnosis of Sjogren's syndrome.

### Blood tests

## Your doctor might order blood tests to check for:

## Levels of different types of blood cells

## Presence of antibodies common in Sjogren's syndrome

## Evidence of inflammatory conditions

## Indications of problems with your liver and kidneys

### Eye tests

## Your doctor can measure the dryness of your eyes with a test called a Schirmer tear test. A small piece of filter paper is placed under your lower eyelid to measure your tear production.

## A doctor specializing in the treatment of eye disorders (ophthalmologist) might also examine the surface of your eyes with a magnifying device called a slit lamp. He or she may place drops in your eye that make it easier to see damage to your cornea.

### Imaging

## Certain imaging tests can check the function of your salivary glands.

## Sialogram. This special X-ray can detect dye that's injected into the salivary glands in front of your ears. This procedure shows how much saliva flows into your mouth.

## Salivary scintigraphy. This nuclear medicine test involves the injection into a vein of a radioactive isotope, which is tracked over an hour to see how quickly it arrives in all your salivary glands.

### Biopsy

## Your doctor might also do a lip biopsy to detect the presence of clusters of inflammatory cells, which can indicate Sjogren's syndrome. For this test, a sliver of tissue is removed from salivary glands in your lip and examined under a microscope.

## Treatment

## Treatment for Sjogren's syndrome depends on the parts of the body affected. Many people manage the dry eye and dry mouth of Sjogren's syndrome by using over-the-counter eye drops and sipping water more frequently. But some people need prescription medications, or even surgical procedures.

### Medications

## Depending on your symptoms, your doctor might suggest medications that:

## Decrease eye inflammation. Prescription eye drops such as cyclosporine (Restasis) or lifitegrast (Xiidra) may be recommended by your eye doctor if you have moderate to severe dry eyes.

## Increase production of saliva. Drugs such as pilocarpine (Salagen) and cevimeline (Evoxac) can increase the production of saliva, and sometimes tears. Side effects can include sweating, abdominal pain, flushing and increased urination.

## Address specific complications. If you develop arthritis symptoms, you might benefit from nonsteroidal anti-inflammatory drugs (NSAIDs) or other arthritis medications. Yeast infections in the mouth should be treated with antifungal medications.

## Treat systemwide symptoms. Hydroxychloroquine (Plaquenil), a drug designed to treat malaria, is often helpful in treating Sjogren's syndrome. Drugs that suppress the immune system, such as methotrexate (Trexall), also might be prescribed.

### Surgery

## A minor procedure to seal the tear ducts that drain tears from your eyes (punctal occlusion) might help relieve your dry eyes. Collagen or silicone plugs are inserted into the ducts to help preserve your tears.

## Lifestyle and home remedies

## Many Sjogren's syndrome symptoms respond well to self-care measures.

## To relieve dry eyes:

## Use artificial tears, an eye lubricant or both. Artificial tears — in eye drop form — and eye lubricants — in eye drop, gel or ointment form — help relieve the discomfort of dry eyes. You don't have to apply eye lubricants as often as artificial tears. Because of their thicker consistency, eye lubricants can blur your vision and collect on your eyelashes, so you might want to use them only overnight. Your doctor might recommend artificial tears without preservatives, which can irritate the eyes of people with dry eye syndrome.

## Increase humidity. Increasing the indoor humidity and reducing your exposure to blowing air can help keep your eyes and mouth from getting uncomfortably dry. For example, avoid sitting in front of a fan or air conditioning vent, and wear goggles or protective eyewear when you go outdoors.

## To help with dry mouth:

## Don't smoke. Smoking can irritate and dry out your mouth.

## Increase your fluid intake. Take sips of fluids, particularly water, throughout the day. Avoid drinking coffee or alcohol since they can worsen dry mouth symptoms. Also avoid acidic beverages such as colas and some sports drinks because the acid can harm the enamel of your teeth.

## Stimulate saliva flow. Sugarless gum or citrus-flavored hard candies can boost saliva flow. Because Sjogren's syndrome increases your risk of dental cavities, limit sweets, especially between meals.

## Try artificial saliva. Saliva replacement products often work better than plain water because they contain a lubricant that helps your mouth stay moist longer. These products come as a spray or lozenge.

## Use nasal saline spray. A nasal saline spray can help moisturize and clear nasal passages so that you can breathe freely through your nose. A dry, stuffy nose can increase mouth breathing.

### Oral health

## Dry mouth increases your risk of dental cavities and tooth loss. To help prevent those types of problems:

## Brush your teeth and floss after every meal

## Schedule regular dental appointments, at least every six months

## Use daily topical fluoride treatments and antimicrobial mouthwashes

### Other areas of dryness

## If dry skin is a problem, avoid hot water when you bathe and shower. Pat your skin — don't rub — with a towel, and apply moisturizer when your skin is still damp. Use rubber gloves when doing dishes or house cleaning. Vaginal moisturizers and lubricants help women who have vaginal dryness.

## Complications

The most common complications of Sjogren's syndrome involve your eyes and mouth.

* Dental cavities. Because saliva helps protect the teeth from the bacteria that cause cavities, you're more prone to developing cavities if your mouth is dry.
* Yeast infections. People with Sjogren's syndrome are much more likely to develop oral thrush, a yeast infection in the mouth.
* Vision problems. Dry eyes can lead to light sensitivity, blurred vision and corneal damage.

Less common complications might affect:

* Lungs, kidneys or liver. Inflammation can cause pneumonia, bronchitis or other problems in your lungs; lead to problems with kidney function; and cause hepatitis or cirrhosis in your liver.
* Lymph nodes. A small percentage of people with Sjogren's syndrome develop cancer of the lymph nodes (lymphoma).
* Nerves. You might develop numbness, tingling and burning in your hands and feet (peripheral neuropathy).

**DIFFERENTIAL DIAGNOSIS**

* Sarcoidosis
* Rosacea
* Mumps
* Dehydration
* Use of medications- antidepressants, anticholinergics
* Mouth breathing
* Lymphoma
* Advanced age
* Parkinson disease
* Scleroderma
* Rheumatoid arthritis
* AIDS
* Lupus

**EPIDEMIOLOGY**

Sjogren syndrome is far from a rare disorder with an incidence approaching approximately one-half of that of rheumatoid arthritis (RA) or affecting 0.5% to 1.0% of the population.

Between 400,000 and 3.1 million adults have Sjögren's syndrome. This condition can affect people of any age, but symptoms usually appear between the ages of 45 and 55. About half of patients also have rheumatoid arthritis or other connective tissue diseases, such as lupus.

Sjogren has been reported worldwide in adults and more rarely in children, and there appears to be no racial, or geographic bias in incidence. The disorder, however, has a marked predilection for women and similar to SLE, the female:male ratio is approximately 9:1. The disease usually presents in middle age but may occur in children as well as the elderly.

As there is no evidence-based standardized screening tool to decide which dry eye patients to refer for Sjogren syndrome workup, there is an under referral of dry eye patients for Sjogren syndrome workups: hence there is continued underdiagnosis of the disease.

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**SCLERODERMA**

**DEFINITION AND DESCRIPTION**

Scleroderma (sklair-oh-DUR-muh), also known as **systemic sclerosis**, is a group of rare diseases that involve the hardening and tightening of the skin. Scleroderma also may cause problems in the blood vessels, internal organs and digestive tract.

Scleroderma is often categorized as limited or diffuse, which refers only to the degree of skin involvement. Both types can involve any of the other vascular or organ symptoms that are part of the disease. Localized scleroderma, also known as morphea, affects only the skin.

While there is no cure for scleroderma, treatments can ease symptoms, slow progression and improve quality of life.

**Causes**

Scleroderma happens when the body produces too much collagen and it builds up in body tissues. Collagen is a fibrous type of protein that makes up the body's connective tissues, including the skin.

Experts don't know exactly what causes this process to begin, but the body's immune system appears to play a role. Most likely, scleroderma is caused by a combination of factors, including immune system problems, genetics and environmental triggers.

**Risk factors**

Anyone can get scleroderma, but it is more common in people assigned female at birth. People typically get scleroderma between ages 30 and 50. Black people often have earlier onset and are more likely to have more skin involvement and lung disease.

Several other combined factors appear to influence the risk of having scleroderma:

* **Genetics.** People who have certain gene changes appear to be more likely to develop scleroderma. This may explain why scleroderma appears to run in families in a small number of people and why some types of scleroderma are more common for people in certain racial and ethnic groups.
* **Environmental triggers.** Research suggests that in some people, scleroderma symptoms may be triggered by exposure to certain viruses, medicines or drugs. Repeated exposure, such as at work, to certain harmful substances or chemicals also may increase the risk of scleroderma. An environmental trigger is not identified for most people.
* **Immune system conditions.** Scleroderma is believed to be an autoimmune disease. This means that it occurs in part because the body's immune system begins to attack the connective tissues. People who have scleroderma also may have symptoms of another autoimmune disease such as rheumatoid arthritis, lupus or Sjogren syndrome.

**Complications**

Scleroderma complications range from mild to serious and can affect the:

* **Fingertips.** In systemic sclerosis, Raynaud's phenomenon can become so severe that the restricted blood flow permanently damages the tissue at the fingertips, causing pits or skin sores. In some people, the tissue on the fingertips may die.
* **Lungs.** Scarring of lung tissue can impact the ability to breathe and tolerance for exercise. High blood pressure in the arteries to the lungs also may happen.
* **Kidneys.** A serious kidney complication, called scleroderma renal crisis, involves a sudden increase in blood pressure and rapid kidney failure. Prompt treatment of this condition is important to preserve kidney function.
* **Heart.** Scarring of heart tissue increases the risk of irregular heartbeats and heart failure. Scleroderma also can cause inflammation of the sac surrounding the heart.
* **Teeth.** Serious tightening of facial skin can cause the mouth to become smaller and narrower. This may make it hard to brush the teeth or to have them professionally cleaned or restored. People who have scleroderma often don't make typical amounts of saliva, so the risk of dental decay increases even more.
* **Digestive system.** Digestive complications of scleroderma can include heartburn and difficulty swallowing. Scleroderma also can cause bouts of cramps, bloating, constipation or diarrhea. Some people who have scleroderma also may have problems absorbing nutrients due to overgrowth of bacteria in the intestine.
* **Joints.** The skin over joints can become so tight that it restricts flexibility and movement, particularly in the hands.

**Symptoms**

Scleroderma symptoms vary from person to person, depending on which parts of the body are affected.

### Skin-related symptoms

Nearly everyone who has scleroderma experiences hardening and tightening of the skin.

The first parts of the body to be affected are usually the fingers, hands, feet and face. In some people, the skin thickening also can involve the forearms, upper arms, chest, abdomen, lower legs and thighs. Early symptoms may include swelling and itchiness. The color of affected skin can become lighter or darker, and skin may look shiny because of the tightness.

Some people also have small red spots, called telangiectasia, on their hands and face. Calcium deposits can form under the skin, particularly at the fingertips, causing bumps that can be seen on X-rays.

### Raynaud's phenomenon

Raynaud's phenomenon is common in scleroderma. It happens because of an exaggerated contraction of the small blood vessels in the fingers and toes in response to cold temperatures or emotional distress. When this happens, the digits may feel painful or numb and turn white, blue, gray or red. Raynaud's phenomenon also can occur in people who don't have scleroderma.

### Digestive symptoms

Scleroderma can affect any part of the digestive system, from the esophagus to the rectum. Depending on which parts of the digestive system are affected, symptoms may include:

* Heartburn.
* Difficulty swallowing.
* Bloating.
* Diarrhea.
* Constipation.
* Fecal incontinence.

### Heart- and lung-related symptoms

When scleroderma affects the heart or lungs, it can cause shortness of breath, decreased exercise tolerance and dizziness. Scleroderma can cause scarring in the lung tissues that may result in increasing shortness of breath over time. There are medicines that may help slow the progression of this lung damage.

Scleroderma also can cause the blood pressure to increase in the circulation that goes between the heart and the lungs. This is called pulmonary hypertension. In addition to causing shortness of breath, pulmonary hypertension also can cause excess fluid to build up in the legs, feet and sometimes around the heart.

When scleroderma affects the heart, heartbeats can become irregular. Heart failure also may happen in some people.

## Diagnosis and tests

Because scleroderma can take so many forms and affect so many different areas of the body, it can be difficult to diagnose.

After a thorough physical exam, your healthcare professional may suggest blood tests to check for elevated levels of certain antibodies made by the immune system.

Your healthcare professional also may suggest other blood tests, imaging or organ function tests. These tests may help determine whether your digestive system, heart, lungs or kidneys are affected.

**Treatment**

There is no treatment that can cure or stop the overproduction of collagen that happens in scleroderma. But a variety of treatments can help control symptoms and prevent complications.

### Medicines

Because scleroderma can affect so many different parts of the body, the choice of medicine varies depending on the symptoms. Examples include medicines that:

* **Dilate blood vessels.** Blood pressure medicines that dilate blood vessels may help treat Raynaud's phenomenon.
* **Suppress the immune system.** Medicines that suppress the immune system, such as those taken after organ transplants, may help reduce progression of some scleroderma symptoms, such as the thickening of the skin or worsening of lung damage.
* **Reduce digestive symptoms.** Pills to reduce stomach acid can help relieve heartburn. Antibiotics and medicines that help move food through the intestines may help reduce bloating, diarrhea and constipation.
* **Prevent infections.** Recommended vaccinations are important to protect people with scleroderma from infectious diseases. Talk with your healthcare professional about vaccines for influenza, pneumonia, shingles, HPV, COVID-19 and RSV.
* **Relieve pain.** If pain relievers available without a prescription don't help enough, your healthcare professional might suggest prescription medicines to control pain.

### Therapies

Physical or occupational therapists can help you improve your strength and mobility and maintain independence with daily tasks. Hand therapy may help prevent hand stiffness, also called contractures.

### Surgical and other procedures

Stem cell transplants might be an option for people who have serious symptoms that haven't responded to more-common treatments. If the lungs or kidneys have been badly damaged, organ transplants might be considered.

**Lifestyle and home remedies**

You can take a number of steps to help manage your symptoms of scleroderma:

* **Stay active.** Exercise keeps your body flexible, improves circulation and eases stiffness. Range-of-motion exercises can help keep your skin and joints flexible. This is always very important, especially early in the disease course.
* **Protect your skin.** Take good care of dry or stiff skin by using lotion and sunscreen regularly. Avoid hot baths and showers and exposure to strong soaps and household chemicals, which can irritate and further dry out your skin.
* **Don't smoke.** Nicotine causes blood vessels to contract, making Raynaud's phenomenon worse. Smoking also can cause permanent narrowing of the blood vessels and cause or worsen lung problems. Quitting smoking can be difficult. Ask your healthcare professional for help.
* **Manage heartburn.** Avoid foods that give you heartburn or gas. Also avoid late-night meals. Elevate the head of your bed to keep stomach acid from backing up into your esophagus as you sleep. Antacids may help relieve symptoms.
* **Protect yourself from the cold.** Wear warm mittens for protection anytime your hands are exposed to cold — even when you reach into a freezer. It also is important to keep your core body temperature warm to help prevent Raynaud's phenomenon. When you're outside in the cold, wear warm boots, cover your face and head, and wear layers of warm clothing.

## Outlook / Prognosis

You should expect to manage scleroderma and its symptoms for the rest of your life. Even though there’s no cure, most people find treatments and lifestyle tweaks to minimize how much their symptoms impact their day-to-day lives.

Living with a chronic condition can be extremely frustrating. Ask your healthcare provider about additional resources like support groups or educational opportunities to help you manage stress and your mental health.

## Prevention

Because experts don’t know what causes it, there’s no way to prevent scleroderma.

## Living With

In addition to your regular treatments, you might be able to manage some of your symptoms by making some changes in your daily routine, including:

* Following a diet and exercise plan that’s healthy for you.
* Avoiding intense physical activity when you’re not feeling well.
* Protecting your skin with the right clothing for your environment and wearing high-quality sunscreen when you’re outside.
* Visiting a dental care provider for regular cleaning and checkups.

### When should I see my healthcare provider?

Scleroderma can cause so many different symptoms that it’s sometimes hard to notice at first. Visit a healthcare provider if you notice any new pain or other symptoms, especially if they’re getting worse. Even if something else is causing your symptoms, a provider will diagnose the cause and suggest treatments to manage them.

Talk to your provider if you feel like your scleroderma treatments aren’t working as well or if your symptoms are changing or getting worse — especially if they affect your ability to breathe or swallow.

**Epidemiology of Scleroderma (Systemic Sclerosis and Localized Scleroderma)**

Systemic Sclerosis (SSc)

* Prevalence:
  + Global prevalence ranges from approximately 17.6 to 24 per 100,000 individuals.
  + Meta-analyses report pooled prevalence around 17.6 to 18.9 per 100,000.
  + Regional variation exists:
    - North America: ~26 per 100,000
    - Europe: ~15 per 100,000
    - Asia: ~6.8 per 100,000
    - South America: ~25 per 100,000
  + No data reported from Africa.
* Incidence:
  + Global incidence is estimated between 1.4 and 8.6 per 100,000 person-years.
  + Higher incidence reported in North America and Europe compared to Asia.
* Demographics:
  + Predominantly affects women (female-to-male ratio approximately 3:1 or higher).
  + Most commonly diagnosed in middle-aged and older adults, with peak incidence in the 50–70 years age group.
  + Incidence and prevalence are increasing, likely due to improved diagnosis and awareness.
* Mortality:
  + Mortality remains high, though younger age mortality has decreased over time.
  + Leading causes of death include interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH).
  + Standardized mortality ratios show excess mortality especially in females aged 40–59 years.
* Subtypes:
  + Limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) differ in skin involvement and organ manifestations.

## Diagnostic Considerations

The following disorders may present clinical similarities with systemic sclerosis (“scleroderma mimics”) and need to be included in the differential diagnosis:

* Nephrogenic Systemic Fibrosis
* Eosinophilic Fasciitis
* Eosinophilia-Myalgia Syndrome
* Graft Versus Host Disease
* Reflex Sympathetic Dystrophy
* Generalized morphea
* Diabetic cheiroarthropathy
* Porphyria cutanea tarda
* Morphea
* Linear scleroderma
* Radiation exposure
* Scleromyxedema (generalized lichen myxedematosus)
* Scleredema adultorum of Buschke
* Scleredema diabeticorum

Gadolinium-based contrast agents, bleomycin, pentazocine, and several other drugs and chemicals have been shown to cause

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### Dermatomyositis

**Definition and description**

Dermatomyositis is a rare disease that causes muscle weakness and rashes on your skin. It’s a form of myopathy. It can also cause severe symptoms that affect your ability to breathe and swallow.

Dermatomyositis is a form of polymyositis that affects your skin in addition to your muscles.

See your provider right away if you experience any symptoms of dermatomyositis. Some cases take months to develop, but dermatomyositis can develop quickly. The sooner you begin treatment, the more likely it is you can avoid having severe complications.

In rare cases, dermatomyositis can be fatal, especially in the first year after symptoms start. It can also increase your risk of developing certain kinds of cancer.

#### **Dermatomyositis vs lupus**

Dermatomyositis is similar to lupus and other autoimmune diseases. However, experts aren’t sure what causes dermatomyositis, so it’s not classified as an autoimmune condition.

If you have lupus, you might experience joint pain, skin sensitivities and rashes, and issues with your internal organs (brain, lungs, kidneys and heart). Many of your symptoms might come and go in waves — often called flare-ups.

Dermatomyositis causes muscle weakness and degeneration (tissue death) and a rash on your skin. It’s diagnosed with blood tests, biopsies and imaging tests.

Both dermatomyositis and lupus need to be diagnosed and treated as soon as possible. Visit your provider right away if you notice any new symptoms.

### How common is dermatomyositis?

Dermatomyositis is very rare. Around 1 in every 100,000 people develop it each year.

### How does this condition affect my body?

Dermatomyositis could affect your body for the rest of your life.

If it damages your muscles badly enough you might lose the ability to move or use a part of your body the way you used to. This usually takes years to develop, but some people experience severe muscle weakness earlier than others.

Dermatomyositis has also been found to increase your risk of developing certain types of cancer.

#### **Dermatomyositis and cancer**

Around 15% of people with dermatomyositis develop cancer later in their life. Some of the most common cancers people with dermatomyositis develop include:

* Ovarian cancer.
* Lung cancer.
* Lymphoma.
* Breast cancer.
* Colon cancer.

Talk to your healthcare provider about your cancer risk and any screenings you need.

## Symptoms and Causes

The most common symptoms of dermatomyositis are muscle weakness and a rash on your skin.

Some people notice muscle weakness and a rash around the same time. You might have one symptom for weeks, months or even years without the other.

Muscle weakness might make it hard for you to do common motions, including:

* Sitting upright.
* Getting up from a seated position (like standing up from a chair or couch).
* Climbing stairs.
* Getting up after lying down.
* Washing your hair.

Dermatomyositis may cause a rash on your skin (especially on parts of your body exposed to the sun). Areas with a rash will be discolored and might be swollen. The most common locations include:

* Eyelids and around your eyes.
* Chest and the front of your shoulders (sometimes referred to as a v-sign rash).
* Neck and the back of your shoulders (a shawl sign rash).
* Scalp.

Other symptoms of dermatomyositis include:

* Discoloration and bumps (sometimes referred to as Gottron papules) on your hands, especially near your knuckles.
* Calcium deposits under your skin, in your muscles or in your connective tissue.
* Bumps on your knees or elbows.
* Ragged cuticles and prominent blood vessels on your fingernail folds.
* Joint pain.

Some people (especially kids) diagnosed with dermatomyositis grow out of it and never have symptoms again. However, 80% of cases are chronic (they come back over time) and cause lifelong symptoms.

### Causes of dermatomyositis

Experts aren’t certain what causes dermatomyositis, but a few causes might include:

* Genetic factors: Some studies indicate dermatomyositis is a genetic disorder.
* Autoimmune issues: Dermatomyositis is similar to many autoimmune diseases that make your body's immune system attack healthy tissue.
* Viral infections: There’s some evidence that suggests a viral infection can trigger dermatomyositis in some people, even after the infection itself is cured.
* Environmental factors: Studies have found that living in areas with higher pollution or lower air quality might make you more likely to develop dermatomyositis.

## Diagnosis and Tests

Dermatomyositis is usually diagnosed with blood tests and biopsies of your skin and muscles.

Your provider will test your blood for:

* Increased amounts of specific muscle enzymes that means something is damaging them.
* Autoantibodies (cells that show your immune system is reacting to something it detects as harmful).

You’ll also need a skin biopsy of any rashes. Your provider might also biopsy your muscles to confirm inflammation inside them.

You might need one of a few imaging tests. Your provider will use these to evaluate your muscles, nerves, lungs and other organs. These tests can help them determine if your symptoms are caused by dermatomyositis or another issue. The most common imaging tests used to diagnose dermatomyositis include:

* Magnetic resonance imaging (MRI).
* Chest X-rays.

In some cases, your provider may request an electromyography (EMG). This test measures electrical activity in response to muscle or nerve stimulation.

## Management and Treatment

Dermatomyositis treatments include:

* Corticosteroids: Corticosteroids will decrease the inflammation in your muscles.
* Physical therapy: Physical therapy (and exercise in general) can help rebuild damage in your muscles. The stronger your muscles are, the better equipped they are to handle any damage from dermatomyositis.
* Immunosuppressant medicines: Immunosuppressants stop your immune system from damaging healthy cells and tissues. They can slow down any damage your body’s defenses are causing in your muscles.
* Intravenous immunoglobulin (IVIg): IVIg is an infusion of extra immunoglobulin, a naturally occurring element of your blood’s plasma. IVIg treatments can work alongside immunosuppressants, or as an alternate treatment.
* Speech therapy: If you have muscle weakness in or around your throat, speech therapy can help you strengthen the muscles in your throat that help you swallow.

Which treatments you need depends on where you’re having symptoms, and how severe they are. Talk to your provider about what to expect and when you’ll need certain treatments.

### How do I manage my dermatomyositis symptoms?

Managing your dermatomyositis symptoms will likely be a long-term process — possibly for the rest of your life.

* If your provider, physical therapist or speech therapist gives you exercises, do them as often as they suggest. This will help keep your muscles as strong as possible.
* Take any medications as often as you should for as long as your provider prescribes.
* Avoid UV exposure. Minimize your time in the sun, don’t use indoor tanning beds and take breaks indoors or under shade as often as possible while you’re outside.
* Use sunscreen whenever you know you’ll be outdoors. Make sure your sunscreen has an SPF rating of at least 50 and reapply it every two hours.

If you have dermatomyositis, it’s important to see your healthcare provider regularly. They’ll need to monitor your symptoms and make sure your condition isn’t spreading or getting more severe.

### How soon after treatment will I feel better?

It might take a few months for your symptoms to improve after you start treatment. Most people living with dermatomyositis feel better as they regain their original levels of muscle strength after treatment.

How long it takes you to feel better depends on which treatments you need, which symptoms you’re experiencing and how severe they are.

Talk to your provider about what to expect and when you should notice your symptoms getting better.

## Outlook / Prognosis

There’s no cure for dermatomyositis. You should expect to manage your symptoms for the rest of your life.

Even with treatment, 80% of people have chronic dermatomyositis (sometimes referred to as polycyclic dermatomyositis). Your symptoms might come and go in waves throughout your life. Visit your provider right away as soon as you notice the signs of a symptom flare up.

Two-thirds of people living with dermatomyositis develop a physical disability because of the damage to their muscles.

#### **What is the life expectancy of someone with dermatomyositis?**

Dermatomyositis is fatal for approximately 5% of people diagnosed with it. This is especially true in the first year after being diagnosed. But, about 20% of people with dermatomyositis go into long-term remission.

Some symptoms and other factors can increase your risk of dying, including if you:

* Wait more than six months to start treatment.
* Are older than 60.
* Experience severe symptoms.
* Have symptoms in your throat, lungs or heart.
* Have or develop cancer.

## Prevention

There’s no known way to prevent dermatomyositis. Because experts don’t know what causes it, there’s nothing you can do to prevent it.

## Living With

Visit your provider right away if you notice new weakness in your muscles, especially if you have a rash on your skin around the same time. The sooner dermatomyositis is diagnosed, the faster you can start treatment. This can decrease your chances of experiencing severe symptoms and other complications.

Ask your provider how often you should schedule follow-up visits so they can track your symptoms and any changes in your muscles or on your skin.

**DIFFERENTIAL DIAGNOSIS**

The following conditions can also present with muscle weakness and should be excluded by history, physical exam, and investigations before a definitive diagnosis of dermatomyositis can be made:

* *Inclusion body myositis:* unlike the symmetric and proximal involvement in dermatomyositis, muscle weakness in inclusion body myositis is usually asymmetric and involves distal muscles like the wrist and finger flexors. Muscle atrophy may be prominent during the examination, which is rare in dermatomyositis. A muscle biopsy will show the characteristic inclusion bodies. Unlike dermatomyositis, inclusion body myositis is refractory to treatment with corticosteroids.
* *Drug-induced myopathy:* Eliciting a drug history is essential to rule out drug-induced myopathies. The most common offending drugs are statins, alcohol, penicillamine, colchicine, glucocorticoids, zidovudine, and antimalarials. Drug-induced myopathy may cause mild myalgia, or it may even be severe enough to cause rhabdomyolysis. The absence of skin findings and muscle biopsy can differentiate this condition from dermatomyositis.
* *Hypothyroidism*: like dermatomyositis, hypothyroidism can present with proximal weakness and elevated muscle enzymes. The presence of other signs and symptoms of hypothyroidism, muscle biopsy, and serum thyroid-stimulating hormone levels can be used to differentiate this condition from dermatomyositis.
* *Myasthenia gravis:* Unlike dermatomyositis, myasthenia gravis predominantly causes muscle weakness of the ocular and bulbar muscles, is associated with anti-acetylcholine receptor antibodies, and does not cause elevation of muscle enzymes.
* *Polymyalgia rheumatica*: can present with pain and stiffness of the muscles around the shoulder and pelvic girdle. This condition can be differentiated from dermatomyositis by the presence of inflammatory markers, absence of elevated muscle enzymes, and normal muscle strength. Moreover, this condition mainly affects people more than 50 years of age.

Other differential diagnoses include muscular dystrophies, motor neuron disease, neuropathy, inherited metabolic myopathies, and myasthenia gravis.

The presence of characteristic skin findings in addition to symmetric muscle weakness should help to distinguish dermatomyositis from these conditions. Electromyography helps differentiate dermatomyositis from neuropathic causes of weakness. Muscle biopsy showing the hallmark pathological features of dermatomyositis also helps to exclude other causes.

EPIDEMIOLOGY

Dermatomyositis is a rare condition. A retrospective study conducted between 1967 and 2007 in Olmsted county, Minnesota, estimated an incidence rate of 9.63 per 1,000,000 people. The same study also found that 21% of all cases were of the amyopathic subtype. Dermatomyositis commonly affects persons between the ages of 40 and 50 with a mean age at diagnosis of 44.0 ± 18.3 years. The condition is more common in women than in men, with incidence rates being 3.98 and 4.68 per 1,000,000, respectively.

In Europe, a higher prevalence of dermatomyositis has been noted in Southern Europe compared to Northern Europe. A study conducted in Quebec showed a higher prevalence of dermatomyositis in urban areas. A cohort study conducted in Pennsylvania also showed clusters of clinically amyopathic dermatomyositis (CADM) in regions with high airborne pollution. These studies point towards the possibility of environmental factors acting as triggers for the condition.

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**POLYMYOSITIS**

**DEFINITION AND DESCRIPTION**

Polymyositis (pol-e-my-o-SY-tis) is an uncommon inflammatory disease that causes muscle weakness affecting both sides of your body. Having this condition can make it difficult to climb stairs, rise from a seated position, lift objects or reach overhead.

Polymyositis most commonly affects adults in their 30s, 40s or 50s. Women are affected more often than men. Signs and symptoms usually develop gradually, over weeks or months.

While there is no cure for polymyositis, treatment — ranging from medications to physical therapy — can improve your muscle strength and function.

**Causes**

The exact cause of polymyositis is unknown, but the disease shares many characteristics with autoimmune disorders, in which your immune system mistakenly attacks your own body tissues.

**Risk factors**

Your risk of polymyositis is higher if you have lupus, rheumatoid arthritis, scleroderma, or Sjogren's syndrome.

**Symptoms**

The muscle weakness associated with polymyositis involves the muscles closest to the trunk, such as those in your hips, thighs, shoulders, upper arms and neck. The weakness affects both the left and right sides of your body, and tends to gradually worsen.

## Diagnosis and tests

If your doctor suspects you have polymyositis, he or she might suggest some of the following tests:

* **Blood tests.** A blood test will let your doctor know if you have elevated levels of muscle enzymes, which can indicate muscle damage. A blood test can also detect specific autoantibodies associated with different symptoms of polymyositis, which can help in determining the best medication and treatment.
* **Electromyography.** This test involves inserting a thin needle electrode through the skin into the muscle. Electrical activity is measured as you relax or tighten the muscle, and changes in the pattern of electrical activity can confirm a muscle disease. The doctor can determine the distribution of the disease by testing different muscles.
* **Magnetic resonance imaging (MRI).** A scanner creates cross-sectional images of your muscles from data generated by a powerful magnetic field and radio waves. Unlike a muscle biopsy, an MRI can assess inflammation over a large area of muscle.
* **Muscle biopsy.** During this test, a small piece of muscle tissue is surgically removed for laboratory analysis. Analysis may reveal abnormalities, such as inflammation, damage, certain proteins or enzyme deficiencies.

**Treatment**

Although there's no cure for polymyositis, treatment can improve your muscle strength and function. The earlier treatment is started in the course of polymyositis, the more effective it is — leading to fewer complications.

However, as with many conditions, no single approach is best; your doctor will tailor your treatment strategy based on your symptoms and how well they respond to therapy.

### Medications

The most commonly used medications to treat polymyositis include:

* **Corticosteroids.** Drugs such as prednisone can be very effective in controlling polymyositis symptoms. But prolonged use of these drugs can have serious and wide-ranging side effects, which is why your doctor may gradually taper the dose of medication down to lower levels.
* **Corticosteroid-sparing agents.** When used in combination with a corticosteroid, these drugs can decrease the dose and potential side effects of the corticosteroid. The two most common medications used for polymyositis are azathioprine (Azasan, Imuran) and methotrexate (Trexall). Other medications prescribed for polymyositis include mycophenolate mofetil (CellCept), cyclosporine and tacrolimus.
* **Rituximab (Rituxan).** More commonly used to treat rheumatoid arthritis, rituximab is an option if initial therapies don't adequately control your polymyositis symptoms.

### Therapy

Depending on the severity of your symptoms, your doctor might suggest:

* **Physical therapy.** A physical therapist can show you exercises to maintain and improve your strength and flexibility and advise an appropriate level of activity.
* **Speech therapy.** If your swallowing muscles are weakened by polymyositis, speech therapy can help you learn how to compensate for those changes.
* **Dietetic assessment.** Later in the course of polymyositis, chewing and swallowing can become more difficult. A registered dietitian can teach you how to prepare easy-to-eat, nutritious foods.

### Surgical and other procedures

Intravenous immunoglobulin (IVIg) is a purified blood product that contains healthy antibodies from thousands of blood donors. These healthy antibodies can block the damaging antibodies that attack muscle in polymyositis. Given as an infusion through a vein, IVIg treatments may need to be repeated regularly for the effects to continue.

### When to see a doctor

Seek medical attention if you develop unexplained muscle weakness.

**Complications**

Possible complications of polymyositis include:

* **Difficulty swallowing.** If the muscles in your esophagus are affected, you may have problems swallowing (dysphagia), which in turn may cause weight loss and malnutrition.
* **Aspiration pneumonia.** Difficulty swallowing may also cause you to breathe food or liquids, including saliva, into your lungs (aspiration), which can lead to pneumonia.
* **Breathing problems.** If your chest muscles are affected by the disease, you may experience breathing problems, such as shortness of breath or, in severe cases, respiratory failure.

### Associated conditions

Although these are not complications, polymyositis is often associated with other conditions that may cause further complications of their own, or in combination with polymyositis symptoms. Associated conditions include:

* **Raynaud's phenomenon.** This is a condition in which your fingers, toes, cheeks, nose and ears initially turn pale when exposed to cold temperatures.
* **Other connective tissue diseases.** Other conditions, such as lupus, rheumatoid arthritis, scleroderma and Sjogren's syndrome, can occur in combination with polymyositis.
* **Cardiovascular disease.** Polymyositis may cause the muscular walls of your heart to become inflamed (myocarditis). In a small number of people who have polymyositis, congestive heart failure and heart arrhythmias may develop.
* **Lung disease.** A condition called interstitial lung disease may occur with polymyositis. Interstitial lung disease refers to a group of disorders that cause scarring (fibrosis) of lung tissue, making lungs stiff and inelastic. Signs and symptoms include a dry cough and shortness of breath.
* **Cancer.** People who have polymyositis have an elevated risk of cancer.

## Epidemiology

### Frequency

Idiopathic inflammatory myopathies are relatively rare diseases, with an incidence in the United States that ranges from 0.5-8.4 cases per million population. Polymyositis is more common in the United States within the Black population, with the estimated Black-to-White incidences for polymyositis and dermatomyositis being 5:1 and 3:1, respectively. Internationally, polymyositis is less common among the Japanese.

### Sex- and age-related demographics

Polymyositis and dermatomyositis are more common in women than in men (2:1 ratio), while inclusion body myositis is twice as common in men.

Polymyositis usually affects adults older than 20 years, especially those aged 45-60 years. Polymyositis rarely affects children. The age of onset of polymyositis with another collagen vascular disease is related to the associated condition.

Although dermatomyositis is primarily a disease of adults, it can be seen in children, usually those aged 5-14 years. Eighty percent of patients with inclusion body myositis are older than 50 years at onset.

## Diagnostic Considerations

Conditions to consider in the differential diagnosis of polymyositis include the following:

* Hypokalemia
* Hypophosphatemia
* Hypothyroidism
* Myasthenia gravis
* Myopathies
* Inclusion body myositis
* Eosinophilic myositis
* Myositis ossificans
* Focal myositis
* Giant cell myositis
* Diabetic polyradiculopathy
* Metabolic myopathy
* Muscular dystrophy
* Myasthenia gravis
* Overlap connective-tissue diseases

Drug-induced myopathy may result from the following:

* Ethanol
* Antimalarials
* Clofibrate

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### Granulomatosis with polyangiitis (GPA)

**Definition and description**

Granulomatosis with polyangiitis (GPA) is a type of vasculitis — chronic inflammation in your blood vessels. It was formerly called Wegener’s granulomatosis, but the new name describes it more precisely. GPA involves:

* Inflammation in many different types of blood vessels throughout your body (polyangiitis)
* Inflammatory masses called granulomas forming in your blood vessels and organs (granulomatosis)

Different types of vasculitis affect different blood vessels. GPA affects the many smaller blood vessels throughout your body. This means it can cause issues throughout your body, but especially in organs that rely on many small blood vessels. GPA tends to affect your respiratory system and kidneys the most.

Inflammation in your blood vessels can cause them to swell, break and bleed. It can also cause scarring that restricts the blood flow through your vessels, depriving your tissues of oxygen and nutrients. GPA can cause bleeding and organ damage in your renal and pulmonary systems (pulmonary-renal syndrome).

## Symptoms and Causes

### (Wegener’s granulomatosis)

GPA affects your respiratory system and kidneys the most. But it can also affect many other organs and tissues, and how you feel overall. The smaller blood vessels that it targets travel throughout your body.

Vasculitis in your connective tissues may cause muscle pain and joint pain, along with an overall feeling of unwellness (malaise). Other general symptoms may include fatigue, loss of appetite and weight loss.

#### **Respiratory symptoms**

Many people with GPA first notice and seek treatment for symptoms in their respiratory system. Early symptoms might resemble a cold or infection, but they linger too long. They might include:

* Sinus headaches or pressure
* Persistent sinus infections
* Persistent runny nose, with crusting around your nostrils
* Nasal congestion
* Unexplained, repeated nosebleeds
* Earache
* Chest pain
* Chronic cough
* Shortness of breath

As granulomatosis with polyangiitis worsens, you might develop inflammation of the cartilage in your ears, nose and throat (polychondritis). This can cause more severe symptoms, including:

* Nasal swelling so severe that your nose bridge collapses (saddle nose)
* Narrowing in your throat (subglottic stenosis), causing hoarseness, wheezing or stridor
* Inner ear inflammation, causing vertigo and hearing loss

You can also bleed in your lungs, which may cause shortness of breath or coughing up blood.

#### **Kidney symptoms**

You may not experience kidney pain with GPA. But you may notice changes in your pee, like foamy pee or blood in your pee. Swelling in your face or feet (edema) is another symptom of kidney disease.

If you have GPA, healthcare providers will continue to check on your kidneys, even if you never develop symptoms. While kidneys aren’t always involved in GPA early on, they almost always are eventually.

#### **Eye symptoms**

GPA can affect your eyes, causing inflammation on the surface or the inner parts of your eye. This can cause eye pain and pressure and make your eyes red and swollen. Severe cases can lead to vision loss.

#### **Skin symptoms**

Vasculitis in your skin may show up as:

* Mottled skin, with a bluish-red pattern.
* Purple, red or brown splotches (purpura).
* Skin lesions, like hard nodules or papules.
* Open sores (ulcers).

#### **Nervous system symptoms**

Granulomatosis with polyangiitis may affect your nervous system. It usually affects your peripheral nervous system — the nerves that extend from your spinal cord to the rest of your body.

Inflammation and swelling may compress or damage just one nerve, causing symptoms in just one area (mononeuropathy). More commonly, it may affect multiple nerves (polyneuropathy). Symptoms can include:

* Motor symptoms, like muscle weakness
* Sensory symptoms, like numbness and tingling or nerve pain
* Loss of autonomic control of your blood pressure, bladder or sweating

#### **Serious complications of granulomatosis with polyangiitis (Wegener’s)**

Severe GPA can be organ-threatening and life-threatening. Complications can include:

* Bleeding in your lungs (pulmonary hemorrhage), which can lead to respiratory failure
* Rapidly progressive glomerulonephritis (kidney disease), which can lead to kidney failure
* Permanent vision loss or hearing loss
* Loss of skin sensation or muscle control (peripheral neuropathy)

### Causes granulomatosis with polyangiitis (GPA)

GPA, like other types of vasculitis, is an autoimmune disease. This means your immune system generates ongoing inflammation in your blood vessels. Normally, your immune system sends inflammation to target infections. But in autoimmune diseases, it targets your healthy tissues by mistake.

#### **What triggers granulomatosis with polyangiitis?**

Researchers aren’t sure why autoimmune diseases occur. There are probably multiple factors involved. Sometimes, extra stress on your immune system seems to push it into overdrive, triggering dysfunction. Researchers have associated the onset of GPA with certain severe bacterial and viral infections.

Granulomatosis with polyangiitis (GPA) belongs to a group of conditions called ANCA-associated vasculitis, or AAV. These are types of vasculitis that involve a specific antibody called ANCA. Researchers believe this antibody plays a role in triggering the inflammation in these conditions, including GPA.

## Diagnosis and Tests

A healthcare provider will begin by asking about your symptoms and physically examining you. If your symptoms and medical history suggest GPA, they’ll follow up with tests to investigate further.

Tests for granulomatosis with polyangiitis include:

* Blood tests, including testing for ANCA antibodies
* Urinalysis, including testing your urine for blood and protein
* Chest X-ray and CT scans to look at your lungs
* Biopsy of lung, sinus or kidney tissue to look for specific types of inflammation

## Management and Treatment

### (Wegener’s)

Healthcare providers treat granulomatosis with polyangiitis (Wegener’s) with anti-inflammatory and immune system-suppressing drugs (corticosteroids and other immunosuppressants).

Some of these medications are stronger than others. Which combination your provider prescribes will depend on how severe your condition is and how much you’re at risk of the side effects.

Initial treatment for active GPA includes:

* High doses of corticosteroids, such as prednisone. These doses will eventually taper off.
* Rituximab. This newer biologic medication is now standard treatment.
* Cyclophosphamide (for severe disease) or methotrexate (for milder disease). These drugs also treat cancer, but for GPA (at much lower doses), they function as immunosuppressants.
* Avacopan. This drug can be used as an adjuvant treatment to reduce your dosage of corticosteroids.

If you have severe complications, you might need additional treatment, such as:

* Dialysis
* Organ transplantation

Once GPA is in remission, you’ll take milder medications to maintain remission. These typically include:

* Rituximab
* Milder immunosuppressants, such as azathioprine, methotrexate or mycophenolate mofetil

You’ll have ongoing testing during treatment to monitor your condition and response to the treatment. Your healthcare provider will adjust your prescription and dosage according to your response.

Each medication comes with its own potential side effects, and they can occur at any time during your treatment. You might need to change medications to avoid or reduce the risk of certain side effects.

## Outlook / Prognosis

Granulomatosis with polyangiitis is a lifelong condition that requires lifelong care. With treatment, the disease can go into remission and stop causing symptoms. But symptoms can also return (relapse).

You may have to take medications off and on for the rest of your life to manage relapses. Since these medications suppress your immune system, you’ll also have to take extra care to prevent getting sick.

#### **Can you live a normal life with GPA?**

With effective treatment, you can live a relatively normal life with GPA. Most people with chronic diseases have periods of remission and relapse, so the course of the disease can be up and down.

#### **What is the life expectancy of someone with granulomatosis with polyangiitis?**

Without treatment, the average life expectancy is five months, with less than 50% surviving one year. But with treatment, follow-up studies show more than 80% of people are alive at least eight years later.

#### **What is the most common cause of death in granulomatosis with polyangiitis?**

Before treatment, organ failure is the biggest mortality risk with GPA. During treatment, you’re more at risk of life-threatening infections that can take hold when your immune system is suppressed.

## Living With

When you’re living with a chronic autoimmune disease like granulomatosis with polyangiitis, you need to maintain a certain awareness of your body. Even when you’re feeling well, you should live defensively.

Take steps to protect yourself from common illnesses while taking immunosuppressants. Make sure to notice any new or unusual symptoms and let your healthcare provider know about them right away.

**DIFFERENTIAL DIAGNOSIS**

Due to the multisystemic nature of GPA, the differential diagnosis is broad. Several conditions that can mimic GPA must be ruled out before a definitive diagnosis can be made.

* Other forms of ANCA-associated vasculitis:
  + MPA
  + Churg-Strauss syndrome
  + Drug-induced ANCA-associated vasculitis
  + Renal-limited vasculitis
  + Mixed cryoglobulinemia
  + Polyarteritis nodosa
  + Immunoglobulin A vasculitis (Henoch-Schönlein purpura)
  + Goodpasture syndrome
* Other autoimmune disorders:
  + Systemic lupus erythematosus
  + Sarcoidosis
  + Rheumatoid arthritis
  + Amyloidosis
* Infections:
  + Infective endocarditis
  + Sepsis
  + Mycobacterial infections
  + Disseminated fungal infections
  + Disseminated gonococcal infection
  + Streptococcal pneumonia with glomerulonephritis
* Malignancies:
  + Lymphomatoid granulomatosis
  + Lymphomas
  + Castleman's disease
  + Carcinomatosis
* Miscellaneous:
  + Idiopathic pulmonary alveolar hemorrhage

**EPIDEMIOLOGY**

Among the 3 ANCA-associated vasculitides, GPA is the most common. The annual worldwide incidence of GPA is estimated to be 10 to 20 cases per million based on the geographical location. A higher incidence is noted in the colder regions. The prevalence of GPA in European and American populations is about 120 to 140 per million. A national study in the Netherlands on ANCA-associated vasculitis found that 167 patients (73%) were diagnosed with GPA, 54 (24%) with MPA, and 9 (4%) with EGPA. This distribution is similar to other European registries.

GPA is more commonly reported in Whites, although it can be observed in all racial and ethnic groups. The onset of GPA occurs between 45 and 60 years, but a small proportion (3%-7%) affects children and adolescents. Children younger than 18 have a female-to-male predominance of about 2:1, while in adults, the ratio is 1:1

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### EGPA (formerly Churg-Strauss syndrome)

**Definition and description**

EGPA stands for “**eosinophilic granulomatosis with polyangiitis**.” This is a long name, but it’s more specific than the former name, Churg-Strauss syndrome. EGPA is a rare disorder that occurs in people with a history of severe allergies and/or asthma. It affects your blood vessels, especially the ones in your lungs.

Let’s break the name down:

* Eosinophilic: Eosinophilia is an unusually high number of eosinophils in your blood. Eosinophils are a type of white blood cell that supports your immune system. Your eosinophil levels rise when your immune system is highly active. With EGPA, eosinophils are often double the norm.
* Granulomatosis: Granulomas are small masses of immune cells that can form in your tissues when those tissues are inflamed. They’re another tool of your immune system, meant to help “wall off” infections and other threats. Granulomatosis is the process of granulomas forming.
* Polyangiitis: Polyangiitis is a type of vasculitis, or chronic inflammation in your blood vessels. It affects the many small-to-medium-sized blood vessels throughout your body (rather than the relatively few larger ones). *Poly* means many, and *angiitis* is another term for vasculitis.

EGPA seems to start with inflammation in your respiratory system, related to allergies or asthma. Eosinophilia and granulomatosis are signs that your immune system is in overdrive. Polyangiitis is a dysfunctional immune response. It’s inflammation that’s automatic, ongoing and has no real target.

#### **How does eosinophilic granulomatosis with polyangiitis (EGPA) affect my body?**

Chronic vasculitis weakens the walls of your blood vessels. This can cause them to stretch, leading to an aneurysm, or to break, leading to internal bleeding. Inflammation can also cause swelling and scarring that narrows your blood vessels. This can restrict or stop the blood flow to your tissues and organs.

As your smaller blood vessels travel throughout your body, polyangiitis can cause symptoms throughout your body. But it especially affects the organs that rely on many small blood vessels. EGPA affects your respiratory system the most. It may also affect your kidneys, intestines, heart or nerves.

## Symptoms of EGPA (formerly Churg-Strauss syndrome)

EGPA develops gradually, and symptoms tend to occur in phases over several years.

Common early symptoms (phase 1) include:

* Adult-onset asthma with coughing, wheezing and shortness of breath.
* Chronic hay fever with sneezing, nasal itching and congestion.
* Chronic sinusitis (inflammation in your sinuses) and sinus pressure.
* Nasal polyps (noncancerous growths in your nose).
* Generalized joint pain and/or muscle pain.
* Fever, malaise (general unwellness) and fatigue.

As the condition progresses, you may develop eosinophilic infiltrates — clusters or masses of eosinophils that infiltrate your lungs and other tissues. This can lead to additional (phase 2) symptoms, including:

* Chest pain and difficulty breathing.
* Heart palpitations.
* Skin rashes or lesions.
* Gastrointestinal symptoms, like stomach pain and diarrhea.

Vasculitis (polyangiitis) is usually the last stage (phase 3) of the disease. It can cause:

* Symptoms of internal bleeding, like blood in your stool or coughing up blood or discolored spots under your skin.
* Symptoms of nerve inflammation or damage, like numbness and tingling, weakness or nerve pain.
* Symptoms of heart disease, like irregular heartbeats, faintness, shortness of breath and swelling (edema).

Polyangiitis will often affect your kidneys as well, but usually without symptoms.

### Causes of EGPA (formerly Churg-Strauss syndrome)

Eosinophilic polyangiitis with granulomatosis (EGPA) develops from an overreaction from your immune system. Your immune system generates the inflammation in your blood vessels, the granulomas in your tissues and the eosinophilia that cause your symptoms. But researchers aren't sure why this happens.

Diseases that involve chronic inflammation from your immune system are sometimes called autoimmune diseases. One common feature of autoimmune diseases is that your body can develop antibodies that target certain cells in your body with inflammation. This may be one factor in EGPA.

Researchers have grouped EGPA together with a handful of similar conditions that all involve a certain autoimmune antibody, called ANCA. They call these conditions ANCA-associated vasculitis, or AAV. However, only about 40% of people with EGPA have the ANCA antibody, so it’s not the only factor.

Eosinophilia seems to be a separate cause of symptoms that often occur long before vasculitis does. When eosinophils accumulate in your tissues, they trigger inflammation and damage them. Eosinophilia is related to asthma and allergies. People with asthma are 34 times more at risk of EGPA than others.

### Serious complications of EGPA (formerly Churg-Strauss syndrome)

If it goes untreated, EGPA can cause serious damage to your organs and tissues, including:

* Pleural effusion.
* Pericardial effusion.
* Peripheral neuropathy.
* Chronic kidney disease.
* Chronic respiratory failure.
* Congestive heart failure.

## Diagnosis and Tests

EGPA can be tricky to diagnose. You might have different symptoms at different times, and you and your healthcare provider might not connect them all together right away. Symptoms of EGPA can also resemble many other conditions. Your provider might suspect EGPA if you have most of these:

* A history of asthma or chronic hay fever.
* Evidence of eosinophilia on a blood test.
* Evidence of eosinophilic infiltrates on imaging tests.
* Evidence of granulomas and/or vasculitis on a tissue biopsy.

## Management and Treatment

Treatment for EGPA begins with a high dose of corticosteroids to reduce inflammation and eosinophils. When they’ve reduced enough to relieve your symptoms, your disease is in remission. At this point, your provider will begin reducing your dose. Most people continue to take a low dose of corticosteroids to maintain remission.

Your provider may prescribe additional medications if corticosteroids alone aren’t effective enough, or if you want to avoid taking a high dose of corticosteroids.

Additional medications include immunosuppressants and biologics. Mepolizumab is the first U.S. Food and Drug Administration (FDA)-approved biologic therapy for EGPA. Benralizumbab, another biologic agent, performed equally well in a recent clinical trial. These recent breakthroughs in research offer new treatment options for people with EGPA.

## Outlook / Prognosis

## EGPA is treatable, but not curable. Most people can manage their symptoms with medications and even achieve remission, meaning symptoms go away. But when you stop treatment, symptoms may start again (relapse). Your healthcare provider will continue to monitor your condition throughout your life.

### Can you live a long life with EGPA?

With effective treatment, you can have a normal life expectancy with EGPA. In the advanced stages of the disease, complications like organ failure can affect your life expectancy. But treatment can often stop or reverse organ failure. With treatment, EGPA survival rates after five years are over 80%.

## Prevention

As we don’t know what causes EGPA, we don’t know any way to prevent it. However, recognizing it and treating it earlier can prevent it from worsening. By paying close attention to your symptoms and reporting them to your healthcare provider, you may be able to prevent the complications of EGPA.

## Living With

Medications for EGPA reduce your immunity, which makes it easier for you to get sick and harder for you to get better. When you’re taking these medications, you’ll need to take extra care to protect yourself from common illnesses, because you won’t be able to “bounce back” as easily as before.

Long-term treatment with corticosteroids can also cause side effects, including high blood sugar and weight gain, bone thinning and mood changes. Your provider will work with you to manage side effects while managing EGPA. Stay in touch with your provider about all your symptoms, especially new ones.

## Epidemiology

The incidence and prevalence of EGPA is approximately 1.7 and 14.25 cases per million persons, respectively, making EGPA the least common of all the ANCA vasculitides. In comparison, the incidence and prevalence of GPA per million persons is 9.0 and 96.8 cases, respectively, and that of MPA is 5.9 and 39.2 cases.

The country with the highest overall incidence is the United States, at 4 cases per million persons. The prevalence is highest in Norway, with 30.4 cases per million persons, and within Europe, Norway has the highest incidence at 2.5 cases per million persons.There are very few cases to determine the true incidence and prevalence of EGPA in the global south; however, a nationwide population-based study from Korea reported an increase in the incidence per million persons from 1.1 in 2007 to 1.6 in 2017, and an increase in prevalence over that time from 1.1 to 11.2.

The prevalence of EGPA is equal in men and women. Onset occurs most often between the ages of 40-60 years, with the mean age at diagnosis being 50 years.

## Differential Diagnosis List for EGPA (Churg-Strauss Syndrome)

1. Chronic Eosinophilic Pneumonia (CEP)
2. Hypereosinophilic Syndrome (HES)
3. Granulomatosis with Polyangiitis (GPA, Wegener’s Granulomatosis)
4. Microscopic Polyangiitis (MPA)
5. Allergic Bronchopulmonary Aspergillosis (ABPA)
6. Asthma with Sinusitis and Nasal Polyps (without vasculitis)
7. Parasitic and Helminthic Infections
8. Drug-Induced Eosinophilia and Vasculitis
9. Malignancies (e.g., Leukemias, Lymphomas, Myeloproliferative Neoplasms)
10. Myelodysplastic Syndromes
11. IgG4-Related Disease
12. Other Small-Vessel Vasculitides (e.g., IgA Vasculitis, Cryoglobulinemic Vasculitis)
13. Infectious Diseases Mimicking Vasculitis (e.g., fungal infections)
14. Autoimmune Disorders with Eosinophilia (rare overlaps)

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**KAWASAKI DISEASE**

**DEFINITION AND DESCRIPTION**

Kawasaki disease causes swelling, called inflammation, in the walls of small to medium-sized blood vessels that carry blood throughout the body. Kawasaki disease most often affects the heart arteries in children. Those arteries supply oxygen-rich blood to the heart.

Kawasaki disease is sometimes called mucocutaneous lymph node syndrome. That's because it also causes swelling in glands, called lymph nodes, and mucous membranes inside the mouth, nose, eyes and throat.

Children with Kawasaki disease might have high fever, swollen hands and feet with skin peeling, and red eyes and tongue. But Kawasaki disease is often treatable. With early treatment, most children get better and have no long-lasting problems.

**Causes**

No one knows what causes Kawasaki disease. But experts don't believe the disease spreads from person to person. Some think that Kawasaki disease happens after a bacterial or viral infection, or that it's linked to factors in the environment. Certain genes might make children more likely to get Kawasaki disease.

**Risk factors**

Three things are known to increase a child's risk of developing Kawasaki disease.

* **Age.** Children under 5 years old are at highest risk of Kawasaki disease.
* **Sex.** Children who are assigned male at birth are slightly more likely to get Kawasaki disease.
* **Ethnicity.** Children of Asian or Pacific Islander descent have higher rates of Kawasaki disease.

Kawasaki disease tends to occur seasonally. In North America and countries with similar climates, it most often happens in the winter and early spring.

**Symptoms**

Symptoms of Kawasaki disease include a fever greater than 102.2 degrees Fahrenheit (39 degrees Celsius) for five or more days. And the child has at least four of the following symptoms.

* A rash on the main part of the body or in the genital area.
* An enlarged lymph node in the neck.
* Very red eyes without a thick discharge.
* Red, dry, cracked lips and a red, swollen tongue.
* Swollen, red skin on the palms of the hands and the soles of the feet. Later the skin on fingers and toes peels.

The symptoms might not happen at the same time. Let your child's healthcare professional know about a symptom that has gone away.

Other symptoms might include:

* Belly pain.
* Diarrhea.
* Fussiness.
* Joint pain.
* Vomiting.

Some children get a high fever for five or more days but have fewer than four of the symptoms needed for a diagnosis of Kawasaki disease. They might have what's called incomplete Kawasaki disease. Children with incomplete Kawasaki disease are still at risk of damage to the heart arteries. They still need treatment within 10 days of when symptoms appear.

Kawasaki disease can have symptoms like those of a condition called multisystem inflammatory syndrome in children. The syndrome happens in children with COVID-19.

## Diagnosis and tests

There's no single test to diagnose Kawasaki disease. Diagnosis involves ruling out other diseases that cause the same symptoms. These diseases include:

* Scarlet fever.
* Juvenile rheumatoid arthritis.
* Stevens-Johnson syndrome — a disorder of the mucous membranes.
* Toxic shock syndrome.
* Measles.
* Some illnesses are caused by ticks, such as Rocky Mountain spotted fever.

A member of your child's healthcare team will do an exam and order blood and urine tests to help in the diagnosis. Tests might include:

* **Blood tests.** Blood tests help rule out other diseases and check blood cell count. A high white blood cell count, anemia and inflammation are signs of Kawasaki disease.
* **Electrocardiogram (ECG or EKG).** This quick test checks the heart's electrical activity. It shows how the heart is beating. Sticky patches called electrodes are attached to the chest and sometimes to the arms or legs. Wires connect the patches to a computer. The computer prints or displays results. An ECG can diagnose an irregular heartbeat. Kawasaki disease can cause heart rhythm problems.
* **Echocardiogram.** This test uses sound waves to make pictures of the heart in motion. It sees how blood flows through the heart and heart valves. An echocardiogram shows how well the heart is working. It also can help see problems with the heart arteries.

**Treatment**

It's best to start treatment for Kawasaki disease as early as possible, when your child still has a fever. Treatment for Kawasaki disease often happens in a hospital. The goals of treatment are to lower fever, reduce swelling and prevent heart damage.

### Medication

Treatment for Kawasaki disease can include:

* **Gamma globulin.** A protein called gamma globulin is given through a vein. This treatment lowers inflammation in the blood vessels. It can lower the risk of problems with the heart artery.  
  With treatment, a child might start to improve soon after one gamma globulin treatment. Without treatment, Kawasaki disease lasts about 12 days. However, heart complications might last longer.  
  After getting gamma globulin, wait at least 11 months to get a live vaccine, such as the chickenpox or measles vaccine. Gamma globulin can affect how well these vaccines work.
* **Aspirin.** High doses of aspirin might help treat inflammation. Aspirin also can decrease pain, joint swelling and fever. The aspirin dose will likely be lowered once the fever has been gone for 48 hours.  
  For most other conditions, aspirin shouldn't be given to children. Aspirin has been linked to Reye's syndrome, a rare life-threatening condition, in children or teenagers who have the flu or chickenpox.  
  A healthcare professional needs to oversee giving aspirin to children with Kawasaki disease. Children who get flu or chickenpox during treatment might need to stop taking aspirin.

### After the first treatment

Once the fever goes down, a child might need to take low-dose aspirin for at least six weeks. This can be longer if there are problems with the heart artery. Aspirin helps prevent blood clotting.

With treatment, a child might start to improve soon after one gamma globulin treatment. Without treatment, Kawasaki disease lasts about 12 days. However, heart problems might last longer.

### Watching heart problems

If your child has any signs of heart problems, the healthcare professional might suggest follow-up tests to check your child's heart health. Tests are often done 6 to 8 weeks after the illness began, and then again after six months.

If heart problems keep on, your child might be sent to a specialist who treats heart disease in children, called a pediatric cardiologist. Treatment for heart issues linked to Kawasaki disease depends on the type of heart condition.

### When to see a doctor

If your child has a fever that lasts more than three days, contact your child's healthcare professional. Treating Kawasaki disease within 10 days of when it began may reduce the chances of lasting damage to the arteries that supply the heart.

**Complications**

Kawasaki disease is a leading cause of heart disease in children who live in developed countries. But, with treatment, few children have lasting damage.

Heart complications include:

* Swelling of blood vessels, most often the arteries that send blood to the heart.
* Swelling of the heart muscle.
* Heart valve problems.

Any of these complications can damage the heart. Swelling of the heart arteries can weaken them and cause a bulge in the artery wall, called an aneurysm. Aneurysms raise the risk of blood clots. These can lead to a heart attack or cause bleeding inside the body.

Rarely, for children who get heart artery problems, Kawasaki disease can cause death.

**DIFFERENTIAL DIAGNOSIS**

Various infections can mimic Kawasaki Disease including:

* Preseptal cellulitis
* Peritonsillar abscess
* Retropharyngeal Abscess
* Cervical lymphadenitis
* Group A streptococcal infection
* Adenovirus, Enterovirus, Parvovirus B19
* Measles
* Mononucleosis (Epstein-Barr virus)
* Scarlet Fever
* Rheumatic fever
* Toxic Shock Syndrome
* Meningitis
* Rocky Mountain Spotted Fever
* Staphylococcal scalded skin syndrome (SSSS)
* Toxic epidermal necrolysis (TEN)
* Lyme disease
* Leptospirosis

Both KD and adenovirus present with conjunctival injection, however, the important differentiation is that adenovirus causes conjunctival exudates and KD does not.The differentiation of KD from lymphadenitis by observing whether the lymphadenopathy is bilateral or unilateral; Kawasaki typically presents unilaterally in over half of cases. KD can cause retropharyngeal edema which may present concerns for possible retropharyngeal abscess (RPA). However, true RPA will have clinical symptoms and abnormal imaging, whereas KD will not.Toxic shock syndrome and scarlet fever lack the ocular and joint involvement that KD has.

Kawasaki disease' presentation also overlaps with other immunologic reactions such as multiple drug hypersensitivity reactions, juvenile idiopathic arthritis, infantile polyarteritis nodosa, and systemic lupus erythematosus. These can be differentiated from KD by the absence of classic clinical criteria and by chronicity and the number of joints affected.

**EPIDEMIOLOGY**

This disease is most common in children younger than five years of age, but it can present at any age, even in adults.There is a slight male predominance (male to female = 1.5 to 1). Boys are also more likely to suffer from complications and death. It is rare to see Kawasaki disease in children less than 4 months, possibly pointing to protection from maternal antibodies. It is most commonly seen in children of Asian descent, particularly Japanese, and is least common in Caucasian children.There also appears to be a higher prevalence of the disease in the winter and spring months. Incidence varies from 10 to 20 in 100,000 children aged < 5 years in the U.S. and Canada to 50 to 250 in 100,000 in Japan, Taiwan or Korea.

**CARE GUIDELINES**

Kawasaki Disease (KD) Care Guideline Initial Treatment ≤ 6 months

• IV Infliximab 5mg/kg - given first

• IVIG 2gm/kg over 10-12 hours (Premedicated with Acetaminophen and Diphenhydramine) o PO Acetaminophen 15 mg/kg, one time PRN premed o IV Diphenhydramine 1 mg/kg PRN premed > 6 months

• IVIG 2gm/kg over 10-12 hours (Premedicate with Acetaminophen and Diphenhydramine) o PO Acetaminophen 15 mg/kg, one time PRN premed o IV Diphenhydramine 1 mg/kg PRN premed

• PO Aspirin 30-50 mg/kg/day divided q6 hours

• PO Aspirin 30-50 mg/kg/day divided q6 hours

• Infliximab IV 5 mg/kg can be given in patients with coronary involvement at discretion of ID. o If given as part of primary therapy, should be given before IVIG

• Patients will be watched for 24 hours from time of IVIG completion

• If afebrile and clinically improved, will be candidate for discharge

• Any fever in first 24 hours after completion of IVIG will require an additional 24 hours of inpatient observation and consideration for retreatment if fevers persist beyond 36 hours post IVIG completion

• If fever at 36 hours, will need repeat labs: o CBC with diff, CRP, CMP and repeat echo Retreatment Options • IV Infliximab: 10 mg/kg (if not given as part of initial treatment)

• IV Cyclosporine: 3 mg/kg/day divided q12 hours

• Switch to PO Cyclosporine once afebrile > 24 hours (if already afebrile at start of therapy, then start with oral therapy) o PO Cyclosporine (10mg/mL liquid formulation): 4 - 6 mg/kg/day by mouth divided every 12 hours (we start with 5 mg/kg/day and that usually achieves good levels). Discharge Criteria

• Afebrile for at least 24 hours after IVIG completed with improvement of clinical signs

• If received Infliximab, will watch for 48 hours post Infliximab.

• All patients with abnormal coronaries (Z-score > 2) will need repeat echo prior to discharge to document stabilization of coronaries.

• Patients will be discharged on low dose aspirin with echo follow ups in 2 and 6 weeks and f/u with ID and Cardiology. o More frequent follow up may be arranged if abnormal Z-scores, at the discretion of Cardiology. Patient and Family Education

• Kids Health o Kawasaki Disease for Parents

• Lexicomp o Kawasaki Disease o Kawasaki Disease Discharge Instruction

REFERENCES

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[Kawasaki disease - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/kawasaki-disease/diagnosis-treatment/drc-20354603)

**HENOCH SCHONLEIN PURPURA**

**DEFINITION AND DESCRIPTION**

Henoch-Schonlein purpura (also known as IgA vasculitis) is a disorder that causes the small blood vessels in your skin, joints, intestines and kidneys to become inflamed and bleed.

The most striking feature of this form of vasculitis is a purplish rash, typically on the lower legs and buttocks. Henoch-Schonlein purpura can also cause abdominal pain and aching joints. Rarely, serious kidney damage can occur.

Henoch-Schonlein purpura can affect anyone, but it's most common in children under 10. The condition usually improves on its own. Medical care is generally needed if the disorder affects the kidneys.

## 

## Causes

In Henoch-Schonlein purpura, some of the body's small blood vessels become inflamed, which can cause bleeding in the skin, abdomen and kidneys. It's not clear why this initial inflammation develops. It may be the result of the immune system responding inappropriately to certain triggers.

Nearly half the people who have Henoch-Schonlein purpura developed it after an upper respiratory infection, such as a cold. Other triggers include chickenpox, strep throat, measles, hepatitis, certain medications, food, insect bites and exposure to cold weather.

**Risk factors**

Factors that increase the risk of developing Henoch-Schonlein purpura include:

* **Age.** The disease mainly affects children younger than 10.
* **Sex.** Henoch-Schonlein purpura is slightly more common in males than in females.
* **Race.** White and Asian children are more likely to develop Henoch-Schonlein purpura than are black children.

## 

## Symptoms

The four main characteristics of Henoch-Schonlein purpura include:

* **Rash (purpura).** Reddish-purple spots that look like bruises develop on the buttocks, legs and feet. The rash can also appear on the arms, face and trunk and may be worse in areas of pressure, such as the sock line and waistline.
* **Swollen, sore joints (arthritis).** People with Henoch-Schonlein purpura often have pain and swelling around the joints — mainly in the knees and ankles. Joint pain sometimes precedes the classical rash by one or two weeks. These symptoms subside when the disease clears and leave no lasting damage.
* **Digestive tract symptoms.** Many children with Henoch-Schonlein purpura develop belly pain, nausea, vomiting and bloody stools. These symptoms sometimes occur before the rash appears.
* **Kidney involvement.** Henoch-Schonlein purpura can also affect the kidneys. In most cases, this shows up as protein or blood in the urine, which you may not even know is there unless you have a urine test done. Usually this goes away once the illness passes, but some people develop persistent kidney disease.

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## Diagnosis and tests

Your doctor will be able to diagnose the condition as Henoch-Schonlein purpura if the classic rash, joint pain and digestive tract symptoms are present. If one of these signs and symptoms is missing, your doctor may suggest one or more of the following tests.

### Lab tests

No single laboratory test can confirm Henoch-Schonlein purpura, but certain tests can help rule out other diseases and make a diagnosis of Henoch-Schonlein seem likely. They may include:

* **Blood tests.** Your blood may be tested if your diagnosis isn't clear based on your signs and symptoms.
* **Urine tests.** Your urine may be tested for evidence of blood, protein or other abnormalities to determine if your kidneys are still working properly.

### Biopsies

People who have Henoch-Schonlein purpura often have deposits of a certain protein, IgA (immunoglobulin A), on the affected organ. Your doctor may take a small sample of skin so that it can be tested in a lab. In cases of severe kidney involvement, your doctor may suggest a kidney biopsy to help guide treatment decisions.

### Imaging tests

Your doctor may recommend an ultrasound to rule out other causes of abdominal pain and to check for possible complications, such as a bowel obstruction.

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## Treatment

Henoch-Schonlein purpura usually goes away on its own within a month with no lasting ill effects. Rest, plenty of fluids and over-the-counter pain relievers may help with symptoms.

### Medications

Corticosteroids, such as prednisone, may help shorten the time and intensity of joint and abdominal pain. Because these drugs can have serious side effects, discuss the risks and benefits of using them with your doctor.

### Surgery

If a section of the bowel has folded in on itself or ruptured, surgery may be needed.

### When to see a doctor

See your doctor if you have Henoch-Schonlein purpura and it's causing serious problems with your digestive tract.

If your child develops the rash associated with this condition, see your doctor as soon as possible.

## 

## Complications

For most people, symptoms improve within a month, leaving no lasting problems. But recurrences are fairly common.

Complications associated with Henoch-Schonlein purpura include:

* **Kidney damage.** The most serious complication of Henoch-Schonlein purpura is kidney damage. This risk is greater in adults than in children. Occasionally the damage is severe enough that dialysis or a kidney transplant is needed.
* **Bowel obstruction.** In rare cases, Henoch-Schonlein purpura can cause intussusception — a condition in which a section of the bowel folds into itself like a telescope, which prevents matter from moving through the bowel.

**PROGNOSIS**

IgA vasculitis is typically a self-limited illness that demonstrates an excellent prognosis in patients without renal involvement. The majority of patients fully recover in four weeks. IgA vasculitis recurs in approximately one-third of patients within 4 to 6 months after the initial onset.

The long-term morbidity of vasculitis is dependent on the extent of renal involvement. Approximately 1% of patients with IgA vasculitis will develop end-stage renal disease (ESRD) and require renal transplantation.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of IgAV includes the following:

* IgA nephropathy
* Acute renal failure
* Acute glomerulonephritis
* Idiopathic thrombocytopenic purpura
* Disseminated intravascular coagulation
* Thrombotic thrombocytopenic purpura
* Hemolytic uremic syndrome
* Meningococcal meningitis
* Hypersensitivity vasculitis
* Systemic lupus erythematosus
* Polyarteritis nodosa
* Bacterial endocarditis
* Inflammatory bowel disease
* Wegener granulomatosis
* Rocky Mountain spotted fever

**EPIDEMIOLOGY**

IgAV is a rare disorder that typically affects children; however, the condition can also be seen in adults and adolescents. The majority of children are aged younger than 10. It is often more severe and likely to cause long-term renal disease in adults. It is the most common vasculitis among children, affecting 10 to 20 per 100,000 per year. IgAV is slightly more common among boys than girls but with about equal predilection in adults.

REFERENCES

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[Henoch-Schonlein purpura - Diagnosis & treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/henoch-schonlein-purpura/diagnosis-treatment/drc-20354045)

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### Primary biliary cholangitis

**Definition and description**

Primary biliary cholangitis (PBC) is a liver disease that affects the bile ducts that run through your liver. It slowly degrades those bile ducts, making it harder for bile to flow through. Bile backs up inside your liver, which damages the tissues. Scar tissue gradually replaces healthy tissue and your liver gradually loses its functionality. This is known as cirrhosis. PBC was formerly known as primary biliary cirrhosis.

“Cholangitis” means inflammation in your bile ducts. “Biliary” means the bile ducts, and “primary” means original. This means that the disease itself is the original cause of inflammation in your bile ducts. There isn’t some other condition causing inflammation, such as an infection or a blockage. Since the inflammation isn’t responding to anything in particular, it doesn’t know when to stop.

### How does primary biliary cholangitis affect my body?

Chronic inflammation degrades your body’s tissues over time. While temporary inflammation can be part of the normal healing process, constant inflammation causes overactive healing in the form of scarring. When your bile ducts are scarred, they become narrowed and distorted, which obstructs the flow of bile. Bile backs up into your liver, causing inflammation and eventually, scarring (cirrhosis).

### Is primary biliary cholangitis serious?

Primary biliary cholangitis is a chronic and progressive condition, which means it doesn’t go away and can get worse over time. It progresses slowly through several stages. At the beginning, you might not notice it at all. But in the end, it can cause liver failure, which is fatal without a liver transplant. Fortunately, medication helps slow the progress of the disease, and not everyone will reach this stage.

### What is the difference between primary biliary cholangitis vs. primary sclerosing cholangitis?

The two conditions are very similar. One major difference is that primary biliary cholangitis (PBC) affects only your intrahepatic bile ducts, the bile ducts within your liver. Primary sclerosing cholangitis (PSC) affects all of your bile ducts, including your extrahepatic ducts. The two conditions also tend to affect different populations. And while you can treat PBC with medication, PSC has no effective treatment.

## Symptoms of primary biliary cholangitis

Many people with PBC have no symptoms in the early stages. As the disease progresses, signs of biliary disease begin to appear. The earliest and most common symptoms of people with PBC are:

* Fatigue (65%).
* Itchy skin (55%).

These symptoms affect different people to different degrees. They can occur later or earlier in the course of your disease, and they can be mild to severe at any stage. How your symptoms present doesn’t seem to be related to how advanced your disease is. However, some research has suggested that more severe symptoms earlier on may predict a faster progression overall.

### Complications of biliary disease

You may not notice biliary disease in the early stages. But as it progresses, complications can begin to develop. Bile that can’t flow will begin to leak into your bloodstream, causing illness. Bile that can’t flow also can’t reach your digestive system, where it’s needed to aid digestion. In later stages, scar tissue in your liver begins to affect the blood vessels that pass through it, causing portal hypertension.

#### **Fat malabsorption**

When your digestive system lacks the bile it needs, it has trouble breaking down and absorbing fats. Fat malabsorption can cause:

* High blood cholesterol.
* Fat deposits under your skin.
* Fatty poop or diarrhea.
* Weight loss.
* Low levels of fat-soluble vitamins A, D, E and K.
* Osteoporosis (from failure to absorb fat-soluble vitamin D).

#### **Portal hypertension**

When scar tissue in your liver begins to obstruct the blood vessels that run through it, it causes portal hypertension — high blood pressure in those veins and the veins that branch off from them. Portal hypertension can lead to:

* Enlarged liver.
* Enlarged spleen.
* More frequent colds and infections (reduced immunity).
* Easy bleeding and bruising (thrombocytopenia).
* Spider angiomas (red, spiderlike blood vessels under the surface of your skin).
* Swollen veins (varices) in your esophagus and abdomen.
* Gastrointestinal bleeding.
* A buildup of fluid in your abdomen (ascites).
* Swelling in your lower body (edema).
* Occasional mental confusion (from the buildup of toxins in your blood).

### Causes of primary biliary cholangitis

In PBC, it appears that your own immune system attacks the cells lining your intrahepatic bile ducts, causing inflammation. It’s as if your immune system mistakes these cells for foreign invaders. This is called autoimmune disease. Your immune system acts automatically to destroy healthy cells without any apparent reason, or any regulation telling it when to stop. Chronic inflammation leads to scarring.

We don’t know why autoimmune disease occurs. There does appear to be a genetic factor. People who get autoimmune diseases often have a family history of autoimmune diseases, and they often get more than one type. There also seems to be an environmental factor, meaning that it may take something in your environment to trigger the disease. It may be a chemical or infection that you’re exposed to.

## Diagnosis and Tests

Your healthcare provider will ask about your medical history and symptoms and physically examine you. Then they’ll test a sample of your blood for evidence of PBC. They look for particular antibodies in your blood that are associated with PBC, especially one called antimitochondrial antibody (AMA). They also look for elevated liver enzymes that indicate liver stress, especially alkaline phosphatase.

If your test results are positive for PBC, your provider will want to look at images of your liver and biliary system next. This helps to rule out other possible causes of your symptoms, and can also help show how advanced the disease is. They’ll usually begin with a simple test like an abdominal ultrasound. But sometimes, they may need to take clearer images with some type of MRI (magnetic resonance imaging).

About 5% of people with PBC test negative for AMA but have other signs and symptoms. In this case, your provider may need to take a liver biopsy to confirm you have PBC. They can usually do this as a bedside procedure using a needle inserted into your liver. The needle will withdraw a tiny tissue sample, and your provider will send the sample to a lab for examination under a microscope.

## Management and Treatment

Providers use the following treatments for primary biliary cholangitis:

#### **Medication**

There’s no cure for PBC, but you can slow it down and improve your condition with medication. Ursodeoxycholic acid (UDCA) is a type of bile salt that can help clear bile from your liver and reduce liver damage. It works well for about half of people with PBC, especially in the early stages. For those who don’t benefit from UDCA, doctors sometimes recommend a different bile salt called obeticholic acid.

Doctors can also treat some of your individual symptoms with different medications. For itching, they may recommend antihistamines such as diphenhydramine (Benadryl® or Aler-Dryl®), ultraviolet light therapy or bile acid sequestrants such as cholestyramine. Vitamin supplements can help prevent vitamin deficiencies and side effects such as osteoporosis. Some people with fatigue benefit from stimulants such as modafinil.

#### **Surgery**

If medication doesn’t improve your condition and your liver function continues to decline, your doctor may put you on the liver transplant waiting list. Liver transplant surgery has excellent results for people with PBC. Although, like other autoimmune diseases, PBC may return after your liver transplant, but it tends to progress much more slowly the second time around. Life expectancy after your transplant is normal.

## Outlook / Prognosis

In most cases, primary biliary cholangitis progresses slowly. With earlier diagnosis and treatment, you can often prevent or at least delay the later stages and complications of the disease. Many people are able to effectively control their symptoms with medications, although fatigue in PBC continues to be difficult to treat. Many people live for years without too much interference from PBC in their daily lives.

However, not everyone discovers PBC in time to treat it in the early stages. And some people simply have a more aggressive form of the disease. Higher levels of fatigue and higher levels of bilirubin in your blood predict a faster progression to liver failure. If you reach this stage, you’ll need a liver transplant to survive. But for those with PBC who have successful liver transplants, the prognosis is excellent.

### How long can you live with primary biliary cholangitis?

It takes an average of 15 to 20 years for PBC to progress to the terminal stage. The first stage, when you test positive for PBC but you don’t yet have symptoms, can last a long time. About half of people will begin having symptoms in the next five to 10 years. Once you have symptoms, the average life expectancy is about 10 years. For those who have successful liver transplants, the 10-year survival rate is 65%.

## Living With

A healthy diet and lifestyle can help you keep your liver as healthy as possible for as long as possible.

For example:

* Quit smoking, drinking alcohol and improperly or recreationally using drugs and medications.
* Eat more whole foods and fewer processed and packaged foods.
* Eat more healthy unsaturated fats and fewer saturated fats.
* Take a brisk walk each day. Weight-bearing exercise may help preserve bone health.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnoses of primary biliary cholangitis comprise all the diseases resulting in cholestasis, pruritis, and a deranged liver profile. All middle-aged women presenting with pruritis and jaundice must be evaluated in the context of primary biliary cholangitis. Some of the more significant differentials are given below:

* Biliary obstruction/stricture
* Primary sclerosing cholangitis
* Hepatitis
* Drug-induced liver disease

**EPIDEMIOLOGY**

The true incidence of primary biliary cholangitis is rising as more screening tests, such as liver chemistry and lipid profiles, are performed in otherwise healthy persons. Primary biliary cholangitis is common among women of middle age worldwide. The disease ratio among females to males is 9:1. The diagnosis is usually made in women aged between 30 and 60. Primary biliary cholangitis is mostly considered a disease of Europe and North America. However, incidence and prevalence are widely variable across different countries. The age-adjusted incidence of primary biliary cirrhosis in the United States per 1 million person-years for women is 45, and 7 for men, the prevalence per 1 million persons is 654 for women and 121 for men

RECOMMENDATIONS

### First-line therapy

UDCA is the first-line therapy for PBC. Several randomized controlled trials (RCTs) have demonstrated that UDCA (13–15 mg/kg/d) significantly improved liver biochemistry, delayed the progression of the disease to death, and reduced the need for transplantation. A low dose of UDCA (≤10 mg/kg/d) had inadequate efficacy. High-dose UDCA (28–30 mg/kg/d) did not have more benefits and was associated with serious adverse reactions, as demonstrated in primary sclerosing cholangitis (PSC) patients. UDCA at a dose of 13–15 mg/kg/d is recommended by all the major practice guidelines of PBC. UDCA should be continued indefinitely and can be given one, two, or three times per day, as per the patient’s choice. In addition, it is necessary to monitor the change in body weight and adjust the UDCA dose accordingly. Cholestyramine may interfere with the absorption of UDCA, therefore, they should be taken 4-6 hours apart. UDCA is well tolerated. The side effects are limited to diarrhea, abdominal distension, weight gain, and aggravation of pruritus, which usually does not need UDCA withdrawal. Very few patients are intolerant or allergic to UDCA.

### Second-line therapy

Patients with suboptimal response to UDCA are at risk of disease progression, so a second-line treatment should be considered. Biochemical response to UDCA is usually assessed after 1 year of treatment in most criteria, but some studies have shown that the biochemical response at 6 months has similar predictability to that at 12 months.27 In the clinical trial of new agents for PBC, ALP ≥1.67 ULN is an important criterion for patient enrollment.. For patients with an insufficient response to UDCA, adding a second-line therapy such as obeticholic acid, fibrates, and budesonide can be considered.

#### **Obeticholic acid (OCA)**

OCA is the only second-line therapy approved by the US Food and Drug Administration (FDA). As a semisynthetic hydrophobic bile acid analog that is highly selective for farnesol X receptor (FXR), OCA inhibits the expression of genes for rate-limiting enzymes for bile acid synthesis, thereby regulating the metabolism of bile acids and affecting inflammation, and liver fibrosis. Several phase II and phase III clinical trials have demonstrated that adding or switching to OCA (10 mg or 5–10 mg dose titration) significantly improved serum ALP and total bilirubin (TBIL) levels in patients with a suboptimal biochemical response or intolerant to UDCA. An open-label extension study and a randomized, double-blind phase III clinical trial also reported that OCA significantly reduced ALP, TBIL, direct bilirubin, GLOBE score, and UK-PBC score in PBC patients with UDCA intolerance or poor response. A subanalysis of data from a phase III clinical trial found 3 years of OCA treatment in PBC patients (*n*=17) was associated with improvement or stabilization of fibrosis and ductular injury.

OCA is generally well tolerated, with pruritus (77%) and fatigue (33%) being the most common side effects.The incidence and severity of pruritus were dose-dependent. OCA treatment results in a reduction of high-density cholesterol, but whether that increases the risk of cardiovascular events is unclear. Another safety concern is that OCA can cause serious liver decompensation events.Therefore, the FDA issued a new warning regarding OCA use in patients with advanced liver cirrhosis (e.g. decompensation events such as hepatic encephalopathy, ascites, esophageal and gastric varices, or persistent thrombocytopenia).Thus, the use of OCA in patients with decompensated cirrhosis is not recommended. In addition, clinicians should be cautious about using OCA even in patients with well-compensated cirrhosis.

#### **Fibrates**

Fibrates, including fenofibrate and bezafibrate, regulate bile acid synthesis by activating the peroxisome proliferator-activated receptor pathway. A recent meta-analysis showed that the combination therapy of UDCA and fenofibrate was superior to UDCA monotherapy in reducing ALP, GGT, IgM, and triglyceride, but not pruritus. Bezafibrate improved the liver chemistries of patients with a suboptimal response to UDCA. A recent phase III trial confirmed that patients on a combination of UDCA and bezafibrate had substantial remission in ALP and other biochemical markers.Furthermore, an RCT showed bezafibrate led to a ≥ 50% reduction of severe or moderate pruritus in 45% of patients compared with 11 % of the those in the placebo group. Bezafibrate also reduced the intensity of pruritus in the morning and evening and improved responses to the validated 5D-Itch Questionnaire. In addition, a large retrospective cohort study in Japan found that bezafibrate significantly reduced all-cause and liver-related mortality or liver transplantation rates in PBC patients with suboptimal responses to UDCA.

Fibrates appear to be safe and well tolerated in PBC patients. The most commonly reported side effects were gastrointestinal and musculoskeletal abnormalities. In addition, the use of fibrates can lead to the elevation of transaminases and serum creatinine. A single-center study reported that both fenofibrate and bezafibrate induced significant biochemical improvement, but that the former could better reduce the low-density lipoprotein cholesterol and uric acid. However, fenofibrate treatment was associated with higher rates of side effects and withdrawal events than bezafibrate.

#### **Budesonide**

Budesonide is a second-generation glucocorticoid with high first-pass elimination in the liver and with relatively few systemic side effects. Budesonide regulates bile acid synthesis, transport, and metabolism through the glucocorticoid receptor/pregnane X receptor pathway. Two multicenter prospective RCTs showed that combination therapy of budesonide (6–9 mg/d) and UDCA (15 mg/kg/d) was superior to UDCA monotherapy in improving the liver chemistries and histological progress.Another placebo-controlled, double-blind trial found that budesonide (9 mg/d) combined with UDCA (12–16 mg/kg/d) was associated with improved biochemical markers, but not liver histology. Therefore, further studies are warranted to explore the effect of budesonide on improving mortality and liver transplantation in PBC patients. In advanced PBC patients, the plasma concentration of budesonide increases significantly, and serious adverse events such as portal vein thrombosis may occur. Therefore, budesonide is not recommended for patients with cirrhosis or portal hypertension.

#### **Liver transplantation**

Indications for liver transplantation for PBC patients include decompensated cirrhosis (e.g. ascites, variceal hemorrhage, and hepatic encephalopathy), a Model for End-stage Liver Disease (MELD) score >15, or a Mayo risk score of PBC of at least 7.8. Intractable severe pruritus is an additional indication for liver transplantation specific to PBC patients.

The outcome of liver transplantation for patients with PBC is generally good, but the recurrence of PBC exists, which is associated with graft loss. The incidence of recurrent PBC (rPBC) after a liver transplant is 22% at 5 years, 21–37% at 10 years, and 40% at 15 years. Clinical and biochemical features are often absent, and AMA alone cannot be used for the diagnosis of rPBC since it could be persistently positive in both patients with or without rPBC. Therefore, the diagnosis of rPBC depends on the histological features, including granulomatous cholangitis and/or florid duct lesions.Risk factors of PBC recurrence include younger age at liver transplantation, use of tacrolimus, and occurrence of cholestasis. The association between the immunosuppressive regimen and recurrent PBC remains controversial. Some studies found tacrolimus was associated with an increased risk of rPBC when compared with cyclosporine. In contrast, one study suggested that tacrolimus and cyclosporine had no significant influence on the rate of rPBC. Meanwhile, tacrolimus showed fewer side effects than that cyclosporine. Studies showed that the conventional use of UDCA after liver transplant could effectively decrease the rate of rPBC.

## Recommendations

1. UDCA at 13–15 mg/kg/d for life-long is a standard therapy for all PBC patients, which can be taken in single or divided doses. It is necessary to monitor the change in body weight and adjust the dose of UDCA in time. (A1)
2. Biochemical response to UDCA should be assessed 6–12 months after treatment initiation. Paris II criteria are suitable for patients with early-stage (I-II) PBC with ALP and AST ≤1.5 times the ULN, normalization of TBIL after 1 year of UDCA treatment. Paris I criteria are suitable for advanced stage (III-IV) PBC with ALP ≤3 times the ULN, AST ≤2 times the ULN, normalization of TBIL after 1 year of UDCA treatment. (B2)
3. OCA at a dose of 5–10 mg/d is recommended for patients with suboptimal biochemical response to UDCA. OCA should not be used in patients with current or previous evidence of decompensation (e.g, ascites, encephalopathy, gastroesophageal varices bleeding), abnormal coagulation function, and persistent thrombocytopenia. Patients with compensated cirrhosis need to be closely monitored during the use of OCA. (A1)
4. Bezafibrate (400 mg/d) or fenofibrate (200 mg/d) are off-label therapies for patients with a suboptimal biochemical response to UDCA. Fibrates are contraindicated for patients with decompensated cirrhosis. It is necessary to monitor drug-induced liver injury (especially the elevation of bilirubin) and other related side effects during fibrate therapy. (B1)
5. Decompensated PBC patients with MELD score >15 or Mayo score >7.8, or patients with severe intractable pruritus, should be evaluated for liver transplantation. (C1)

UDCA is recommended for post-transplant patients to prevent and reduce the recurrence of PBC. (A1)

1. The available data are not sufficient to recommend the best immunosuppressive drugs and regimens for liver transplantation patients. (C2)

REFERENCES

[Primary Biliary Cholangitis: What It Is, Symptoms, Treatment](https://my.clevelandclinic.org/health/diseases/17715-primary-biliary-cholangitis-pbc)

**PRIMARY SCLEROSING CHOLANGITIS**

Primary sclerosing (skluh-ROHS-ing) cholangitis (koh-lan-JIE-tis) is a disease of the bile ducts. Bile ducts carry the digestive liquid bile from your liver to your small intestine. In primary sclerosing cholangitis, inflammation causes scars within the bile ducts. These scars make the ducts hard and narrow and gradually cause serious liver damage. A majority of people with primary sclerosing cholangitis also have inflammatory bowel disease, such as ulcerative colitis or Crohn's disease.

In most people with primary sclerosing cholangitis, the disease progresses slowly. It can eventually lead to liver failure, repeated infections, and tumors of the bile duct or liver. A liver transplant is the only known cure for advanced primary sclerosing cholangitis, but the disease may recur in the transplanted liver in a small number of patients.

Care for primary sclerosing cholangitis focuses on monitoring liver function, managing symptoms and, when possible, doing procedures that temporarily open blocked bile ducts.

**Causes**

It's not clear what causes primary sclerosing cholangitis. An immune system reaction to an infection or toxin may trigger the disease in people who are genetically predisposed to it.

A large proportion of people with primary sclerosing cholangitis also have inflammatory bowel disease, an umbrella term that includes ulcerative colitis and Crohn's disease.

Primary sclerosing cholangitis and inflammatory bowel disease don't always appear at the same time, though. In some cases, primary sclerosing cholangitis is present for years before inflammatory bowel disease occurs. If primary sclerosing cholangitis is diagnosed, it's important to look for inflammatory bowel disease because there is a greater risk of colon cancer.

Somewhat less often, people being treated for inflammatory bowel disease turn out to have primary sclerosing cholangitis as well. And rarely, people with primary sclerosing cholangitis develop inflammatory bowel disease only after having a liver transplant.

**Risk factors**

Factors that may increase the risk of primary sclerosing cholangitis include:

* **Age.** Primary sclerosing cholangitis can occur at any age, but it's most often diagnosed between the ages of 30 and 40.
* **Sex.** Primary sclerosing cholangitis occurs more often in men.
* **Inflammatory bowel disease.** A large proportion of people with primary sclerosing cholangitis also have inflammatory bowel disease.
* **Geographical location.** People with Northern European heritage have a higher risk of primary sclerosing cholangitis.

**Symptoms**

Primary sclerosing cholangitis is often diagnosed before symptoms appear when a routine blood test or an X-ray taken for an unrelated condition shows liver abnormalities.

Early signs and symptoms often include:

* Fatigue
* Itching
* Yellow eyes and skin (jaundice)
* Abdominal pain

Many people diagnosed with primary sclerosing cholangitis before they have symptoms continue to feel generally well for several years. But there's no reliable way to predict how quickly or slowly the disease will progress for any individual.

Signs and symptoms that may appear as the disease progresses include:

* Fever
* Chills
* Night sweats
* Enlarged liver
* Enlarged spleen
* Weight loss

**DIAGNOSIS AND TEST**

Tests and procedures used to diagnose primary sclerosing cholangitis include:

* **Liver function blood test.** A blood test to check your liver function, including levels of your liver enzymes, can give your doctor clues about your diagnosis.
* **MRI of your bile ducts.** Magnetic resonance cholangiopancreatography (koh-lan-jee-o-pan-cree-uh-TOG-ruh-fee) uses magnetic resonance imaging (MRI) to make images of your liver and bile ducts and is the test of choice to diagnose primary sclerosing cholangitis.
* **X-rays of your bile ducts.** A type of bile duct X-ray called endoscopic retrograde cholangiopancreatography (ERCP) in addition to, or instead of, an MRI may be needed. But this test is rarely used for diagnosis because of the risk of complications.  
  To make your bile ducts visible on an X-ray, your doctor uses a flexible tube passed down your throat to inject dye into the area of your small intestine where your bile ducts empty.  
  An ERCP is the test of choice if signs and symptoms persist despite no abnormalities on an MRI. An ERCP is often the initial test if you're unable to have an MRI because of a metal implant in your body.
* **Liver biopsy.** A liver biopsy is a procedure to remove a piece of liver tissue for laboratory testing. Your doctor inserts a needle through your skin and into your liver to extract a tissue sample.  
  A liver biopsy can help determine the extent of damage to your liver. The test is used only when the diagnosis of primary sclerosing cholangitis is still uncertain after less-invasive tests.

**Treatment**

Treatments for primary sclerosing cholangitis focus on managing complications and monitoring liver damage. Many medications have been studied in people with primary sclerosing cholangitis, but so far none have been found to slow or reverse the liver damage associated with this disease.

### Treatment for itching

* **Bile acid sequestrants.** Medications that bind to bile acids — the substances thought to cause itching in liver disease — are the first line treatment for itching in primary sclerosing cholangitis.
* **Antibiotics.** If you have trouble tolerating a bile acid-binding drug or if it doesn't help, your doctor may prescribe rifampin (Rifadin, Rimactane, others), an antibacterial drug. Exactly how rifampin reduces itching is unknown, but it may block the brain's response to itch-inducing chemicals in your circulation.
* **Antihistamines.** This type of medication may help reduce mild itching caused by primary sclerosing cholangitis. Whether these medications are effective for this condition is unknown.  
  Antihistamines may worsen the liver disease symptoms of dry eyes and dry mouth. On the other hand, antihistamines can help with sleep if itching keeps you awake.
* **Opioid antagonists.** Itching related to liver disease may also respond to opioid antagonist drugs, such as naltrexone. Like rifampin, these drugs seem to reduce the itch sensation by acting on your brain.
* **Ursodeoxycholic acid (UDCA).** Also known as ursodiol, UDCA is a naturally occurring bile acid that may help relieve itching symptoms caused by liver disease by increasing the absorbability of bile.

### Treatment for infections

Bile that backs up in narrowed or blocked ducts causes frequent bacterial infections. To prevent and treat these infections, people with primary sclerosing cholangitis may take repeated courses of antibiotics or continue taking antibiotics for long periods.

Before any procedure that could cause an infection, such as an endoscopic procedure or abdominal surgery, you'll also need to take antibiotics.

### Nutrition support

Primary sclerosing cholangitis makes it difficult for your body to absorb certain vitamins. Even though you may eat a healthy diet, you may find that you can't get all the nutrients you need.

Your doctor may recommend vitamin supplements that you take as tablets or that you receive as an infusion through a vein in your arm. If the disease weakens your bones, you may take calcium and vitamin D supplements as well.

### Treatment for bile duct blockages

Blockages that occur in your bile ducts may be due to disease progression but can be a sign of cancer of the bile duct. Endoscopic retrograde cholangiopancreatography (ERCP) can help determine the cause, and bile duct blockage can be treated with:

* **Balloon dilation.** This procedure can open blockages in the larger bile ducts outside the liver. In balloon dilation, your doctor runs a slender tube with an inflatable balloon at its tip (balloon catheter) through an endoscope and into a blocked bile duct. Once the balloon catheter is in place, the balloon is inflated.
* **Stent placement.** In this procedure, your doctor uses an endoscope and attached instruments to place a small plastic tube called a stent in a blocked bile duct to hold the duct open.

### Liver transplant

A liver transplant is the only treatment known to cure primary sclerosing cholangitis. During a liver transplant, surgeons remove your diseased liver and replace it with a healthy liver from a donor.

A liver transplant is reserved for people with liver failure or other severe complications of primary sclerosing cholangitis. Though uncommon, it's possible for primary sclerosing cholangitis to recur after a liver transplant.

### When to see a doctor

Make an appointment with your doctor if you have severe, unexplained itching on much of your body — itching that persists no matter how much you scratch. Also see your doctor if you feel extremely tired all the time, no matter what you do.

It's particularly important to bring unexplained fatigue and itching to your doctor's attention if you have ulcerative colitis or Crohn's disease, both of which are types of inflammatory bowel disease. A majority of people with primary sclerosing cholangitis also have one of these diseases.

**Complications**

Complications of primary sclerosing cholangitis may include:

* **Liver disease and failure.** Chronic inflammation of the bile ducts throughout your liver can lead to tissue scarring (cirrhosis), liver cell death and, eventually, loss of liver function.
* **Repeated infections.** If scarring of the bile ducts slows or stops the flow of bile out of the liver, you may experience frequent infections in the bile ducts. The risk of infection is particularly high after you've had a surgical procedure to expand a badly scarred bile duct or remove a stone blocking a bile duct.
* **Portal hypertension.** Your portal vein is the major route for blood flowing from your digestive system into your liver. Portal hypertension refers to high blood pressure in this vein.  
  Portal hypertension can cause fluid from the liver to leak into your abdominal cavity (ascites). It can also divert blood from the portal vein to other veins, causing these veins to become swollen (varices). Varices are weak veins and tend to bleed easily, which can be life-threatening.
* **Thinning bones.** People with primary sclerosing cholangitis may experience thinning bones (osteoporosis). Your doctor may recommend a bone density exam to test for osteoporosis every few years. Calcium and vitamin D supplements may be prescribed to help prevent bone loss.
* **Bile duct cancer.** If you have primary sclerosing cholangitis, you have an increased risk of developing cancer in the bile ducts or gallbladder.
* **Colon cancer.** People with primary sclerosing cholangitis associated with inflammatory bowel disease have an increased risk of colon cancer. If you've been diagnosed with primary sclerosing cholangitis, your doctor may recommend testing for inflammatory bowel disease, even if you have no signs or symptoms, since the risk of colon cancer is elevated if you have both diseases.

**Lifestyle and home remedies**

If you've been diagnosed with primary sclerosing cholangitis, take steps to care for your liver, such as:

* Don't drink alcohol.
* Get vaccinated against hepatitis A and B.
* Use care with chemicals at home and at work.
* Maintain a healthy weight.
* Follow directions on all medications, both prescription and over-the-counter. Make sure your pharmacist and any doctor prescribing for you know that you have a liver disease.
* Talk to your doctor about any herbs or supplements you're taking since some can be harmful to your liver.

**Alternative medicine**

No alternative medicine treatments have been found to treat primary sclerosing cholangitis. But some complementary and alternative therapies may help you cope with the signs and symptoms of the disease. Talk to your doctor about your options.

Fatigue is common in people with primary sclerosing cholangitis. While doctors can treat some factors that may contribute to fatigue, your signs and symptoms may persist. You might find relief with complementary and alternative treatments that have shown some benefit for fatigue, such as:

* Regular exercise done more than two hours before you go to bed, which can help promote better sleep
* A well-balanced diet that includes fruit, vegetables, whole grains and protein
* Stress management techniques, such as meditation and relaxation exercises

## Epidemiology

In the United States, the prevalence of primary sclerosing cholangitis (PSC) is not known. Inferences have been drawn on the basis of the strong relationship with inflammatory bowel disease (IBD), which has a prevalence of 60-80% in patients with PSC in western countries.

The prevalence of PSC is estimated to be 6.3 cases per 100,000 population. Western Europe is thought to have approximately the same prevalence as in the United States, although Scandinavian countries report a somewhat higher rate. In many developing countries with limited access to advanced health care, the prevalence of PSC is probably underestimated, as the diagnosis cannot be confirmed without endoscopic retrograde cholangiopancreatography (ERCP). The association of PSC with IBD may vary; for example, in Japan, only 34-37% of patients with PSC have IBD.The disease normally starts at age 20-30 years, although it may begin in childhood. PSC may be active for a long time before it is noticed or diagnosed.

A survey of the literature has not revealed a racial bias for PSC, but studies on this aspect of the disease are rather limited. Based on the epidemiologic data available for IBD, the Jewish population might be expected to have a 2- to 4-fold higher prevalence, followed by, in descending order of frequency, white persons, black individuals, Hispanic people, and Asian populations.

## Differential Diagnoses

* Abdominal Vascular Injuries
* Acalculous Cholecystitis
* Autoimmune Hepatitis
* Bile Duct Strictures
* Bile Duct Tumors
* Biliary Obstruction
* Biliary Trauma
* Cholangiocarcinoma
* Cholangitis
* Common Bile Duct Stones
* Gallbladder Cancer
* Gallstones (Cholelithiasis)
* IgG4 Cholangitis
* Mirizzi Syndrome
* Pancreatic Necrosis and Pancreatic Abscess
* Papillary Tumors
* Primary Biliary Cholangitis (Primary Biliary Cirrhosis)

**GUIDELINE of Primary Sclerosing Cholangitis**

Cholestatic liver biochemistry with typical cholangiographic features in the absence of other identifiable causes of secondary sclerosing cholangitis is usually sufficient for a diagnosis of primary sclerosing cholangitis (PSC).

Magnetic resonance cholangiopancreatography (MRCP) is recommended as the principal imaging modality for investigating suspected PSC.

Liver biopsy should be reserved for possible small duct PSC, assessment of suspected possible overlap variants, or when the diagnosis is unclear.

Risk stratification based on non-invasive assessment is recommended.

Do not use ursodeoxycholic acid (UDCA) for the prevention of colorectal cancer or cholangiocarcinoma.

Corticosteroids and immunosuppressants are not recommended for the treatment of classic PSC; however, corticosteroids may be indicated in patients with additional features of autoimmune hepatitis (AIH) or IgG4-related sclerosing cholangitis (IgG4-SC).

Perform endoscopic screening for esophageal varices in line with international guidelines where there is evidence of cirrhosis and/or portal hypertension.

Use colonoscopy and colonic biopsies to seek colitis in all patients with PSC.

Patients with suspected PSC undergoing endoscopic retrograde cholangiopancreatography (ERCP) should receive prophylactic antibiotics.

Non-invasive investigations such as MRCP, dynamic liver MRI, and/or contrast CT should be performed in patients who have new or changing symptoms or evolving abnormalities.

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**PEMPHIGUS AND PEMPHIGOID**

**DEFINITION AND DESCRIPTION**

Pemphigus and pemphigoid are rare autoimmune blistering diseases of the skin and/or mucous membranes. Pemphigus affects the outer layer of the skin (epidermis) and causes lesions and blisters that easily rupture. Pemphigoid affects a lower layer of the skin, between the epidermis and the dermis, creating tense blisters that do not break easily. Sometimes pemphigoid may look like hives or eczema without blisters.

The term “pemphigus” is used in a very specific way to describe blistering disorders caused by autoantibodies such as desmoglein 1 and desmoglein 3 that recognize components of the epidermis and lead to disruption of the intercellular junctions, loss of integrity and formation of blisters.

Pemphigoid is a group of subepidermal, blistering autoimmune diseases that primarily affect the skin, especially in the lower abdomen, groin and flexor surfaces of the extremities. Here, autoantibodies (anti-BPA-2 and anti-BPA-1) are directed against the basal layer of the epidermis and mucosa.

The patient’s immune system makes antibodies, which attack viruses and harmful bacteria. In the context of pemphigus and pemphigoid, the immune system is overactive, and antibodies instead attack healthy cells in the skin or mucous membranes. As a result, skin cells separate from each other, fluid collects between skin layers and blisters form and may cover a large area of skin.

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### Signs & Symptoms

There are several different types of pemphigus.

*Pemphigus Vulgaris (PV)*PV is the most common of these conditions. Blisters are soft and fragile and may form at the mouth first and then spread to the skin and even the genitals. Blisters are frequently painful but not itchy, and in the mouth make chewing and swallowing difficult. PV does not cause permanent scarring unless there is an infection associated with the sore.

*Pemphigus Foliaceus (PF)*PF is a less severe type. Blisters may form on the scalp and face first and then spread to the chest and back. Blisters do not occur in the mouth. Blisters are not usually painful and are superficial and form crusts.

*Pemphigus Vegetans*This type results in thicker sores, mainly in the groin and under the arms.

*IgA Pemphigus*This type is caused by the IgA antibody binding to epidermal cell proteins. It may resemble pemphigus foliaceus or may appear as small pustules.

*Paraneoplastic Pemphigus (PNP)*PNP is associated with certain forms of cancer. Blisters form inside the mouth and may affect the lungs, leading to a fatal outcome. Sores of the mouth, lips and esophagus are almost always present and skin lesions of different types occur. PNP can affect the lungs. In some patients, the diagnosis will prompt doctors to search for a hidden tumor. In some patients, the tumor will be benign, and the disease will improve if the tumor is surgically removed.

*Mucous Membrane Pemphigoid (MMP)*MMP affects the eyes, mouth and throat. A clinical form called ocular cicatricial pemphigoid (OCP) can result in blindness if it involves the eyes and respiratory compromise if it involves the deeper parts of the throat.

*Bullous Pemphigoid (BP)*BP is frequently limited to the skin with blisters presenting predominantly on the abdomen, groin, back, arms and legs. The blisters may itch and be painful.

*Gestational Pemphigoid (GP)*GP is characterized by a blistering rash starting around the navel and spreading to the entire body, typically in the second or third trimester of pregnancy.

*Epidermolysis Bullosa Acquisita (EBA)*EBA involves a blistering rash on the skin and/or mucosal surfaces. Blisters are usually smaller than in pemphigoid.

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### Causes

Pemphigus and pemphigoid are not inherited but there can be a genetic predisposition to develop the disease. A person who is genetically predisposed to a disorder carries a gene (or genes) for the disease, but it may not be expressed unless it is triggered or “activated” under certain circumstances, such as due to particular environmental factors. It is not currently possible to predict who may get these diseases.

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### Affected populations

Males and females are equally affected. The conditions are known to affect people from all racial and cultural backgrounds. However, there are certain groups of people (Ashkenazi Jews, people of Mediterranean, North Indian and Persian descent) who have a higher incidence of pemphigus.

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### Diagnosis and tests

Pemphigus and pemphigoid are diagnosed through special testing and clinical presentation. Types of testing include:

Lesion biopsy — a sample of skin is removed by biopsy and examined under the microscope. Additionally, the layer of skin in which cell-to-cell separation occurs can be determined.

Direct immunofluorescence — the skin sample is treated to detect desmoglein autoantibodies in the skin. The presence of these antibodies indicates pemphigus. In pemphigoid and other basement membrane autoimmune blistering diseases, other autoantibodies can be detected.

Indirect immunofluorescence or antibody titer test — this measures desmoglein autoantibodies in the blood serum in pemphigus. In bullous pemphigoid BP180 and BP230 antibodies can be measured in the serum. Anti-type VII collagen is found in EBA. It may be used to obtain a more complete understanding of the course of the disease.

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### Standard Therapies

**Treatment**  
There is currently no cure for pemphigus or pemphigoid, but these conditions can usually be controlled. A decrease in or disappearance of signs and symptoms (remission) is possible. The treatment of pemphigus and pemphigoid is directed toward suppressing the skin and mucosal lesions of the disease and preventing complications potentially associated with its treatment. Most patients will eventually enter a complete remission in which they are off all therapy and there is no evidence of the disease. Generally, the less widespread the pemphigus is, the easier it is to control. The development, severity and progression of the diseases are not uniform and the response to therapies can vary among individuals. Consequently, physicians will take several different factors into account when planning an individual’s treatment, which will be tailored to the individual’s specific needs and situation.

Treatment is usually separated into phases: control, consolidation and maintenance. In the control phase, high-intensity therapy is used to bring the disorder under control by initiating the clearance of current lesions, reducing or suppressing new lesion formation, and improving other symptoms such as itch relief. In the consolidation phase, a consistent dose of medication is used until a significant portion of lesions have healed. In the maintenance phase, the dose of medication is gradually reduced until a minimal level is achieved that is successful in preventing the development of new lesions.

The mainstay of treatment is the use of corticosteroids such as prednisone, which are anti-inflammatory medications that also suppress the normal function of the immune system. Steroids may be applied directly to the affected areas (topically) or may be taken by mouth or given by injection (systemic steroids). Topical therapy is generally given to reduce pain and prevent or treat infection. Most individuals will receive systemic steroids to bring about control of pemphigus. The dose of steroids used can be tapered once control of the disorder is achieved.

Rituximab is now considered a first-line therapy for pemphigus, and it was recently approved by the FDA for this indication. Rituximab can prevent new autoantibodies from forming. It takes 3-4 months for the existing autoantibody levels to fall, during which time some dose of steroids may be required.

Other medications that may be used in combination with corticosteroids to treat individuals with pemphigus include drugs that suppress the immune system (immunosuppressive drugs) such as mycophenolate mofetil, azathioprine, methotrexate or cyclophosphamide; drugs that modify or regulate the immune system (immunomodulatory drugs) dapsone; or antibiotics such as doxycycline. These medications may be used to allow physicians to lower the overall dose of steroids. Some individuals respond to therapy quickly; others respond more slowly or do not respond at all. In severe cases or in cases where individuals fail to respond to other therapies, pulse steroids, plasmapheresis or intravenous immunoglobulin therapy (IVIG) may be used.

Research has indicated that IVIG therapy can markedly decrease levels of the abnormal antibodies associated with pemphigus without decreasing the levels of normal, healthy antibodies. IVIG is normally given with other therapy such as steroids and immunosuppressive drugs, to prevent rebound of disease as the therapy is tapered.

Pulse-steroid therapy refers to the administration of extremely high levels of steroids given for a short period of time. Plasmapheresis is a method for removing unwanted substances (e.g., autoantibodies) from the blood, and is not used as much now because of increased risk of infections. Blood is removed from the patient and blood cells are separated from plasma. The patient’s plasma is then replaced with other human plasma and the blood is transfused into the patient. These approaches are most frequently used now only if rituximab is not tolerated or is ineffective.

The conditions themselves are rarely fatal, and most deaths occur from infections of compromised tissues. If left untreated, these diseases may be fatal.

## Pemphigus Differential Diagnoses

* Bullous Pemphigoid
  + Tense blisters, subepidermal cleavage; pemphigus has fragile, easily ruptured blisters with intraepidermal cleavage.
* Dermatitis Herpetiformis
  + Intensely pruritic grouped vesicles, associated with gluten sensitivity.
* Drug-Induced Pemphigus
  + Similar clinical features but triggered by medications.
* Erythema Multiforme
  + Target lesions with mucosal involvement but no autoantibodies.
* Hailey-Hailey Disease (Benign Familial Pemphigus)
  + Recurrent erosions in flexural areas, genetic disorder without autoantibodies.
* Paraneoplastic Pemphigus
  + Associated with malignancies; polymorphic skin lesions and severe mucositis.
* Pemphigus Foliaceus
  + Superficial blistering limited to skin, no mucosal involvement.
* IgA Pemphigus
  + Presents with pustules; IgA autoantibodies detected.

**Pemphigoid Differential Diagnoses**

* Pemphigus Vulgaris
  + Flaccid blisters and erosions; pemphigoid blisters are tense and subepidermal.
* Bullous Systemic Lupus Erythematosus (BSLE)
  + Autoimmune blistering in lupus patients; immunofluorescence and serology differentiate.
* Cicatricial (Mucous Membrane) Pemphigoid
  + Chronic mucosal blistering with scarring; overlaps with pemphigoid spectrum.
* Dermatitis Herpetiformis
  + Pruritic vesicles, associated with gluten sensitivity.
* Linear IgA Bullous Dermatosis
  + IgA-mediated subepidermal blistering disease.
* Epidermolysis Bullosa Acquisita (EBA)
  + Autoantibodies against type VII collagen; subepidermal blisters.
* Bullous Drug Eruptions
  + Drug-induced blistering mimicking pemphigoid.
* Contact Dermatitis and Other Bullous Dermatoses
  + May mimic early or non-bullous pemphigoid.

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**Polyendocrine autoimmune syndromes**

**Definition and description**

Autoimmune Polyendocrine Syndrome is a rare disorder where the immune system mistakenly attacks healthy tissues in different organs of the body. This results in dysfunction of various endocrine glands, leading to abnormal hormone levels and affecting the body's ability to regulate essential functions. The primary impact of this syndrome on health is the disruption of hormone production and balance, which can cause a range of symptoms and complications that impact overall well-being and quality of life.

## Symptoms of Autoimmune Polyendocrine Syndrome

Autoimmune Polyendocrine Syndrome typically presents with a variety of symptoms affecting multiple organs and systems in the body.

* Fatigue
* Weight loss
* Low blood pressure
* Dizziness
* Nausea and vomiting
* Diarrhea
* Joint and muscle pain
* Skin discoloration
* Shakiness or tremors
* Loss of appetite

## Causes of Autoimmune Polyendocrine Syndrome

Autoimmune Polyendocrine Syndrome is primarily caused by the immune system mistakenly attacking the body's own tissues and organs, leading to dysfunction in multiple endocrine glands. Causes of Autoimmune Polyendocrine Syndrome:

* Genetic predisposition
* Environmental triggers
* Autoimmune dysfunction in the body

Types of Autoimmune Polyendocrine Syndrome

Autoimmune Polyendocrine Syndrome encompasses a variety of conditions that involve the immune system mistakenly attacking multiple organs in the body.

* Autoimmune Polyendocrine Syndrome Type 1 (APS1): A rare genetic disorder characterized by the presence of multiple autoimmune conditions affecting various endocrine glands.
* Autoimmune Polyendocrine Syndrome Type 2 (APS2): Involves autoimmune destruction of multiple endocrine glands, commonly affecting the adrenal glands and thyroid.
* Autoimmune Polyendocrine Syndrome Type 3 (APS3): Features a combination of autoimmune thyroid disease with other autoimmune conditions such as type 1 diabetes and autoimmune gastritis.
* Autoimmune Polyendocrine Syndrome Type 4 (APS4): Involves autoimmune thyroid disease along with other autoimmune conditions like type 1 diabetes and various skin disorders.
* Autoimmune Polyendocrine Syndrome Type 5 (APS5): A less common form characterized by autoimmune thyroid disease in combination with other autoimmune disorders affecting the endocrine system.

## Risk Factors

Autoimmune Polyendocrine Syndrome risk factors are primarily linked to genetic predisposition, family history of autoimmune diseases, and environmental triggers.

* Genetic predisposition
* Family history of autoimmune diseases
* Certain infections
* Exposure to environmental factors
* Gender (more common in females)

## Diagnosis of Autoimmune Polyendocrine Syndrome

Autoimmune Polyendocrine Syndrome is typically diagnosed through a combination of medical history, physical examination, and specific laboratory tests.

* Blood tests
* Imaging studies
* Hormone level testing
* Genetic testing

## Treatment for Autoimmune Polyendocrine Syndrome

The treatment for Autoimmune Polyendocrine Syndrome focuses on managing symptoms and addressing any hormone deficiencies.

* Hormone Replacement Therapy: Essential for managing hormone deficiencies in Autoimmune Polyendocrine Syndrome, involves taking synthetic hormones to replace the ones the body is not producing adequately.
* Immunomodulatory Therapy: Helps regulate the immune system's abnormal response, often using medications like corticosteroids or immunosuppressants to reduce inflammation and slow down autoimmune activity.
* Regular Monitoring and Blood Tests: Crucial for adjusting treatment regimens and ensuring hormone levels are within the target range to prevent complications and maintain overall health.
* Symptom Management: Addressing specific symptoms such as diabetes, thyroid dysfunction, or adrenal insufficiency through medications or lifestyle modifications.
* Patient Education and Lifestyle Modifications: Educating patients on the importance of adherence to treatment, healthy eating, stress management, and regular exercise to support overall wellbeing and symptom control.

## Epidemiology

### United States statistics

Approximately 14-20 people per million population are affected by polyglandular autoimmune syndrome type II. Observations have revealed, however, that the disease is much more prevalent if subclinical forms are included.

### Sex- and age-related demographics

The female-to-male ratio of polyglandular autoimmune syndrome type II is 3-4:1.

Polyglandular autoimmune syndrome type II occurs in the third or fourth decade of life.

## Differential Diagnosis for Autoimmune Polyendocrine Syndrome (APS)

1. Thymoma (Paraneoplastic Autoimmune Syndromes)
2. Kearns–Sayre Syndrome (Mitochondrial Disorder)
3. POEMS Syndrome (Paraneoplastic Syndrome)
4. Wolfram Syndrome (DIDMOAD Syndrome)
5. Severe Combined Immunodeficiency (SCID) and Other Immunodeficiencies
6. IPEX Syndrome (Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked)
7. Other Genetic Syndromes with Endocrinopathies
8. Isolated Autoimmune Endocrinopathies (e.g., isolated Addison’s disease, autoimmune thyroiditis)
9. Drug-Induced Endocrinopathies or Autoimmune Reactions
10. Infectious Causes Mimicking Endocrine Dysfunction (e.g., tuberculosis, HIV)

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### Food intolerance

**Definition and description**

When you have a food intolerance, it means your digestive system has a hard time digesting (breaking down) food. Another word for food intolerance is food sensitivity.

Food intolerance means your gut is sensitive to certain foods and can’t tolerate them. When you eat these foods, you may experience uncomfortable symptoms like gas, diarrhea and abdominal pain.

### Food intolerance and food allergies

Food intolerance, or food sensitivity, is not the same thing as having a food allergy.

A food intolerance:

* Affects your digestive system.
* Occurs when your digestive system can’t break down certain foods.
* Causes symptoms like an upset stomach that aren’t life-threatening.
* Brings on symptoms within a few hours after eating as the food makes its way through the digestive tract.
* May not cause symptoms if you eat just a small amount of a food.

A food allergy:

* Affects the immune system.
* Occurs when your immune system mistakes a protein or other ingredient in food as a threat. Your immune system releases antibodies (proteins) called immunoglobulin E (IgE) to fight the threat.
* Causes an allergic reaction, such as hives and swelling, shortness of breath or wheezing.
* Brings on symptoms within minutes of consuming even a small amount of an allergy-inducing food.
* May cause a severe, life-threatening reaction called anaphylaxis. Without an epinephrine treatment, this reaction can be fatal.

### Most common types of food intolerance

Common food sensitivities include:

* Lactose: People who are lactose intolerant don’t make enough lactase enzyme to break down lactose, a sugar found in milk and dairy products. This food intolerance is the most common.
* Histamine: Histamines are naturally occurring chemicals in foods like cheese, pineapples, bananas, avocados and chocolate. Red wine and some white wines also have histamines. People who are histamine intolerant don’t make enough diamine oxidase enzyme to break down this chemical.
* Gluten: Gluten is a protein in wheat, rye and barley. Gluten sensitivity isn’t the same as having celiac disease, a type of autoimmune disease. When you have celiac disease, gluten damages the small intestines. If you have a non-celiac gluten sensitivity, your body has a harder time digesting gluten.

## Causes of food intolerance

People with food intolerances often don’t make enough of a particular enzyme that the digestive system needs to break down a certain food or ingredient. Experts aren’t sure why some people develop food intolerances.

Certain gastrointestinal conditions may make you more prone to food sensitivities. These conditions include:

* Celiac disease.
* Inflammatory bowel disease (IBD), including Crohn’s disease and ulcerative colitis.

### symptoms of a food intolerance

Symptoms of a food intolerance include:

* Abdominal (belly) pain.
* Diarrhea.
* Gas and bloating.
* Headaches or migraines.
* Heartburn.
* Nausea.
* Upset stomach.

## Diagnosis and Tests

A hydrogen breath test can detect lactose intolerance. During this test, you drink a liquid that has lactose. Then you breathe into a balloon-like container every 30 minutes for a few hours. If you’re lactose intolerant, the undigested lactose will cause high levels of hydrogen in your breath. You may also develop symptoms from drinking the lactose solution.

There isn’t a test for gluten sensitivity or histamine intolerance. An allergy test can detect food allergies but not a food intolerance. Your healthcare provider may ask you to keep a food diary to track meals and symptoms.

You may also try an elimination diet to remove certain foods from your diet for two to six weeks. If symptoms go away during this time — and then return when you start eating the food again — you may have a food intolerance.

## Management and Treatment

You may need to change your diet to limit or eliminate problem foods. Many people with food intolerances find that consuming small amounts of food causes few symptoms if any. When symptoms occur, over-the-counter medicines like antacids or antidiarrheals can help.

People who are lactose intolerant can consume lactose-free milk and dairy products. You can also buy lactase enzymes at drugstores. You can take lactase pills before consuming dairy products or add lactase drops directly to milk to break down the lactose.

### Complications of food intolerance

People who are lactose intolerant may not get enough calcium and vitamin D if they completely cut out dairy products. You can take supplements or use over-the-counter lactase enzymes to consume dairy products without getting an upset stomach.

People who cut back on products with gluten may need to eat more fresh vegetables, fruit and gluten-free whole grains to make sure they get enough fiber and other nutrients such as B vitamins in their diets, which are important for health.

## Outlook / Prognosis

## Food intolerances tend to be lifelong. Most people can manage symptoms if they reduce or cut out foods that cause digestive problems. Food intolerance may be an inconvenience (and the symptoms unpleasant), but it isn’t a life-threatening problem like a food allergy.

## Living With

You should call your healthcare provider if you experience:

* Extreme abdominal pain or diarrhea.
* Severe reaction to food.
* Unexplained weight loss.

**Epidemiology of Food Intolerance**

* Prevalence:
  + Food intolerance is common, with self-reported rates ranging from 4% to 20% in the general population across various countries.
  + A US-based survey found a self-reported food intolerance prevalence of about 24.8% among adults.
  + European studies show variability, with lower rates in Spain and Ireland compared to higher rates in Scandinavia and Germany.
  + Australia and Mexico report higher food hypersensitivity rates of approximately 19.1% and 30.1%, respectively.
  + Food intolerance is generally more frequently reported than food allergy, but objective diagnostic tools are limited.
* Symptoms and Impact:
  + Symptoms typically involve the gastrointestinal tract, including bloating, abdominal pain, flatulence, and diarrhea.
  + Symptoms usually resolve with elimination of the offending food and recur upon reintroduction.
  + Unlike food allergy, food intolerance is not immune-mediated and does not cause anaphylaxis.
* Common Types:
  + Lactose intolerance is the most common enzymatic food intolerance worldwide.
  + Other types include reactions to food additives, fermentable carbohydrates (FODMAPs), and food chemicals.
* Age and Geographic Variation:
  + Prevalence varies by region and dietary habits.
  + Higher prevalence reported in Western countries, possibly related to diet and microbiome differences.
  + Data from developing countries are limited.
* Comparison with Food Allergy:
  + Food allergy affects about 3–10% of children worldwide, with lower prevalence in adults (~1–2%).
  + Food allergy is immune-mediated (IgE or non-IgE), whereas food intolerance involves non-immune mechanisms.

## Differential Diagnoses of Food Intolerance

1. Food Allergy
   * Immune-mediated reaction (IgE or non-IgE) with symptoms such as urticaria, angioedema, anaphylaxis, respiratory symptoms, and sometimes GI symptoms.
   * Food intolerance is non-immunologic and does not cause anaphylaxis.
2. Carbohydrate Malabsorption
   * Lactose intolerance, fructose malabsorption, sorbitol intolerance causing bloating, diarrhea, and gas due to enzyme deficiencies or transporter defects.
3. Histamine Intolerance
   * Reaction to histamine-rich foods or impaired histamine degradation causing flushing, headaches, rashes, abdominal symptoms.
4. Pharmacological Food Reactions
   * Sensitivity to food additives (e.g., monosodium glutamate), preservatives (sulfites), caffeine, tyramine causing flushing, headaches, GI symptoms.
5. Gastrointestinal Disorders
   * Irritable Bowel Syndrome (IBS)
   * Inflammatory Bowel Disease (IBD)
   * Celiac Disease
   * Small Intestinal Bacterial Overgrowth (SIBO)
   * Pancreatic insufficiency
   * Chronic infections or parasitic infestations
6. Mastocytosis
   * Excess mast cells releasing histamine causing symptoms mimicking food intolerance.
7. Food Poisoning and Toxic Reactions
   * Scombroid poisoning (histamine toxicity from spoiled fish), lectin toxicity from undercooked beans.
8. Psychological Factors
   * Food aversion, eating disorders, somatization disorders.
9. Other Allergic or Atopic Conditions
   * Atopic dermatitis, eosinophilic esophagitis which may coexist or mimic food intolerance.

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**DRUG ALLERGY**

**DEFINITION AND DESCRIPTION**

A drug allergy is the reaction of the immune system to a medicine. Any medicine — over-the-counter, prescription or herbal — can trigger a drug allergy. However, a drug allergy is more likely with certain medicines.

The most common symptoms of drug allergy are hives, rash and fever. But a drug allergy also may cause serious reactions. This includes a severe, life-threatening condition known as anaphylaxis.

A drug allergy is not the same as a medicine side effect. A side effect is a known possible reaction to a medicine. Side effects to medicines are listed on their labels. A drug allergy also is different from drug toxicity. Drug toxicity is caused by an overdose of medicine.

**Causes**

A drug allergy happens when the immune system mistakenly identifies a medicine as a harmful substance, such as a virus or bacterium. Once the immune system detects a medicine as a harmful substance, it develops an antibody specific to that medicine. This can happen the first time you take a medicine, but sometimes an allergy doesn't develop until there have been repeated exposures.

The next time you take the medicine, these specific antibodies flag the medicine and direct immune system attacks on the substance. Chemicals released by this activity cause the symptoms associated with an allergic reaction.

You may not be aware of your first exposure to a medicine, however. Some evidence suggests that trace amounts of a medicine in the food supply, such as an antibiotic, may be enough for the immune system to create an antibody to it.

Some allergic reactions may result from a somewhat different process. Researchers believe that some medicines can bind directly to a certain type of immune system white blood cell called a T cell. This event causes the release of chemicals that can result in an allergic reaction the first time you take the medicine.

### Medicines commonly linked to allergies

Although any medicine can cause an allergic reaction, some medicines are more commonly associated with allergies. These include:

* Antibiotics, such as penicillin.
* Pain relievers, such as aspirin, ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve).
* Chemotherapy drugs for treating cancer.
* Medicines for autoimmune diseases, such as rheumatoid arthritis.

### Non Allergic drug reactions

Sometimes a reaction to a medicine can produce symptoms that are virtually the same as those of a drug allergy. However, a drug reaction isn't triggered by immune system activity. This condition is called a nonallergic hypersensitivity reaction or pseudoallergic drug reaction.

Medicines that are more commonly associated with this condition include:

* Aspirin.
* Dyes used in imaging tests, known as radiocontrast media.
* Opiates for treating pain.
* Local anesthetics.

**Risk factors**

While anyone can have an allergic reaction to a drug, a few factors can increase someone's risk. These include:

* A history of other allergies, such as a food allergy or hay fever.
* A personal or family history of drug allergy.
* Increased exposure to a medicine because of high doses, repeated use or prolonged use.
* Certain infections commonly associated with allergic drug reactions, such as HIV infection or Epstein-Barr virus infection.

**Symptoms**

Symptoms of a serious drug allergy often happen within an hour after taking a medicine. Other reactions, particularly rashes, can happen hours, days or weeks later.

Drug allergy symptoms may include:

* Skin rash.
* Hives.
* Itching.
* Fever.
* Swelling.
* Shortness of breath.
* Wheezing.
* Runny nose.
* Itchy, watery eyes.

### Anaphylaxis

Anaphylaxis is a rare, life-threatening drug allergy reaction that causes widespread changes in the way body systems function. Symptoms of anaphylaxis include:

* Tightening of the airways and throat, causing trouble breathing.
* Nausea or belly cramps.
* Vomiting or diarrhea.
* Dizziness or lightheadedness.
* Weak, fast pulse.
* Drop in blood pressure.
* Seizure.
* Loss of consciousness.

### Other conditions resulting from drug allergy

Less common drug allergy reactions happen days or weeks after exposure to a medicine and may last for some time after you stop taking the medicine. These include:

* **Serum sickness,** which may cause fever, joint pain, rash, swelling and nausea.
* **Drug-induced anemia,** a reduction in red blood cells, which can cause fatigue, irregular heartbeats, shortness of breath and other symptoms.
* **Drug rash with eosinophilia and systemic symptoms, also called (DRESS),** which results in rash, high white blood cell count, general swelling, swollen lymph nodes and hepatitis infection that comes back after being dormant.
* **Inflammation in the kidneys, also called nephritis,** which can cause fever, blood in the urine, general swelling, confusion and other symptoms.

## Diagnosis and tests

An accurate diagnosis is essential. Research has suggested that drug allergies may be overdiagnosed and that patients may report drug allergies that have never been confirmed. Misdiagnosed drug allergies may result in the use of less appropriate or more-expensive medicines.

A healthcare professional typically does a physical exam and asks you questions. Details about when symptoms started, the time you took the medicine, and improvement or worsening of symptoms are important clues for helping your health professional make a diagnosis.

Your health professional may order more tests or refer you to an allergy specialist, called an allergist, for tests. These may include the following.

### Skin test

With a skin test, the allergist or a nurse administers a small amount of a suspect medicine to the skin with a tiny needle that scratches the skin, a shot or a patch. A positive reaction to a test often causes a red, itchy, raised bump.

A positive result suggests that you may have a drug allergy.

A negative result isn't as clear-cut. For some medicines, a negative test result usually means that you're not allergic to the medicine. For other medicines, a negative result may not completely rule out the possibility of a drug allergy.

### Blood tests

A healthcare professional may order blood tests to rule out other conditions that could be causing symptoms.

While there are blood tests for detecting allergic reactions to a few medicines, these tests aren't used often because of the relatively limited research on their accuracy. They may be used if there's concern about a serious reaction to a skin test.

### Results of diagnostic work-up

After looking at your symptoms and test results, a healthcare professional can usually reach one of the following conclusions:

* You have a drug allergy.
* You don't have a drug allergy.
* You may have a drug allergy — with varying degrees of certainty.

These conclusions can help when making future treatment decisions.

**Treatment**

Treatments for a drug allergy can be divided into two general strategies:

* Treatment for present allergy symptoms.
* Treatment that may enable you to take an allergy-causing medicine if it's medically necessary.

### Treating current symptoms

The following treatments may be used to treat an allergic reaction to a medicine:

* **Stopping the medicine.** If a healthcare professional determines that you have a drug allergy — or likely allergy — stopping the medicine is the first step in treatment. For many people, this may be the only intervention necessary.
* **Antihistamines.** Your health professional may prescribe an antihistamine or recommend a nonprescription antihistamine such as diphenhydramine (Benadryl). An antihistamine can block immune system chemicals triggered during an allergic reaction.
* **Corticosteroids.** Corticosteroids given as a shot or taken by mouth may be used to treat symptoms associated with more-serious reactions.
* **Treatment of anaphylaxis.** Anaphylaxis requires an immediate epinephrine shot. Hospital care also is needed to maintain blood pressure and support breathing.

### Taking allergy-causing medicines

If you have a confirmed drug allergy, a healthcare professional likely would not prescribe the medicine that causes a reaction unless it is necessary. Sometimes — if the diagnosis of drug allergy is uncertain or there's no other treatment — your health professional may use one of two strategies to give you the suspect medicine.

With either strategy, your health professional provides careful supervision. Supportive care also is available in the event of an adverse reaction. These treatments are generally not used if medicines have caused serious, life-threatening reactions in the past.

### Graded challenge

If the diagnosis of a drug allergy is uncertain and a healthcare professional judges that an allergy is unlikely, a graded drug challenge may be an option. With this procedure, you receive 2 to 5 doses of the medicine, starting with a small dose and increasing to the desired dose, also called the therapeutic dose.

If you reach the therapeutic dose with no reaction, then your health professional may recommend that you take the medicine as prescribed.

### Drug desensitization

If it's necessary for you to take a medicine that has caused an allergic reaction, your care professional may recommend a treatment called drug desensitization. With this treatment, you receive a very small dose and then increasingly larger doses every 15 to 30 minutes over several hours or days. If you can reach the desired dose with no reaction, then you can continue the treatment.

**Prevention**

If you have a drug allergy, the best prevention is to avoid using the problem medicine. Steps you can take to protect yourself include the following:

* **Inform healthcare professionals.** Be sure that your drug allergy is clearly identified in your medical records. Inform other healthcare professionals, such as your dentist or any medical specialist.
* **Wear a bracelet.** Wear a medical alert bracelet that identifies your drug allergy. This information can ensure proper treatment in an emergency.

### When to see a doctor

Call 911 or emergency medical help if you experience signs of a severe reaction or suspected anaphylaxis after taking a medicine.

If you have milder symptoms of a drug allergy, see a healthcare professional as soon as possible.

**PROGNOSIS**

The outcome of most cutaneous drug allergies is good after immediate cessation of the drug and symptom relief.

Drug-induced anaphylaxis is potentially fatal, as it is characterized by a high frequency of rapid-onset (within minutes) cardiovascular collapse, especially in older patients. Other risk factors for death include cardiopathies associated with beta-blocker therapy. The true prevalence of fatal drug-induced anaphylaxis is unknown, as the patients studied varied from children to adults, and from emergency room attendees to inpatients, and most studies included all causes of anaphylaxis rather than drug-induced anaphylaxis specifically.

In SJS/TEN, the reported mortality rate varies from 30% to 50%. The effect of IVIG on mortality in patients with TEN remains indeterminate. Ocular complications (i.e., non healing epithelial defects and visual impairment) are major but relatively uncommon long-term sequelae of SJS/TEN. A persistent dry eye is the most common.

Drug allergy may result in anxiety and impairment in health related quality of life for sufferers. Health care professionals involved in the care of patients with a history of drug allergy/hypersensitivity must be aware of potential long-term psychological sequelae and effects on the doctor-patient relationships especially when new drugs have to be prescribed again.

**EPIDEMIOLOGY**

ADRs account for 3% to 6% of all hospital admissions and occur in 10% to 15% of hospitalized patients and up to 25% of outpatients. Drug allergy is relatively uncommon, accounting for less than 10% of all ADRs. Drug allergy occurs in 1% to 2% of all admissions and 3% to 5% of hospitalized patients, respectively but the true incidence of drug allergy in the community, and among children and adults, is unknown. Many children are misdiagnosed as being “allergic” to various medications, particularly antibiotics and end up carrying this label into adulthood. These patients are frequently treated with alternate medication that may be more toxic, less effective and more expensive – this in turn may result in increased morbidity, mortality and cost (economic) .

The true incidence of drug-induced anaphylaxis is also unknown, as most studies have been based on all causes of anaphylaxis or all causes (both allergic and nonallergic) of ADRs.

The estimated incidence of SJS, which may occur secondary to ADR, is 0.4 to 1.2 per 1 million people per year; the estimated incidence for TEN is 1.2 to 6 per 1 million people per year. An increase in SCARs among children (reaching 100 cases/year) has been observed, probably due to the active pharmacovigilance programmes

## Differential Diagnoses for Drug Allergy

## 1. IgE-Mediated Reactions (Urticaria, Angioedema, Anaphylaxis, Bronchospasm)

* Carcinoid syndrome
* Insect bites or stings
* Mastocytosis
* Asthma exacerbations
* Food allergy
* Scombroid fish poisoning (histamine toxicity)
* Latex allergy
* Infections (e.g., Epstein-Barr virus, hepatitis A/B/C, gastrointestinal parasites)

## 2. Non-IgE-Mediated Reactions (Exanthema, DRESS, SJS, TEN)

* Acute graft-versus-host disease
* Kawasaki disease
* Still’s disease
* Psoriasis
* Insect bites or stings
* Viral infections (e.g., measles, herpes viruses)
* Streptococcal infections

## 3. Other Conditions Mimicking Drug Allergy

* Idiopathic urticaria and angioedema
* Serum sickness and serum sickness-like reactions (immune complex-mediated)
* Drug-induced autoimmune syndromes (e.g., drug-induced lupus erythematosus)
* Vasculitis (drug-induced or primary)
* Infectious exanthems
* Contact dermatitis or allergic contact dermatitis
* Other dermatologic conditions (e.g., erythema multiforme, pityriasis rosea)

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## 

## 

## Hereditary Angioedema (HAE)

**Definition and description**

Hereditary angioedema (HAE) is a rare, genetic condition that causes episodes of swelling in different parts of your child’s body, including their face, hands or feet. Sometimes, swelling can happen in areas you can’t see, like in the tissues that line your child’s airways or digestive organs.

This swelling occurs because fluid leaks out of tiny blood vessels in your child’s body. The fluid builds up in the nearby tissues, which can prevent blood or lymph from moving along as it should. Episodes of swelling and related symptoms (HAE attacks) can be unpredictable and range in severity from mild to life-threatening.

“Angio-” refers to blood vessels, and “-edema” is the medical term for swelling due to fluid buildup within bodily tissues. There are many types of angioedema, each with different causes. HAE is one of the rarer types. It’s congenital, which means a person is born with it.

If your child has been diagnosed with HAE, you might feel uncertain of what comes next. It may help to know that research continues to provide new treatments for people of all ages with HAE — including children. Your child’s care team can help you learn which treatments are suitable for them and what you can expect down the road.

### Types of hereditary angioedema

HAE is one type of angioedema, but healthcare providers also divide HAE into different types:

* Type I HAE. This is the most common type, responsible for about 85% of all HAE cases. It’s when your child’s body doesn’t make enough of a certain protein called C1-Inhibitor (C1-INH). Without enough C1-INH, inflammation and related swelling can occur in your child’s body. Providers also call this type C1-INH deficiency.
* Type II HAE. This is the next most common type. Your child’s body can make enough C1-INH, but the protein doesn’t function as it should.
* HAE with normal C1-INH. This type is the least common. Your child has normal levels of C1-INH, and the protein functions normally. However, other factors cause swelling to happen.

Taken together, types I and II HAE affect 1 in every 50,000 people. This means about 6,000 people in the U.S. have one of these types of HAE. Researchers don’t know how many people have HAE with normal C1-INH, but they know it’s very rare.

## Symptoms and Causes

Hereditary angioedema (HAE) causes swelling you might notice in different parts of your child's body.

### Symptoms of hereditary angioedema

HAE signs and symptoms vary from person to person and may include:

* Visible swelling in various parts of your child’s body, including their hands, feet, eyelids, lips and genitals
* Symptoms related to swelling in your child’s gastrointestinal (GI) tract, which include nausea, vomiting, diarrhea and abdominal pain
* Symptoms related to swelling in your child’s mouth, throat and airways — including difficulty swallowing, swelling of your child’s tongue, a gasping sound when your child inhales and a change in how their voice sounds

Call your local emergency number immediately if your child struggles to breathe or swallow. Swelling affecting the airways is a life-threatening complication of HAE that can be fatal without treatment.

HAE doesn’t cause hives. This makes HAE different from other forms of angioedema, like acute allergic angioedema. However, some people with HAE develop a non-itchy rash as an early warning sign before swelling develops.

HAE attacks typically last three to five days. The attacks come and go and can be hard to predict.

#### **When do HAE symptoms begin?**

HAE symptoms usually begin during childhood or adolescence and often worsen at puberty. They may start as early as age 2. About 50% of people with type I or type II HAE develop symptoms by age 10. Attacks may happen more often and with greater severity after puberty. Nearly everyone with type I or type II HAE shows symptoms by age 20.

People who have HAE with normal C1-INH start to show symptoms a bit later in life — usually in their late teens or early adulthood.

#### **What are the triggers for HAE attacks?**

It’s not always clear what triggers an HAE attack. Some known triggers include:

* Physical injury or minor trauma
* Dental procedures
* Surgery
* Anxiety or emotional stress
* Viral infections, like a cold or flu
* Certain physical activities, like typing, hammering or shoveling

You may not be able to tell what triggers an attack in your child. But it may help to keep a journal of when the attacks happen and what’s going on at the time (for example, if your child is sick or dealing with a stressful situation).

### Hereditary angioedema causes

A mutation (change) to the *SERPING1* gene causes both type I and type II HAE. This gene tells your child’s body how to create the C1-INH protein. If your child has type I HAE, that means the mutation prevents their body from making enough C1-INH. If your child has type II HAE, their body can produce enough C1-INH, but the mutation prevents the protein from functioning normally.

Researchers continue to explore the causes of HAE with normal C1-INH. They know mutations to the following genes can cause it:

* *F12*
* *ANGPT1*
* *PLG*
* *KNG1*

In some cases, people have HAE without an identifiable gene mutation. Healthcare providers call this HAE-unknown.

The genetic mutations that cause HAE prevent certain proteins in your child’s body from working as they should. These proteins help fluids flow normally through your child’s tiny blood vessels, known as capillaries. But when these proteins aren’t working right, fluid leaks and builds up in the tissues surrounding your child’s blood vessels, leading to HAE symptoms.

#### **Hereditary angioedema inheritance**

HAE occurs through an autosomal dominant pattern of inheritance. This means just one copy of an abnormal gene is enough to cause the condition. A child can inherit this abnormal gene from either parent.

Most people with HAE have a family history of the condition. But sometimes, a genetic mutation can spontaneously occur (de novo or “new”). This means a mutation happens for the first time in a person without a known family history.

## Diagnosis and Tests

If your child has signs or symptoms of HAE, a provider will:

* Do a physical exam
* Talk to you about your child’s symptoms and their medical history
* Do blood tests to check their C1-INH levels and function
* In some cases, do genetic testing to look for the mutations that cause HAE

## Management and Treatment

There are two main categories of medications available for people with HAE:

* On-demand medications, like Berinert® or Kalbitor®. These treat an HAE attack right when it happens. Taking these medications as soon as possible after symptoms begin can reduce an attack’s severity and prevent life-threatening complications.
* Prophylactics (preventive medications), like Cinryze®, Haegarda® or Takhzyro®. These medications lower the risk of an attack happening. Your child’s provider may prescribe a prophylactic medication in the context of a known trigger (like a dental procedure). Or they may prescribe it long-term, depending on your child’s needs.

Experts agree that on-demand medications are crucial and potentially lifesaving. Your child needs these medications on hand at all times and in all settings (like home and school), even if they’re also taking prophylactic medications.

Your child’s provider will tell you exactly which medications your child needs, how they should receive them and when. They’ll also explain which medications your child is eligible to take according to their age. Be sure to follow their instructions closely and ask if anything is unclear.

#### **How soon after treatment will my child feel better?**

On-demand medication to help treat an HAE attack will help your child feel better relatively quickly. Once they begin treatment, their symptoms should improve within 30 minutes to two hours. Your child’s provider can tell you more about what to expect and how to manage at-home treatment.

### How do I take care of my child if they have HAE?

Seeing your child experience an HAE attack may make you feel helpless. But there’s a lot you can do to take care of your child before, during and after an attack:

* Keep on-demand medications available. These can be lifesaving. Make sure you can recognize when your child needs the medications. Also, be sure you know how to administer them. Your provider will tell you more.
* Don’t treat an HAE attack as an allergy. Medications like antihistamines and epinephrine — commonly used for allergies — won’t help an HAE attack. So, don’t give these medications to your child.
* Be aware of what triggers an attack. Triggers can vary from person to person. Keep a list of triggers that cause your child to have an attack and share these with their healthcare provider. Try to help your child avoid these triggers. When they’re unavoidable, ask your provider if prophylactic medications are appropriate.

### When should I seek care for my child?

Call a healthcare provider if:

* You believe your child has symptoms of hereditary angioedema
* Your child has new or changing symptoms associated with an HAE attack
* Your child’s medications aren’t working as expected

## Epidemiology

## Hereditary angioedema (HAE) is a rare disorder characterized by recurrent episodes of severe swelling in various locations throughout the body, including the face, extremities, gastrointestinal tract, and airways. Mutations in the *SERPING1* and *F12* genes result in 3 types of HAE: type 1 and 2 from *SERPING1* mutations and type 3 from *F12* mutations.

## Approximately 75% of individuals with HAE inherit the disorder in an autosomal dominant pattern, while the remaining 25% undergo spontaneous mutations in these genes and do not have a previous family history.

## These mutations encode for deficient or dysfunctional C1-esterase inhibitor proteins, which normally regulate inflammatory responses in the body. When these proteins are deficient or dysfunctional, inflammatory responses increase, allowing the excessive release of bradykinin, an inflammatory peptide that promotes vascular permeability. This leakage of fluid through blood vessel walls leads to the collection of fluid within the body’s tissues, becoming visible as excessive swelling.

## Incidence

## Hereditary angioedema accounts for approximately 2% of clinical angioedema cases, and angioedema affects around 20% of the global population.

## Prevalence

## Hereditary angioedema affects 1 in every 50,000 people globally, with reported prevalence ranges from 1:10,000 to 1:150,000. In the United States, HAE episodes result in 15,000 to 30,000 annual emergency department admissions.

## Diagnostic delays impact the accuracy of incidence and prevalence estimates. An online survey of US physicians revealed that the average time to diagnosis for HAE ranged from 0 to 6 months in 5.8% of cases to over 10 years in another 5.8% of cases. This survey demonstrated that less than 38% of patients obtained an accurate diagnosis of HAE within 1 to 3 years following symptom onset.

## Race

## Hereditary angioedema affects people of all races and ethnicities, with no bias toward any ethnic group.

## A study conducted in Norway estimated an HAE prevalence of 1.75 in every 100,000 people.

## Another study conducted in Spain estimated an HAE prevalence of 1.09 in every 100,000 people.

## Sex

## Hereditary angioedema occurs in men and women at equal rates, although women experience more severe attacks. Type 3 HAE was initially believed to occur only in women, however, reports of families with men who have type 3 HAE exist.

## Type 3 HAE attacks often follow elevations in estrogen levels in women during pregnancy or in those taking estrogen hormone replacement therapy, which may offer an explanation as to why type 3 attacks occur more frequently in women.

## Age

## Although mutations in the *SERPING1* and *F12* genes are present at birth in many patients with HAE, symptoms caused by C1-esterase inhibitor protein deficiency usually appear in the first or second decade of life. The severity of attacks increases around puberty, whereas swelling during childhood tends to be milder, less frequent, and less visible as abdominal symptoms are more common.

## In one study, researchers analyzed symptom presentation in 209 patients with HAE. In most patients, symptoms began during childhood or adolescence, with an average age of onset of 11.2±7.7 years (range, 1-40 years). Initial HAE attacks began in the first decade of life in 107 (51.2%) patients, in the second decade of life in 79 (37.8%) patients, and at later ages in 23 (11%) patients. In 15 (7.2%) patients, symptoms began within the first year of life. Patients with an earlier onset of symptoms typically experienced a more severe course of the disease than those with a later onset.

## Spontaneously acquired forms of HAE typically present after the fourth decade of life.11 Although HAE causes lifelong symptoms, some people with HAE report decreasing severity of symptoms with aging.

## Differential Diagnosis

## Several disorders have clinical features similar to those of hereditary angioedema (HAE). Cutaneous and/or upper airway edema without urticaria (wheals) can be seen in several diseases.

## Anaphylaxis and Acute Hypersensitivity (Allergic) Reactions

## Anaphylaxis, classified as a type 1 hypersensitivity reaction, is a relatively common medical emergency. In type 1 hypersensitivity reactions, which are mediated by immunoglobulin E, the degranulation of sensitized basophils and mast cells leads to the release of numerous vascular mediators upon re-exposure to a specific antigen. The mediators include histamine, tryptase, carboxypeptidase A, and proteoglycans. Activation of phospholipase A, lipoxygenases, and cyclooxygenases results in the formation of arachidonic acid-derived metabolites such as leukotrienes, prostaglandins, and platelet-activating factors. The mechanism of action behind the swelling associated with HAE is distinct and does not involve histamine or any of the mediators previously listed. Rather, HAE attacks are mediated primarily by the release of bradykinin. Key features that distinguish anaphylaxis from HAE are the following:

1. Usually, a clear trigger can be associated with anaphylaxis (eg, bee sting, food allergen, medication). It is noteworthy that only one group of medications, the angiotensin receptor blockers, may precipitate an HAE attack.
2. Urticaria (wheals), flushing, and itching are common in allergic reactions, whereas HAE attacks characteristically lack wheals and are not pruritic.
3. Usually, a patient with HAE has a clear family history of recurrent episodes of angioedema.
4. HAE does not respond to antihistamines, epinephrine, or corticosteroids.

## Non-hereditary (Acquired) Angioedema

## Acquired angioedema (C1-INH-AAE) is a deficiency of C1-esterase inhibitor (C1-INH) acquired through the consumption of C1-INH. Like HAE, it is not mediated by IgE and is characterized by recurrent episodes of asymmetric edema of the face, lips, tongue, limbs, genitals, upper airway, and gastrointestinal tract without urticaria. C1-INH-AAE is classified into 2 types.3 Type 1 C1-INH-AAE is usually associated with a lymphoproliferative malignancy causing the production of complement-activating factors, idiotype/anti-idiotype antibodies against C1-INH, or other destructive immune complexes that compromise C1-INH function. The most common associated malignancy is B-cell lymphoma, which produces anti-idiotype antibodies that cause C1-INH deficiency. In type 2 C1-INH-AAE, autoantibodies against C1-INH are produced for unknown reasons.In general, the onset of C1-INH-AAE is later (usually in individuals at least 40 years old) than that of HAE. Additionally, a clear family history of recurrent episodes of angioedema is usually lacking. The clinician should look for a history of lymphoproliferative disease in a patient with type 1 C1-INH-AAE. A determination of the C1 esterase and C4 levels makes it possible to differentiate HAE and AAE from angioedema with other causes.5 The serum C1q level is decreased in C1-INH-AAE, and measurement of this level is a useful laboratory study to differentiate between the 2 conditions.

## ACE Inhibitor-Induced Angioedema

## Angiotensin-converting enzyme (ACE) inhibitors are drugs that act at the level of the renin-angiotensin-aldosterone system to reduce systemic blood pressure. In addition to inhibiting the conversion by ACE of angiotensin I to angiotensin II, ACE inhibitors prevent the catabolism of bradykinin and substance P by ACE. Patients with intrinsic defects in the degradation of bradykinin are prone to the development of ACE inhibitor-induced angioedema. The overall incidence of ACE inhibitor-induced angioedema is low, ranging from 1 to 7 events per 1000 patients, and ACE inhibitor-induced angioedema is most likely to occur during the first month of treatment with an ACE inhibitor. The condition is more frequent in African Americans, individuals who have a history of drug rash or seasonal allergies, persons older than 40 years, smokers, women, and those on immunosuppressive therapy. The risk for ACE inhibitor-induced angioedema is highest in patients taking enalapril.

## Other HAE Differential Diagnoses

## Thyroid disorders. Thyroid dysfunction may cause cutaneous manifestations resembling those of angioedema, including non pitting, nonpruritic edema of the extremities without urticaria. The changes are gradual, occur over weeks to months, and are not episodic; in contrast, HAE attacks develop acutely over minutes.

## Allergic contact dermatitis. Pruritus is a hallmark feature of contact dermatitis and responds to corticosteroids and antihistamines, unlike HAE.

## Cheilitis granulomatosa (Miescher cheilitis) and Melkersson-Rosenthal syndrome. These are rare conditions characterized by persistent angioedema of the lips. Melkersson-Rosenthal syndrome is characterized by the triad of familial relapsing peripheral facial palsy, facial edema, and lingua plicata. Miescher cheilitis is considered to be a monosymptomatic form of Melkersson-Rosenthal syndrome; it is described as an association of recurrent labial and/or facial edema, relapsing facial paralysis, and fissured tongue. Complement studies are normal in both conditions.

## GUIDELINES

The guidelines recommend that all patients with suspected type 1 or type 2 HAE undergo tests to measure blood levels of C4 and C1-INH as well as C1-INH function. Confirmation of diagnosis is recommended for patients testing positive in any of the previous assessments. Patients with normal C1-INH levels and activity should undergo further evaluation of genetic variations that may be responsible for the disease.

On-demand treatment should be considered for all HAE attacks, and any episode affecting the upper airway must be treated. All attacks should be treated early with intravenous C1-INH, ecallantide, or icatibant. Procedures like endotracheal intubation, esophagogastroduodenoscopy, or bronchoscopy may precipitate angioedema near the site of intervention within 48 h. Rapid treatment with an effective HAE on-demand medication can lower the mortality associated with upper airway angioedema. Early intubation or tracheostomy are recommended in patients with progressive edema of the upper airway. It is recommended that patients with HAE always carry enough medication for on-demand treatment of at least 2 HAE episodes.

Short-term prophylaxis with C1-INH as a first-line therapy is recommended before medical procedures such as dental surgery. For any situation to which the patient may be exposed that is considered a potential trigger of an episode, a prophylactic approach is also recommended.Long-term prophylaxis with C1-INH, berotralstat, or lanadelumab as a first-line therapy can be also considered for patients with HAE at every follow-up visit and after the evaluation of disease activity and control. Androgens are only recommended as a second-line therapy for long-term prophylaxis, while antifibrinolytics are not recommended in these situations. Monitoring patients undergoing long-term prophylaxis is also suggested.

Screening for HAE is recommended for all family members of patients with HAE, and it should be carried as soon as possible in children.2 C1-INH or icatibant should be used to treat HAE episodes in children under 12 years of age. Plasma-derived C1-INH is also recommended for women who are pregnant or lactating.

It is recommended that all patients consult specialists with expertise in HAE and follow an established action plan. Patients should be educated on potential triggers for HAE episodes, and they may self-administer on-demand therapy when properly taught.

The US HAEA MAB recommends that serum levels of C4 and C1-INH and the functionality of C1-INH are determined for HAE diagnosis. To reach a diagnosis of HAE in the presence of normal C1-INH levels, additional genetic testing for mutations in genes encoding for factor XII, plasminogen, angiopoietin-1, and kininogen should be performed. Screening for HAE is recommended for all first-degree relatives of the patient. An early diagnosis in children is important for reducing morbidity and mortality.

To address HAE attacks, patients must carry effective on-demand medication. All HAE attacks should be treated. C1-INH replacement therapy, ecallantide, or icatibant should be the first-line treatment in these episodes. When possible, on-demand therapy should be self-administered or administered by a caregiver.

Short-term prophylaxis is recommended for patients who are at risk of experiencing an episode following exposure to a known trigger (including dental surgery). Long-term prophylaxis should be performed using C1-INH or lanadelumab as the first-line treatment; however, in cases of HAE with normal levels of C1-INH, initial treatment should include progestin-based medication or an antifibrinolytic. The use of C1-INH is recommended for pregnant or breastfeeding women, either as prophylactic or on-demand therapy. If first-line therapies are not available, HAE attacks can be treated with solvent detergent-treated plasma (SDP). Fresh frozen plasma (FFP) can also be used to treat HAE attacks, if SDP is not available.

Patients with HAE must follow individualized management plans after consulting HAE specialists. These plans must detail the use of effective on-demand therapy, the potential use of prophylactic medication, and the prophylactic procedure before medical procedures or exposure to triggers.

Regular follow-ups are important, and their frequency varies according to the status of the disease. Patients with well-controlled HAE may follow up every 6 to 12 months. Patients are to be encouraged to keep a registry of their symptoms, medications used, and adverse effects. This information should be shared and reviewed with the care team.

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### Guillain-Barré syndrome

**DEFINITION AND DESCRIPTION**

Guillain-Barré syndrome (pronounced “ghee-AHN buh-RAY”) is a rare autoimmune condition in which your immune system attacks your peripheral nerves. It leads to symptoms like numbness, tingling and muscle weakness that can progress to paralysis. But with treatment, most people fully recover from the condition.

#### **Who typically gets Guillain Barré syndrome?**

Guillain-Barré syndrome (GBS) can occur at any age, but it most commonly affects people between 30 and 50.

## Symptoms and Causes

Guillain-Barré syndrome is a rare autoimmune condition in which your immune system attacks your peripheral nerves.

### symptoms of Guillain-Barré syndrome

Guillain-Barré syndrome affects your peripheral nerves, which control muscle movement, pain signals, and temperature and touch sensations. Thus, GBS causes issues related to these functions.

The first symptoms of Guillain-Barré syndrome are muscle weakness and/or tingling sensations (paresthesia). These symptoms typically come on suddenly. They usually affect both sides of your body and start in your feet and legs and spread up to your arms and face. Muscle weakness in your legs may make it difficult to walk or climb stairs.

The severity of GBS can range from very mild to severe. Depending on the severity of the condition, other symptoms may include:

* Deep muscular pain in your back and/or legs.
* Paralysis of your legs, arms and/or facial muscles. In severe cases, you may experience near-total paralysis.
* Chest muscle weakness, which can make it difficult to breathe. This affects about 1 in 3 people with GBS.
* Difficulty speaking and swallowing (dysphagia).
* Difficulty moving your eyes and vision issues.

The symptoms of GBS can progress over hours, days or a few weeks. Most people reach the most severe stage of weakness within the first two weeks after symptoms appear. By the third week, about 90% of people are at their weakest.

If you experience sudden muscle weakness that gets worse over hours or days, see a healthcare provider right away. It’s important to start treatment for GBS as soon as possible.

#### **Complications of Guillain-Barré syndrome**

If GBS affects your autonomic nerves, it can lead to life-threatening complications. Your autonomic nervous system controls the automatic functions of your body that you need to survive, like your heart rate, blood pressure and digestion. When you have issues with this system, it’s called dysautonomia.

Complications due to GBS-related dysautonomia can include:

* Cardiac arrhythmias.
* Unstable blood pressure.
* Digestion issues (gastrointestinal stasis).
* Bladder control issues, like urinary retention.

### Causes of Guillain-Barré syndrome

Guillain-Barré syndrome is a post-infectious, immune-mediated neuropathy. This means:

* Post-infectious: The condition typically develops after you’ve had some type of infection (“post-” means “after”). In up to 70% of people who’ve had GBS, their symptoms started within one to six weeks of an illness. Researchers don’t know why GBS affects some people after they get sick and not others.
* Immune-mediated: An immune-mediated condition results from an abnormal immune system response. For some people, after they get sick, their immune system responds abnormally and attacks and damages their peripheral nerves, leading to GBS. This is another way of saying it’s an autoimmune condition. But unlike most autoimmune conditions, GBS isn’t chronic (lifelong).
* Neuropathy: “Neuropathy” is an umbrella term for conditions that damage your nerves. In the case of GBS, it’s peripheral nerves. Your immune system attacks your nerves rapidly over days and causes loss of myelin — the “insulation” of your nerves.

Researchers have identified some infections and other immune system-related factors that can trigger Guillain-Barré syndrome, including:

* Diarrhea or a respiratory infection: About 2 in 3 people with GBS had diarrhea or a respiratory infection weeks before developing GBS symptoms. Infection with the bacteria *Campylobacter jejuni*, which causes diarrhea, is one of the most common triggers of GBS.
* Viral infections: Some people with GBS have had the flu or infections with cytomegalovirus, Epstein-Barr virus, Zika virus or other viruses.
* Vaccines: In very rare cases, people have developed GBS in the days or weeks after getting certain vaccines. It’s important to know that the benefits of vaccination far outweigh the possible risks. Studies show that you have a greater chance of getting GBS after getting the flu than you do after getting vaccinated against the flu.
* Surgery: Very rarely, GBS can develop after any surgery.

## Diagnosis and Tests

Healthcare providers typically diagnose Guillain-Barré syndrome based on your symptoms and medical history. They’ll ask how and when your symptoms started and if you’ve been sick recently. They’ll also do physical and neurological exams to look for signs of muscle weakness and weak or absent deep-tendon reflexes (hyporeflexia or areflexia).

However, many other neurological conditions share the same symptoms as GBS. So, your provider will likely do other tests to rule out other possible conditions. These tests may include:

* Electromyography (EMG) and nerve conduction tests: These tests evaluate the health and function of your skeletal muscles and the nerves that control them.
* Spinal tap (lumbar puncture): For this procedure, your healthcare provider inserts a needle into your lower back to get a sample of cerebrospinal fluid (CSF). They send the sample to a lab where a pathologist examines the substances in it. In about 80% of GBS cases, there’s a normal amount of white blood cells and an elevated CSF protein level. Other abnormalities in CSF may point to other conditions.
* Imaging test: Your provider may recommend an MRI (magnetic resonance imaging) of your spine.

## Management and Treatment

If you have Guillain-Barré syndrome, you’ll likely need to receive medical care in a hospital’s intensive care unit (ICU). This is so your healthcare team can monitor you for any complications of GBS, like difficulty breathing or blood pressure fluctuations.

There’s no known cure for Guillain-Barré syndrome. But some therapies can lessen the severity of the condition and shorten your recovery time. The main treatment for GBS includes one of two options:

* Plasma exchange (plasmapheresis): In this treatment, a machine separates the plasma from your blood, treats it, and then returns the plasma and blood to your body. Plasma exchange filters out the antibodies in your plasma that are attacking your nerves.
* Intravenous immunoglobulin therapy (IVIG): This treatment involves intravenous (IV) injections of immunoglobulins, which are proteins that your immune system naturally makes to attack invading organisms. The immunoglobulins come from a collection of thousands of healthy donors. IVIG can lessen your immune system’s attack on your nerves.

Both of these treatments usually shorten your recovery time if you start one of them within two weeks of developing GBS symptoms.

#### **Treatment for complications**

Complications of GBS can develop if the condition affects your autonomic nerves, causing near-total paralysis. Your healthcare team will carefully monitor your breathing, heart rate and blood pressure. They’ll act quickly if any complications develop. Examples of treatments for complications include:

* Respiratory care: If GBS affects the muscles you need for breathing, you may need mechanical ventilation. Respiratory failure affects up to 30% of people with GBS.
* Blood clot prevention: Your provider may give you heparin (an anticoagulant) to help prevent deep vein thrombosis. This can happen if you have near-total paralysis and are in a medical bed for an extended period of time.
* IV fluids and tube feeding: If it’s difficult to swallow, you may need IV fluids to prevent dehydration and a nasogastric tube to prevent malnutrition. These can also help prevent aspiration pneumonia.

#### **Rehabilitation**

As you begin to improve, your healthcare team may transfer you to a rehabilitation setting. Here, you’ll work with physical therapists and other therapists to regain strength and resume activities of daily living. Types of therapy include:

* Physical therapy: This helps you improve how your body moves. A physical therapist will help you manage symptoms like pain, stiffness and discomfort. They’ll also help you with exercises to regain muscle strength.
* Occupational therapy: This type of therapy helps you improve your ability to do daily tasks. An occupational therapist will help you learn how to stand, sit, move or use different tools to participate in your activities safely.
* Speech therapy: If GBS affects the muscles in your mouth or throat, a speech-language pathologist can help you regain skills of swallowing and speaking.
* Mobility aids: Devices such as canes, braces, walkers and wheelchairs can improve your mobility and help prevent falls. They can also help reduce fatigue.

## Outlook / Prognosis

The prognosis (outlook) for Guillain-Barré syndrome can vary. Most people with GBS improve considerably over a period of months. But about 30% of adults — and even more children — have some remaining muscle weakness three years after diagnosis.

In the majority of cases, the symptoms of Guillain-Barré syndrome improve significantly with time and treatment. Most people start to recover two to three weeks after symptoms first start. The length of total recovery can vary from months to a year or more depending on the severity.

#### **Guillain-Barré syndrome life expectancy**

People who recover from Guillain-Barrésyndrome have a normal life expectancy. Less than 2% of people die from GBS in the acute phase — when symptoms are at their worst. Common causes of death related to GBS include:

* Pneumonia.
* Sepsis.
* Acute respiratory distress syndrome (ARDS).
* Blood clots in your lungs (pulmonary embolism).
* Cardiac arrest.

## Prevention

In most cases, Guillain-Barré syndrome isn’t preventable. Researchers don’t know why some people develop GBS after they get sick and others don’t. But one way you can try to lower your risk of GBS is to stay as healthy as possible. These steps can help:

* Wash your hands often.
* Keep away from those who have the stomach flu or other infections.
* Eat healthily and exercise regularly to help boost your immune system.
* Clean and disinfect common surfaces such as tables and countertops, toys, door handles, phones and bathroom fixtures.
* Stay up-to-date with all vaccines.

## Living With

The recovery process for Guillain-Barré syndrome can be slow for some. Don’t hesitate to lean on loved ones for support — both physically and emotionally. Your healthcare team will also be by your side.

Suddenly and unexpectedly developing weakness or paralysis can be overwhelming. Consider talking to a mental health professional, like a psychologist, if GBS is causing distress. A support group may also help you relate to others who are going through similar experiences and feelings.

**Epidemiology of Guillain-Barré Syndrome (GBS)**

* Incidence:
  + The overall global incidence of GBS ranges between 1.1 and 1.8 cases per 100,000 person-years.
  + A recent meta-analysis estimated a pooled incidence of about 1.12 per 100,000 person-years (95% CI: 0.98 to 1.27)
  + Incidence increases with age, especially after 50 years, rising from about 1.7 to 3.3 per 100,000 person-years in older adults.
  + Incidence varies by region, with cohort studies reporting a wide range from 0.3 to 6.6 per 100,000 person-years depending on the population and study design.
  + Higher incidence rates have been reported in some countries:
    - United States: ~1.1 per 100,000
    - Canada: ~1.6 per 100,000
    - United Kingdom: ~1.3 per 100,000
    - Denmark: ~1.6 per 100,000
    - Taiwan: ~1.7 per 100,000 (with rising trends)
    - Korea: increased from 1.28 to 1.82 per 100,000 between 2010 and 2016.
* Prevalence and Burden:
  + In 2019, there were approximately 150,000 cases of GBS worldwide, with an age-standardized point prevalence of 1.9 per 100,000 population.
  + GBS caused about 44,000 years lived with disability (YLDs) globally in 2019
  + The age-standardized prevalence and disability burden have increased by about 6.4% since 1990
  + Higher prevalence and burden are observed in high-income Asia Pacific regions (e.g., Japan) compared to East Asia (e.g., China)
* Demographics:
  + GBS affects all ages but incidence increases with age, especially after 50 years.
  + Males have a slightly higher incidence and prevalence than females in all age groups.
  + Geographic variation is noted, with higher incidence and prevalence in developed regions, possibly reflecting better diagnosis and reporting.
* Outbreaks and Clusters:
  + Epidemics have been reported, such as a notable outbreak in Peru in 2019 with about 700 cases.
  + Seasonal variation and associations with preceding infections (e.g., Campylobacter jejuni, viruses) are common.

## Diagnostic Considerations

Problems to consider in the differential diagnosis of Guillain-Barré syndrome (GBS) include the following:

* Acute myelopathy (eg, from compression, transverse myelitis, vascular injury)
* Chronic inflammatory demyelinating polyneuropathy
* Conversion disorder/hysterical paralysis
* Human immunodeficiency virus (HIV) peripheral neuropathy
* Neurotoxic fish or shellfish poisoning
* Paraneoplastic neuropathy
* Poliomyelitis
* Porphyria polyneuropathy
* Spinal cord compression
* Spinal cord syndromes, particularly postinfection
* Tick paralysis
* Toxic neuropathies (eg, arsenic, thallium, organophosphates, lead)
* Vasculitic neuropathies
* Vitamin deficiency (eg, vitamin B-12, folate, thiamine)
* West Nile encephalitis
* Bilateral strokes
* Acute cerebellar ataxia syndromes
* Posterior fossa structural lesion

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## Differential Diagnoses

* Botulism
* Cauda Equina and Conus Medullaris Syndromes
* Chronic Inflammatory Demyelinating Polyradiculoneuropathy
* Emergent Management of Myasthenia Gravis
* Heavy Metal Toxicity
* Lyme Disease
* Metabolic Myopathies
* Multiple Sclerosis
* Nutritional Neuropathy
* Vasculitic Neuropathy

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### Paraneoplastic syndrome

**Definition and description**

A paraneoplastic syndrome is a set of signs and symptoms that can occur when you have cancer. The symptoms develop when a malignant tumor causes changes in your body that aren’t directly caused by the cancer itself. The tumor may secrete a hormone or protein that affects a particular body system. Often with paraneoplastic syndromes, your immune system releases antibodies to destroy the tumor. During this process, the antibodies also damage healthy cells (autoimmune response).

Paraneoplastic syndromes can affect multiple body systems and organs, including your nervous system, endocrine system (hormones), kidneys, bones, joints, skin and blood, etc.

Often, the symptoms of paraneoplastic syndrome are the first signs of cancer.

#### **Who is affected by paraneoplastic syndromes?**

You’re more likely to have paraneoplastic syndrome if you’re middle-aged or older and you have lung, lymphatic, ovarian or breast cancer. The same factors that increase your cancer risk can increase your chances of developing a paraneoplastic syndrome.

##### **How common are paraneoplastic syndromes?**

About 8% to 20% of people with cancer develop paraneoplastic syndromes.

#### **Cancers are associated with paraneoplastic syndromes**

Anyone with a cancerous tumor can develop a paraneoplastic syndrome. The types of cancer most commonly associated with paraneoplastic syndromes are:

* Breast cancer.
* Stomach cancer.
* Leukemia.
* Lymphoma.
* Lung cancer (especially small-cell lung cancer).
* Ovarian cancer.
* Pancreatic cancer.
* Prostate cancer.
* Kidney cancer.
* Testicular cancer.

## Causes of paraneoplastic syndromes

Some cancerous tumors secrete substances, like hormones or proteins, that cause certain organs in your body to work atypically. As a result, you may experience symptoms that wouldn’t occur without the tumor. These substances can permanently damage an organ or system without treatment.

Often, paraneoplastic syndromes occur because your body’s immune system mistakenly harms healthy tissue. Your immune system makes a substance called antibodies. Antibodies protect you from disease by identifying and destroying abnormal cells, like cancer cells. Sometimes, the signals get crossed, and antibodies attack healthy cells and tissue instead, causing symptoms associated with a paraneoplastic syndrome.

### Symptoms of paraneoplastic syndromes

Symptoms of paraneoplastic syndromes vary depending on the organ systems affected. In more than half of cases (60%), people experience symptoms before receiving a cancer diagnosis. Identifying a paraneoplastic syndrome early can help your healthcare provider diagnose cancer in its early stages when it’s easiest to treat.

Common symptoms of a paraneoplastic syndrome include:

* Fever.
* Loss of appetite and weight.
* Night sweats.

Paraneoplastic syndromes that affect particular organs or body systems may cause system-specific symptoms.

#### **Nervous system**

Paraneoplastic syndromes affecting your central nervous system (brain, spinal cord) and your peripheral nervous system (nerves outside of your brain and spinal cord) may cause:

* Dizziness.
* Double vision.
* Speech difficulty.
* Memory loss.
* Seizures.
* Muscle weakness.
* Reduced reflexes, sensation or coordination.
* Loss of feeling in your arms and legs.

#### **Endocrine system**

Paraneoplastic syndromes affecting your endocrine system may cause:

* Fatigue.
* High blood pressure.
* Muscle weakness.
* Nausea and vomiting.
* Unexplained weight gain.

#### **Joints, bones and muscles (rheumatologic)**

Paraneoplastic syndromes affecting your joints, bones, muscles and connective tissue may cause:

* Arthritis.
* Joint pain, swelling or stiffness.

#### **Skin**

Paraneoplastic syndromes affecting your skin may cause:

* Itching.
* Flushing (redness).
* Thickened skin.
* Benign (noncancerous) skin growths.

### Types of paraneoplastic syndromes

There are several paraneoplastic syndromes, including those that affect your nervous system, endocrine system, joints, blood, skin, kidneys, etc.

#### **Nervous system paraneoplastic syndromes**

Examples include:

* Cerebellar degeneration.
* Dysautonomia.
* Encephalitis.
* Encephalomyelitis.
* Lambert-Eaton myasthenic syndrome (LEMS).
* Myasthenia gravis (MG).
* Myelopathy.
* Neuromyotonia.
* Opsoclonus-myoclonus syndrome.
* Neuropathy (peripheral neuropathy).
* Stiff-person syndrome.

#### **Endocrine system paraneoplastic syndromes**

Examples include:

* Cushing’s syndrome.
* Hypercalcemia.
* Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH).

#### **Rheumatic paraneoplastic syndromes**

Examples include:

* Eosinophilic fasciitis.
* Erythromelalgia.
* Hypertrophic osteoarthropathy.
* Palmar fasciitis.
* Paraneoplastic polyarthritis.

#### **Blood paraneoplastic syndromes**

Examples include:

* Paraneoplastic erythrocytosis.
* Paraneoplastic thrombocytosis.

#### **Skin paraneoplastic syndromes**

Examples include:

* Acanthosis nigricans.
* Dermatomyositis.
* Leukocytoclastic vasculitis.
* Paraneoplastic pemphigus.
* Sweet syndrome.

Paraneoplastic glomerulonephritis is a paraneoplastic syndrome that affects your kidneys.

## Diagnosis and Tests

Your healthcare provider will diagnose paraneoplastic syndromes with a medical history, physical exam and several tests.

* Neurological exam: Paraneoplastic syndromes often affect your nervous system, impacting your brain and muscle function. Your provider may ask you to perform specific tasks to check how your nervous system functions. They’ll want to judge any change in your abilities related to strength, memory and coordination.
* Imaging: Your provider may use imaging tests such as CT scans, MRIs and ultrasounds to look for a tumor that may be causing symptoms.
* Blood tests: Blood tests can reveal suspicious findings that suggest a tumor or that confirm you have antibodies linked to paraneoplastic syndromes. Blood tests can also help your provider rule out other conditions that may be causing your symptoms, like an infection, a hormone disorder or a metabolic disorder.
* Spinal tap: In some instances, your provider may perform a spinal tap (lumbar puncture) to test your cerebrospinal fluid for signs of antibodies attacking healthy cells. During a spinal tap, your provider inserts a needle into your lower back to withdraw a fluid sample. Later, your healthcare provider will test the liquid for antibodies.

## Management and Treatment

Your healthcare provider will treat the underlying cancer that’s causing your symptoms. They’ll also work to manage your symptoms to decrease any damage to your body’s organs or systems.

Therapies used to manage paraneoplastic syndromes include:

* Corticosteroids: Medications, such as cortisone or prednisone, that reduce inflammation (swelling).
* Immunosuppression: Drugs that decrease your body’s immune response. The drug therapies your provider prescribes will be tailored to your paraneoplastic syndrome.
* Intravenous immunoglobulin: Treatment that destroys the harmful antibodies causing the syndrome. During the procedure, your provider gives you a shot of healthy antibodies that destroy the harmful ones.
* Plasmapheresis: A procedure that decreases the number of antibodies by removing plasma (liquid) from your blood. The plasma contains the antibodies that damage healthy tissue.
* Physical and speech therapy: Muscle exercises that can help improve functions like speech and movement. You may need this therapy if you have a neurological paraneoplastic syndrome.

## Outlook / Prognosis

Your prognosis mostly depends on your cancer. In some instances, paraneoplastic syndromes cause mild, temporary symptoms. In others, paraneoplastic syndromes cause severe symptoms that must be managed long-term.

Talk to your healthcare provider about how your stage of cancer and response to treatment will affect your prognosis.

### What complications are associated with paraneoplastic syndromes?

You may experience a broad range of complications, some of which are minor and some that may be more serious or even life-threatening without treatment. Your healthcare provider will discuss potential complications and treatment options with you.

## Living With

Contact your healthcare provider if you notice symptoms of a paraneoplastic syndrome that don’t have a clear cause. If you’re experiencing symptoms and you’ve been treated for cancer within the last five years, it’s a good idea to get re-screened. Re-screening can alert your provider that the cancer has returned.

DIFFERENTIAL DIAGNOSIS

**Toxic-metabolic encephalopathy:** rule out underlying infections and electrolyte abnormalities.

**Infectious Encephalitis:** rule out any bacterial, viral, or fungal etiologies.

**Personality disorders:** patients may have underlying depression.

**Myelitis:** rule out infectious or inflammatory causes.

**Bone marrow failure:** rule out other causes, may need a bone marrow biopsy.

**Chronic fatigue syndrome:** patients may present with non-specific symptoms. They need close follow-ups.

**Mixed connective tissue disorder:** check for specific antibodies, anti-ribonucleic acid Ab ( anti-RNP). They may have co-existing rheumatological disorders like systemic lupus erythematosus, scleroderma, and polymyositis.

**Non-tumor-related dermatomyositis:** check for specific antibodies; they have anti-Jo-1 and anti-Mi-2 antibodies. Rule out ovarian, breast, and gastrointestinal cancers.

**Polymyalgia rheumatica:** mostly seen in elderly patients and involves shoulder girdle. These patients have elevated erythrocyte sedimentation rate (ESR) and respond dramatically to low-dose steroids.

**Nephrotic syndrome:** rule out all other etiologies.

**EPIDEMIOLOGY**

The precise incidence and prevalence of paraneoplastic syndrome are unknown because of the rarity of the disease; however, it can occur with any malignancy. A literature review suggests that paraneoplastic syndrome occurs in up to 8% of cancer patients. Neurological manifestations in the form of neuropathies are the most common presentation. Males and females are affected equally.

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### Lymphoproliferative disorders

**Definition and description**

Lymphoproliferative disorders (LPDs) are groups of rare diseases that happen when lymphocytes, a type of white blood cell, don’t work as they should. Your lymphocytes help your body’s immune system fight intruders like cancer, viruses and bacteria.

Some LPDs are immunologic, meaning they affect how your immune system reacts to intruders. Other types are lymphoid blood cancers, like leukemia and lymphoma, which are serious illnesses that happen when abnormal lymphocytes multiply uncontrollably. In all, more than a dozen different diseases are lymphoproliferative disorders.

### Types of lymphoproliferative disorders

There are two groups of lymphoproliferative disorders: immunologic disorders and lymphoid blood cancers. Lymphoid blood cancers include B-cell and T-cell cancers.

#### **Immunologic disorders**

Immunologic disorders affect how your immune system reacts to intruders. People with these LPDs have an increased risk of developing lymphoma:

* X-linked lymphoproliferative disorder (XLP): If you have this disorder, exposure to Epstein-Barr virus may lead to lymphoma.
* Autoimmune lymphoproliferative syndrome (ALPS): In ALPS, large numbers of lymphocytes build up in your lymph nodes, spleen and liver, making your lymph nodes, spleen and liver get bigger.
* Post-transplant lymphoproliferative disorders (PTLD): PTLDs are rare but serious complications of solid organ transplants or allogeneic (donated) stem cell transplantations that can happen if you or the organ or stem cell donor have B-cells with Epstein-Barr virus.

#### **Lymphoid blood cancers**

These disorders happen when white blood cells change and become abnormal cells that multiply in your bone marrow and blood. These cells are B-cells, T-cells and natural killer cells. Healthcare providers may call these conditions lymphocytic disorders. In some cases, diseases involving these white blood cells are curable. But they’re serious illnesses that may be life-threatening.

##### **B-cell non-Hodgkin lymphomas**

Some common non-Hodgkin lymphomas that are lymphoproliferative disorders include:

* Diffuse large B-cell lymphoma.
* Follicular lymphoma.
* Mantle cell lymphoma.

##### **B-cell lymphocytic leukemias**

These disorders include:

* Chronic lymphocytic leukemia (CLL): Normal B-cells in your bone marrow multiply, crowding out healthy blood cells and platelets.
* B-cell prolymphocytic leukemia: Abnormal B-cells form in your bone marrow so there’s no room for healthy blood cells and platelets.
* Hairy cell leukemia: Your bone marrow makes abnormal white blood cells that multiply. The abnormal cells appear hairy when viewed under a microscope.

##### **T-cell non-Hodgkin lymphomas**

T-cell lymphocytic disorders are generally divided into systemic and cutaneous T-cell disorders:

* Systemic T-cell lymphomas affect your lymph nodes, spleen, bone marrow, blood and other organs in your body.
* Cutaneous T-cell lymphomas mainly affect your skin, but in some cases, can involve lymph nodes, blood, bone marrow and other internal organs.

###### **Systemic T-cell lymphomas**

There are many kinds of systemic T-cell lymphomas. Common types include:

* Peripheral T-cell lymphoma not otherwise specified (PTCL NOS).
* Angioimmunoblastic T-cell lymphoma (AITL).
* Anaplastic large cell lymphoma.
* Follicular helper T-cell lymphoma (FHTCL).
* Follicular T-cell lymphoma (FTCL).

Some rare types include:

* Hepatosplenic T-cell lymphoma (HSTCL).
* Enteropathy-associated T-cell lymphoma (EATL).
* Monomorphic epithelioid tropic intestinal T-cell lymphoma (MEITL).

Some systemic T-cell lymphomas are called chronic T-cell leukemias. Examples are:

* T-cell prolymphocytic leukemia (T-PLL).
* T-cell large granular lymphocytic leukemia (T-LGL).

###### **Cutaneous T-cell lymphomas**

The two most common subtypes of cutaneous T-cell lymphoma are:

* Mycosis fungoides.
* Sézary syndrome.

##### **NK-cell lymphocytic disorders**

These are very rare disorders that affect NK cells. They include:

* Extranodal NK T-cell lymphoma nasal type.
* Aggressive NK-cell leukemia (AKNL).
* NK-cell large granular lymphocytic leukemia (NK-LGL).

## Symptoms and Causes

The symptoms vary widely depending on the type of lymphoproliferative disorder you have. Some common symptoms of LPDs are:

* Drenching night sweats.
* Enlarged or swollen lymph nodes, liver or spleen.
* Excessive or unusual bleeding and bruising.
* Fatigue.
* Fever.
* Frequent viral infections.
* Loss of appetite.
* Unexplained weight loss.

### Causes lymphoproliferative disorders

There’s no single cause for most lymphoproliferative disorders. Potential causes of LPDs include:

* Infections: Epstein-Barr virus or *H. pylori* may cause some types of lymphoproliferative disorders.
* Certain autoimmune diseases: Rheumatoid arthritis or lupus may cause some types of marginal zone lymphomas.
* Medication: Immunosuppressant drugs may lead to hepatosplenic T-cell lymphoma.
* Certain genetic mutations: Rarely, you may inherit a mutation that causes a lymphoproliferative disorder. For example, people with X-linked lymphoproliferative disorder carry one of two genetic mutations that cause them to have an unusually severe reaction to the Epstein-Barr virus that can lead to lymphoma. Likewise, genetic mutations that affect white blood cell growth play a role in lymphoma and leukemia.

## Diagnosis and Tests

There are many different types of LPDs, so the diagnosis process focuses on finding out which disorder is causing your symptoms.

To do that, a healthcare provider will consider symptoms like swollen lymph nodes and signs that your liver or spleen is bigger than normal. They’ll also ask about your medical history.

They may order the following tests:

* Biopsy: Your provider may order a bone marrow biopsy to look for signs of blood cancer like leukemia or lymphoma.
* Blood tests: Blood tests may include a complete blood count (CBC), comprehensive metabolic panel (CMP), Epstein-Barr antibody test, hepatitis test, human immunodeficiency virus HIV test or lactate dehydrogenase (LDH) test.
* Imaging tests: Tests may include computed tomography (CT) scans and positron emission tomography (PET) scans.
* Lab tests: Your provider may order a flow cytometry test to help diagnose specific disorders.

## Management and Treatment

LPD treatment depends on the specific disorder. For example, if you have a type of leukemia or lymphoma, your treatments may include:

* Chemotherapy.
* Immunotherapy.
* Radiation therapy.
* Stem cell (bone marrow) transplant.
* Targeted therapy.

## Outlook / Prognosis

It depends. There are many types of LPDs and many factors that may affect your prognosis, or what you can expect after treatment.

#### **Can lymphoproliferative disorders be cured?**

That depends on the type of disorder that you have. For example, chemo-immunotherapy may cure certain lymphomas like large B-cell lymphoma, Burkitt lymphoma and Hodgkin lymphoma. If you have X-linked lymphoproliferative disorder, a stem cell transplant may cure the condition.

In some cases, treatment may put certain lymphomas into remission but can’t cure the disease. Remission means you don’t have symptoms and tests don’t find signs or evidence of disease. But some LPDs can come back months or years after you finish treatment.

It’s understandable that you’d want to know about a cure or how long you may live. If you have a type of LPD, ask your healthcare provider what you can expect. They’re your best resource for information because they know you and your situation.

## Living With

Lymphoproliferative disorders are serious illnesses. While there are treatments that ease symptoms and may cure the conditions, you might find some challenges as you go through treatment. Here are some suggestions that may help you:

* Ask about palliative care. If you have an LPD, you may need help managing symptoms and treatment side effects. Your palliative care team will have recommendations and suggestions.
* Eat well. Being sick and/or undergoing treatment can affect your appetite. If that’s your situation, ask a nutritionist for suggestions.
* Get some exercise. Light exercise may help you deal with the stress that can come with having a serious illness. But be sure to talk to your healthcare provider before starting a new exercise program.
* Protect against infection. Your immune system may be weak from illness or treatment. Ask your healthcare provider about ways to avoid viral infections.

### When should I see my healthcare provider?

If you’re receiving treatment for a lymphoproliferative disorder, ask your healthcare provider to explain the kinds of changes in your body that may be signs that your condition is getting worse, like having a fever that won’t go away. That way, you’ll know when you should contact them.

## Differential Diagnoses

* Epstein-Barr Virus (EBV) Infectious Mononucleosis (Mono)
* Pediatric Non-Hodgkin Lymphoma

**EPIDEMIOLOGY**

LPD is a disease caused by cells of the lymphatic system that grow excessively. B-cell neoplasms are much more common than T-cell neoplasms in the United States and Europe.

Epstein-Barr virus (EBV) is an etiological factor for most lymphoproliferative disorders. EBV infects 90% of people during their lives. It presumably spreads by saliva or droplets. It has an incubation period of 4 to 5 weeks. In early childhood, it causes few symptoms, but in adolescents and young adults, it may cause infectious mononucleosis.

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**ASPERGILLOSIS**

Aspergillosis is an infection caused by a type of mold (fungus). The illnesses resulting from aspergillosis infection usually affect the respiratory system, but their signs and severity vary greatly.

The mold that triggers the illnesses, aspergillus, is everywhere — indoors and outdoors. Most strains of this mold are harmless, but a few can cause serious illnesses when people with weakened immune systems, underlying lung disease or asthma inhale their fungal spores.

In some people, the spores trigger an allergic reaction. Other people develop mild to serious lung infections. The most serious form of aspergillosis — invasive aspergillosis — occurs when the infection spreads to blood vessels and beyond.

Depending on the type of aspergillosis, treatment may involve observation, antifungal medications or, in rare cases, surgery.

## Causes

Aspergillus mold is unavoidable. Outdoors, it's found in decaying leaves and compost and on plants, trees and grain crops.

Everyday exposure to aspergillus is rarely a problem for people with healthy immune systems. When mold spores are inhaled, immune system cells surround and destroy them. But people who have a weakened immune system from illness or immunosuppressant medications have fewer infection-fighting cells. This allows aspergillus to take hold, invading the lungs and, in the most serious cases, other parts of the body.

Aspergillosis is not contagious from person to person.

## Risk factors

Your risk of developing aspergillosis depends on your overall health and the extent of your exposure to mold. In general, these factors make you more vulnerable to infection:

* **Weakened immune system.** People taking immune-suppressing drugs after undergoing transplant surgery — especially bone marrow or stem cell transplants — or people who have certain cancers of the blood are at highest risk of invasive aspergillosis. People in the later stages of AIDS also may be at increased risk.
* **Low white blood cell level.** People who have had chemotherapy, an organ transplant or leukemia have lower white cell levels, making them more susceptible to invasive aspergillosis. So does having chronic granulomatous disease — an inherited disorder that affects immune system cells.
* **Lung cavities.** People who have air spaces (cavities) in their lungs are at higher risk of developing aspergillomas.
* **Asthma or cystic fibrosis.** People with asthma and cystic fibrosis, especially those whose lung problems are long-standing or hard to control, are more likely to have an allergic response to aspergillus mold.
* **Long-term corticosteroid therapy.** Long-term use of corticosteroids may increase the risk of opportunistic infections, depending on the underlying disease being treated and what other drugs are being used.

## 

## Symptoms

The signs and symptoms of aspergillosis vary with the type of illness you develop:

### Allergic reaction

Some people with asthma or cystic fibrosis have an allergic reaction to aspergillus mold. Signs and symptoms of this condition, known as allergic bronchopulmonary aspergillosis, include:

* Fever
* A cough that may bring up blood or plugs of mucus
* Worsening asthma

### Aspergilloma

Certain chronic lung (pulmonary) conditions, such as emphysema, tuberculosis or advanced sarcoidosis, can cause air spaces (cavities) to form in the lungs. When people with lung cavities are also infected with aspergillus, fungus fibers may find their way into the cavities and grow into tangled masses (fungus balls) known as aspergillomas.

Aspergillomas may produce no symptoms or cause only a mild cough at first. Over time and without treatment, however, aspergillomas can worsen the underlying chronic lung condition and possibly cause:

* A cough that often brings up blood (hemoptysis)
* Wheezing
* Shortness of breath
* Unintentional weight loss
* Fatigue

### Invasive aspergillosis

This is the most severe form of aspergillosis. It occurs when the infection spreads rapidly from the lungs to the brain, heart, kidneys or skin. Invasive aspergillosis occurs only in people whose immune systems are weakened as a result of cancer chemotherapy, bone marrow transplantation or a disease of the immune system. Untreated, this form of aspergillosis may be fatal.

Signs and symptoms depend on which organs are affected, but in general, invasive aspergillosis can cause:

* Fever and chills
* A cough that brings up blood (hemoptysis)
* Shortness of breath
* Chest or joint pain
* Headaches or eye symptoms
* Skin lesions

### Other types of aspergillosis

Aspergillus can invade areas of your body other than your lungs, such as your sinuses. In your sinuses, the fungus can cause a stuffy nose sometimes accompanied by drainage that may contain blood. Fever, facial pain and headache may also occur.

## 

## Diagnosis

Diagnosing an aspergilloma or invasive aspergillosis can be difficult. Aspergillus is common in all environments but difficult to distinguish from certain other molds under the microscope. The symptoms of aspergillosis are also similar to those of other lung conditions such as tuberculosis.

Your doctor is likely to use one or more of the following tests to pinpoint the cause of your symptoms:

* **Imaging test.** A chest X-ray or computerized tomography (CT) scan — a type of X-ray that produces more-detailed images than conventional X-rays do — can usually reveal a fungal mass (aspergilloma), as well as characteristic signs of invasive aspergillosis and allergic bronchopulmonary aspergillosis.
* **Respiratory secretion (sputum) test.** In this test, a sample of your sputum is stained with a dye and checked for the presence of aspergillus filaments. The specimen is then placed in a culture that encourages the mold to grow to help confirm the diagnosis.
* **Tissue and blood tests.** Skin testing, as well as sputum and blood tests, may be helpful in confirming allergic bronchopulmonary aspergillosis. For the skin test, a small amount of aspergillus antigen is injected into the skin of your forearm. If your blood has antibodies to the mold, you'll develop a hard, red bump at the injection site. Blood tests look for high levels of certain antibodies, indicating an allergic response.
* **Biopsy.** In some cases, examining a sample of tissue from your lungs or sinuses under a microscope may be necessary to confirm a diagnosis of invasive aspergillosis.

## 

## TREATMENT

Aspergillosis treatments vary with the type of disease. Possible treatments include:

* **Observation.** Simple, single aspergillomas often don't need treatment, and medications aren't usually effective in treating these fungal masses. Instead, aspergillomas that don't cause symptoms may simply be closely monitored by chest X-ray. If the condition progresses, then antifungal medications may be recommended.
* **Oral corticosteroids.** The goal in treating allergic bronchopulmonary aspergillosis is to prevent existing asthma or cystic fibrosis from worsening. The best way to do this is with oral corticosteroids. Antifungal medications by themselves aren't helpful for allergic bronchopulmonary aspergillosis, but they may be combined with corticosteroids to reduce the dose of steroids and improve lung function.
* **Antifungal medications.** These drugs are the standard treatment for invasive pulmonary aspergillosis. The most effective treatment is a newer antifungal drug, voriconazole (Vfend). Amphotericin B is another option.  
  All antifungal drugs can have serious side effects, including kidney and liver damage. Interactions between antifungal drugs and other medications are also common.
* **Surgery.** Because antifungal medications don't penetrate an aspergilloma very well, surgery to remove the fungal mass is the first-choice treatment when an aspergilloma causes bleeding in the lungs.
* **Embolization.** This procedure stops lung bleeding caused by an aspergilloma. A radiologist injects a material through a catheter that has been guided into an artery feeding a lung cavity where an aspergilloma is causing blood loss. The injected material hardens, blocking the blood supply to the area and stopping the bleeding. This treatment works temporarily, but the bleeding is likely to start again.

**When to see a doctor**

If you have asthma or cystic fibrosis, see your doctor whenever you notice a change in your breathing. Although aspergillosis may not be the cause, it's important to have breathing problems evaluated.

If you have a weakened immune system and develop an unexplained fever, shortness of breath or a cough that brings up blood, get immediate medical care. In the case of invasive aspergillosis, prompt treatment is crucial. In some cases, treatment with antifungal medication begins as soon as aspergillosis is suspected, even before testing has confirmed the diagnosis.

## Complications

Depending on the type of infection, aspergillosis can cause a variety of serious complications:

* **Bleeding.** Both aspergillomas and invasive aspergillosis can cause severe, and sometimes fatal, bleeding in your lungs.
* **Systemic infection.** The most serious complication of invasive aspergillosis is the spread of the infection to other parts of your body, especially your brain, heart and kidneys. Invasive aspergillosis spreads rapidly and may be fatal.

**Prevention**

It's nearly impossible to avoid exposure to aspergillus, but if you have had a transplant or are undergoing chemotherapy, try to stay away from places where you're likely to encounter mold, such as construction sites, compost piles and buildings that store grain. If you have a weakened immune system, your doctor may advise you to wear a face mask to avoid being exposed to aspergillus and other airborne infectious agents.

## Differential Diagnoses

* Acute Respiratory Distress Syndrome (ARDS)
* Allergic and Environmental Asthma
* Assessment and Management of the Kidney Transplant Patient
* Asthma
* Bacterial Pneumonia
* Bronchiectasis
* Eosinophilia
* Eosinophilic Pneumonia
* Fungal Pneumonia
* Granulomatosis with Polyangiitis (GPA, formerly Wegener Granulomatosis)
* Heart Transplantation
* Heart-Lung Transplantation
* Hypersensitivity Pneumonitis
* Liver Transplantation
* Lung Abscess
* Mucormycosis (Zygomycosis)
* Mycetoma
* Myocardial Abscess
* Neutropenia
* Nocardiosis
* Hospital-Acquired Pneumonia (Nosocomial Pneumonia) and Ventilator-Associated Pneumonia
* Pulmonary Embolism (PE)
* Pulmonary Eosinophilia
* Sarcoidosis
* Tuberculosis (TB)
* Viral Pneumonia
* Zygomycosis

## Epidemiology

### United States

Although allergy to *Aspergillus,* as manifested by a positive skin test reaction to *Aspergillus* antigen, is present in approximately 25% of people with asthma and 50% of patients with CF, ABPA is much less common. From surveys and an ABPA registry, 0.25-0.8% of people with asthma and approximately 7% of patients with CF are estimated to have ABPA. The incidence of ABPA in people with asthma who are steroid-dependent or have associated central bronchiectasis is higher, estimated at 7-10%.

CNPA is rare. Frequently undetected in life and found at autopsy, the frequency of chronic necrotizing *Aspergillus* pneumonia may be underestimated.

The frequency of invasive aspergillosis reflects disease states and treatments that result in prolonged neutropenia and immunosuppression. Invasive aspergillosis is estimated to occur in 5-13% of recipients of bone marrow transplants, 5-25% of patients who have received heart or lung transplants, and 10-20% of patients who are receiving intensive chemotherapy for leukemia. Although it has been described in individuals who are immunocompetent, invasive aspergillosis is exceedingly uncommon in this population.

Aspergilloma is not rare in patients with chronic cavitary lung disease and CF. In one survey of patients with cavitary lung disease due to tuberculosis, 17% developed aspergilloma.

***GUIDELINE***

*Aspergillus* sensitization should be evaluated in all newly diagnosed asthmatic adults and in children with difficult to treat asthma. The initial evaluation should be only for *A. fumigatus* sensitization. Assessment of sensitization to other fungi is suggested for patients with difficult to treat asthma and negative *A. fumigatus* sensitization. Fungus-specific IgE is preferred over a skin prick test for documenting fungal sensitization.

Serum total IgE, *A. fumigatus*-specific IgG and peripheral blood eosinophil count should be performed in patients with asthma and *Aspergillus* sensitization; population-specific cut-offs should be used to interpret *Aspergillus*-specific IgG. When data are unavailable, manufacturer-recommended cut-offs may be used. The following cut-offs are recommended for diagnosing ABPA:

* Serum total IgE ≥500 IU·mL−1
* Blood eosinophil count ≥500 cells·µL−1

Sputum fungal culture may help identify the species or guide therapy. A thin-section chest CT should be performed at baseline to identify and characterize bronchiectasis, mucus plugging, HAM and other abnormalities.

Serum galactomannan and bronchoscopy are not routinely recommended for diagnosing ABPA .

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### Severe combined immunodeficiency

**Definition and description**

Severe combined immunodeficiency (SCID) is a rare condition that causes babies to be born with little or no immune system.

SCID is a primary immunodeficiency disorder. Immunodeficiency disorders suppress your immune system and keep it from working properly. Immunodeficiency disorders weaken your body’s natural ability to defend itself.

Babies born with SCID can’t fight off infections, even common illnesses that are usually not severe or dangerous. If it’s not treated, SCID is fatal in most children within a year or two.

#### **Types of SCID**

Your immune system is like your body’s built-in security system. Usually, it automatically detects substances that shouldn’t be in your body (like viruses, bacteria, fungi, protozoa or toxins) and sends out white blood cells called lymphocytes to eliminate them. The three types of lymphocytes include:

* T-cells.
* B-cells.
* Natural killer (NK) cells.

Babies with SCID are usually missing T-cells. Because T-cells are critical for B-cells to work, these babies will have problems with the types of infections B-cells are supposed to handle, too. That’s what the “combined” in SCID’s name comes from — missing a combination of these important defense cells.

There are different types of severe combined immunodeficiency, depending on which immune cells your child is missing. All of them are equally serious. Your healthcare provider will tell you which type your child has.

## Symptoms and Causes

SCID doesn’t cause many symptoms you’ll notice. Your baby getting sick much more often than usual is the most obvious sign.

### SCID symptoms

SCID may not cause any symptoms you can notice. If it does, they usually include:

* Your child not gaining weight at a typical healthy rate.
* Chronic diarrhea.
* Frequent, severe infections.

Your baby’s immune response to infections will be dramatically reduced or absent. That means your child will be much more likely than usual to get sick. And when they do, their symptoms will be much more severe than usual.

Babies with SCID have a higher risk for all types of infections, including:

* Bacterial infections.
* Viral infections.
* Fungal infections.
* Parasitic infections.

Any illness can cause severe symptoms, but some types of infections are more common in babies with SCID, including:

* Yeast infections (thrush or diaper rash).
* Chickenpox.
* Cold sores (herpes simplex).
* Ear infections.
* Pneumonia.
* Meningitis.

### Causes of SCID

Severe combined immunodeficiency is a genetic disorder. That means genetic mutations cause it. Experts have identified more than a dozen mutated genes that can cause SCID.

The genetic mutations that cause SCID are passed from biological parents to their children. It can be either autosomal recessive or X-linked. A recessive trait means both biological parents must have the mutated gene that causes a condition. X-linked cases of SCID happen when a mutation on an X chromosome causes it. X-linked conditions usually affect male babies because they only have one X chromosome, while female babies have two.

### Complications of SCID

Not having a strong (or any) immune response to infections is the most important SCID complication. Because your child’s body can’t fight off even mild infections, their risk of severe complications is much higher than most children’s.

Illnesses that would normally not be a cause for concern can cause life-threatening complications in children born with SCID.

SCID is almost always fatal if it’s not diagnosed and treated right after a baby is born.

## Diagnosis and Tests

Providers diagnose SCID with a blood test. Your provider will take a small blood sample from your baby right after birth (usually from your child’s heel).

All 50 states in the U.S. screen every baby born for SCID. This is important to help identify babies that need treatment right away so they don’t get a severe infection immediately after birth.

## Management and Treatment

Babies with SCID need a stem cell transplant (bone marrow transplant) as soon as possible. A stem cell transplant will replace your baby’s stem cells with a sample from a donor. The healthy stem cells will replace your child’s immune system and help their body fight infections.

Biological siblings that don’t have SCID are the best stem cell donors. If you don’t have another biological child who can donate stem cells, your healthcare providers will check stem cell registries — databases that allow providers to look for matching stem cells donated by the public.

Your child might need other treatments while they’re waiting for a stem cell transplant, including:

* Antibiotics.
* Antivirals.
* Antifungals.
* IVIG infusions.
* Gene therapy.

These are all temporary treatments that won’t cure the SCID, but can help your child fight infections before their stem cell transplant. Only a stem cell transplant can permanently cure SCID.

Your child might also need to stay in sterile isolation while they’re waiting for a stem cell transplant. This means they’ll stay in a medically sterile environment where everything that enters their room or space will be sterilized to make sure it doesn’t have any germs on it.

People sometimes refer to SCID as “bubble baby disease” because babies with SCID have to stay in sterile isolation to keep them safe. This name isn’t medically accurate, and is potentially hurtful. You and your baby didn’t do anything wrong, and there’s nothing funny about your child’s health condition.

## Outlook / Prognosis

SCID can be fatal if it’s not treated right away. If you live in the U.S., your baby will be screened for it when they’re born. Knowing they have SCID right away is extremely important. The sooner your providers diagnose it and get your child scheduled for a stem cell transplant, the better their chances of survival are.

You might not be able to hold or visit with your baby the way you expected. If they’re in sterile isolation, you’ll have to follow strict health and safety rules to keep them protected from germs and getting sick. Your providers will tell you how you can keep your baby safe, and what you can expect before and after they receive a stem cell transplant.

#### **What is the life expectancy of a baby with SCID?**

Babies with untreated SCID usually die within a year or two. Children who’ve had a successful stem cell transplant have a typical life expectancy. Once their body develops a stronger, complete immune system, they usually don’t have long-term complications.

## Prevention

Because genetic mutations you can’t control cause SCID, there’s nothing you can do to prevent it. Talk to your healthcare provider about genetic counseling if you’re worried about the risk of passing genetic conditions to your biological children.

## Living With

Visit a healthcare provider if your baby gets sick often, or if they’re experiencing severe symptoms of an illness.

If you know your child has SCID, call your provider right away if you notice any changes in your child’s health. Getting antibiotics or other medications as soon as possible is an emergency because their body can’t fight infections on its own.

**DIFFERENTIAL DIAGNOSIS**

At the top of the differential for SCID are other forms of combined immunodeficiency. These patients have several characteristics that overlap in their clinical presentation. Patients with agenesis of the thymus or T cell deficiency (such as in DiGeorge syndrome or CHARGE syndrome) may present with opportunistic infections similar to SCID.

Additional immunodeficiencies that merit consideration in the differential include the following:

* Calcium channel deficiencies
* Wiskott-Aldrich syndrome
* NF-kappa-B essential modifier (NEMO) deficiency
* Zeta-chain-associated protein 70 deficiency
* HIV/AIDS

Malabsorption syndromes that cause extreme malnutrition may also have similar presentations to SCID

## Epidemiology

### Frequency

United States

The accurate incidence of SCID in the United States is unknown, but it has been estimated to be in 1 per 50,000-100,000 births across all ethnic groups. A postulated reason for the lack of exact epidemiologic information is that infants with SCID may die of infections without having been diagnosed with the condition.

With implementation of SCID newborn screening in unbiased populations, Kwan et al reported that 1 in 58,000 infants (95% CI 1/46,000–80,000) are born with SCID or leaky SCID (ie, forms of SCID, such as Omenn syndrome, characterized by normal or elevated levels of nonfunctional T cells, in contrast to the low or absent T cell counts of typical SCID). That prevalence rate is nearly twice the previous estimates based on population data or experience of centers performing hematopoietic cell transplantation therapy for SCID.

The approximate frequency of the most common forms of SCID is as follows:

* X-linked SCID - 42%
* Autosomal recessive SCID - 22%
* ADA deficiency - 15%
* JAK3 deficiency - 6%

The incidence of reticular dysgenesis and CHH are less than 1% each. In approximately 14% of cases, the etiology remains unknown.

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**PRIMARY IMMUNODEFICIENCY DISORDER**

Primary immunodeficiency disorders — also called primary immune disorders or primary immunodeficiency — weaken the immune system, allowing infections and other health problems to occur more easily.

Many people with primary immunodeficiency are born missing some of the body's immune defenses or with the immune system not working properly, which leaves them more susceptible to germs that can cause infections.

So far, researchers have identified more than 300 forms of primary immunodeficiency disorders. Some forms are so mild they can go unnoticed until adulthood. Other types are severe enough that they're discovered soon after an affected baby is born.

Treatments can boost the immune system in many types of primary immunodeficiency disorders. Research is ongoing, leading to improved treatments and enhanced quality of life for people with the condition.

**Signs and Symptoms**

One of the most common signs of primary immunodeficiency is having infections that are more frequent, longer lasting or harder to treat than are the infections of someone with a typical immune system. You may also get infections that a person with a healthy immune system likely wouldn't get (opportunistic infections).

Signs and symptoms differ depending on the type of primary immunodeficiency disorder, and they vary from person to person.

Signs and symptoms of primary immunodeficiency can include:

* Frequent and recurrent pneumonia, bronchitis, sinus infections, ear infections, meningitis or skin infections
* Inflammation and infection of internal organs
* Blood disorders, such as low platelet count or anemia
* Digestive problems, such as cramping, loss of appetite, nausea and diarrhea
* Delayed growth and development
* Autoimmune disorders, such as lupus, rheumatoid arthritis or type 1 diabetes

**When to see a doctor**

If you or your child has frequent, recurrent or severe infections or infections that don't respond to treatments, talk to your health care provider. Early diagnosis and treatment of primary immune deficiencies can prevent infections that can cause long-term problems.

**Causes**

Many primary immunodeficiency disorders are inherited — passed down from one or both parents. Problems in the genetic code that acts as a blueprint for producing the cells of the body (DNA) cause many of these immune system defects.

There are more than 300 types of primary immunodeficiency disorders, and researchers continue to identify more. They can be broadly classified into six groups based on the part of the immune system that's affected:

* B cell (antibody) deficiencies
* T cell deficiencies
* Combination B and T cell deficiencies
* Defective phagocytes
* Complement deficiencies
* Unknown (idiopathic)

**Risk factors**

The only known risk factor is having a family history of a primary immune deficiency disorder, which increases your risk of having the condition.

If you have a type of primary immune deficiency disorder, you might want to seek genetic counseling if you plan to have a family.

**Complications**

Complications caused by a primary immunodeficiency disorder vary depending on what type you have. They can include:

* Recurrent infections
* Autoimmune disorders
* Damage to the heart, lungs, nervous system or digestive tract
* Slowed growth
* Increased risk of cancer
* Death from serious infection

**Prevention**

Because primary immune disorders are caused by genetic changes, there's no way to prevent them. But when you or your child has a weakened immune system, you can take steps to prevent infections:

* **Practice good hygiene.** Wash your hands with mild soap after using the toilet and before eating.
* **Take care of your teeth.** Brush your teeth at least twice a day.
* **Eat right.** A healthy, balanced diet can help prevent infections.
* **Be physically active.** Staying fit is important to your overall health. Ask your doctor what activities are appropriate for you.
* **Get enough sleep.** Try to go to sleep and get up at the same time daily, and get the same number of hours of sleep every night.
* **Manage stress.** Some studies suggest that stress can hamper your immune system. Keep stress in check with massage, meditation, yoga, biofeedback or hobbies. Find what works for you.
* **Avoid exposure.** Stay away from people with colds or other infections and avoid crowds.
* **Ask your doctor about vaccinations.** Find out which ones you should have.

**Epidemiology of Primary Immunodeficiency Disorders (PIDs)**

* Prevalence:
* Primary immunodeficiencies (PIDs) affect approximately 6 million people worldwide, but 70 to 90% remain undiagnosed
* The prevalence of PIDs is about 1 in 10,000 people globally, but this is likely underestimated due to missed diagnoses . In France, the prevalence is 4.4 cases per 100,000 inhabitants
* Disease registries suggest a prevalence of 1:8,500 to 1:100,000 persons .
* A U.S. study using healthcare data estimated the prevalence of any PIDD diagnosis increased from 38.9 to 50.5 per 100,000 among privately insured and from 29.1 to 41.1 per 100,000 among publicly insured persons between 2001 and 2007 .
* One study estimated the prevalence of PIDs to be around 3.9 per 100,000 in the population . Another estimated the prevalence to be 1.1 per 100,000 children less than 19 years of age .
* Types of PIDs:
* Predominantly antibody deficiencies are the most common PIDs .
* Selective IgA deficiency is the most prevalent specific defect, with 16.4% in the US, 13.0% internationally, and 14.1% globally .
* Common variable immunodeficiency (CVID) showed a prevalence of 15.4% in the US, 11.2% internationally, and 12.6% globally. Canada and Australia had higher CVID prevalence, at 25.5% and 39.5%, respectively.
* Regional Differences:
* The Middle East reports 30.5% Familial Mediterranean fever compared to 3.3% globally .
* Africa reports 6.5% Ataxia telangiectasia (A-T) compared to 2.6% globally, and 8.7% other combined immunodeficiencies compared to 1.5% globally.
* Trends and Market Growth:
* The global primary immunodeficiency disorders market was valued at USD 7.15 billion in 2023 . It is projected to grow at a CAGR of 6.4% from 2024 to 2030, reaching USD 11.14 billion by 2030 .
* Factors driving market growth include the rising incidence of PID, greater awareness, advances in biotechnology, and increased research funding .
* The Asia Pacific market is experiencing robust growth due to increased R&D incentives in developing economies like China and India

**HASHIMOTO DISEASE**

**DEFINITION AND DESCRIPTION**

Hashimoto's disease is an autoimmune disorder affecting the thyroid gland. The thyroid is a butterfly-shaped gland located at the base of the neck just below the Adam's apple. The thyroid produces hormones that help regulate many functions in the body.

An autoimmune disorder is an illness caused by the immune system attacking healthy tissues. In Hashimoto's disease, immune-system cells lead to the death of the thyroid's hormone-producing cells. The disease usually results in a decline in hormone production (hypothyroidism).

Although anyone can develop Hashimoto's disease, it's most common among middle-aged women. The primary treatment is thyroid hormone replacement.

Hashimoto's disease is also known as Hashimoto's thyroiditis, chronic lymphocytic thyroiditis and chronic autoimmune thyroiditis.

**CAUSES**

Hashimoto's disease is an autoimmune disorder. The immune system creates antibodies that attack thyroid cells as if they were bacteria, viruses or some other foreign body. The immune system wrongly enlists disease-fighting agents that damage cells and lead to cell death.

What causes the immune system to attack thyroid cells is not clear. The onset of disease may be related to:

* Genetic factors
* Environmental triggers, such as infection, stress or radiation exposure
* Interactions between environmental and genetic factors

**RISK FACTOR**

The following factors are associated with an increased risk of Hashimoto's disease:

* **Sex.** Women are much more likely to get Hashimoto's disease.
* **Age.** Hashimoto's disease can occur at any age but more commonly occurs during middle age.
* **Other autoimmune disease.** Having another autoimmune disease — such as rheumatoid arthritis, type 1 diabetes or lupus — increases your risk of developing Hashimoto's disease.
* **Genetics and family history.** You're at higher risk for Hashimoto's disease if others in your family have thyroid disorders or other autoimmune diseases.
* **Pregnancy.** Typical changes in immune function during pregnancy may be a factor in Hashimoto's disease that begins after pregnancy.
* **Excessive iodine intake.** Too much iodine in the diet may function as a trigger among people already at risk for Hashimoto's disease.
* **Radiation exposure.** People exposed to excessive levels of environmental radiation are more prone to Hashimoto's disease.

**SIGNS AND SYMPTOMS**

Hashimoto's disease progresses slowly over the years. You may not notice signs or symptoms of the disease. Eventually, the decline in thyroid hormone production can result in any of the following:

* Fatigue and sluggishness
* Increased sensitivity to cold
* Increased sleepiness
* Dry skin
* Constipation
* Muscle weakness
* Muscle aches, tenderness and stiffness
* Joint pain and stiffness
* Irregular or excessive menstrual bleeding
* Depression
* Problems with memory or concentration
* Swelling of the thyroid (goiter)
* A puffy face
* Brittle nails
* Hair loss
* Enlargement of the tongue

**DIAGNOSIS AND TESTS**

A number of conditions may lead to the signs and symptoms of Hashimoto's disease. If you're experiencing any of these symptoms, your health care provider will conduct a thorough physical exam, review your medical history and ask questions about your symptoms.

### Testing thyroid function

To determine if hypothyroidism is the cause of your symptoms, your provider will order blood tests that may include the following:

* **TSH test.** Thyroid stimulating hormone (TSH) is produced by the pituitary gland. When the pituitary detects low thyroid hormones in the blood, it sends TSH to the thyroid to prompt an increase in thyroid hormone production. High TSH levels in the blood indicates hypothyroidism.
* **T-4 tests.** The main thyroid hormone is thyroxine (T-4). A low blood level of T-4 confirms the findings of a TSH test and indicates the problem is within the thyroid itself.

### Antibody tests

More than one disease process can lead to hypothyroidism. To determine if Hashimoto's disease is the cause of hypothyroidism, your health care provider will order an antibody test.

The intended purpose of an antibody is to flag disease-causing foreign agents that need to be destroyed by other actors in the immune system. In an autoimmune disorder, the immune system produces rogue antibodies that target healthy cells or proteins in the body.

Usually in Hashimoto's disease, the immune system produces an antibody to thyroid peroxidase (TPO), a protein that plays an important part in thyroid hormone production. Most people with Hashimoto's disease will have TPO antibodies in their blood. Lab tests for other antibodies associated with Hashimoto's disease may need to be done.

## 

## Treatment

Most people with Hashimoto's disease take medication to treat hypothyroidism. If you have mild hypothyroidism, you may have no treatment but get regular thyroid stimulating hormone (TSH) tests to monitor thyroid hormone levels.

### T-4 hormone replacement therapy

Hypothyroidism associated with Hashimoto's disease is treated with a synthetic hormone called levothyroxine (Levoxyl, Synthroid, others). The synthetic hormone works like the thyroxine (T-4) hormone naturally produced by the thyroid.

The treatment goal is to restore and maintain adequate T-4 hormone levels and improve symptoms of hypothyroidism. You will need this treatment for the rest of your life.

### Monitoring the dosage

Your heath care provider will determine a dosage of levothyroxine that's appropriate for your age, weight, current thyroid production, other medical conditions and other factors. Your provider will retest your TSH levels about 6 to 10 weeks later and adjust the dosage as necessary.

Once the best dosage is determined, you will continue to take the medication once a day. You'll need follow-up tests once a year to monitor TSH levels or any time after your provider changes your dosage.

A levothyroxine pill is usually taken in the morning before you eat. Talk to your doctor if you have any questions about when or how to take the pill. Also, ask what to do if you accidentally skip a dose. If your health insurance requires you to switch to a generic drug or a different brand, talk to your doctor.

### Precautions

Because levothyroxine acts like natural T-4 in the body, there are generally no side effects as long as the treatment is resulting in "natural" levels of T-4 for your body.

Too much thyroid hormone can worsen bone loss that causes weak, brittle bones (osteoporosis) or cause irregular heartbeats (arrhythmias).

### Effects of other substances

Certain medications, supplements and foods may affect your ability to absorb levothyroxine. It may be necessary to take levothyroxine at least four hours before these substances. Talk to your doctor about any of the following:

* Soy products
* High-fiber foods
* Iron supplements, including multivitamins that contain iron
* Cholestyramine (Prevalite), a medication used to lower blood cholesterol levels
* Aluminum hydroxide, which is found in some antacids
* Sucralfate, an ulcer medication
* Calcium supplements

### T-3 hormone replacement therapy

Naturally produced T-4 is converted into another thyroid hormone called triiodothyronine (T-3). The T-4 replacement hormone is also converted into T-3, and for most people the T-4 replacement therapy results in an adequate supply of (T-3) for the body.

For people who need better symptom control, a doctor also may prescribe a synthetic T-3 hormone (Cytomel) or a synthetic T-4 and T-3 combination. Side effects of T-3 hormone replacement include rapid heartbeat, insomnia and anxiety. These treatments may be tested with a trial period of 3 to 6 months.

**COMPLICATION**

Thyroid hormones are essential for the healthy function of many body systems. Therefore, when Hashimoto's disease and hypothyroidism are left untreated, many complications can occur. These include:

* **Goiter.** A goiter is enlargement of the thyroid. As thyroid hormone production declines due to Hashimoto's disease, the thyroid receives signals from the pituitary gland to make more. This cycle may result in a goiter. It's generally not uncomfortable, but a large goiter can affect your appearance and may interfere with swallowing or breathing.
* **Heart problems.** Hypothyroidism can result in poor heart function, an enlarged heart and irregular heartbeats. It can also result in high levels of low-density lipoprotein (LDL) cholesterol — the "bad" cholesterol — that is a risk factor for cardiovascular disease and heart failure.
* **Mental health issues.** Depression or other mental health disorders may occur early in Hashimoto's disease and may become more severe over time.
* **Sexual and reproductive dysfunction.** In women, hypothyroidism can result in a reduced sexual desire (libido), an inability to ovulate, and irregular and excessive menstrual bleeding. Men with hypothyroidism may have a reduced libido, erectile dysfunction and a lowered sperm count.
* **Poor pregnancy outcomes.** Hypothyroidism during pregnancy may increase the risk of a miscarriage or preterm birth. Babies born to women with untreated hypothyroidism are at risk for decreased intellectual abilities, autism, speech delays and other developmental disorders.
* **Myxedema (miks-uh-DEE-muh).** This rare, life-threatening condition can develop due to long-term, severe, untreated hypothyroidism. Its signs and symptoms include drowsiness followed by profound lethargy and unconsciousness. A myxedema coma may be triggered by exposure to cold, sedatives, infection or other stress on your body. Myxedema requires immediate emergency medical treatment.

## 

## Alternative medicine

Products with triiodothyronine (T-3) and thyroxine (T-4) hormones derived from pigs or other animals are available as prescriptions or as dietary supplements, such as Armour Thyroid, in the United States. Concerns about these products include the following:

* The balance of T-4 and T-3 in animals isn't the same as in humans.
* The exact amount of T-4 and T-3 in each batch of a natural extract product can vary, leading to unpredictable levels of these hormones in your blood.

## Outlook / Prognosis

With lifelong monitoring and treatment, the prognosis (outlook) for people with Hashimoto’s disease is excellent.

If you have hypothyroidism from Hashimoto’s disease that’s untreated, it can lead to certain health problems, including:

* High cholesterol.
* Heart disease and heart failure.
* High blood pressure.
* Depression.
* Myxedema coma. This is a rare complication of severe hypothyroidism. Your body’s functions slow down so much that it can be deadly.

Without treatment, hypothyroidism can also cause problems during pregnancy.

#### **Hashimoto’s disease during pregnancy**

Untreated hypothyroidism during pregnancy can increase the risk of:

* Miscarriage.
* Premature birth.
* Stillbirth.

Or it may cause a dangerous rise in your blood pressure in late pregnancy called preeclampsia. Untreated hypothyroidism can also affect the fetus’s growth and brain development. Your providers will work with you to make sure your hypothyroidism is well-managed during pregnancy.

Hypothyroidism during pregnancy isn’t common. But it can be easy to miss its symptoms that are also common during pregnancy, like fatigue and weight gain. Let your providers know right away if you notice any hypothyroidism symptoms or feel like you’re developing a goiter.

## Prevention

Unfortunately, there’s nothing you can do to prevent Hashimoto’s disease. The risk factors for it — like your genetics and age — aren’t modifiable.

## Living With

If you have Hashimoto’s disease, you’ll need to see your healthcare provider regularly. They’ll perform routine thyroid hormone blood tests to make sure your levels are in range and that the dose of medication you’re taking is right for you.

Otherwise, see your healthcare provider if you develop new or worsening symptoms or notice a change in your thyroid.

#### **When should I go to the ER?**

If you have symptoms of myxedema coma, call 911 or get to the emergency room as soon as possible. This complication of severe hypothyroidism is life-threatening.

Symptoms include:

* A body temperature below 95 degrees Fahrenheit or 35 degrees Celsius (hypothermia).
* Swelling (edema) in your body, especially your face, tongue and lower legs.
* A slow heart rate and faint pulse.
* Slowed breathing (bradypnea) and difficulty breathing (dyspnea).
* Confusion or loss of consciousness.

## When to see a doctor

Signs and symptoms of Hashimoto's disease vary widely and are not specific to the disorder. Because these symptoms could result from any number of disorders, it's important to see your health care provider as soon as possible for a timely and accurate diagnosis.

## 

## Differential Diagnoses

* Diffuse Toxic Goiter (Graves Disease)
* Euthyroid Sick Syndrome
* Goiter
* Hypopituitarism (Panhypopituitarism)
* Lithium-Induced Goiter
* Nontoxic Goiter
* Thyroid Lymphoma
* Toxic Nodular Goiter
* Type I Polyglandular Autoimmune Syndrome
* Type II Polyglandular Autoimmune Syndrome

## 

## Epidemiology

### Occurrence in the United States

Hashimoto thyroiditis is the most common cause of hypothyroidism in the United States after age 6 years, with the incidence estimated to be 1.3% in a series of 5000 children aged 11-18 years. In adults, the incidence is estimated to be 3.5 per 1000 per year in women and 0.8 per 1000 per year in men. The incidence may be as high as 6% in the Appalachian region.

In the Colorado Thyroid Disease Prevalence Study, involving 25,862 adults, the prevalence of elevated TSH in symptomatic and asymptomatic adults was 9.5%, with a greater percentage of those involved being women. The prevalence of hypothyroidism and of thyroid disease in general increases with age.

### International occurrence

Worldwide, the most common cause of hypothyroidism is iodine deficiency. However, Hashimoto thyroiditis remains the most common cause of spontaneous hypothyroidism in areas of adequate iodine intake. The annual incidence of Hashimoto thyroiditis worldwide is estimated to be 0.3-1.5 cases per 1000 persons.

Climate conditions have been thought to play a role in pathogenesis of Hashimoto thyroiditis, as Siberian women have higher TPO titers than does the general population.

### Sex- and age-related demographics

The incidence of Hashimoto thyroiditis is estimated to be 10-15 times higher in females.

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**RHEUMATOID ARTHRITIS**

**DEFINITION AND DESCRIPTION**

Rheumatoid arthritis is an ongoing, called chronic, condition that causes pain, swelling and irritation, called inflammation, in the joints. But it also can damage other parts of the body. These may include the skin, eyes, lungs, heart and blood vessels.

Rheumatoid arthritis happens when the immune system attacks its own body's tissues by mistake. This is called an autoimmune condition.

Rheumatoid arthritis differs from the more common osteoarthritis. Some people have both. Osteoarthritis causes damage to joints from overuse. Rheumatoid arthritis affects the lining of the joints and eats away at the bone under them. This causes a painful swelling that can cause joints to bend out of shape over time, called deformity.

The inflammation of rheumatoid arthritis also can damage other parts of the body. New medicines have improved treatment choices greatly. But rheumatoid arthritis still can cause long-term damage and increase the risk of heart disease.

**CAUSES**

Experts don't know the cause of rheumatoid arthritis. But it's a condition in which the immune system attacks healthy joint tissue by mistake, called autoimmune.

The cause is likely a mix of genetic changes and factors from outside the body, called environmental. Hormones may play a role. An infection with certain viruses may start rheumatoid arthritis in people whose genes make them more likely to get it.

**RISK FACTORS**

Factors that may increase your risk of rheumatoid arthritis include:

* **Your sex.** People assigned female at birth are more likely than those assigned male at birth to get rheumatoid arthritis.
* **Age.** Rheumatoid arthritis can happen at any age. But most often it begins in middle age. Children and young teens may get a related condition called juvenile idiopathic arthritis.
* **Family history.** Having a family member with rheumatoid arthritis or other autoimmune conditions may raise the risk of the condition.
* **Smoking.** Cigarette smoking over time raises the risk of getting rheumatoid arthritis. Smoking also seems to make the condition worse in people who keep smoking.
* **Gum infection.** A serious gum infection, called periodontal disease, can damage the soft tissue around teeth and raise the risk of getting rheumatoid arthritis.
* **Excess weight.** People who are overweight seem to be at a somewhat higher risk of getting rheumatoid arthritis.

**SIGNS AND SYMPTOMS**

Symptoms of rheumatoid arthritis may include:

* Painful, warm, swollen joints.
* Joint stiffness that most often is worse in the mornings and after periods of rest. It can last for 45 minutes or longer.
* Tiredness, fever and not wanting to eat.

Rheumatoid arthritis may affect just a few joints at first. Most often, these are the small joints of the hands and the feet.

As the disease gets worse, symptoms may spread to more joints. These most often include the wrists, elbows, hips, knees and ankles. Most of the time, symptoms affect the same joints on both sides of the body.

Many people who have rheumatoid arthritis also have symptoms that affect more than the joints. Areas that may be affected include:

* Skin.
* Eyes.
* Lungs.
* Heart.
* Nerve tissue.
* Blood.

Rheumatoid arthritis symptoms may vary in how bad they are. They may come and go. Periods when the condition becomes more active, called flares, follow periods of less or no swelling and pain. This is called remission.

Over time, rheumatoid arthritis can cause joints to bend out of shape and shift out of place. The joints can be hard to use for daily activities at home or at work.

## Diagnosis and tests

Rheumatoid arthritis can be hard to diagnose in its early stages. That's because the early symptoms can be like those of other common conditions.

During the physical exam, your healthcare professional checks your joints for swelling, redness and warmth. Your healthcare professional also may check your reflexes and muscle strength.

### Blood tests

People with rheumatoid arthritis often have an elevated erythrocyte sedimentation rate (ESR), also called sed rate, or C-reactive protein (CRP) level. This may show a higher level of inflammation in the body. Other blood tests look for rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies.

### Imaging tests

You may have X-rays to track rheumatoid arthritis in your joints over time. MRI scans and ultrasound tests may help with diagnosis. They can show how bad the condition is.

**Treatment**

There is no cure for rheumatoid arthritis. Joint damage can happen quickly without treatment. But clinical studies show that easing of symptoms, called remission, is more likely with early treatment with medicines called disease-modifying antirheumatic drugs (DMARDs).

Treatment of rheumatoid arthritis also involves regular follow-up with your healthcare team. This is to watch for joint damage, to see whether treatment is working and to look for possible side effects of treatment.

### Medications

Your healthcare professional will suggest medicines based on how bad your symptoms are and how long you've had rheumatoid arthritis. You and your healthcare professional will decide on treatment. Medicines might include:

* **NSAIDs.** Nonsteroidal anti-inflammatory drugs (NSAIDs) can relieve pain and ease swelling and irritation. NSAIDs you can get without a prescription include ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve).  
  There also are stronger prescription NSAIDs. Side effects for all NSAIDs may include stomach upset, heart problems and kidney damage.
* **Steroids.** Corticosteroid medicines, such as prednisone (Rayos), ease inflammation and pain and slow joint damage. There can be serious side effects. The risk of side effects rises when taken at high doses over a long time. Side effects may include thinning of bones, fractures, easy bruising from skin thinning, weight gain, diabetes, cataracts and glaucoma, among others.  
  Healthcare professionals often prescribe a corticosteroid for quick symptom relief. The goal is to taper off the medicine when the condition is under control.
* **Conventional DMARDs.** These drugs can slow the progression of rheumatoid arthritis and save the joints and other tissues from long-term damage. Common DMARDs include methotrexate (Trexall, Otrexup, others), leflunomide (Arava), hydroxychloroquine (Plaquenil, Sovuna) and sulfasalazine (Azulfidine). Side effects vary but may include liver damage and severe lung infections.
* **Biologic agents.** Also known as biologic response modifiers, this newer class of DMARDs includes abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara) and tocilizumab (Actemra).  
  Biologic DMARDs most often work best when used with a conventional DMARD, such as methotrexate. Biologic agents also raise the risk of rare infections such as tuberculosis, also called TB, or fungal infections. If you take biologic agents, you need to be watched closely.
* **Targeted synthetic DMARDs.** Healthcare professionals may prescribe these human-made medicines if conventional DMARDs and biologics haven't worked. They include baricitinib (Olumiant), tofacitinib (Xeljanz) and upadacitinib (Rinvoq).  
  Higher doses of tofacitinib may raise the risk of blood clots in the lungs, serious heart-related events and cancer.

### Therapy

A physical or occupational therapist can teach you exercises to help keep your joints moving. The therapist also may suggest ways to do daily tasks that are easier on your joints. For instance, you may pick up an object using your forearms instead of your hands.

Assistive devices can make it easier to keep from stressing painful joints. For instance, a kitchen knife with a hand grip helps protect finger and wrist joints. Certain tools, such as buttonhooks, can make it easier to get dressed. Look for ideas in medical supply brochures and stores.

### Surgery

Better medicines to treat rheumatoid arthritis have lowered the need for surgery. But if medicines fail to prevent or slow joint damage, you and your healthcare professional may think about surgery for damaged joints.

Rheumatoid arthritis surgery may involve replacing or repairing a damaged joint. The type of surgery may depend on the joint involved. Surgery may help you use a joint again. It also can ease pain.

**Complications**

Rheumatoid arthritis increases the risk of getting:

* **Osteoporosis.** Rheumatoid arthritis itself, and some medicines used to treat it, can increase the risk of this condition. Osteoporosis weakens bones and makes them more likely to break.
* **Rheumatoid nodules.** These firm bumps of tissue most often form around pressure points, such as the elbows. But these nodules can form anywhere in the body, including the heart and lungs.
* **Dry eyes and mouth.** People who have rheumatoid arthritis are much more likely to get a condition that lowers the amount of moisture in the eyes and mouth. This is called secondary Sjogren's syndrome.
* **Infections.** Rheumatoid arthritis and many of the medicines used to treat it can harm the immune system. This can lead to more infections. Vaccinations can help prevent infections such as the flu, pneumonia, shingles and COVID-19.
* **Carpal tunnel syndrome.** If rheumatoid arthritis affects the wrists, the swelling can press on the nerve to the hand and fingers.
* **Heart problems.** Rheumatoid arthritis can raise the risk of hardened and blocked arteries. It also can raise the risk of swelling and irritation, called inflammation, of the sac around the heart.
* **Lung disease.** People with rheumatoid arthritis have a higher risk of swelling and irritation, called inflammation, of lung tissues. This can cause scarring and lead to shortness of breath that gets worse over time.
* **Lymphoma.** Rheumatoid arthritis raises the risk of a group of blood cancers that happen in the lymph system. This is called lymphoma. People with rheumatoid arthritis may have a higher risk of other cancers, as well.

**Lifestyle and home remedies**

Self-care measures, when used with your rheumatoid arthritis medicines, can help you manage your symptoms:

* **Exercise regularly.** Gentle exercise can help strengthen the muscles around your joints. And it can help you feel less tired. Check with your healthcare team before you start exercising. Walking is a good way to begin. Don't exercise tender, injured or inflamed joints.
* **Apply heat or cold.** Heat can help ease your pain and relax tense, painful muscles. Cold may dull pain. Cold also numbs and can ease swelling.
* **Relax.** Find ways to cope with pain by lowering your stress. Techniques such as guided imagery, deep breathing and muscle relaxation all can help control pain.
* **Don't smoke.** Smoking can make rheumatoid arthritis worse. If you smoke, ask your healthcare team to help you quit.

**Alternative medicine**

Some common complementary and alternative treatments that have shown promise for rheumatoid arthritis include:

* **Fish oil.** Some studies have found that fish oil supplements may ease rheumatoid arthritis pain and stiffness. Side effects can include nausea, belching and a fishy taste in the mouth. Fish oil can get in the way of medicines you take. So check with your healthcare professional before trying it.
* **Tai chi.** This movement therapy involves gentle exercises and stretches and deep breathing. Many people use tai chi to relieve stress. Small studies have found that tai chi may improve mood and quality of life in people with rheumatoid arthritis. When led by a trained leader, tai chi is safe. But don't do any moves that cause pain or make it worse.

## Outlook / Prognosis

Although there isn’t currently a cure for rheumatoid arthritis, there are many effective methods for decreasing your pain and inflammation and slowing down the disease process. Early diagnosis and effective treatment are very important.

If you don’t see a provider for RA treatment, the disease can cause permanent damage to your cartilage and, eventually, your joints. RA can also harm organs like your lungs and heart.

## Living With

It’s important to see your healthcare provider on a regular basis to monitor your symptoms. They’ll also want to know about any side effects you may experience from your medications. Your provider can adjust your dosage or change the types of medications you take. Continue to take your medications until you speak with your provider.

You can also take care of yourself by following a healthy eating plan and getting some physical activity every day. If you smoke, it’s important that you quit.

**DIFFERENTIAL DIAGNOSIS**

* Osteoarthritis
* Psoriatic arthritis
* Systemic lupus erythematosus
* Sjogren syndrome
* Polymyalgia rheumatic
* Chronic gouty arthritis
* Calcium pyrophosphate deposition disease

## Epidemiology

Worldwide, the annual incidence of RA is approximately 3 cases per 10,000 population, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years. RA affects all populations, though it is much more prevalent in some groups (eg, 5-6% in some Native American groups) and much less prevalent in others (eg, Black persons from the Caribbean region).

First-degree relatives of individuals with RA are at 2- to 3-fold higher risk for the disease. Disease concordance in monozygotic twins is approximately 15-20%, suggesting that non genetic factors play an important role. Because the worldwide frequency of RA is relatively constant, a ubiquitous infectious agent has been postulated to play an etiologic role.

Women are affected by RA approximately 3 times more often than men are.For example, a nationwide study from Norway reported that the point prevalence of RAl was 1.10% in women and 0.46% in men.However, sex differences in RA diminish in older age groups.In investigating whether the higher rate of RA among women could be linked to certain reproductive risk factors, a study from Denmark found that the rate of RA was higher in women who had given birth to just 1 child than in women who had delivered 2 or 3 offspring.

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**CRYOGLOBULINEMA**

**DEFINITION AND DESCRIPTION**

Cryoglobulinemia is a family of rare conditions, called vasculitis. Vasculitis causes irritation and swelling, called inflammation, of the blood vessels.

Cryoglobulins are atypical proteins in the blood. For people who have cryoglobulinemia (kry-o-glob-u-lih-NEE-me-uh), these proteins may clump together at body temperatures below 98.6 F (37 C).

These clumps can block blood flow. This can damage the skin, joints, nerves and organs, mainly the kidneys and liver.

#### **Cryoglobulinemia types**

Cryoglobulins are a kind of antibody. Cryoglobulinemia can be divided into three main types, depending on which kind of antibody your body produces.

Type I cryoglobulinemia is frequently associated with an underlying health condition, such as cancer of your blood or immune system.

Type II cryoglobulinemia and type III cryoglobulinemia are often seen in people with long-term (chronic) inflammatory conditions, such as autoimmune diseases. Type II cryoglobulinemia is very common in people with hepatitis C virus (HCV). Another name for types II and III cryoglobulinemia is mixed cryoglobulinemia.

### causes cryoglobulinemia

Researchers don’t know the exact cause of cryoglobulinemia. But the condition is a type of vasculitis, which is an autoimmune disease. Autoimmune disorders occur when your body’s immune system attacks healthy tissue. Factors that may trigger this reaction include:

* Genetics.
* Certain medications.
* Infections and viruses.
* Environmental factors.

Cryoglobulinemia can be present alone (“idiopathic”), but it’s frequently associated with other diseases, such as:

* Hepatitis C infection.
* Blood cell abnormalities like lymphoma and multiple myeloma.
* Connective tissue diseases, like lupus.

**Risk factors**

Risk factors of cryoglobulinemia may include:

* **Sex.** Cryoglobulinemia happens more often in women than in men.
* **Age.** Symptoms of cryoglobulinemia most often begin in middle age.
* **Other diseases.** Cryoglobulinemia is linked with diseases such as hepatitis C, HIV, multiple myeloma, Waldenstrom macroglobulinemia, lupus and Sjogren syndrome.

### symptoms of cryoglobulinemia

People with cryoglobulinemia may or may not experience symptoms. When symptoms are present, they most commonly include a particular rash called purpura that looks like red spots or purple bruises, usually over your lower legs. You may also have fatigue and joint pain.

Other cryoglobulinemia symptoms may include:

* Spasms in the blood vessels of your hands and/or feet with cold temperatures that cause them to turn blue (Raynaud’s phenomenon).
* Weight loss.
* High blood pressure (hypertension).
* Swelling (edema) of your ankles and legs.
* Skin ulcers and gangrene.
* Enlarged liver (hepatomegaly) or enlarged spleen (splenomegaly).
* Numbness, tingling or weakness in your hands or feet.
* Kidney damage.

## Diagnosis and Tests

Your healthcare provider will ask about your medical history and perform a physical exam. They’ll order a specific blood test that detects the presence of cryoglobulins in your blood. Learning the type of cryoglobulins you have can sometimes help determine the cause and how to treat it.

In addition to this blood test, your provider may request the following to help diagnose your condition:

* Urinalysis.
* Chest X-ray.
* Computed tomography (CT) scan.
* Angiogram.
* MRA (magnetic resonance angiogram).
* CT angiogram.
* Nerve conduction test.
* Electromyography (EMG).
* Biopsy.

## Management and Treatment

Cryoglobulinemia treatment depends on the organs it affects, the degree of damage and the presence of other medical conditions. It’s very important not only to treat cryoglobulinemia but also to address any other associated disorders. When you treat your other conditions, the symptoms of cryoglobulinemia may improve.

For mild cases of cryoglobulinemia, your healthcare provider may recommend over-the-counter (OTC) anti-inflammatory drugs (NSAIDs) for pain, along with avoiding cold temperatures. They’ll want to monitor your disease with regular checkups.

For more moderate to severe cases of cryoglobulinemia, treatments may include:

* Immunosuppressive drugs: The mainstay of treatment is corticosteroids such as prednisone, with or without other medications, depending on the affected organ and the extent of involvement.
* Antiviral medications: If your provider found another medical condition like hepatitis C, they may recommend antiviral therapy. They may also refer you to a hepatologist (liver specialist).
* Biologics: The biologic rituximab is a common treatment for cryoglobulinemia. Biologics are complex proteins derived from living organisms that target certain parts of your immune system to control inflammation.
* Plasmapheresis: Another form of treatment that decreases the amount of cryoglobulins in your blood. This procedure, called plasmapheresis, removes cryoglobulins from your plasma (the liquid in your blood). This helps prevent cryoglobulins from clogging your arteries, which could block your blood flow and lead to organ damage.

#### **Complications and side effects of treatment**

The medications your healthcare provider recommends for the treatment of cryoglobulinemia may cause serious side effects. These side effects include potential bone loss (osteoporosis) and lowering your body’s ability to fight infection. Because of this, it’s important to see your provider for routine checkups. They may be able to prescribe medications to offset the side effects. It’s also important to prevent infection, so talk to your provider about vaccinations to lower your risk of infection.

## Outlook / Prognosis

Your prognosis depends on several factors, including:

* Other underlying conditions.
* The extent of your organ damage.
* How well you respond to treatment.

In addition, the severity of the condition varies. Some people don’t have any symptoms or have a very mild case that doesn’t require treatment. For people with moderate to severe cases, prompt diagnosis and treatment can help relieve symptoms and prevent long-term complications. If you haven’t experienced any permanent damage to your organs, your prognosis is very good.

## Prevention

Researchers don’t know the cause of cryoglobulinemia, so there’s no way to prevent it. But staying out of the cold may help prevent some symptoms, including Raynaud's phenomenon. It’s also important to get tested and treated for hepatitis C infection.

## Living With

The best way to take care of yourself is to actively work with your healthcare providers. Depending on which organs cryoglobulinemia affects, you may work with a team of specialists that includes:

* Rheumatologists.
* Dermatologists.
* Hematologists.
* Nephrologists.
* Cardiologists.
* Neurologists.
* Hepatologists (liver specialists).

Get to know the members of your team. And be sure to advocate for yourself. Ask questions. If you have concerns about your treatment plan, speak up. Your providers are there to listen and make sure you fully understand everything that affects your health and care.

**Complications**

Cryoglobulinemia can affect the kidneys. The main symptoms are protein or blood in the urine. High blood pressure most often goes with the kidney symptoms. In time, kidney failure might happen.

**DIFFERENTIAL DIAGNOSIS**

Cryoglobulinemia must be diagnosed carefully, as its clinical presentation is similar to other vasculitides affecting small- or medium-sized vessels. The differential diagnoses of cryoglobulinemia include:

* Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (such as granulomatosis with polyangiitis [Wegener], eosinophilic granulomatosis with polyangiitis [Churg-Strauss], and microscopic polyangiitis).
* IgA vasculitis (Henoch-Schönlein purpura); Henoch Schlein purpura (HSP) causes palpable purpura in lower extremities but can be differentiated by immunofluorescence of skin biopsy. In HSP, immunofluorescence usually shows the deposition of IgA and not immune complexes.
* Cutaneous small-vessel vasculitis.
* Hypersensitivity vasculitis.
* Vasculitis is associated with a connective tissue disorder (such as SLE, rheumatoid arthritis, and Sjögren syndrome). Systemic lupus erythematosus can cause cutaneous vasculitis, cytopenias, arthralgias, positive RF, and glomerulonephritis. Further, there can be overlap with patients with underlying systemic lupus erythematosus developing cryoglobulinemic vasculitis. Systemic lupus erythematosus is usually associated with low complements, both C3 and C4, and not just isolated C4 depletion. Serum cryoglobulin detection and pathological evaluation are critical in differentiating these two conditions.  
  Rheumatoid arthritis is associated with joint pain and a positive RF. Rarely, leukocytoclastic vasculitis can be seen in rheumatoid arthritis as well. However, rheumatoid arthritis is associated with the presence of inflammatory arthritis and synovitis, which is usually absent in cryoglobulinemic vasculitis, where patients have arthralgias but usually lacks true synovitis. Further, anti-CCP antibodies are specific for rheumatoid arthritis and are not seen in cryoglobulinemic vasculitis. Renal involvement is rare in rheumatoid arthritis. Complements are usually normal in rheumatoid arthritis. Cryoglobulins will be absent.  
  Systemic sclerosis can cause cutaneous manifestations like digital ulcers and gangrene. However, other clinical features of systemic sclerosis, including sclerodactyly, calcinosis, interstitial lung disease, gastrointestinal dysmotility, are not seen in cryoglobulinemic vasculitis. Renal involvement in systemic sclerosis is rare and is manifested as scleroderma renal crisis which is different from cryoglobulinemic vasculitis induced glomerulonephritis. Both of these can be differentiated by kidney biopsy.

Other thrombotic and embolic disorders, such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, should also be considered in the differential diagnosis. Additionally, patients affected by chronic HCV infection may develop arthralgias and membranoproliferative nephritis even without cryoglobulinemia. Therefore, further testing is necessary to reach a definitive diagnosis.

**EPIDEMIOLOGY**

Cryoglobulinemia is a rare condition and is clinically significant in about 1 in 100,000 individuals, with a higher prevalence observed in southern Europe. Cryoglobulins have been identified in several patient populations, specifically 15% to 20% of HIV-infected individuals, 40% to 65% of HCV-infected patients, and over 90% of HIV/HCV-coinfected individuals. In addition, the condition is also linked to autoimmune diseases, such as SLE and Sjögren syndrome, as well as hematologic malignancies, such as multiple myeloma and lymphoma.

Cryoglobulinemia predominantly affects adults, with a higher incidence observed in females than males. Based on the currently available case series, patients with type 1 cryoglobulin account for 5% to 25% of the cases. Geographic variations in prevalence are noted, correlating with the distribution of HCV infection and other associated diseases. Due to its association with various underlying conditions, the epidemiology of cryoglobulinemia reflects a complex interplay between genetic, environmental, and infectious factors.

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**GLOMERULONEPHRITIS**

**DEFINITION AND DESCRIPTION**

Glomerulonephritis is a type of kidney disease. It involves damage to the glomeruli (tiny filters) inside your kidneys. If you have glomerulonephritis, your kidneys can have trouble removing waste and fluid from your body. Many mild cases resolve with treatment. If the condition becomes severe, it can lead to kidney failure.

#### **How do glomeruli help your kidneys?**

Glomeruli are tiny filtering units made of capillaries (tiny blood vessels) in your kidneys. You have almost a million of them. Their job is to remove waste and extra fluid from your blood. It’s the first step in the process of making pee. If something damages them, they can’t do their job. This means your kidneys may not work as well.

#### **Are there different types of glomerulonephritis?**

When glomerulonephritis starts suddenly, it’s called acute glomerulonephritis. When it happens slowly and lasts a while, it’s called chronic glomerulonephritis. Some people can have an acute attack and then a chronic condition years later.

## Symptoms and Causes

### Symptoms of glomerulonephritis

People with glomerulonephritis often don’t experience any warning signs of the disease. But symptoms can include:

* Blood in your pee, which may make it look brown, pink or red.
* Nausea.
* Rash
* Shortness of breath.
* Pain in your joints or abdomen.
* Peeing less often or more often than usual.
* Swelling in your legs or face.
* Pee that appears foamy or bubbly.
* High blood pressure.
* Jaundice.
* Weight loss or loss of appetite.

Contact a healthcare provider if you have one or more of these symptoms. Many other health conditions can cause similar symptoms. Your healthcare provider can evaluate your symptoms and tell you if glomerulonephritis is a possible diagnosis.

### Causes glomerulonephritis

The reason glomerulonephritis appears is often unknown. But causes may include:

* A complication of bacterial endocarditis, an infection in your heart valves.
* A complication of infections like strep throat, HIV or hepatitis C.
* Problems with your immune system attacking healthy parts of your body, such as with lupus.
* Anti-GBM disease (formerly Goodpasture syndrome), a group of autoimmune diseases that affect your lungs and kidneys.
* IgA nephropathy, a kidney disease caused by a buildup of abnormal IgA antibody (immunoglobulin A).
* Rare diseases that inflame blood vessels like granulomatosis with polyangiitis (formerly Wegener’s disease), microscopic polyangiitis, Henoch-Schönlein purpura, or eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome).
* Genetics, meaning it runs in your biological family (this is rare).
* Certain types of cancer (like multiple myeloma).

#### **Risk factors for glomerulonephritis**

Not everyone with risk factors will develop glomerulonephritis. And, not everyone with the condition has a risk factor. But, the following are known risk factors:

* A personal or family history of kidney disease.
* Taking certain medications.
* Exposure to specific toxins.
* Having certain viral infections (like strep) or bacterial infections (bacterial endocarditis).
* Having an autoimmune condition.

### Complications of glomerulonephritis

Some people develop complications from glomerulonephritis. Glomerulonephritis affects your kidney’s ability to remove waste from your bloodstream. Specific complications include:

* Blood clots, including deep vein thrombosis (DVT) or pulmonary embolism (PE).
* Chronic kidney disease (CKD).
* Hypertension (high blood pressure).
* High cholesterol.
* Kidney failure, which can happen quickly or after several years.
* Nephrotic syndrome (nephrosis), with protein in your pee, often leading to foamy pee and swelling in your body.

## Diagnosis and Tests

Glomerulonephritis may not produce symptoms. That’s why it’s often discovered during tests for another concern. If a healthcare provider suspects you have glomerulonephritis, they may refer you to a kidney specialist and/or you may have the following tests:

* Urine test: This test will determine if you have protein or blood in your urine.
* Blood test: This test will measure the level of creatinine (a waste product your kidneys filter) in a sample of your blood.
* Kidney biopsy: A healthcare provider will use a needle to remove a piece of tissue from your kidney and send it to a lab for analysis.
* Imaging tests: Your provider may order imaging tests such as ultrasound, X-ray or CT scan. These tests check the size and shape of your kidneys, look for blockages and help diagnose other problems.

## Management and Treatment

Treatment depends on what’s causing the condition and if you have kidney damage. The goal of treatment is to reduce any further damage.

Sometimes, treating the underlying cause, like taking medication to manage high blood pressure, is all that’s necessary. If the cause is due to infection, antibiotics can treat the infection.

At other times, your healthcare provider may recommend:

* Changes to your diet so that you eat less protein and salt, which put extra strain on your kidneys.
* Immunosuppressants, if a problem with your immune system causes glomerulonephritis.
* Medicine to lower your blood pressure, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin blockers (ARB).
* Corticosteroids to decrease inflammation.
* Dialysis, which helps clean your blood, remove extra fluid and control blood pressure.
* Diuretics (water pills) to reduce swelling and remove excess fluid from your body.
* Plasmapheresis, a special process that filters protein from your blood.

## Outlook / Prognosis

Different people have different outcomes with glomerulonephritis depending on what kind of glomerulonephritis you have. Some cases go away over time without any treatment. Some people have no symptoms of the disease and only find out because they have a blood or urine test for another condition. But it can cause kidney damage and lead to kidney failure without treatment.

## Prevention

There’s no proven way to prevent glomerulonephritis. Adopting a healthy lifestyle is the best approach, though some practices may help, such as:

* Eating a balanced diet and unprocessed food.
* Managing high blood pressure with a low-salt diet, exercise and medication.
* Managing diabetes.
* Preventing infections by practicing good hygiene and safe sex.
* Seeing a healthcare provider whenever you think you have an infection like strep throat.
* Using any over-the-counter (OTC) pain medication as directed.

## Living With

If you have glomerulonephritis, get your kidneys checked on a regular basis. Follow medical advice and take medication as prescribed by your provider to manage the cause. You also may have to limit the amount of salt and protein you eat. These ingredients put stress on your kidneys.

### Is glomerulonephritis a serious disease?

It can lead to kidney disease or kidney failure in some people. Both of these conditions are serious. It’s important to see your healthcare provider each year so they can be made aware of changes in your body or health history. This can help them detect conditions like glomerulonephritis, which causes no symptoms in some people.

### When should I see my healthcare provider?

Contact your healthcare provider if you have symptoms like:

* Blood in your pee (hematuria) or other changes in the appearance of your pee.
* Changes in how often you pee.
* Joint pain.
* Swelling in your legs or face.
* Shortness of breath.

**DIFFERENTIAL DIAGNOSIS**

Based on the clinical presentation, differentiation needs to be drawn between the nephrotic and the nephritic spectrum. This is important as it helps to narrow down the differentials of the underlying glomerular pathology. Also, differential diagnoses will include primary versus secondary causes depending on the age group and clinical picture.

Primary glomerulonephritis presenting as the nephrotic syndrome in young patients is likely to be minimal change disease, while in adults, membranous variety is more likely. In the secondary category, diabetes mellitus has to be ruled out.

When nephritic syndrome is the main presentation in children, it is likely post-infectious. In adults, however, IgA nephropathy should be considered. When systemic vasculitis involves glomeruli, the cause in the younger age group is Henoch Schonlein purpura, while in adults, granulomatosis with polyangiitis should be suspected. Lupus nephritis is seen more commonly in young women (20 to 30 years).

**Differential Diagnoses**

Following are some important differentials to be considered while making the diagnosis of glomerulonephritis:

* Acute kidney injury
* Crescentic glomerulonephritis
* Diffuse proliferative glomerulonephritis
* Focal segmental glomerulonephritis
* Glomerulonephritis associated with non streptococcal infection
* Goodpasture syndrome
* Lupus nephritis
* Membranoproliferative glomerulonephritis
* Poststreptococcal glomerulonephritis
* Rapidly progressive glomerulonephritis

The following renal syndromes frequently mimic the early stages of acute GN:

* Idiopathic hematuria
* Chronic GN with an acute exacerbation
* Anaphylactoid purpura with nephritis
* Familial nephritis

**EPIDEMIOLOGY**

Glomerulonephritis (GN) is a prominent cause of renal impairment. It leads to 10% to 15% of end-stage renal disease cases in the United States. In most instances, the disease becomes progressive without timely intervention, eventually leading to morbidity. This makes chronic glomerulonephritis the third most common cause of end-stage renal disease in the United States, following diabetes mellitus and hypertension, accounting for 10% of patients on dialysis.

Glomerulonephritis constitutes 25% to 30% of all end-stage renal disease cases—about a quarter of patients present with nephritic syndrome. Progression, in most cases, is relatively quick, and end-stage renal disease may ensue within weeks or months of the beginning of acute nephritic syndrome.

IgA nephropathy has been found to be the most common cause of glomerulonephritis worldwide. However, the incidence of post-streptococcal glomerulonephritis has declined in most developed countries. As reported by Japanese researchers, the incidence of postinfectious glomerulonephritis in their country climaxed in the 1990s. Post-streptococcal glomerulonephritis, which accounted for nearly all cases of postinfectious GN in the 1970s, has reduced to about 40-50% since the 1990s, while the percentage of *Staphylococcus aureus*–related nephritis rose to 30%, and hepatitis C virus-associated glomerulonephritis also increased.

Post-streptococcal glomerulonephritis remains much more prevalent in regions such as the Caribbean, Africa, India, Pakistan, Papua New Guinea, South America, and Malaysia. In Port Harcourt, Nigeria, acute glomerulonephritis in the pediatric age group 3-16 years was 15.5 cases/year, with a male-to-female ratio of 1.1:1; it is not much different currently.

An Ethiopian study from a regional dialysis center found that acute glomerulonephritis was the second most common cause of acute kidney failure requiring dialysis, comprising about 22% of cases. Geographic and seasonal variations in the occurrence of PSGN are more pronounced for pharyngeal-associated GN than in cutaneously-associated disease.

**Age-, Gender-, and Race-related Demographics**

Acute nephritis can appear at any age, including infancy. Post-streptococcal glomerulonephritis usually develops in the pediatric population aged 5-15 years. Only 10% of cases occur in patients 40 years old or above. Outbreaks are common in children around six years old.

Acute glomerulonephritis affects males more than females, with a male-to-female ratio of 2 to 1. Postinfectious glomerulonephritis has no predilection for racial or ethnic groups.

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**SIMPLE PULMONARY EOSINOPHILIA**

**DEFINITION AND DESCRIPTION**

Simple pulmonary eosinophilia (SPE), also known as Loeffler syndrome, is a rare, temporary (transient) respiratory disorder characterized by the accumulation of eosinophils in the lungs (pulmonary eosinophilia). Eosinophils are a type of white blood cell and are part of the immune system. They are usually produced in response to allergens, inflammation or infection and are particularly active in the respiratory tract. Most cases of SPE are thought to be due to an allergic reaction to drugs or infection (mainly parasites). SPE usually ranges in severity from no symptoms to development of mild respiratory symptoms. In rare cases, more significant complications can occur. Generally, no specific therapy is required as symptoms usually go away spontaneously without treatment.

Introduction

Simple pulmonary eosinophilia was first described in the medical literature in 1932. It is classified as a form of eosinophilic lung disease. SPE is considered a benign, self-limiting disorder.

### Causes

Generally, SPE is caused by an allergic reaction. A variety of factors including parasitic infection, exposure to certain drugs or exposure to certain fungi have been linked to SPE. In some people with SPE, the triggering event or cause of SPE is unknown (idiopathic). The exact reason why there is an overproduction and accumulation of eosinophils in the lungs in individuals with SPE is not fully understood.

The passage of parasitic larvae through the lungs causes most cases, which results in an allergic reaction. Parasitic worms (helminths) such as nematodes are the most common parasitic cause associated with SPE. The term nematode is a classification (i.e., phylum) of worms characterized by long, round, generally smooth bodies. Nematodes that have been linked to SPE include hookworms and Ascaris lumbricoides, a type of roundworm.

Drugs that have been linked to cases of SPE include nonsteroidal anti-inflammatory drugs (NSAIDs), certain antibiotics, anti-microbialsand anti-seizure medications (anticonvulsants).

Some cases of SPE have been caused by exposure to certain fungi such as Aspergillus fumigatus.

### Signs & Symptoms

SPE usually presents as a mild lung disorder characterized by a dry, unproductive cough, wheezing and a slight fever. Some affected individuals may cough up a mixture of saliva and mucus (sputum). Symptoms usually resolve on their own without treatment (spontaneous resolution) within two weeks to a month. In some people, symptoms can persist for months, especially if the person is exposed to the allergen again.

Additional symptoms can occur including chest pain, wheezing, shortness of breath (dyspnea) and a rapid breathing rate. Some individuals may complain of a general feeling of poor health (malaise). Inflammation of the mucous membranes of the nose (rhinitis), unintended weight loss and night sweats have also been reported.

Some individuals with SPE develop acute eosinophilic pneumonia (AEP). AEP is a rare, serious lung disorder that can quickly progress to cause acute respiratory failure. (For more information on AEP, see the related disorders section below).

### Diagnosis

A diagnosis of SPE is based upon identification of characteristic symptoms (e.g., eosinophilic pneumonia), a detailed patient history, a thorough clinical evaluation, the absence of other known causes of eosinophilic lung disease and a variety of specialized tests. A physical examination may reveal wheezing and/or a rattling sound in the lungs (rales). Distinguishing SPE from other, more severe forms of pulmonary eosinophilia is especially important when obtaining a diagnosis.

*Clinical Testing and Work-Up*Imaging techniques may be used to help confirm a diagnosis of SPE including chest x-ray or computerized tomography (CT) scanning. Chest x-rays in individuals with SPE generally show white patches or shadows (infiltrates) in the lungs. These infiltrates may disappear but can reappear in different areas of the lungs. A CT scan may reveal hazy areas (ground-glass opacities) that are not seen on traditional x-rays. During CT scanning, a computer and x-rays are used to create a film showing cross-sectional images of tissue structures such as the lungs. A CT scan can also show airspace consolidation, in which the tiny air sacs of the lungs (alveolar) become abnormally filled (as with eosinophils).

A procedure known as bronchoalveolar lavage (BAL) may also be used to help obtain a diagnosis of SPE. During BAL, a narrow tube (bronchoscope) is slid down the windpipe into the lungs and a sterile solution is passed through the tube washing out (lavaging) cells. This fluid is collected and then the tube is removed, allowing the cells to be studied. BAL in individuals with SPE reveals abnormally high levels of eosinophils.

Blood tests may reveal elevated levels of eosinophils (i.e., eosinophilia) and/or serum immunoglobulin E (IgE) and may coincide with pulmonary manifestations. A stool examination may reveal the presence of parasites. Analysis of sputum or fluid obtained from pumping the stomach (gastric lavage) may reveal parasitic larvae.

Additional tests may be performed to rule out other causes of pulmonary eosinophilia.

### Standard Therapies

Treatment

In most patients, no treatment is required and SPE goes away on its own (spontaneous remission). Cases due to active parasitic infection should be treated with appropriate anti-parasitic medications. Drug-induced cases should be treated by stopping the suspected offending drug. Respiratory symptoms such as wheeze and cough may be managed with inhaled bronchodilators. In rare cases, after active infection has been ruled out, corticosteroid therapy may be required and is generally effective.

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## Outlook (Prognosis)

The disease often goes away without treatment. If treatment is needed, the response is usually good. But, the disease can come back, especially if the condition does not have a specific cause and needs to be treated with corticosteroids.

## Possible Complications

A rare complication of simple pulmonary eosinophilia is a severe type of pneumonia called acute idiopathic eosinophilic pneumonia.

## When to Contact a Medical Professional

See your provider if you have symptoms that may be linked with this disorder.

## Prevention

This is a rare disorder. Many times, the cause cannot be found. Minimizing exposure to possible risk factors, such as certain medicines or parasites, may reduce the chance of developing this disorder.

## Alternative Names

Pulmonary infiltrates with eosinophilia; Loffler syndrome; Eosinophilic pneumonia; Pneumonia - eosinophilic

## Differential Diagnoses of SPE

1. Parasitic Infections
   * Ascariasis (larval migration causing transient infiltrates)
   * Strongyloidiasis
   * Other helminthic infections causing pulmonary eosinophilia
2. Allergic Bronchopulmonary Aspergillosis (ABPA)
   * Asthma or cystic fibrosis patients with bronchiectasis, elevated IgE, and eosinophilia.
   * Radiology shows tubular opacities and mucus plugging.
3. Acute Eosinophilic Pneumonia (AEP)
   * Rapid onset respiratory failure, often after inhalation exposures (smoking, dust).
   * Peripheral eosinophilia may be absent early.
4. Chronic Eosinophilic Pneumonia (CEP)
   * Subacute to chronic symptoms (>1 month), marked peripheral eosinophilia, asthma history common.
   * Peripheral lung consolidation on imaging.
5. Eosinophilic Granulomatosis with Polyangiitis (EGPA / Churg-Strauss Syndrome)
   * Systemic vasculitis with asthma, eosinophilia, neuropathy, and other organ involvement.
   * Positive ANCA in many cases.
6. Hypereosinophilic Syndrome (HES)
   * Persistent eosinophilia with multi-organ involvement including lungs, heart, and skin.
7. Drug-Induced Pulmonary Eosinophilia
   * Reactions to medications such as sulfonamides, NSAIDs, antibiotics.
8. Fungal Infections
   * Other than ABPA, fungal pneumonias with eosinophilic response (e.g., coccidioidomycosis).
9. Other Causes of Pulmonary Infiltrates with Eosinophilia
   * Sarcoidosis (rarely eosinophilic)
   * Lymphoma or other malignancies with eosinophilic infiltration
   * Idiopathic eosinophilic lung diseases

**Epidemiology of Simple Pulmonary Eosinophilia (SPE / Loeffler Syndrome)**

* Prevalence and Incidence:
  + The exact incidence and prevalence of SPE in the general population are unknown due to its transient and often mild nature.
  + SPE is considered the most common form of eosinophilic lung disease.
  + It can affect individuals of any age and occurs equally in males and females.
  + SPE is generally rarely symptomatic and often self-limited, which may contribute to underdiagnosis.
* Demographics:
  + No clear sex or racial predilection has been identified for SPE.
  + It can occur worldwide and is not restricted to specific geographic regions.
* Relation to Other Eosinophilic Lung Diseases:
  + SPE is distinct from chronic eosinophilic pneumonia (CEP), which is rarer and shows a female predominance (2:1) and peak incidence in the 30–45 years age group.
  + Unlike CEP, SPE usually resolves within weeks without treatment.
* Etiology and Risk Factors:
  + SPE often results from transient eosinophilic infiltration triggered by parasitic infections (e.g., Ascaris), drug reactions, or unknown causes.
  + It is sometimes linked to parasitic larval migration in endemic areas.
* Imaging and Laboratory Findings:
  + Radiographically, SPE shows transient migratory pulmonary infiltrates.
  + Peripheral blood eosinophilia is typically mild to moderate.

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**GRAVES DISEASE**

**DEFINITION AND DESCRIPTION**

Graves’ disease is an autoimmune disease that leads to a generalized overactivity of the entire thyroid gland (*hyperthyroidism*). It is the most common cause of hyperthyroidism in the United States. It is named after Robert Graves, an Irish physician, who described this form of hyperthyroidism about 150 years ago. It is 7-8 times more common in women than men.

**CAUSES**

Graves’ disease is triggered by a process in the body’s immune system, which normally protects us from foreign invaders such as bacteria and viruses. The immune system destroys foreign invaders with substances called antibodies produced by blood cells known as lymphocytes. Sometimes the immune system can be tricked into making antibodies that cross-react with proteins on our own cells. In many cases these antibodies can cause destruction of those cells. In Graves’ disease these antibodies (called the thyrotropin receptor antibodies (TRAb) or thyroid stimulating immunoglobulins (TSI) do the opposite – they cause the cells to work overtime. The antibodies in Graves’ disease bind to receptors on the surface of thyroid cells and stimulate those cells to overproduce and release thyroid hormones. This results in an overactive thyroid (*hyperthyroidism*)

**Risk factors**

Factors that can increase the risk of Graves' disease include:

* **Family history.** People who get Graves' disease often have a family history of thyroid conditions or an autoimmune condition.
* **Sex.** Women are much more likely to get Graves' disease than are men.
* **Age.** Graves' disease mostly happens between the ages of 30 and 60.
* **Another autoimmune condition.** People with other conditions of the immune system, such as type 1 diabetes or rheumatoid arthritis, have a higher risk.
* **Smoking.** Cigarette smoking, which can affect the immune system, raises the risk of Graves' disease. People who smoke and have Graves' disease are at higher risk of getting thyroid eye disease.

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**SIGNS AND SYMPTOMS**

Common symptoms of Graves' disease include:

* Feeling nervous and irritable.
* Having a slight tremor of the hands or fingers.
* Being sensitive to heat with an increase in sweating or warm, moist skin.
* Losing weight, despite wanting to eat more.
* Having an enlarged thyroid gland, also called goiter.
* Having changes in menstrual cycles.
* Not being able to get or keep an erection, called erectile dysfunction, or having less desire for sex.
* Having bowel movements often.
* Having bulging eyes — a condition called thyroid eye disease or Graves' ophthalmopathy.
* Being tired.
* Having thick, discolored skin mostly on the shins or tops of the feet, called Graves' dermopathy.
* Having fast or irregular heartbeat, called palpitations.
* Not sleeping well.
* *Hyperthyroidism*The majority of symptoms of Graves’ disease are caused by the excessive production of thyroid hormones by the thyroid gland. These may include, but are not limited to, racing heartbeat, hand tremors, trouble sleeping, weight loss, muscle weakness, neuropsychiatric symptoms and heat intolerance.
* *Eye disease*Graves’ disease is the only kind of hyperthyroidism that can be associated with inflammation of the eyes, swelling of the tissues around the eyes and bulging of the eyes (called *Graves’ ophthalmopathy or orbitopathy*). Overall, a third of patients with Graves’ disease develop some signs and symptoms of Graves’ eye disease but only 5% have moderate-to-severe inflammation of the eye tissues to cause serious or permanent vision trouble. Patients who have any suggestion of eye symptoms should seek an evaluation with an eye doctor (an ophthalmologist) as well as their endocrinologist.  
  Eye symptoms most often begin about six months before or after the diagnosis of Graves’ disease has been made. Seldom do eye problems occur long after the disease has been treated. In some patients with eye symptoms, hyperthyroidism never develops and, rarely, patients may be hypothyroid. The severity of the eye symptoms is not related to the severity of hyperthyroidism.  
  Early signs of trouble might be red or inflamed eyes, a bulging of the eyes due to inflammation of the tissues behind the eyeball or double vision. Diminished vision or double vision are rare problems that usually occur later, if at all. We do not know why, but problems with the eyes occur much more often and are more severe in people with Graves’ disease who smoke cigarettes.
* *Skin disease*Rarely, patients with Graves’ disease develop a lumpy reddish thickening of the skin in front of the shins known as pretibial myxedema (called Graves’ dermopathy). This skin condition is usually painless and relatively mild, but it can be painful for some. Like the eye trouble of Graves’ disease, the skin problem does not necessarily begin precisely when the hyperthyroidism starts. Its severity is not related to the level of thyroid hormone.

**DIAGNOSIS AND TESTS**

The diagnosis of hyperthyroidism is made on the basis of your symptoms and findings during a physical exam and it is confirmed by laboratory tests that measure the amount of thyroid hormones (thyroxine, or T4, and triiodothyronine, or T3) and thyroid-stimulating hormone (TSH) in your blood Clues that your hyperthyroidism is caused by Graves’ disease are the presence of Graves’ eye disease and/or dermopathy (see above), a symmetrically enlarged thyroid gland and a history of other family members with thyroid or other autoimmune problems, including type 1 diabetes, rheumatoid arthritis, pernicious anemia (due to lack of vitamin B12) or painless white patches on the skin known as vitiligo.

The choice of initial diagnostic testing depends on cost, availability and local expertise. Measurement of antibodies, such as TRAb or TSI, is cost effective and if positive, confirms the diagnosis of Graves’ disease without further testing needed. If this test is negative (which can also occur in some patients with Graves’ disease), or if this test is not available, then your doctor should refer you to have a radioactive iodine uptake test (RAIU) to confirm the diagnosis.

Also, in some patients, measurement of thyroidal blood flow with ultrasonography may be useful to establish the diagnosis if the above tests are not readily available.

TREATMENT

All hyperthyroid patients should be initially treated with beta-blockers. Treatment options to control Graves’ disease hyperthyroidism include antithyroid drugs (generally methimazole [Tapazole®], although propylthiouracil [PTU] may be used in rare instances such as the first trimester of pregnancy), radioactive iodine and surgery.

Antithyroid medications are typically preferred in patients who have a high likelihood of remission (women, mild disease, small goiters, negative or low titer of antibodies). These medications do not cure Graves’ hyperthyroidism, but when given in adequate doses are effective in controlling the hyperthyroidism.

If methimazole is chosen, it can be continued for 12-18 months and then discontinued if TSH and TRAb levels are normal at that time. If TRAb levels remain elevated, the chances of remission are much lower and prolonging treatment with antithyroid drugs is safe and may increase chances of remission. Long term treatment of hyperthyroidism with antithyroid drugs may be considered in selected cases.

If your hyperthyroidism due to Graves’ disease persists after 6 months, then your doctor may recommend definitive treatment with either radioactive iodine or surgery.

If surgery (thyroidectomy) is selected as the treatment modality, the surgery should be performed by a skilled surgeon with expertise in thyroid surgery to reduce the risk of complications.

Your doctor should discuss each of the treatment options with you including the logistics, benefits and potential side effects, expected speed of recovery and costs. Although each treatment has its advantages and disadvantages, most patients will find one treatment plan that is right for them. Hyperthyroidism due to Graves’ disease is, in general, controllable and safely treated and treatment is almost always successful.

**Complications of Graves' disease can include**:

* **Pregnancy health concerns.** Graves' disease during pregnancy can cause miscarriage, early birth, fetal thyroid issues and poor fetal growth. It also can cause heart failure and preeclampsia in the pregnant person. Preeclampsia leads to high blood pressure and other serious symptoms.
* **Heart conditions.** Graves' disease that isn't treated can lead to irregular heart rhythms and changes in the heart and how it works. The heart might not be able to pump enough blood to the body. That condition is called heart failure.
* **Thyroid storm.** This rare but deadly complication of Graves' disease also is called accelerated hyperthyroidism or thyrotoxic crisis. It's more likely to happen when severe hyperthyroidism is not treated or not treated well enough.  
  Thyroid storm happens when a sudden and drastic rise in thyroid hormones causes a number of effects in the body. They include fever, sweating, confusion, delirium, severe weakness, tremors, irregular heartbeat, severe low blood pressure and coma. Thyroid storm needs medical attention right away.
* **Brittle bones.** Hyperthyroidism that isn't treated can lead to weak, brittle bones — a condition called osteoporosis. The strength of the bones depends, in part, on the amount of calcium and other minerals they hold. Too much thyroid hormone makes it hard for the body to get calcium into the bones.

**Lifestyle and home remedies**

If you have Graves' disease, it's important to take care of your mental and physical health. This includes:

* **Eating well and exercising.** These can help ease some symptoms during treatment and help you feel better overall. Your thyroid controls how you burn calories. So you may gain weight when the hyperthyroidism is corrected.  
  Brittle bones also can happen with Graves' disease. Weight-bearing exercises can help keep bones strong.
* **Easing stress.** Stress can trigger Graves' disease or make it worse. Listening to music, taking a warm bath or walking can help you relax and put you in a better mood.

Work with your healthcare team to design a plan that makes eating well, exercising and relaxing part of each day.

**PROGNOSIS**

If you receive definitive treatment for your Graves’ hyperthyroidism (such as radioactive iodine or surgery), you will eventually develop hypothyroidism (underactive thyroid). Even if you are treated with antithyroid drugs alone, hypothyroidism can still occur. Your doctor will check your *thyroid function tests* frequently to assess thyroid function following treatment. When hypothyroidism occurs, you will need to take a thyroid hormone tablet once a day at the right dose

**Diagnostic Considerations**

A summary of the differential diagnosis for thyrotoxicosis is as follows:

* Graves disease: Special features include a diffusely enlarged thyroid gland, thyroid bruits, ophthalmopathy, pretibial myxedema, and the presence of TSIs.
* Subacute thyroiditis: Special features include a history of antecedent respiratory tract infection, neck tenderness, elevated sedimentation rate, low or absent radioactive iodine uptake, and a self-limited course.
* Silent thyroiditis: Special features include painless thyroiditis, which may be seen in postpartum women (postpartum thyroiditis); a self-limited course; and low radioiodine uptake.
* Multinodular toxic goiter: Special features include a propensity to occur in elderly individuals and multiple nodules palpated or observed after thyroid scanning.
* Toxic adenoma: Special features include a solitary palpable nodule and a hot nodule observed after thyroid scanning.
* Factitious thyrotoxicosis: Special features include no goiter, a low thyroglobulin level, and low radioiodine uptake.
* Iatrogenic thyrotoxicosis: The special feature is a history of thyroid hormone intake.
* Iodide-induced thyrotoxicosis: The special feature is a propensity to occur in patients with a history of nodular thyroid disease who have been exposed to iodine-containing contrast agents or drugs such as amiodarone.
* TSH-secreting pituitary adenoma: Special features include inappropriately elevated or normal TSH levels in the setting of elevated free levothyroxine (T4) and free triiodothyronine (T3) levels, evidence of other pituitary hormone deficiencies, elevated alpha subunit level, and compressive symptoms.

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## Epidemiology

### Frequency

*United States*

Graves disease is the most common cause of hyperthyroidism in the United States. A study conducted in Olmstead County, Minnesota estimated the incidence to be approximately 30 cases per 100,000 persons per year.The prevalence of maternal thyrotoxicosis is approximately 1 case per 500 persons, with maternal Graves disease being the most common etiology. Commonly, patients have a family history involving a wide spectrum of autoimmune thyroid diseases, such as Graves disease, Hashimoto thyroiditis, or postpartum thyroiditis, among others.

*International*

Among the causes of spontaneous thyrotoxicosis, Graves disease is the most common. Graves disease represents 60-90% of all causes of thyrotoxicosis in different regions of the world. In the Wickham Study in the United Kingdom, the incidence was reported to be 100-200 cases per 100,000 population per year.The incidence in women in the UK has been reported to be 80 cases 100,000 per year.

### Mortality/Morbidity

If left untreated, Graves disease can cause severe thyrotoxicosis. A life-threatening thyrotoxic crisis (ie, thyroid storm) can occur. Long-standing severe thyrotoxicosis leads to severe weight loss with catabolism of bone and muscle.Cardiac complications and psycho cognitive complications can cause significant morbidity. Graves disease is also associated with ophthalmopathy, dermopathy, and acropachy.

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**CELIAC DISEASES**

**DEFINITION AND DESCRIPTION**

Celiac disease is an illness caused by an immune reaction to eating gluten. Gluten is a protein found in foods containing wheat, barley or rye.

If you have celiac disease, eating gluten triggers an immune response to the gluten protein in your small intestine. Over time, this reaction damages your small intestine's lining and prevents it from absorbing nutrients, a condition called malabsorption.

The intestinal damage often causes symptoms such as diarrhea, fatigue, weight loss, bloating or anemia. It also can lead to serious complications if it is not managed or treated. In children, malabsorption can affect growth and development in addition to gastrointestinal symptoms.

There's no definite cure for celiac disease. But for most people, following a strict gluten-free diet can help manage symptoms and help the intestines heal.

**CAUSES**

Your genes, combined with eating foods with gluten and other factors, can contribute to celiac disease. However, the precise cause isn't known. Infant-feeding practices, gastrointestinal infections and gut bacteria may contribute, but these causes have not been proved. Sometimes celiac disease becomes active after surgery, pregnancy, childbirth, viral infection or severe emotional stress.

When the body's immune system overreacts to gluten in food, the reaction damages the tiny, hairlike projections, called villi, that line the small intestine. Villi absorbs vitamins, minerals and other nutrients from the food you eat. If your villi are damaged, you can't get enough nutrients, no matter how much you eat.

**RISK FACTOR**

Celiac disease tends to be more common in people who have:

* A family member with celiac disease or dermatitis herpetiformis.
* Type 1 diabetes.
* Down syndrome, William syndrome or Turner syndrome.
* Autoimmune thyroid disease.
* Microscopic colitis.
* Addison's disease.

**Symptoms**

The symptoms of celiac disease can vary greatly. They also may be different in children and adults. Digestive symptoms for adults include:

* Diarrhea.
* Fatigue.
* Weight loss.
* Bloating and gas.
* Abdominal pain.
* Nausea and vomiting.
* Constipation.

However, more than half the adults with celiac disease have symptoms that are not related to the digestive system, including:

* Anemia, usually from iron deficiency due to decreased iron absorption.
* Loss of bone density, called osteoporosis, or softening of bones, called osteomalacia.
* Itchy, blistery skin rash, called dermatitis herpetiformis.
* Mouth ulcers.
* Headaches and fatigue.
* Nervous system injury, including numbness and tingling in the feet and hands, possible problems with balance, and cognitive impairment.
* Joint pain.
* Reduced functioning of the spleen, known as hyposplenism.
* Elevated liver enzymes.

### Children

Children with celiac disease are more likely than adults to have digestive problems, including:

* Nausea and vomiting.
* Chronic diarrhea.
* Swollen belly.
* Constipation.
* Gas.
* Pale, foul-smelling stools.

The inability to absorb nutrients might result in:

* Failure to thrive for infants.
* Damage to tooth enamel.
* Weight loss.
* Anemia.
* Irritability.
* Short stature.
* Delayed puberty.
* Neurological symptoms, including attention-deficit/hyperactivity disorder (ADHD), learning disabilities, headaches, lack of muscle coordination and seizures.

### Dermatitis herpetiformis

Gluten intolerance can cause this blistery skin disease. The rash usually occurs on the elbows, knees, torso, scalp or buttocks. This condition is often associated with changes to the lining of the small intestine identical to those of celiac disease, but the skin condition might not cause digestive symptoms.

Health care professionals treat dermatitis herpetiformis with a gluten-free diet or medicine, or both, to control the rash.

**DIAGNOSIS AND TESTS**

Many people with celiac disease don't know they have it. Two blood tests can help diagnose it:

* **Serology testing** looks for antibodies in your blood. Elevated levels of certain antibody proteins indicate an immune reaction to gluten.
* **Genetic testing** for human leukocyte antigens (HLA-DQ2 and HLA-DQ8) can be used to rule out celiac disease.

It's important to be tested for celiac disease before trying a gluten-free diet. Eliminating gluten from your diet might make the results of blood tests appear in the standard range.

If the results of these tests indicate celiac disease, one of the following tests will likely be ordered:

* **Endoscopy.** This test uses a long tube with a tiny camera that's put into your mouth and passed down your throat. The camera enables the practitioner to view your small intestine and take a small tissue sample, called a biopsy, to analyze for damage to the villi.
* **Capsule endoscopy.** This test uses a tiny wireless camera to take pictures of your entire small intestine. The camera sits inside a vitamin-sized capsule, which you swallow. As the capsule travels through your digestive tract, the camera takes thousands of pictures that are transmitted to a recorder. This test is used in some situations where an exam of the entire or end of the small intestine is desired.

If you might have dermatitis herpetiformis, your health care professional may take a small sample of skin tissue to examine under a microscope.

If you're diagnosed with celiac disease, additional testing may be recommended to check your nutritional status. This includes levels of vitamins A, B-12, D and E, as well as mineral levels, hemoglobin and liver enzymes. Your bone health also may be checked with a bone density scan.

**Treatment**

A strict, lifelong gluten-free diet is the only way to manage celiac disease. Besides wheat, foods that contain gluten include:

* Barley.
* Bulgur.
* Durum.
* Farina.
* Graham flour.
* Malt.
* Rye.
* Semolina.
* Spelt (a form of wheat).
* Triticale.

A dietitian who works with people with celiac disease can help you plan a healthy gluten-free diet. Even trace amounts of gluten in your diet can be damaging, even if they don't cause symptoms.

Gluten can be hidden in foods, medicines and nonfood products, including:

* Modified food starch, preservatives and food stabilizers.
* Prescription and over-the-counter medications.
* Vitamin and mineral supplements.
* Herbal and nutritional supplements.
* Lipstick products.
* Toothpaste and mouthwash.
* Communion wafers.
* Envelope and stamp glue.
* Play dough.
* Certain makeup products.

Removing gluten from your diet will typically reduce inflammation in your small intestine, causing you to feel better and eventually heal. Children tend to heal more quickly than adults.

### Vitamin and mineral supplements

If your anemia or nutritional deficiencies are severe, supplements may be recommended, including:

* Copper.
* Folic acid.
* Iron.
* Vitamin B-12.
* Vitamin D.
* Vitamin K.
* Zinc.

Vitamins and supplements are usually taken in pill form. If your digestive tract has trouble absorbing vitamins, you might be able to get them by injection.

### Follow-up care

Medical follow-up at regular intervals can ensure that your symptoms have responded to a gluten-free diet. Your health care team may monitor your response with blood tests. Nutritional markers also are checked regularly.

For most people with celiac disease, eating a gluten-free diet allows the small intestine to heal. For children, that usually takes 3 to 6 months. For adults, complete healing might take several years.

If you continue to have symptoms or if symptoms recur, you might need an endoscopy with biopsies to determine whether your intestine has healed.

### Medications to control intestinal inflammation

If your small intestine is severely damaged or you have refractory celiac disease, steroids may be recommended to control inflammation. Steroids can ease severe symptoms of celiac disease while the intestine heals.

Other drugs, such as azathioprine (Azasan, Imuran) or budesonide (Entocort EC, Uceris), might be used.

### Treating dermatitis herpetiformis

If you have this skin rash, a medicine called dapsone may be recommended in addition to a gluten-free diet. Dapsone is taken by mouth. If you take dapsone, you'll need regular blood tests to check for side effects.

### Refractory celiac disease

With refractory celiac disease, the small intestine doesn't heal. Refractory celiac disease can be quite serious, and there is currently no proven treatment. If you have refractory celiac disease, you may want to seek medical care at a specialized center.

**Lifestyle and home remedies**

If you've been diagnosed with celiac disease, you'll need to avoid all foods that contain gluten. Ask your health care team for a referral to a dietitian, who can help you plan a healthy gluten-free diet.

### Read labels

Avoid packaged foods unless they're labeled as gluten-free or have no gluten-containing ingredients, including emulsifiers and stabilizers that can contain gluten. In addition to cereals, pastas and baked goods, other packaged foods that can contain gluten include:

* Beers, lagers, ales and malt vinegars.
* Candies.
* Gravies.
* Imitation meats or seafood.
* Processed luncheon meats.
* Rice mixes.
* Salad dressings and sauces, including soy sauce.
* Seasoned snack foods, such as tortilla and potato chips.
* Seitan.
* Self-basting poultry.
* Soups.

Pure oats aren't harmful for most people with celiac disease, but oats can be contaminated by wheat during growing and processing. Ask your health care team if you can try eating small amounts of pure oat products.

### Allowed foods

Many basic foods are allowed in a gluten-free diet, including:

* Eggs.
* Fresh meats, fish and poultry that aren't breaded, batter-coated or marinated.
* Fruits.
* Lentils.
* Most dairy products, unless they make your symptoms worse.
* Nuts.
* Potatoes.
* Vegetables.
* Wine and distilled liquors, ciders and spirits.

Grains and starches allowed in a gluten-free diet include:

* Amaranth.
* Buckwheat.
* Corn.
* Cornmeal.
* Gluten-free flours (rice, soy, corn, potato, bean).
* Pure corn tortillas.
* Quinoa.
* Rice.
* Tapioca.
* Wild rice.

**Complications**

Celiac disease that is not treated can lead to:

* **Malnutrition.** This occurs if your small intestine can't absorb enough nutrients. Malnutrition can lead to anemia and weight loss. In children, malnutrition can cause slow growth and short stature.
* **Bone weakening.** In children, malabsorption of calcium and vitamin D can lead to a softening of the bone, called osteomalacia or rickets. In adults, it can lead to a loss of bone density, called osteopenia or osteoporosis.
* **Infertility and miscarriage.** Malabsorption of calcium and vitamin D can contribute to reproductive issues.
* **Lactose intolerance.** Damage to your small intestine might cause you abdominal pain and diarrhea after eating or drinking dairy products that contain lactose. Once your intestine has healed, you might be able to tolerate dairy products again.
* **Cancer.** People with celiac disease who don't maintain a gluten-free diet have a greater risk of developing several forms of cancer, including intestinal lymphoma and small bowel cancer.
* **Nervous system conditions.** Some people with celiac disease can develop conditions such as seizures or a disease of the nerves to the hands and feet, called peripheral neuropathy.

### Nonresponsive celiac disease

Some people with celiac disease don't respond to what they consider to be a gluten-free diet. Nonresponsive celiac disease is often due to contamination of the diet with gluten. Working with a dietitian can help you learn how to avoid all gluten.

People with nonresponsive celiac disease might have:

* Bacterial overgrowth in the small intestine.
* Microscopic colitis.
* Poor pancreas function, known as pancreatic insufficiency.
* Irritable bowel syndrome.
* Difficulty digesting sugar found in dairy products (lactose), table sugar (sucrose), or a type of sugar found in honey and fruits (fructose).
* Truly refractory celiac disease that is not responding to a gluten-free diet.

### Refractory celiac disease

In rare instances, the intestinal injury of celiac disease doesn't respond to a strict gluten-free diet. This is known as refractory celiac disease. If you still have symptoms after following a gluten-free diet for 6 months to 1 year, you should talk to your health care team to see if you need further testing to look for explanations for your symptoms.

### When to see a doctor

Consult your health care team if you have diarrhea or digestive discomfort that lasts for more than two weeks. Consult your child's health care team if your child:

* Is pale.
* Is irritable.
* Is failing to grow.
* Has a potbelly.
* Has foul-smelling, bulky stools.

Be sure to consult your health care team before trying a gluten-free diet. If you stop or even reduce the amount of gluten you eat before you're tested for celiac disease, you can change the test results.

Celiac disease tends to run in families. If someone in your family has the condition, ask a member of your health care team if you should be tested. Also ask about testing if you or someone in your family has a risk factor for celiac disease, such as type 1 diabetes.

**Differential Diagnosis for Celiac Disease (Sprue)**:

1. Tropical sprue
2. Adult-onset autoimmune enteropathy
3. Hypogammaglobulinemia (e.g., Common Variable Immunodeficiency)
4. Idiopathic AIDS enteropathy
5. Food protein hypersensitivity (food allergy)
6. Eosinophilic gastroenteritis
7. Whipple disease
8. Abetalipoproteinemia
9. Intestinal lymphoma
10. Collagenous sprue
11. Intestinal tuberculosis
12. Giardiasis
13. Crohn’s disease
14. Small-bowel bacterial overgrowth
15. Infectious enteritis
16. Parasitic infestation
17. Severe malnutrition
18. Small-bowel ischemia
19. Inflammatory bowel disease (IBD)
20. Irritable bowel syndrome (IBS)
21. Cystic fibrosis
22. Microscopic colitis
23. Diverticular disease
24. Peptic ulcer disease
25. Small bowel adenocarcinoma (malignancy)

**EPIDEMIOLOGY**

Celiac disease affects approximately 1% of the global population. Serologic testing estimates its prevalence at 1.4%, while small intestinal biopsy, performed less frequently, indicates a prevalence of 0.7%. The occurrence varies by geographic region, with higher rates observed in populations of European descent, as well as in individuals from Saudi Arabia and the Saharawi, an ethnic group indigenous to the Western Sahara. Women are diagnosed more frequently than men, possibly due to hormonal influences, genetic susceptibility, and a greater tendency to seek medical care for symptoms.

Celiac disease is more prevalent among individuals with other autoimmune disorders, such as type-1 diabetes, with rates ranging from 1.6% to 16.4%, significantly higher than in the general population. This association is likely due to shared genetic susceptibility, particularly the *HLA-DQ2* and *HLA-DQ8* haplotypes, which are common in both celiac disease and various autoimmune conditions. First-degree relatives of individuals with celiac disease have an increased prevalence of approximately 7.5%, with the highest risk seen in monozygotic twins (>70%), followed by siblings (8.9%), offspring (7.9%), and parents (3.0%).

Pediatric patients are more likely to receive an earlier diagnosis than adults due to differences in clinical presentation. Children often exhibit classic signs of malabsorption, such as chronic diarrhea and growth failure, which prompt earlier evaluation. In contrast, adults frequently present with nonspecific symptoms, including abdominal pain, anemia, and chronic fatigue, leading to delayed diagnosis. Additionally, increased awareness and routine screening in pediatric populations facilitate earlier detection, whereas many adult cases go undiagnosed for extended periods.

Adolescents transitioning from pediatric to adult care, no longer under parental supervision, may be less likely to adhere to treatment and miss follow-up appointments, leading to underreporting of the true prevalence of celiac disease in adults. Additionally, some patients diagnosed at a young age strictly follow dietary recommendations, become asymptomatic and seronegative, and no longer report having celiac disease. As celiac disease is a lifelong condition with no known cure, its true prevalence should be similar in children and adults. Reported differences likely reflect diagnostic disparities, underreporting, and suboptimal long-term medical follow-up

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### Myasthenia gravis

**DEFINITION AND DESCRIPTION**

Myasthenia gravis is an autoimmune condition that causes skeletal muscle weakness. These are the muscles that connect to your bones and help you move. Myasthenia gravis usually targets the muscles in your eyes, face, neck, arms and legs. It can affect your ability to:

* Move your eyes or blink.
* Keep your eyes open.
* Make facial expressions.
* Chew, swallow and talk.
* Raise your arms up and lift objects.
* Walk upstairs or get up from a chair.

Muscle weakness gets worse after physical activity and improves after rest. Symptoms usually happen quickly.

Myasthenia gravis is a chronic (long-lasting) neuromuscular condition (it affects the junction between your nerves and muscles). There isn’t a cure, but effective treatment can help you manage your symptoms and function well.

#### **Types of myasthenia gravis**

The types of myasthenia gravis include:

* Autoimmune myasthenia: It’s an autoimmune condition where the cause isn’t well understood but the likely cause is the production of certain types of antibodies (immune system proteins). This is the most common type.
* Neonatal myasthenia: A fetus gets certain antibodies from their birth mother who has myasthenia gravis. An infant may have a weak cry or sucking reflex at birth. These temporary symptoms usually go away after three months.
* Congenital myasthenia: It isn’t an autoimmune condition, and a genetic change causes this type.

There are two subtypes of autoimmune myasthenia:

* Ocular: The muscles that move your eyes and eyelids weaken. Your eyelids may droop, or you may not be able to keep your eyes open. Some people have double vision. Eye weakness is often the first sign of myasthenia. Ocular myasthenia gravis may evolve into the generalized form for nearly half of all people diagnosed with this type.
* Generalized: Muscle weakness affects your eye muscles and others in your face, neck, arms, legs and throat. You may find it difficult to speak or swallow, lift your arms over your head, stand up from a seated position, walk long distances and climb stairs.

#### **How common is myasthenia gravis?**

Myasthenia gravis affects about 20 out of every 100,000 people around the world. The actual number may be higher, as some people with mild cases may not know they have the condition. In the United States, there are approximately 60,000 people affected by myasthenia gravis at any given time.

## Symptoms and Causes

Symptoms associated with myasthenia gravis affect many different areas of your body.

### Symptoms of myasthenia gravis

Symptoms of myasthenia gravis may include:

* Muscle weakness in your arms, hands, fingers, legs and neck.
* Fatigue.
* Droopy eyelids (ptosis).
* Blurry or double vision.
* Limited facial expressions.
* Difficulty speaking, swallowing or chewing.
* Trouble walking.

Initial symptoms of myasthenia gravis happen suddenly. Your muscles usually get weaker when you’re active. Muscle strength returns when you rest. The intensity of muscle weakness often changes from day to day. Most people feel strongest at the start of the day and weakest at the end of the day.

In rare instances, myasthenia gravis affects muscles in your respiratory system. You may have shortness of breath or more serious breathing problems. Contact 911 or your local emergency services number if you have trouble breathing. In general, this doesn’t occur suddenly.

### Causes myasthenia gravis

Myasthenia gravis (autoimmune type) happens when your body’s immune system mistakenly attacks itself. Researchers aren’t sure why this happens. Studies suggest that certain immune system cells in your thymus gland have trouble identifying what’s a threat to your body (like bacteria or viruses) versus healthy components.

A genetic change causes congenital myasthenia. Antibodies passed from a birth mother to a fetus during pregnancy cause neonatal myasthenia.

#### **How does myasthenia gravis affect my body?**

Myasthenia gravis affects communication between nerves and muscles.

When your immune system is working as expected, nerves and muscles work together. It’s similar to a baseball game:

1. Nerves (the pitcher) send signals to muscles (the catcher) across a synapse (field) called the neuromuscular junction. To communicate, nerves release a molecule called acetylcholine (the baseball).
2. Muscles have sites called acetylcholine receptors (the catcher’s glove). The acetylcholine binds to its receptors in the muscle tissue, like a ball landing in a glove.
3. When the acetylcholine binds to its receptor, it triggers the muscle fiber to contract.
4. Nerves signal muscles effortlessly, like one ball player catching a ball and throwing it to a teammate.

If you have myasthenia gravis, antibodies destroy the receptor sites, blocking nerve-muscle communication. The “catcher” can’t catch the ball, and communication becomes sluggish or doesn’t work at all.

#### **Is myasthenia gravis inherited?**

It’s rare to inherit autoimmune myasthenia gravis. You can inherit congenital myasthenia or neonatal myasthenia. Types where inheritance happens usually occur in an autosomal recessive pattern where you need two genes, one from each biological parent, to experience symptoms.

#### **Risk factors for myasthenia gravis**

Myasthenia gravis is most common among females around age 40 and males after age 60. The condition can affect anyone at any age.

You may be more at risk of developing myasthenia gravis if you:

* Have a history of other autoimmune conditions, such as rheumatoid arthritis and lupus.
* Have thyroid disease.

If you have myasthenia gravis, your symptoms could trigger (start) if you:

* Take medications for malaria and heart arrhythmias.
* Underwent surgery.
* Had an infection.

### Complications of myasthenia gravis

Weakness and fatigue from myasthenia gravis can keep you from participating in activities you enjoy. This may lead to stress and depression. However, studies also show that most people with myasthenia gravis can tolerate light activities and exercises on a routine basis.

Up to 1 in 5 people with myasthenia gravis experience a myasthenic crisis or severe respiratory muscle weakness. You may need a respirator or other treatments to help you breathe. This is a life-threatening medical emergency. An estimated 20% of people with myasthenia gravis experience at least one myasthenic crisis in their lifetime.

#### **Connection between the thymus gland and myasthenia gravis**

Many people with myasthenia gravis have thymus gland conditions that may trigger symptoms. The thymus is a small organ in your upper chest. It’s part of your lymphatic system. It makes white blood cells that fight infections. Two-thirds of people with myasthenia gravis have overactive thymic cells (thymic hyperplasia). About 1 in 10 people with myasthenia gravis have thymus gland tumors called thymomas, which may be benign (not cancer) or cancerous.

## Diagnosis and Tests

To diagnose myasthenia gravis, your healthcare provider will perform a physical exam and ask detailed questions to learn more about your symptoms and medical history. Testing confirms a diagnosis. It may include:

* Blood antibody tests: About 85% of people with myasthenia gravis have unusually high levels of acetylcholine receptor antibodies in their blood. Approximately 6% of people diagnosed have muscle-specific kinase (MuSK) antibodies.
* Imaging scans: An MRI or CT scan can check for thymus gland problems like tumors.
* Electromyography (EMG): An EMG measures the electrical activity of muscles and nerves. This test detects communication problems between nerves and muscles.

#### **Myasthenia gravis stages**

There are five main classifications of myasthenia gravis that your healthcare provider may use during a diagnosis:

* Class I: Muscle weakness only affects your eyes (ocular muscle).
* Class II: Muscle weakness is mild.
* Class III: Muscle weakness is moderate.
* Class IV: Muscle weakness is severe.
* Class V: Severe muscle weakness affects how you breathe. You may need intubation or mechanical ventilation.

## Management and Treatment

There’s no cure for myasthenia gravis. But effective treatment is available to help manage your symptoms. Treatments may include:

* Medications: Certain medications can reduce your symptoms.
* Monoclonal antibodies: You’ll receive intravenous (IV) or subcutaneous (SQ) infusions of biologically engineered proteins. These proteins suppress an overactive immune system.
* Plasma exchange (plasmapheresis): An IV connected to a machine removes harmful antibodies from your blood plasma and replaces them with donor plasma or a plasma solution.
* IV or SQ immunoglobulin (IVIG or SCIG): You’ll receive IV infusions of donor antibodies over two to five days. IVIG or SCIG can treat myasthenia crises, as well as generalized myasthenia gravis.
* Surgery: A thymectomy is surgery to remove the thymus gland.

#### **Myasthenia gravis medications**

Common medications to treat myasthenia gravis include:

* Cholinesterase inhibitors (anticholinesterase): They boost signals between nerves and muscles to improve muscle strength.
* Immunosuppressants: Medications like corticosteroids decrease inflammation and reduce your body’s production of abnormal antibodies.

Side effects are possible with these medications. Talk to your healthcare provider to learn more before starting a new medication.

#### **How can I alleviate myasthenia gravis symptoms?**

If you have myasthenia gravis, try these steps to ease fatigue and boost muscle strength:

* Exercise regularly to strengthen muscles, boost your mood and give you more energy. Talk to your healthcare provider before starting an exercise program to make sure it’s safe.
* Avoid going outside in the middle of a hot day. Apply cold compresses to your neck and forehead when you feel overheated. Heat can make your symptoms worse.
* Get plenty of protein and carbohydrates in your meals for added energy.
* Tackle your most exhausting tasks earlier in the day when you feel your best.
* Take naps or rest breaks throughout the day.

## Outlook / Prognosis

Myasthenia gravis is a treatable condition. Symptoms range from mild to severe. Symptoms tend to reach their peak in severity within one to three years of initial diagnosis.

Most people with the condition live full and active lives with treatment.

Some cases go into remission. Remission is when your symptoms stop for a period of time. This could be temporary or permanent. If remission happens, your healthcare provider may adjust your treatment plan.

#### **What is the life expectancy of a person with myasthenia gravis?**

Most people have a normal life expectancy with myasthenia gravis. Life-threatening outcomes may happen during a myasthenic crisis, which affects your ability to breathe.

### How does myasthenia gravis affect pregnancy?

In rare instances, pregnancy brings on myasthenia gravis symptoms for the first time. If you already have this condition, symptoms may worsen during the first trimester or immediately after childbirth. In some cases, myasthenia gravis symptoms improve during pregnancy.

Certain treatments aren’t safe during pregnancy or breastfeeding. Your healthcare provider can guide you through this time, ensuring a healthy pregnancy.

## Living With

You should call your healthcare provider if you experience:

* Blurred or double vision.
* Difficulty walking, talking or eating.
* Extreme muscle fatigue or weakness.
* Shortness of breath.

Call your local emergency services number if you have trouble breathing.

## Epidemiology

## Myasthenia gravis (MG) is a chronic, rare, autoimmune disease in which the immune system attacks components of the neuromuscular junction, disrupting the transmission of signals from nerve to muscle. MG manifests as weakness and fatigue in voluntary skeletal muscles, particularly those of the eyes, throat, face, jaw, and limbs.

## Incidence of MG

## A systematic review published in 2010 pooled epidemiological data from 55 studies conducted from 1950 to 2007. Across these studies, the incidence rate of MG varied between 1.7 and 21.3 cases per 1,000,000 person-years, resulting in a global pooled incidence rate of 5.3 cases per 1,000,000 person-years.A study published in 2021 compiled data from another 29 studies conducted between 2007 and 2019, reporting MG incidence rates ranging from 0.15 to 61.33 cases per 1,000,000 person-years. Another 2021 study cites the incidence rate of MG as ranging from 4.1 to 30 cases per 1,000,000 person-years.

## Incidence of MG in the United States

## Researchers conducting a retrospective, claims-based analysis published in April 2023 collected claims data from 2011 to 2022 from commercial insurance, Medicare, and Medicaid databases, as well as population estimates from the 2021 US census to calculate the most up-to-date incidence and prevalence of MG in the US. In 2021, the overall incidence of MG in the US was 3.2 cases per 100,000 persons.

## Incidence of MG in Europe

## Researchers conducting a similar retrospective, claims-based analysis published in March 2023 collected claims data in Germany. They found the incidence of MG in Germany to be 4.6 cases per 100,000 persons in 2019.

## Incidence of MG in Asia

## A nationwide, population-based study in China published in December 2020 indicated that the incidence of MG was 0.68 per 100,000 persons, with the highest incidence occurring in people aged 70 to 74 years. This study cited similar incidence findings from previous studies conducted throughout Asia. The incidence of MG in Japan is estimated between 0.69 and 0.87 cases per 100,000 persons. The incidence of MG in Korea is estimated around 0.69 cases per 100,000 persons.

## Prevalence of MG

## The reported prevalence of MG over the past 50 years has been increasing and varies based on location. Global prevalence rates range from 150 to 200 cases per 1,000,000 persons.4 Researchers performing a 2021 systematic review and meta-analysis estimated that the global prevalence of MG was 12.4 per 100,000 persons.

## Prevalence of MG in the US

## In 2006, the prevalence of MG in the US was reported to be 20 per 100,000 persons, with an estimated 53,000 to 59,900 people living with MG in the US. Similarly, in 2015, the prevalence of MG in the US was estimated at 14 to 20 cases per every 100,000 persons, or between 36,000 and 60,000 cases. A retrospective claims-based study reported that the total prevalence of MG in 2021 was 37.0 per 100,000 persons. This increased prevalence may be attributed to several factors, including increased survival, more effective treatments, and/or improved diagnosis of MG

## Prevalence of MG in Europe

## In Europe, an estimated 56,000 to 123,000 individuals live with MG. In the province of Ourense in Galicia, Spain, the prevalence of MG was calculated to be one of the highest published figures at 260 cases per 1,000,000 persons, rising to 517.9 per 1,000,000 persons in individuals aged 65 years or over. Early onset of MG by the age of 50 years or under occurred in approximately 29.1% of these cases. The 2023 German study calculated that the prevalence of MG in Germany was 39.3 per 100,000 persons as of December 31, 2019.

## Race Factors of MG

## Specific ethnic backgrounds may factor into MG onset, presentation, and disease progression. White patients demonstrate a higher age of onset than other races by approximately 17.3 years. Black women demonstrated a higher incidence of MG at 0.01 per 1000 persons per year, compared to White patients and Black men who have an estimated incidence of 0.007 to 0.009 per 1000 persons per year.Black patients are more likely to develop treatment-resistant ocular MG than White patients, who show higher probabilities of developing more severe forms of generalized MG, which often respond poorly to treatment.Overall, there is a lower incidence and prevalence of MG among individuals of Asian descent.4 However, Asian populations demonstrate a higher incidence of early-onset ocular MG, including juvenile- and infantile-onset MG. Approximately 80.6% of Asian patients with infantile-onset MG develop ocular MG, compared with 14% to 30% of patients with infantile-onset MG in Europe and North America.14 An estimated 10% to 15% of MG cases in White individuals represent juvenile-onset MG, while up to 50% of MG cases in Asian individuals are juvenile-onset, particularly in the southern Chinese population.

## Sex Factors of MG

## Women are more affected by MG than men, with a 3:1 sex ratio prior to 40 years of age. However, as the population ages, men are increasingly more affected after age 50, resulting in closer to a 1:1 sex ratio at advanced ages.1,2,4 Scientists hypothesize that stress, viral infections, pregnancy, and childbirth trigger the development of MG, contributing to the middle-age sex disparities.In 2021, the incidence of MG among men and women in the US was estimated at 3.2 and 3.1 per 100,000 persons, respectively. In the US, the prevalence of MG was estimated at 37.3 per 100,000 persons for men and 36.7 per 100,000 persons for women. In China, the incidence of MG among women was estimated at 0.76 cases per 100,000 persons, while the incidence among men was estimated at 0.60 cases per 100,000 persons.

## Age Factors of MG

## While women most commonly manifest MG symptoms in their 20s and 30s, men are more commonly diagnosed in their 70s and 80s.1 Researchers calculated a 99.6% probability that the mean difference in age between the sexes at MG diagnosis was greater than 10 years. Current evidence is contributing to a growing recognition of late-onset MG in individuals over 50 years of age.16 In the US, the incidence and prevalence of MG increased with age as follows5:

* Patients aged less than 2 years: incidence of 0.3 per 100,000 and prevalence of 0.4 per 100,000 persons
* Patients aged 2 to 5 years: incidence of 0.5 per 100,000 and prevalence of 2.1 per 100,000 persons
* Patients aged 6 to 11 years: incidence of 0.2 per 100,000 and prevalence of 3.7 per 100,000 persons
* Patients aged 12 to 17 years: incidence of 0.4 per 100,000 and prevalence of 5.6 per 100,000 persons
* Patients aged 18 to 49 years: incidence of 1.5 per 100,000 and prevalence of 18.3 per 100,000 persons
* Patients aged 50 to 64 years: incidence of 4.0 per 100,000 and prevalence of 47.9 per 100,000 persons
* Patients aged 65 years and over: incidence of 10.2 per 100,000 and prevalence of 116.8 per 100,000 persons

Similar trends of increased MG incidence with increasing age have also been observed in China,7 Spain,10 and Japan.

## Subtype Factors of MG

## The most prevalent subtype of MG is the anti-acetylcholine receptor (AChR) subtype. Anti-AChR antibodies are detected in 85% to 95% of patients with generalized MG, while they are present in 40% to 70% of patients with ocular MG.The second most prevalent subtype is the muscle-specific tyrosine kinase (MuSK) subtype. Anti-MuSK antibodies are detected in 7% to 10% of all patients with MG and up to 40% of patients who test negative for anti-AChR antibodies. Women are more likely to develop MuSK-positive MG, accounting for 85% of MuSK MG cases.Lipoprotein receptor-related protein 4 (LRP4) accounts for 2% to 50% of double seronegative MG cases, while up to 10% of patients with MG characteristics exhibit no identifiable autoantibodies.

## 

## Differential Diagnoses

* Amyotrophic Lateral Sclerosis in Physical Medicine and Rehabilitation
* Basilar Artery Thrombosis
* Botulism
* Brainstem Gliomas
* Cavernous Sinus Syndromes
* Chronic Myelogenous Leukemia (CML)
* Ciguatera Toxicity
* Congenital Myasthenic Syndrome
* Dermatomyositis
* Diphtheria
* Graves Disease
* Guillain-Barre Syndrome
* Kearns-Sayre Syndrome
* Lambert-Eaton Myasthenic Syndrome (LEMS)
* Miller-Fisher Syndrome
* Multiple Sclerosis
* Myocardial Infarction
* Neurosarcoidosis
* Organophosphate Toxicity
* Polymyositis
* Pulmonary Embolism (PE)
* Tetrodotoxin Toxicity
* Thyroid Ophthalmopathy
* Tick-Borne Diseases
* Tolosa-Hunt Syndrome

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**MOTOR NEUROPATHY**

**DEFINITION AND DESCRIPTION**

Multifocal Motor Neuropathy (MMN) is a rare but debilitating condition that affects the motor neurons responsible for controlling movement in the limbs. This condition is often misdiagnosed or overlooked due to its similarity with other neurological disorders such as ALS or Guillain-Barre Syndrome. However, early diagnosis and treatment can significantly improve the quality of life for those affected by this condition. In this article, we will explore the causes, symptoms, and treatment options available for MMN. We'll discuss the special challenges faced by those living with this condition and how they can cope with the unique difficulties it presents. Whether you're someone living with MMN or a caregiver seeking to better understand this condition, this article will give you the information you need to make informed decisions about your health and wellbeing. So, let's dive in and learn more about Multifocal Motor Neuropathy, its causes, symptoms, and treatment options.

Motor neuropathy or motor neuropathy, which is distinguished among neurological disorders, is defined as a disorder of the reflex motor functions that are provided by various structures of the nervous system.

The pathologies of movement may involve lesions of subcortical motor nuclei, the cerebellum, the pyramidal system, the reticular formation of the brain stem, innervating the skeletal muscles of the peripheral nerves, motoneurons and their processes (axons) involved in conducting nerve impulses.

## Causes of the motor neuropathy

In many cases, the causes of motor neuropathy are motor neuron diseases. These nerve cells are divided into superior (in the brain) and lower (spinal) cells; the former transmit nerve impulses from the nuclei of the sensorimotor cortex to the spinal cord, and the latter transmit them to the synapses of the muscle fibers.

With degenerative changes of the upper motoneurons, primary lateral sclerosis and hereditary spastic paraplegia are noted. In degenerative lesions of spinal motoneurons, focal syndrome of spinal motor neuron or amyotrophic lateral sclerosis syndrome, multiple motor neuropathy and distal spinal amyotrophy develop. Also distinguished are etiologically homogeneous syndromes: Verdnig- *Hoffman (starts in children up to six months), Dubovitsa (* starts at 6-12 months *),* Kugelberg-Welander (may appear between 2 and 17 years), Friedreich's ataxia (manifested by the end of the first decade of life or later). In adults, the most common type of spinal amyotrophy is slowly progressive Kennedy disease (also called spin-bulbar muscle atrophy).

Motor neuropathy is interrelated with degeneration of the cerebellum, which controls muscle tone and coordination of movements. It manifests itself as a hereditary movement disorder or ataxia, as a symptom of multiple sclerosis, as a neurological consequence of an acute violation of cerebral circulation,

Movement disorders can occur in case of oncological diseases, in particular, in the form of Eaton-Lambert paraneoplastic neurological syndrome. Cm. - Causes of cerebellar ataxia.

Patients who have suffered cranio-cerebral traumas or poisonings with various toxic substances often come across as impaired motor functions as a neurological complication. Infected with infectious diseases, among the causative agents of which the polyomavirus is noted, the viruses Varicella and Herpes zoster, Human immunodeficiency virus (HIV), Cytomegalovirus, and also the bacteria Borrelia burgdorferi, Mycoplasma hominis, Campylobacter jejuni, Treponema pallidum (causing neurosyphilis)

## Risk factors

Among the risk factors for motor neuropathy, experts refer to disorders of the immune system with activation of autoimmune reactions, loss of the myelin sheaths of nerve fibers and axons of motoneurons.

Elderly people, alcohol-dependent children, children in families with hereditary neurological disorders, cancer patients with lymphomas and lung cancer tumors, most patients after cancer treatment with ionizing radiation and cytostatics are at risk.

The risk of neurological movement disorders in diabetics is extremely high. Other diseases with motor neurological complications are celiac disease, amyloidosis, megaloblastic anemia (vitamin B12 deficiency), lupus erythematosus (SLE).

Consider the risk when using certain medications that may cause impaired sensory-motor functions. For example, this means Disulfiram (anti-alcoholism), Phenytoin (anticonvulsant), anticancer drugs (Cisplatin, Vincristine, etc.), the drug for hypertension Amiodarone, etc.

## Symptoms of the motor neuropathy

Different types of motor neuropathy demonstrate some similar manifestations characteristic of disorders of motor function.

Localization and etiology of the disease determine the early symptoms. For example, the first signs of amyotrophic lateral sclerosis are manifested by progressive weakness and stiffness of the arms and legs, which leads to dysbasia - slow walking with poor coordination of movements and balance (a person often stumbles on level ground).



In hereditary spinal muscular atrophy *in adults,* symptoms of motor neuropathy *include*  periodic twitching of the superficial muscle fibers (fasciculation) against the background of their reduced tone and weakened tendon reflexes. At a later stage - as the disease progresses - muscle movement limiting movement begins to be felt not only in the arms and legs, but also in other muscle groups (including intercostal respiratory, pharyngeal, orofacial). Because of this, there are problems with breathing, progressing to respiratory failure, and dysphagia (difficulty swallowing). It also slows down and becomes slurred speech. The list of typical symptoms of Kennedy's disease - with genetically determined degeneration of motoneurons in the spinal cord and brainstem - lists the weakness and atrophy of the muscles of the limbs, face, pharynx, larynx and oral cavity. Speech disorders (dysarthria) and swallowing (dysphagia) are noted.

Multiple or multifocal motor neuropathy manifests itself as a unilateral violation of the movement of the limbs, without sensory symptoms. In eight cases out of ten, the disease begins at 40-50 years of age. Most often affected are the ulnar, median and radial nerves with weakness in the hands and wrists, which impedes fine motor skills. Lewis-Sumner syndrome is distinguished, which is essentially a multiple motor-sensory neuropathy of acquired (inflammatory) character with paresthesia of the upper limbs and a decrease in skin sensitivity of the backs of the hands.

Some immunologically related neuropathies can have acute and chronic forms. Acute axonal motor neuropathy due to dysfunction of neuronal processes is still diagnosed as a subtype or a variant of Landry-Guillain-Barre polyneuropathy or Guillain-Barre syndrome (acute polyradiculoneuritis) - with symptoms in the form of progressive muscular weakness of the distal upper extremities, the fascismus, and anesthesia of the distal parts of the upper extremities, the fascismus. Restrictions on eye movement, lethargic tetraplegia (paralysis of all limbs) in the absence of a conduction block of nerve impulses. Signs of demyelination and sensory impairment in this pathology are absent.

Chronic idiopathic axonal motor polyneuropathy is a frequent neurological disorder in older people (over 65), which manifests itself with symmetrical distal symptoms in the lower limbs in the form of ankle clonus, muscular weakness and restraint of walking, painful cramps of the calf muscles (krampi) in a state of movement, walking, painful cramps of the calf muscles (crampy), and the constraint of movement when walking, painful cramps of the ankle muscles, and weakness and stiffness during walking, and painful cramps in the condition of the ankle, muscle weakness, and stiffness during walking cramps in the front of the tibial muscles after walking.

Due to pathological processes that lead to the violation of certain sections of the myelin sheaths of the processes of motor neurons (as well as the roots and fibers of the spinal nerves that innervate muscles), motor axonal-demyelinating neuropathy can develop with symptoms such as. Involuntary twitching of the muscles of the extremities, their paresthesia (tingling and numbness), impaired tactile and temperature sensitivity (especially of the hands and feet), paresis (partial paralysis), paraplegia (simultaneous paralysis of both arms or both legs), orthostatic dizziness, dysbasia and dysrhea. Vegetative symptoms may manifest by increased sweating and acceleration / deceleration of the heart rate.

## Forms

When efferent (motor) and afferent (sensory) neurons and nerve fibers lose their ability to transmit signals, which most often happens in children and adolescents with hereditary neuropathies , peripheral motor-sensory neuropathy is diagnosed, which is divided into several types of genetically determined diseases.

Motor-sensory neuropathy type 1 - hypertrophic-demyelinating, which accounts for half of all inherited peripheral neuropathies in children - is associated with segmental demyelination due to impaired synthesis of myelin proteins due to gene mutations on chromosomes 17p11.2, 1q21-q23 and 10q21.



This type of pathology, in which hypertrophy of peripheral nerves is noted, is a slowly progressive atrophy of the peroneal (peroneal) muscles of the lower extremities - type 1 Charcot-Marie-Tout disease. When it muscles of the legs atrophy below the knee in the ankle area (with the formation of a pathologically high arch of the foot and a characteristic change in the shape of the toes); often, when tension occurs, tremor; anhidrosis (lack of sweat) and progressive hypesthesia, and in some cases, loss of pain sensation (in the distal lower extremities); tendon reflexes of the Achilles ligament disappear; signs of mental and mental disorders appear; rarely the disease is accompanied by nervous deafness. In the later stages, the muscles of the arms below the elbow with deformity of the hands also atrophy.

Hereditary motor-sensory neuropathy type 2 (Charcot-Marie-Tuat disease type 2) - axonal amyotrophy, that is, associated with dysfunction and degeneration of processes of motor and sensory neurons without loss of the myelin sheath - affects the same muscle group, manifests from 5 to 25 years. At the same time, mutations were detected on chromosomes 1p35-p36, 3q13-q22 and 7p14.



On the background of almost normal speed of nerve impulses (compared with the first type of the disease), clinical manifestations of distal muscular weakness and atrophy are less pronounced; muscle atrophy below the knee symmetrical in 75% of patients; typical first signs are weakness of the feet and ankles, reduction of tendon reflexes with weakness of the dorsiflexia of the foot in the ankle. There are mild sensory symptoms; there may be pain, sleep apnea, restless legs syndrome, depressive state. Atrophy of the muscles of the hands is rarely observed.

## Diagnostics of the motor neuropathy

At an early stage, neurological movement disorders are difficult to diagnose because their symptoms are similar to the symptoms of other conditions, such as multiple sclerosis, neuritis, or Parkinson's disease.



Diagnosis begins with the examination and testing of tendon reflexes. Laboratory studies are required: biochemical and general blood tests, plasma creatinine phosphokinase level analysis, plasma C-reactive protein, antibodies level (in particular, GM1 ganglioside antibodies), C3 complement, etc. If necessary, the analysis of cerebrospinal fluid is taken.

The main instrumental diagnostics used in neurology include: stimulation electromyography (EMG); electroneuromyography (ENMG); myelography; Ultrasound and MRI scans of the brain (to rule out stroke, cerebral neoplasia, blood circulation problems, or structural abnormalities); positron emission tomography (PET).

Some motor neuropathies are classified as variants of amyotrophic lateral sclerosis, but differential diagnosis is necessary. Among neuropathies of immune genesis with destruction of the myelin sheaths, multifocal motor neuropathy and chronic immune demyelinating polyneuropathy should be differentiated.

Loss of the lower motor neurons with the involvement of sensory nerves must be distinguished from paraneoplastic encephalomyelitis and sensory ganglionic syndromes.

In addition, it is necessary to eliminate myopathic syndromes and muscular dystrophies, for which muscle research is carried out, as well as Morvan's disease (syringomyelia) - with the help of MRI of the spine, which visualizes the spinal cord.

## Treatment of the motor neuropathy

Neuropathologists admit that today only symptomatic treatment of motor neuropathy is possible, facilitating the condition of patients and somewhat slowing the progression of pathological processes. And for the treatment of hereditary motor and sensory neuropathies of drugs does not yet exist.

One of the generally accepted methods is periodically conducted plasmapheresis, by means of which autoantibodies are removed from patients' blood.

In multiple motor neuropathy, human immunoglobulin (IVIg) is infused; glucocorticoids (Prednisolone or Methylprednisolone) can be used systemically, providing immunomodulatory effects. For all types of movement disorders, vitamins A, D and groups B are prescribed.

Some other medications are also used. First of all, for oral administration, normalizing tissue metabolism and L-carnitine repairing damaged cells are prescribed: adults in the form of capsules (0.25-0.5 g twice a day), children in the form of syrup (the dose is determined by the doctor depending on age).



To increase the conductivity of nerve impulses, the CNS stimulating inhibitor of the enzyme Ipidacrine cholinesterase (other trade names - Neuroimin, Amipirin, Axamon) is used orally or parenterally: adults - 10-20 mg three times a day (or 1 ml intramuscularly); Only oral administration is allowed for children from one year to 14 years old - a single dose is 10 mg (half a pill) - up to three times a day. The course of treatment lasts one and a half months; Ipidacrine may be reappointed two months after the end of the first course.

This drug is contraindicated in disorders of heart rate, inflammatory gastroenterological and pulmonary diseases and pregnancy. And as its most likely side effects, nausea, diarrhea, dizziness, drooling, bronchial spasms are noted.

Recently, foreign neurologists in patients with amyotrophic lateral sclerosis prescribe a new drug (FDA approved) Riluzole (Rilutec). Its effectiveness and even the mechanism of action are still poorly understood, and a number of serious side effects are noted in the list of complications of its use.

Treatment of hereditary motor-sensory disorders requires the participation of not only a neurologist, but also a physiotherapist. Physiotherapy can play an important role in slowing and preventing disease progression and managing symptoms, and the treatment plan should focus on strengthening the affected muscle group. This may be a therapeutic massage, exercise therapy, ultrasound, electrical stimulation, water treatments, pelotherapy, etc.

Many patients need help from an orthopedist: orthopedic shoes or ankle and foot orthoses are necessary to maintain the arch when walking; often you can not do without crutches, walking sticks or walkers; some need a wheelchair.

And in cases of severe limb deformities, surgical treatment is undertaken.

Those who prefer alternative treatments are advised to use bee venom - bee sting [treatments.](https://iliveok.com/health/bee-sting-treatment_106466i16053.html)

However, it should be borne in mind that the effectiveness of the poison of honeybees (with its active substance melittin) has been proven only in peripheral neuropathies caused by chemotherapy.

But from paresthesia for movement disorders, massage with chamomile and lavender essential oils (a few drops on a dessert spoon of the essential oil) helps.



In the same way, herbal medicine helps with neuropathies induced by the use of anticancer drugs. Used medicinal plants such as:

* Salvia officinalis (Salvia officinalis), which contains apigenin, which has significant antioxidant activity and protects the nerve cells of the peripheral nervous system;
* calamus acorus (Acorus calamus), which extract anesthetizes, soothes and relieves seizures;
* Ginkgo biloba (Ginkgo biloba) contains terpenic trilactones, which have a positive effect on damaged neurons.

In case of progressive spinal amyotrophy, homeopathy can also be applied, recommending to such patients the drugs Argentum nitricum, Plumbum, Phosphorus, Kali phosphoricum, Cuprum, Arnica montana. But they are also not able to help with genetically "programmed" pathologies that cause impaired motor functions.



## Prevention

It is impossible to prevent hereditary spinal amyotrophy or immune-mediated demyelination of motor neurons and their axons.

The question of their prevention is genetic counseling for families in which there are carriers of abnormal genes. To do this, a blood test is performed, and antenatal screening can be performed, that is, a survey of a pregnant woman using chorion biopsy (CVS).

## Complications and consequences

Previously, neuropathologists believed that motor neuron disease did not affect brain function, but research results demonstrated the fallacy of this opinion. It turned out that the negative consequences and complications of amyotrophic lateral sclerosis and degenerative changes in the lower motoneurons in almost half of the patients are manifested by these or other disorders of the central nervous system, and in 15% of cases there is a development of frontotemporal dementia. Changes in personality and emotional state can occur with bouts of uncontrollable crying or laughter.



Violation of contractions of the primary respiratory muscle (diaphragm) causes breathing problems in amyotrophic lateral sclerosis; patients also have increased anxiety and sleep disturbances.

Complications of the axonal-demyelinating form of neuropathy manifest as impaired intestinal motility, urination, and erectile dysfunction.



Damage to the sensory nerves can lead to the loss of pain sensitivity, and neglected injuries and wounds due to infectious inflammation are fraught with the development of gangrene and sepsis.

In case of Charcot-Marie-Tut disease, the joints cannot react normally to the pressure force, which causes microcracks in the bone structures, and destruction of the bone tissue leads to irreversible deformation of the extremities.

Spinal amyotrophy is considered the second most significant cause of infant mortality in the world. If the degree of pathology is insignificant, the patient survives - most often with the subsequent loss of the ability to move independently.

## Epidemiology

According to clinical statistics, peripheral motor neuropathy in diabetes mellitus develops over time in six out of ten patients with this disease.

The human immunodeficiency virus, according to the Journal of Neurology, causes neuropathic conditions in a third of patients, and multiple motor neuropathy is detected in three people per 100,000 of the population and almost three more often affect males.

The most common hereditary disease of the peripheral nerves - Charcot-Marie-Tuta disease - affects about one person in 2.5-5 thousand.



In North America, spinal muscular atrophy annually affects one child from 6-8 thousand babies. According to some information, one of 40-50 people is an asymptomatic carrier of this disease, that is, it has a defective gene that can be transmitted to its children as an autosomal dominant trait.

**Differential diagnosis for Motor Neurone Disease (MND)**

Key differentials are in bold. The examination/investigation which is most helpful in identifying the mimic is below each differential diagnosis.

* **Cervical radiculopathy**
  + MRI spine shows multilevel disc compression
* **Syringomyelia**
  + MRI spine shows syrinx (expansion of the CSF space in the centre of the cord)
* **Syphilic pachymeningitis**
  + Now very rare, untreated syphilis used to be much more common and can cause a patchy meningitis leading to poor function of the exiting nerve roots in the brainstem and spinal cord
  + Test for EIA/VDRL serology
* **Motor neuropathy**
  + **Lead/heavy metal poisoning** is the most common cause of a progressive motor neuropathy – check serum levels
  + **Multifocal Motor Neuropathy** is a rare inflammatory condition involving antibodies to nerve root antigen – check “anti ganglioside antibodies”; MMN has positive anti GM1 antibodies. Also nerve conduction will be different to MND – and show conduction block although this can be difficult to identify
* **Spinal muscular atrophies**
  + Rare genetic disorders causing progressive muscle atrophy, of which there are a range that vary in severity, age of onset and rate of progression. Genetic tests available.
* **Kennedy’s Syndrome** “Spinal and bulbar muscular atrophy”
  + X-linked condition, causing spinal and bulbar muscular atrophy. Only LMN pathology. Pathology is due to a mutation in the androgen receptor and therefore also has endocrine manifestations of androgen insensitivity.
  + Usually presents in young-middle aged adult males.
  + Ask about muscle cramps. Look for chin fasciculations and gynaecomastia

[Differential Diagnosis of Motor Neurone Disease - Oxford Medical Education](https://oxfordmedicaleducation.com/neurology/differential-diagnosis-motor-neurone-disease/)

**HUMAN IMMUNODEFICIENCY VIRUS / ACQUIRED IMMUNODEFICIENCY VIRUS**

**DEFINITION AND DESCRIPTION**

HIV (human immunodeficiency virus) is a virus that attacks the body's immune system. Without treatment, it can lead to AIDS (acquired immunodeficiency syndrome).

There is currently no effective cure. Once people get HIV, they have it for life. But proper medical care can control the virus.

People with HIV who get on and stay on effective HIV treatment can live long, healthy lives and protect their partners.

Acquired immunodeficiency syndrome (AIDS), is an ongoing, also called chronic, condition. It's caused by the human immunodeficiency virus, also called HIV. HIV damages the immune system so that the body is less able to fight infection and disease. If HIV isn't treated, it can take years before it weakens the immune system enough to become AIDS. Thanks to treatment, most people in the U.S. don't get AIDS.

HIV is spread through contact with genitals, such as during sex without a condom. This type of infection is called a sexually transmitted infection, also called an STI. HIV also is spread through contact with blood, such as when people share needles or syringes. It is also possible for a person with untreated HIV to spread the virus to a child during pregnancy, childbirth or breastfeeding.

There's no cure for HIV/AIDS. But medicines can control the infection and keep the disease from getting worse. Antiviral treatments for HIV have reduced AIDS deaths around the world. There's an ongoing effort to make ways to prevent and treat HIV/AIDS more available in resource-poor countries.

**CAUSES**

HIV is caused by a virus. It can spread through sexual contact, shooting of illicit drugs or use of shared needles, and contact with infected blood. It also can spread from parent to child during pregnancy, childbirth or breastfeeding.

HIV destroys white blood cells called CD4 T cells. These cells play a large role in helping the body fight disease. The fewer CD4 T cells you have, the weaker your immune system becomes.

### How does HIV become AIDS?

You can have an HIV infection with few or no symptoms for years before it turns into AIDS. AIDS is diagnosed when the CD4 T cell count falls below 200 or you have a complication you get only if you have AIDS, such as a serious infection or cancer.

### How HIV spreads

You can get infected with HIV if infected blood, semen or fluids from a vagina enter your body. This can happen when you:

* **Have sex.** You may become infected if you have vaginal or anal sex with an infected partner. Oral sex carries less risk. The virus can enter your body through mouth sores or small tears that can happen in the rectum or vagina during sex.
* **Share needles to inject illicit drugs.** Sharing needles and syringes that have been infected puts you at high risk of HIV and other infectious diseases, such as hepatitis.
* **Have a blood transfusion.** Sometimes the virus may be transmitted through blood from a donor. Hospitals and blood banks screen the blood supply for HIV. So this risk is small in places where these precautions are taken. The risk may be higher in resource-poor countries that are not able to screen all donated blood.
* **Have a pregnancy, give birth or breastfeed.** Pregnant people who have HIV can pass the virus to their babies. People who are HIV positive and get treatment for the infection during pregnancy can greatly lower the risk to their babies.

### How HIV doesn't spread

You can't become infected with HIV through casual contact. That means you can't catch HIV or get AIDS by hugging, kissing, dancing or shaking hands with someone who has the infection.

HIV isn't spread through air, water or insect bites. You can't get HIV by donating blood.

**RISK FACTOR**

Anyone of any age, race, sex or sexual orientation can have HIV/AIDS. However, you're at greatest risk of HIV/AIDS if you:

* **Have unprotected sex.** Use a new latex or polyurethane condom every time you have sex. Anal sex is riskier than vaginal sex. Your risk of HIV increases if you have more than one sexual partner.
* **Have an STI.** Many STIs cause open sores on the genitals. These sores allow HIV to enter the body.
* **Inject illicit drugs.** If you share needles and syringes, you can be exposed to infected blood.

**SIGNS AND SYMPTOMS**

The symptoms of HIV and AIDS vary depending on the person and the phase of infection.

### Primary infection, also called acute HIV

Some people infected by HIV get a flu-like illness within 2 to 4 weeks after the virus enters the body. This stage may last a few days to several weeks. Some people have no symptoms during this stage.

Possible symptoms include:

* Fever.
* Headache.
* Muscle aches and joint pain.
* Rash.
* Sore throat and painful mouth sores.
* Swollen lymph glands, also called nodes, mainly on the neck.
* Diarrhea.
* Weight loss.
* Cough.
* Night sweats.

These symptoms can be so mild that you might not notice them. However, the amount of virus in your bloodstream, called viral load, is high at this time. As a result, the infection spreads to others more easily during primary infection than during the next stage.

### Clinical latent infection, also called chronic HIV

In this stage of infection, HIV is still in the body and cells of the immune system, called white blood cells. But during this time, many people don't have symptoms or the infections that HIV can cause.

This stage can last for many years for people who aren't getting antiretroviral therapy, also called ART. Some people get more-severe disease much sooner.

### Symptomatic HIV infection

As the virus continues to multiply and destroy immune cells, you may get mild infections or long-term symptoms such as:

* Fever.
* Fatigue.
* Swollen lymph glands, which are often one of the first symptoms of HIV infection.
* Diarrhea.
* Weight loss.
* Oral yeast infection, also called thrush.
* Shingles, also called herpes zoster.
* Pneumonia.

### Progression to AIDS

Better antiviral treatments have greatly decreased deaths from AIDS worldwide. Thanks to these lifesaving treatments, most people with HIV in the U.S. today don't get AIDS. Untreated, HIV most often turns into AIDS in about 8 to 10 years.

Having AIDS means your immune system is very damaged. People with AIDS are more likely to develop diseases they wouldn't get if they had healthy immune systems. These are called opportunistic infections or opportunistic cancers. Some people get opportunistic infections during the acute stage of the disease.

The symptoms of some of these infections may include:

* Sweats.
* Chills.
* Fever that keeps coming back.
* Ongoing diarrhea.
* Swollen lymph glands.
* Constant white spots or lesions on the tongue or in the mouth.
* Constant fatigue.
* Weakness.
* Rapid weight loss.
* Skin rashes or bumps.

**DIAGNOSIS AND TEST**

HIV can be diagnosed through blood or saliva testing. Tests include:

* **Antigen-antibody tests.** These tests most often use blood from a vein. Antigens are substances on the HIV virus itself. They most often show up in the blood within a few weeks after being exposed to HIV.  
  The immune system makes antibodies when it's exposed to HIV. It can take weeks to months for antibodies to show up in blood. You may not show a positive result on an antigen-antibody test until 2 to 6 weeks after exposure to HIV.
* **Antibody tests.** These tests look for antibodies to HIV in blood or saliva. Most rapid HIV tests are antibody tests. This includes self-tests done at home. You may not show a positive result on an antibody test until 3 to 12 weeks after you've been exposed to HIV.
* **Nucleic acid tests (NATs).** These tests look for the virus in your blood, called viral load. They use blood from a vein.  
  If you might have been exposed to HIV within the past few weeks, your healthcare professional may suggest NAT. NAT is the first test to become positive after exposure to HIV.

Talk with your healthcare professional about which HIV test is right for you. If any of these tests are negative, you may need a follow-up test weeks to months later to confirm the results.

### Tests to stage disease and treatment

If you've been diagnosed with HIV, find a specialist trained in diagnosing and treating HIV to help you:

* Decide whether you need other tests.
* Find which HIV antiretroviral therapy, also called ART, is best for you.
* Watch your progress and work with you to manage your health.

If you get a diagnosis of HIV/AIDS, tests can help your healthcare professional learn the stage of your disease and the best treatment, including:

* **CD4 T cell count.** CD4 T cells are white blood cells that HIV targets and destroys. Even if you have no symptoms, HIV infection becomes AIDS when your CD4 T cell count dips below 200.
* **Viral load, also called HIV RNA.** This test measures the amount of virus in your blood. After starting HIV treatment, the goal is to have a viral load so low that it doesn't show up on the test, called undetectable. This greatly reduces your chances of opportunistic infection and other HIV-related complications.
* **Medicine resistance.** Some strains of HIV are resistant to medicines. This test helps your healthcare professional know if your form of the virus has resistance. This guides treatment decisions.

### Tests for complications

Your healthcare professional also might order lab tests to check for other infections or complications, including:

* Tuberculosis.
* Hepatitis B or hepatitis C virus infection.
* STIs.
* Liver or kidney damage.
* Urinary tract infection.
* Cervical and anal cancer.
* Cytomegalovirus.
* Toxoplasmosis.

**TREATMENT**

There's no cure for HIV/AIDS. Once you have the infection, your body can't get rid of it. But there are medicines that can control HIV and prevent complications.

Everyone diagnosed with HIV should take antiretroviral therapy medicines, also called ART. This is true no matter what stage the disease is in or what the complications are.

ART is usually a mix of two or more medicines from several classes. This approach has the best chance of lowering the amount of HIV in the blood. There are many ART options that mix more than one HIV medicine into a single pill, taken once daily.

Each class of medicines blocks the virus in different ways. Treatment involves mixing medicines from different classes to:

* Account for medicine resistance, called viral genotype.
* Keep from creating new medicine-resistant strains of HIV.
* Suppress the virus in the blood as much as possible.

Two medicines from one class, plus a third medicine from another class, are most often used.

The classes of anti-HIV medicines include the following:

* **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** turn off a protein needed by HIV to make copies of itself.  
  Examples include efavirenz, rilpivirine (Edurant) and doravirine (Pifeltro).
* **Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs)** are faulty versions of the building blocks that HIV needs to make copies of itself.  
  Examples include abacavir (Ziagen), tenofovir disoproxil fumarate (Viread), emtricitabine (Emtriva), lamivudine (Epivir) and zidovudine (Retrovir). Retrovir is no longer suggested for routine use in the U.S. because of high rates of toxic effects.  
  Mixes of medicines also are available, such as emtricitabine-tenofovir disoproxil fumarate (Truvada) and emtricitabine-tenofovir alafenamide fumarate (Descovy).
* **Protease inhibitors (PIs)** make HIV protease inactive. HIV protease is another protein that HIV needs to make copies of itself.  
  Examples include atazanavir (Reyataz), darunavir (Prezista) and lopinavir-ritonavir (Kaletra).
* **Integrase inhibitors** stop the action of a protein called integrase. HIV uses integrase to put its genetic material into CD4 T cells.  
  Examples include bictegravir sodium-emtricitabine-tenofovir alafenamide fumarate (Biktarvy), raltegravir (Isentress), dolutegravir (Tivicay) and cabotegravir (Vocabria).
* **Entry or fusion inhibitors** block HIV's entry into CD4 T cells.  
  Examples include enfuvirtide (Fuzeon) and maraviroc (Selzentry). Newer medicines include ibalizumab-uiyk (Trogarzo) and fostemsavir (Rukobia).

### Starting and staying on treatment

Everyone with HIV infection, no matter what the CD4 T cell count or symptoms are, should be offered antiviral medicine.

Staying on ART that keeps your HIV viral load in the blood from being detected is the best way for you to stay healthy.

For ART to work, you must take the medicines as prescribed. Don't miss or skip doses. Staying on ART with an undetectable viral load helps:

* Keep your immune system strong.
* Lower your chances of getting an infection.
* Lower your chances of getting treatment-resistant HIV.
* Lower your chances of giving HIV to other people.

Staying on HIV therapy can be hard. Talk to your healthcare professional about possible side effects, trouble you have taking medicines, and any mental health or substance use issues that may make it hard for you to stay on ART.

Have regular follow-up appointments with your health professional to check your health and response to treatment. Let your health professional know right away if you have problems with HIV therapy. Then you can work together to find ways to deal with those issues.

### Treatment side effects

Treatment side effects can include:

* Nausea, vomiting or diarrhea.
* Heart disease.
* Kidney and liver damage.
* Weakened bones or bone loss.
* Cholesterol levels that are not typical.
* Higher blood sugar.
* Problems with thinking, emotions and sleep.

### Treatment for age-related diseases

Some health issues that are a part of aging may be harder to manage if you have HIV. Some medicines that are common for age-related heart, bone or metabolic conditions, for example, may not mix well with anti-HIV medicines. Talk with your healthcare professional about your other health conditions and the medicines you take for them.

If another health professional prescribes a medicine for another condition, let that health professional know about your HIV therapy. Then the health professional can make sure there are no problems with taking the medicines together.

### Treatment response

Your healthcare professional will watch your viral load and CD4 T cell counts to see your response to HIV treatment. The first check is at 4 to 6 weeks. After that, you see your health professional every 3 to 6 months.

Treatment should lower your viral load so that it can't be found in the blood. That doesn't mean your HIV is gone. Even if it can't be found in the blood, HIV is still in your body.

**COMPLICATIONS**

HIV infection weakens your immune system. The infection makes you much more likely to get many infections and certain types of cancers.

### Infections common to HIV/AIDS

* **Pneumocystis pneumonia, also called PCP.** This fungal infection can cause severe illness. It doesn't happen as often in the U.S. because of treatments for HIV/AIDS. But PCP is still the most common cause of pneumonia in people infected with HIV.
* **Candidiasis, also called thrush.** Candidiasis is a common HIV-related infection. It causes a thick, white coating on the mouth, tongue, esophagus or vagina.
* **Tuberculosis, also called TB.** TB is a common opportunistic infection linked to HIV. Worldwide, TB is a leading cause of death among people with AIDS. It's less common in the U.S. thanks to the wide use of HIV medicines.
* **Cytomegalovirus.** This common herpes virus is passed in body fluids such as saliva, blood, urine, semen and breast milk. A healthy immune system makes the virus inactive, but it stays in the body. If the immune system weakens, the virus becomes active, causing damage to the eyes, digestive system, lungs or other organs.
* **Cryptococcal meningitis.** Meningitis is swelling and irritation, called inflammation, of the membranes and fluid around the brain and spinal cord, called meninges. Cryptococcal meningitis is a common central nervous system infection linked to HIV. A fungus found in soil causes it.
* **Toxoplasmosis.** This infection is caused by Toxoplasma gondii, a parasite spread primarily by cats. Infected cats pass the parasites in their stools. The parasites then can spread to other animals and humans.  
  Toxoplasmosis can cause heart disease. Seizures happen when it spreads to the brain. And it can be fatal.

### Cancers common to HIV/AIDS

* **Lymphoma.** This cancer starts in the white blood cells. The most common early sign is painless swelling of the lymph nodes most often in the neck, armpit or groin.
* **Kaposi sarcoma.** This is a tumor of the blood vessel walls. Kaposi sarcoma most often appears as pink, red or purple sores called lesions on the skin and in the mouth in people with white skin. In people with Black or brown skin, the lesions may look dark brown or black. Kaposi sarcoma also can affect the internal organs, including the lungs and organs in the digestive system.
* **Human papillomavirus (HPV)-related cancers.** These are cancers caused by HPV infection. They include anal, oral and cervical cancers.

### Other complications

* **Wasting syndrome.** Untreated HIV/AIDS can cause a great deal of weight loss. Diarrhea, weakness and fever often happen with weight loss.
* **Brain and nervous system, called neurological complications.** HIV can cause neurological symptoms such as confusion, forgetfulness, depression, anxiety and difficulty walking. HIV-associated neurological conditions can range from mild symptoms of behavior changes and reduced mental functioning to severe dementia causing weakness and not being able to function.
* **Kidney disease.** HIV-associated nephropathy (HIVAN) is swelling and irritation, called inflammation, of the tiny filters in the kidneys. These filters remove excess fluid and waste from the blood and pass them to the urine. Kidney disease most often affects Black and Hispanic people.
* **Liver disease.** Liver disease also is a major complication, mainly in people who also have hepatitis B or hepatitis C.

**PREVENTION**

There's no vaccine to prevent HIV infection and no cure for HIV/AIDS. But you can protect yourself and others from infection.

To help prevent the spread of HIV:

* **Consider preexposure prophylaxis, also called PrEP.** There are two PrEP medicines taken by mouth, also called oral, and one PrEP medicine given in the form of a shot, called injectable. The oral medicines are emtricitabine-tenofovir disoproxil fumarate (Truvada) and emtricitabine-tenofovir alafenamide fumarate (Descovy). The injectable medicine is called cabotegravir (Apretude). PrEP can reduce the risk of sexually transmitted HIV infection in people at very high risk.  
  PrEP can reduce the risk of getting HIV from sex by about 99% and from injecting drugs by at least 74%, according to the Centers for Disease Control and Prevention. Descovy hasn't been studied in people who have sex by having a penis put into their vaginas, called receptive vaginal sex.  
  Cabotegravir (Apretude) is the first U.S. Food and Drug Administration-approved PrEP that can be given as a shot to reduce the risk of sexually transmitted HIV infection in people at very high risk. A healthcare professional gives the shot. After two once-monthly shots, Apretude is given every two months. The shot is an option in place of a daily PrEP pill.  
  Your healthcare professional prescribes these medicines to prevent HIV only to people who don't already have HIV infection. You need an HIV test before you start taking any PrEP. You need to take the test every three months for the pills or before each shot for as long as you take PrEP.  
  You need to take the pills every day or closely follow the shot schedule. You still need to practice safe sex to protect against other STIs. If you have hepatitis B, you should see an infectious disease or liver specialist before beginning PrEP therapy.
* **Use treatment as prevention, also called TasP.** If you have HIV, taking HIV medicines can keep your partner from getting infected with the virus. If your blood tests show no virus, that means your viral load can't be detected. Then you won't transmit the virus to anyone else through sex.  
  If you use TasP, you must take your medicines exactly as prescribed and get regular checkups.
* **Use post-exposure prophylaxis, also called PEP, if you've been exposed to HIV.** If you think you've been exposed through sex, through needles or in the workplace, contact your healthcare professional or go to an emergency room. Taking PEP as soon as you can within the first 72 hours can greatly reduce your risk of getting HIV. You need to take the medicine for 28 days.
* **Use a new condom every time you have anal or vaginal sex.** Both male and female condoms are available. If you use a lubricant, make sure it's water based. Oil-based lubricants can weaken condoms and cause them to break.  
  During oral sex, use a cut-open condom or a piece of medical-grade latex called a dental dam without a lubricant.
* **Tell your sexual partners you have HIV.** It's important to tell all your current and past sexual partners that you're HIV positive. They need to be tested.
* **Use clean needles.** If you use needles to inject illicit drugs, make sure the needles are sterile. Don't share them. Use needle-exchange programs in your community. Seek help for your drug use.
* **If you're pregnant, get medical care right away.** You can pass HIV to your baby. But if you get treatment during pregnancy, you can lessen your baby's risk greatly.
* **Consider male circumcision.** Studies show that removing the foreskin from the penis, called circumcision, can help reduce the risk of getting HIV infection.

**Lifestyle and home remedies**

Besides getting medical treatment, you need to take an active role in your own care. The following may help you stay healthy longer:

* **Eat healthy foods.** Fresh fruits and vegetables, whole grains, and lean protein help keep you strong, give you more energy and support your immune system. Eat enough calories to keep your weight stable.
* **Avoid raw meat, eggs and more.** Foodborne illnesses can be severe in people who are infected with HIV. Cook meat until it's well done. Don't use dairy products that aren't treated for bacteria, called pasteurized. Don't eat raw eggs and raw seafood such as oysters, sushi or sashimi. Don't drink water you don't know is safe.
* **Get the right vaccinations.** These may prevent common infections such as pneumonia, influenza, COVID-19 and mpox. Your healthcare professional also may suggest other vaccinations, including those for HPV, hepatitis A and hepatitis B. Vaccines that don't have live viruses mostly are safe. But most vaccines with live viruses are not safe because of your weakened immune system.
* **Take care with pets.** Some animals may carry parasites that can cause infections in people who are HIV positive. Cat stool can cause toxoplasmosis, reptiles can carry salmonella, and birds can carry cryptococcus or histoplasmosis. Wash hands thoroughly after handling pets or emptying litter boxes.

**ALTERNATIVE MEDICINE**

People who are infected with HIV sometimes try dietary supplements that claim to boost the immune system or help with side effects of anti-HIV medicines. But there are no studies that show these claims are true. And many supplements can get in the way of other medicines you take.

Always check with your healthcare professional before taking any supplements or alternative therapies to make sure they won't affect the way your medicines work.

### Supplements that may be helpful

There's little evidence to show that any supplements for HIV work. Some examples with limited research include:

* **Acetyl-L-carnitine.** Researchers have used acetyl-L-carnitine to treat nerve pain, numbness or weakness, called neuropathy, in people with diabetes. It may also ease neuropathy linked to HIV for people who don't have enough acetyl-L-carnitine in their bodies.
* **Whey protein and certain amino acids.** Early evidence suggests that whey protein, a cheese byproduct, can help some people with HIV gain weight. The amino acids L-glutamine, L-arginine and hydroxymethylbutyrate (HMB), also may help with weight gain.
* **Probiotics.** There is some evidence that the probiotic Saccharomyces boulardii may help with HIV-related diarrhea. Use only as your healthcare professional directs. Bovine colostrum also is being studied for treating diarrhea. But more research is needed.
* **Vitamins and minerals.** Vitamins A, D, E, C and B and the minerals zinc, iron and selenium may help if you have low levels of them. Talk to your health professional before taking them. Too much of some vitamins and minerals can be harmful.

### Supplements that may be dangerous

* **St. John's wort.** Often used for depression, St. John's wort can reduce how well several types of anti-HIV medicines work by more than half.
* **Garlic supplements.** Garlic itself may help strengthen the immune system. But garlic supplements can reduce how well some anti-HIV medicines work. Eating some garlic in food seems to be safe.
* **Red yeast rice extract.** Some people use this to lower cholesterol. Don't take it if you take a protease inhibitor or a statin.

### Mind-body practices

Practices such as yoga, meditation and massage have been shown to reduce stress as well as provide relaxation and improve quality of life. While they need more study, these practices may be helpful if you're living with HIV/AIDS.

## Outlook / Prognosis

If you’re diagnosed with HIV, it’s important to know that those living with HIV who follow treatment guidelines can live full lives for nearly as long as those without HIV.

If you have a high CD4 count and an undetectable viral load within a year of starting treatment, research suggests you’ll have the best outcomes, as long as you continue your treatment plan.

You can improve your outlook by:

* Getting tested as part of routine healthcare or if you think you’ve been exposed.
* Starting ART soon after being diagnosed.
* Taking your medicine every day.
* Keeping your appointments with your healthcare team.

ART can keep blood levels undetectable but can’t entirely rid your body of the virus (which remains inactive in your cells). If you don’t take your medication every day, the virus can start multiplying again and mutate, which may cause your medications to stop working.

Left untreated, it can take about 10 years for HIV to advance to AIDS. If you progress to AIDS and it goes untreated, you can expect to live about three years more.

For those on treatment, if you have a high CD4 count and undetectable viral load within a year of starting treatment, you can expect to live about as long as someone without HIV. If you have a low CD4 count or a detectable viral load within a year of starting treatment, you may live 10 to 20 years less than someone without HIV.

### Does HIV go away?

HIV doesn’t go away on its own. It inserts itself into your DNA so your cells think that it’s a part of you. There can be many years without symptoms after initial infection, but HIV can still be damaging to your immune system even if you don’t feel sick.

There may be periods while on medication where the virus is not detectable by an HIV test. In these cases, HIV can be hiding in your body, undetected. It can “wake up” and start destroying your cells again in the future.

This is why continuing to take HIV medication, even if you don’t feel sick or the virus is undetectable, is extremely important. Without treatment, HIV will weaken your immune system until you can’t fight off other serious illnesses.

### When should I see my healthcare provider?

Call your healthcare provider immediately if you think you’ve been exposed to HIV. It is important to begin treatment as soon as possible if you do have HIV.

If you already know you have HIV, you should follow your healthcare provider’s instructions on when to call. It is important to treat any type of infection, so call if you have new symptoms like fever, night sweats, diarrhea or anything else that concerns you.

## Recent Epidemiology of HIV (2023–2025)

* Global Prevalence and Burden:
  + Approximately 39.9 million people [36.1–44.6 million] were living with HIV worldwide in 2023, including about 38.6 million adults (≥15 years) and 1.4 million children (<15 years).
  + The global adult (15–49 years) HIV prevalence is about 0.6% [0.6 -- 0.7%], with significant regional variation; the WHO African Region remains the most affected, with 3.4% of adults living with HIV.
  + Since the start of the epidemic, 88.4 million people [71.3 -- 112.8 million] have been infected, and 42.3 million [35.7 -- 51.1 million] have died from AIDS-related illnesses.
* New Infections and Trends:
  + In 2023, an estimated 1.3 million [1.0–1.7 million] people acquired HIV globally, marking a 39% decline since 2010 and a 60% decline since the peak in 1995 (3.3 million infections)
  + Women and girls accounted for 44% of new infections in 2023.
  + New HIV infections among children have declined by 62% since 2010, from 300,000 to 120,000 in 2023.
  + Despite global declines, some regions such as Eastern Europe, Central Asia, the Middle East, North Africa, and Latin America have seen increasing new infections, especially among key populations.
* Mortality:
  + Approximately 630,000 people died from AIDS-related illnesses in 2023, a 51% reduction since 2010 (1.3 million deaths) and a 69% reduction since the 2004 peak (2.0 million deaths).
  + AIDS remains a leading cause of death globally, particularly among women of reproductive age.
* Diagnosis and Treatment Coverage:
  + About 86% of people living with HIV knew their status in 2023, leaving roughly 5.4 million people unaware of their infection[2](https://www.unaids.org/en/resources/fact-sheet).
  + Around 30.7 million people [27–31.9 million] were accessing antiretroviral therapy (ART) in 2023, contributing to reduced mortality and transmission.
* Regional Highlights:
  + Sub-Saharan Africa accounts for about two-thirds of all people living with HIV globally and remains the hardest-hit region.
  + For the first time, more new infections occurred outside sub-Saharan Africa than within it in 2023.
  + Asia and the Pacific had approximately 6.7 million people living with HIV and 300,000 new infections in 2023.
  + The Caribbean and other regions continue to experience significant HIV burdens
* Key Populations and Drivers:
  + Key populations at higher risk include men who have sex with men, sex workers, people who inject drugs, transgender people, and incarcerated individuals.
  + Substance use remains a significant driver of new infections in some regions, with harm reduction and opioid agonist therapies showing effectiveness in reducing infections among people who inject drugs.

## Diagnostic Considerations

Human immunodeficiency virus (HIV) infection should be considered in any patient with unusual or recurrent serious infections without another cause, especially in those with risk factors for HIV infection.

Any of the opportunistic infections or cancers associated with acquired immune deficiency syndrome (AIDS) can occur in the absence of HIV infection, although they usually develop in patients with some other form of immunosuppression or defect. The possibility of HIV infection must be considered on a case-by-case basis. Other causes of immunosuppression (eg, chemotherapy, immune disorders, severe combined immune deficiency [SCID], severe malnutrition) should be considered. For example, a young adult with leukemia undergoing chemotherapy is at high risk for many opportunistic infections.

## Differential Diagnoses

* Burkitt Lymphoma
* Candidiasis
* Coccidioidomycosis and Valley Fever
* Cryptococcosis
* Cryptosporidiosis
* Cytomegalovirus (CMV)
* Herpes Simplex
* High-Grade Malignant Immunoblastic Lymphoma
* Mycobacterium Avium Complex (MAC) (Mycobacterium Avium-Intracellulare [MAI])
* Toxoplasmosis

## 

## **R**EFERENCES

## [About HIV | HIV | CDC](https://www.cdc.gov/hiv/about/index.html)

[HIV & AIDS: Causes, Symptoms, Treatment & Prevention](https://my.clevelandclinic.org/health/diseases/4251-hiv-aids)

[HIV/AIDS - Diagnosis and treatment - Mayo Clinic](https://www.mayoclinic.org/diseases-conditions/hiv-aids/diagnosis-treatment/drc-20373531)

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<https://www.who.int/data/gho/data/themes/hiv-aids>

<https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics>

<https://www.unaids.org/en/resources/fact-sheet>

**AUTOIMMUNE HEPATITIS**

**DEFINITION AND DESCRIPTION**

Autoimmune hepatitis is a liver disease that happens when the body's immune system attacks the liver. This can cause swelling, irritation and damage to the liver. The exact cause of autoimmune hepatitis is unclear, but genetic and environmental factors appear to interact over time to trigger the disease.

Untreated autoimmune hepatitis can lead to scarring of the liver, called cirrhosis. It can also eventually lead to liver failure. When diagnosed and treated early, however, autoimmune hepatitis often can be controlled with medicines that suppress the immune system.

A liver transplant may be an option when autoimmune hepatitis doesn't respond to medicines or liver disease becomes advanced.

**CAUSES**

Autoimmune hepatitis occurs when the body's immune system, which usually attacks viruses, bacteria and other causes of disease, instead targets the liver. This attack on the liver can lead to long-lasting inflammation and serious damage to liver cells. Just why the body turns against itself is unclear, but researchers think autoimmune hepatitis could be caused by the interaction of genes controlling immune system function and exposure to viruses or medicines.

### Types of autoimmune hepatitis

Experts have identified two main forms of autoimmune hepatitis.

* **Type 1 autoimmune hepatitis.** This is the most common type of the disease. It can occur at any age. About half the people with type 1 autoimmune hepatitis have other autoimmune disorders, such as celiac disease, rheumatoid arthritis or ulcerative colitis.
* **Type 2 autoimmune hepatitis.** Although adults can develop type 2 autoimmune hepatitis, it's most common in children and young people. Other autoimmune diseases may accompany this type of autoimmune hepatitis.

**RISK FACTOR**

Factors that may increase your risk of autoimmune hepatitis include:

* **Being female.** Although both males and females can develop autoimmune hepatitis, the disease is most common in females.
* **Genetics.** Evidence suggests that a predisposition to autoimmune hepatitis may run in families.
* **Having an autoimmune disease.** People who already have an autoimmune disease, such as celiac disease, rheumatoid arthritis or hyperthyroidism (Graves' disease or Hashimoto thyroiditis), may be more likely to develop autoimmune hepatitis.

**SIGNS AND SYMPTOMS**

Symptoms of autoimmune hepatitis vary from person to person and may come on suddenly. Some people have few, if any, recognized problems in the early stages of the disease, whereas others experience symptoms that may include:

* Fatigue.
* Belly discomfort.
* Yellowing of the skin and whites of the eyes, called jaundice. Depending on skin color, this change may be harder or easier to see.
* An enlarged liver.
* Irregular blood vessels on the skin, called spider angiomas.
* Skin rash.
* Joint pain.
* Loss of menstrual periods.

**DIAGNOSIS AND TESTS**

ests and procedures used to diagnose autoimmune hepatitis include:

* **Blood tests.** Testing a sample of blood for antibodies can distinguish autoimmune hepatitis from viral hepatitis and other conditions with similar symptoms. Antibody tests also help pinpoint the type of autoimmune hepatitis you have.
* **Liver biopsy.** A sample of liver tissue may be taken to confirm the diagnosis and to determine the degree and type of liver damage. During the biopsy procedure, a thin needle is passed into the liver through a small cut in the skin. The needle is used to take a small sample of liver tissue. The sample is then sent to a laboratory for testing.

**TREATMENT**

The goal of treatment for autoimmune hepatitis is to slow or stop the immune system attack on the liver. This may help increase the time before the disease gets worse. To meet this goal, you'll likely need medicines that lower immune system activity. The first treatment is usually prednisone. A second medicine, azathioprine (Azasan, Imuran), may be recommended in addition to prednisone.

Prednisone, especially when taken long term, can cause a wide range of serious side effects, including diabetes, weakened or broken bones, high blood pressure, cataracts, glaucoma, and weight gain.

Healthcare professionals typically prescribe prednisone at a high dose for about the first month of treatment. Then, to reduce the risk of side effects, they gradually reduce the dose over the next several months until reaching the lowest possible dose that controls the disease. Adding azathioprine also helps you avoid prednisone side effects.

Although you may experience remission a few years after starting treatment, the disease often returns if the drug is discontinued. Depending on your situation, you may need lifelong treatment.

### Liver transplant

When medicines don't stop the disease from getting worse or you get scarring that can't be reversed — called cirrhosis — or liver failure, the remaining option is a liver transplant.

During a liver transplant, your diseased liver is removed and replaced with a healthy liver from a donor. Liver transplants most often use livers from deceased organ donors. In some cases, a living-donor liver transplant can be used. During a living-donor liver transplant, you receive only a part of a healthy liver from a living donor. Both livers begin regenerating new cells almost right away.

#### **Side effects of the medication**

Side effects of long-term steroid use can include:

* Increased appetite and weight gain.
* Mood disorders, such as anxiety and depression.
* Glaucoma (vision blurring).
* Osteopenia or osteoporosis (bone weakening).
* Diabetes.
* High blood pressure.

Side effects of taking immunosuppressants can include:

* Frequent infections.
* Nausea and vomiting.
* Skin rashes.
* Easy bruising and bleeding.
* Impaired kidney function.
* Pancreatitis.

When you take these medications, your healthcare provider will monitor you for side effects. If the side effects of your medication are too severe, or it doesn’t help you enough, they’ll suggest an alternative.

### How long does the treatment take to work?

The goal of the medications is to make the disease go into remission. You may have to take them for several months to years before this happens. Along the way, your healthcare provider will check your liver regularly for signs the treatment is working. Liver function tests will show your liver enzyme levels gradually lowering to normal. Remission means that all symptoms and signs of the disease are gone.

The American Association for the Study of Liver Diseases recommends staying on steroids for at least three years before discontinuing. When you’ve been in remission for at least two years, they’ll consider discontinuing the immunosuppressants. About 50% of people will have a relapse of the disease within three months of discontinuing their medications. Others may relapse years later, or not at all.

Some people have some improvement with treatment, but not enough to achieve remission. In this case, your healthcare provider will try different medications. Some people don’t respond at all to the treatment. In this case, the course of the disease continues to worsen. These people may develop complications that need additional treatment. They may eventually need a liver transplant.

## Outlook / Prognosis

No. It can go into remission. That means the inflammatory process goes away for a time, sometimes for a long time. But after you stop the treatment, it can come back. This is called relapse. Most people (80%) who discontinue their medications will eventually have a relapse and need to start them again. Medications can usually control the disease well, but you may have to take them off and on for life.

### What is the average life expectancy with autoimmune hepatitis?

Without treatment, life expectancy is 50% within five years. But with treatment, life expectancy is 90% in 10 years and 70% in 20. About 15% of people will eventually develop cirrhosis despite treatment, usually after 10 to 20 years. This can happen if the treatment fails, if you have an incomplete response to the treatment or if the disease relapses multiple times. When it relapses, it can come back stronger.

## Living With

* Keep up with your healthcare appointments. Your healthcare provider will need to continue to monitor your liver for the rest of your life. Even if you’ve been in remission for some time, the disease can relapse without warning and without causing noticeable symptoms. Your healthcare provider can monitor the extent of fibrosis (damage that leads to scarring) in your liver through noninvasive elastography. If you do begin to have symptoms again, don’t hesitate to contact your healthcare provider.
* Take care of your diet. A healthy diet is very important for anyone with liver disease. With AIH in particular, studies show that up to 30% of people have signs of non-alcohol related fatty liver disease. That means your body has a tendency to store excess fat in your liver, which is an additional cause of inflammation. You can work against this by maintaining a healthy weight and reducing sugar and saturated fats in your diet. This can also help improve your treatment results.
* Protect your immunity. Both liver disease and immunosuppressant drugs depress your immune system. That means you have to take extra good care of yourself to prevent getting sick. Your healthcare provider may recommend certain vitamin supplements and vaccines to protect you against infections. Make sure you don’t take any supplements that they haven’t approved.
* Avoid alcohol. Alcohol use depresses your immunity and damages your liver.

**COMPLICATIONS**

Autoimmune hepatitis that goes untreated can cause permanent scarring of the liver tissue, known as cirrhosis. Complications of cirrhosis include:

* **Enlarged veins in the esophagus, called esophageal varices.** The portal vein carries blood from the intestine to the liver. When circulation through the portal vein is blocked, blood may back up into other blood vessels, mainly those in the stomach and esophagus.  
  These blood vessels have thin walls. And because they become filled with more blood than they're meant to carry, they're likely to bleed. Massive bleeding in the esophagus or stomach from these blood vessels is a life-threatening emergency that needs immediate medical care.
* **Fluid in the abdomen, called ascites (uh-SY-teez).** Liver disease can cause large amounts of fluid to build up in the belly. Ascites can be uncomfortable and may interfere with breathing. It's usually a sign of advanced cirrhosis.
* **Liver failure.** Liver failure happens when extensive damage to liver cells makes it not possible for the liver to function well. At this point, a liver transplant is needed.
* **Liver cancer.** People with cirrhosis have an increased risk of liver cancer.

**DIFFERENTIAL DIAGNOSIS**

* Primary biliary cirrhosis
* Primary sclerosing cholangitis
* Hepatitis A
* Hepatitis B
* Hepatitis C
* Hepatitis D
* Hepatitis E

**EPIDEMIOLOGY**

Epidemiological data on autoimmune hepatitis is scarce and very likely unreported and underrecognized. Of the two types of autoimmune hepatitis, 80% of cases are diagnosed as type 1. Seventy-five percent of type 1 autoimmune hepatitis is known to manifest in young or middle-aged females. Autoimmune hepatitis is more common in females than males with a ratio of 3.6:1. Due to the lack of exact epidemiological data, the true incidence and prevalence in the United States are unknown. However, it is reported that 100,000 to 200,000 individuals are affected each year. Based on European studies, the incidence of autoimmune hepatitis is 0.9-2/100,000 populations per year and the prevalence of 11-25/100,000 per year. Type 2 autoimmune hepatitis is most commonly diagnosed in children and young adults and usually presents with fulminant hepatic failure.

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**AUTOIMMUNE ENCEPHALITIS**

**DEFINITION AND DESCRIPTION**

Autoimmune encephalitis (en-sef-uh-LIE-tis) is a group of conditions that causes swelling in the brain. This happens because the immune system mistakenly attacks brain cells. Autoimmune encephalitis symptoms can vary but may include memory loss, changes in thinking, changes in behavior and seizures.

Autoimmune encephalitis is different from encephalitis caused by viral or bacterial infections, known as infectious encephalitis. Infectious encephalitis isn't caused by an immune reaction, and it's treated with different medicines. Research has found that the number of people with autoimmune encephalitis is comparable to the number of people with infectious encephalitis.

Experts don't know what causes autoimmune encephalitis, also known as AE. For some people, AE is triggered by certain cancers or infections. Autoimmune encephalitis also may be triggered by medicines. People with an autoimmune disease or a family history of autoimmune disease may be more likely to get AE. Healthcare professionals use several tests to diagnose autoimmune encephalitis.

Without treatment, autoimmune encephalitis can cause serious complications, including death. But treatments can lead to recovery. Many people with AE make a full recovery, but some can have lasting symptoms.

**CAUSES**

Autoimmune encephalitis causes are not known. Autoimmune encephalitis, also known as AE, happens when the immune system mistakenly attacks heathy brain cells.

Antibodies are part of the immune system. They help protect the body from viruses, bacteria and other substances that can cause illnesses. But in autoimmune encephalitis, the antibodies target and attack certain receptors in the brain. This leads to swelling in the brain, also known as inflammation, and other symptoms.

AE may be triggered by:

Certain cancers. When this happens, it's known as paraneoplastic AE.

Infections, such as from the herpes simplex virus.

Certain medicines, such as monoclonal antibodies and medicines to suppress the immune system after a transplant.

Autoimmune encephalitis is more likely to occur in people who have an autoimmune disease or who have a strong family history of autoimmune disease.

Types

There are several different types of AE. Each type of autoimmune encephalitis is caused by the immune system attacking different receptors in the brain. Some of the types and causes include:

Anti-NMDA-receptor autoimmune encephalitis. This is the most common type of AE. In this type, antibodies attack the NMDA receptor in the brain. It often affects young women and children and can cause seizures, facial movements, psychosis and other symptoms.

Anti-GABA-B receptor encephalitis. This type of AE is related to a tumor, often small-cell lung cancer. This type of AE can cause seizures, confusion and memory loss. The average age of diagnosis of this type is 60.

Anti-GABA-A receptor encephalitis. People with this type of AE are usually diagnosed around age 40, but children also can have this type of AE. This type of AE can cause seizures, movement disorders, and changes in thinking and behavior.

Anti-AMPA receptor encephalitis. This type of AE usually affects women and can cause confusion and memory loss. The average age of diagnosis is age 62.

Anti-LGI1 limbic encephalitis. This type of autoimmune encephalitis tends to affect men. It can cause memory loss, confusion and seizures. The average age of diagnosis is age 60.

Anti-CASPR2 associated encephalitis. People with this type of AE often have symptoms that include confusion, memory loss, trouble with sleep, nerve pain and other symptoms. This type also can cause a rare disease known as Morvan syndrome. Morvan syndrome can cause hallucinations, memory loss, changes in blood pressure and painful cramps. Men are more likely to have this type of AE. The average age of diagnosis is 60.

Anti-IgLON5 disease. People who have this type of AE have sleep symptoms that include behaviors and movements after falling asleep. The average age of diagnosis is 64.

**RISK FACTOR**

Risk factors for autoimmune encephalitis, also known as AE, include:

Having had AE in the past, especially if it wasn't treated.

Having had herpes simplex virus encephalitis.

Taking monoclonal antibodies or medicines to suppress the immune system after a transplant.

Having a tumor, especially small-cell lung cancer.

Researchers are studying whether certain genes may be related to autoimmune encephalitis.

**SYMPTOMS**

Autoimmune encephalitis symptoms can vary from person to person. But symptoms can occur in a pattern that is predictable depending on the type of autoimmune encephalitis. Many people have a headache, fever and other symptoms of an infection followed by:

* Psychiatric symptoms that may include anxiety, panic attacks, changes in behavior, agitation, hallucinations, delusions and trouble organizing thoughts.
* Trouble with memory.
* Trouble with language, such as talking less or repeating words or phrases.
* Movements that are not voluntary.
* Seizures.
* Changes in consciousness.
* Less sleep at the beginning of the disease followed by excess sleep during recovery.

Sometimes AE causes serious seizures that need emergency care, known as status epilepticus. These seizures last more than five minutes or occur one after another while the person is not conscious.

Autoimmune encephalitis symptoms can get worse over time. This disease course is known as progressive. Symptoms also might alternate between getting better and getting worse. This course is known as relapsing-remitting. These are similar to the disease courses people experience with multiple sclerosis.

## Diagnosis

Autoimmune encephalitis diagnosis involves a review of your symptoms, a physical exam and several tests. It's important to get an accurate diagnosis because autoimmune encephalitis, also known as AE, can be mistaken for other diseases.

Experts have created autoimmune encephalitis criteria to help healthcare professionals diagnose people with AE. Healthcare professionals look for patterns of symptoms that signal AE. They also test for signs that antibodies are attacking receptors in the brain to cause AE.

Tests also help rule out other possible causes of your symptoms, such as infections or other autoimmune conditions.

Sometimes people are incorrectly diagnosed with autoimmune encephalitis. It's important for healthcare professionals to consider all potential conditions when making a diagnosis.

### Lab tests

Testing for autoimmune encephalitis includes checking for antibodies. AE is caused by antibodies in the brain that attack proteins and receptors in the brain and cause symptoms.

Some tests may be done on your blood. Other tests are done on the fluid that surrounds your brain and spinal cord, known as cerebrospinal fluid. Cerebrospinal fluid is removed using a procedure known as a lumbar puncture. During the procedure, a healthcare professional numbs the lower back and uses a hollow needle to remove cerebrospinal fluid for testing.

### Brain imaging

Your healthcare professional also may recommend an MRI of your brain. MRIs can look for signs of autoimmune encephalitis or rule out other causes of your symptoms.

Other imaging tests may look for signs of cancer that may have triggered AE.

### EEG

An electroencephalogram, also known as an EEG, tests the electrical activity in your brain. It may show seizure activity and may help your healthcare professional diagnose AE. An EEG also can help rule out other conditions.

**TREATMENT**

Autoimmune encephalitis treatment focuses on the immune system, which is mistakenly attacking brain cells. If a tumor is causing autoimmune encephalitis, the first step is to diagnose and treat the tumor.

### Medicines

Immunotherapy works by reducing the immune system's activity and improving inflammation.

Two types of immunotherapy are given through an IV in a vein in the arm. Most people get this therapy in a hospital. Medicines include:

* **Methylprednisolone (Solu-Medrol).** This high-dose steroid is given daily for 3 to 7 days.
* **Immunoglobulin (IVIg).** This medicine may be given daily for 2 to 5 days.

Other treatment options include:

* **Oral corticosteroids.** With this medicine, you start with a larger dose and then slowly lower the dose over weeks to months, known as tapering.
* **Plasma exchange.** This therapy gets rid of antibodies that are causing the immune system to attack brain cells. During plasma exchange, the liquid part of your blood is removed and separated from your blood cells. The blood cells are put back into your body and your body makes more plasma.

If your symptoms respond to immunotherapy, the medicine doses are slowly lowered over time, known as tapering. You may take an oral corticosteroid at a lower dose for several weeks. Or you may get monthly doses of methylprednisolone or immunoglobulin through an IV for several months.

If your symptoms aren't improving, your healthcare professional also may recommend the medicines rituximab (Rituxan, Truxima, others), cyclophosphamide or tocilizumab (Actemra, Tofidence, Tyenne). These medicines can improve symptoms and help lower the chances of AE coming back.

Most people recover with treatment. The earlier you receive treatment, the more quickly you may recover. Early treatment also lowers the chances of having lasting symptoms due to AE or having another bout of autoimmune encephalitis.

### Therapies

You may need treatment for complications, such as epilepsy, sleep conditions and trouble with movements. You also may need rehabilitation if AE affected your memory, thinking skills or speech. Occupational and speech therapists, along with mental health professionals and other specialists, can help in your recovery.

If cancer triggered autoimmune encephalitis, you're treated for the cancer and monitored to check if the cancer comes back. Sometimes people with other symptoms related to AE need to get regular care from specialists.

The long-term outlook can vary from person to person. Full recovery may take months or years. Many people continue to have symptoms related to thinking and behavior for longer than a year. But treatment continues to improve symptoms for 18 months to two years.

Some people fully recover while others may have lasting symptoms that are mild or more serious. Getting treated early helps improve your long-term outlook.

People who have recovered from certain types of autoimmune encephalitis, such as anti-NMDA receptor encephalitis and anti-LGI1 encephalitis, are at risk of symptoms coming back. Sometimes symptoms return after several years.

**Complications**

Serious autoimmune encephalitis, also known as AE, can lead to complications such as:

* **Seizures that need emergency care, known as status epilepticus.** The immune system's attack on the brain during AE can lead to seizures and a condition called autoimmune epilepsy. Sometimes the seizures may last more than five minutes or occur one after another. The person isn't conscious in between the seizures. These serious seizures are known as status epilepticus.
* **Not enough air entering the lungs, known as respiratory failure.** People with respiratory failure may need treatment with a machine that helps them breathe, known as mechanical ventilation.
* **Trouble with heart rate and blood pressure.** AE can affect heart rate, blood pressure, digestion and urination. These are known as autonomic functions.
* **Fevers.** People with AE may have high fevers.

Another possible complication is that the condition may come back after recovery. This is known as a relapse. A relapse is more likely in people who had anti-LGI1 limbic encephalitis or anti-CASPR2 associated encephalitis.

**Prevention**

Autoimmune encephalitis, also known as AE, can't always be prevented. But getting cancer screenings can help your healthcare professional find tumors and treat them early. This could prevent autoimmune encephalitis that is triggered by cancers. Talk with your healthcare professional about your cancer risk and if cancer screening is recommended.

## Outlook / Prognosis

In general, getting treatment early in the course of autoimmune encephalitis tends to decrease your risk of long-term complications and relapse.

But AE affects everyone differently — and other coexisting conditions like cancer may affect your prognosis (outlook). Your healthcare team will be able to give you a better idea of what to expect.

#### **Is autoimmune encephalitis lifelong?**

Autoimmune encephalitis generally responds well to treatment and goes away. But this can take a long time for some people. AE can also relapse (come back), especially if you have cancer that’s not responding to treatment.

### When to see a doctor

Get emergency medical care if you or someone you're with has serious symptoms of AE. This includes having seizures that last more than five minutes or that happen one after another with a loss of consciousness. Also seek emergency medical care for high fevers or trouble breathing.

See your healthcare professional right away if you have any other symptoms of autoimmune encephalitis. AE can become serious quickly if not treated.

### *Best practice recommendations summary for acute management of autoimmune encephalitis*

* *Evaluate the likelihood of AE relative to the patient’s clinical picture.*
* *Perform brain MRI and/or EEG to look for focal or multifocal brain abnormality.*
* *Perform lumbar puncture to support inflammatory etiology and rule out infective/neoplastic causes. Test oligoclonal bands, IgG index, IgG synthesis rate, and neuronal autoantibodies in the cerebrospinal fluid (CSF).*
* *Send blood tests to rule out other potential causes guided by neuroanatomical and clinical data. Test neuronal autoantibodies in the serum.*
* *Consider brain FDG-PET when there is a high clinical suspicion of AE, and other paraclinical studies are uninformative.*
* *Perform cancer screening with CT chest, abdomen, and pelvis with contrast in relevant cases (or MRI when CT is contraindicated or not preferred). If negative, consider further testing with mammogram/breast MRI, pelvic ultrasound, and/or whole body FDG-PET guided by the clinical presentation and each patient’s specific cancer risk factors.*
* *Once infection is ruled out based on basic CSF results (e.g., number of cells) and if a biopsy for primary CNS lymphoma or neurosarcoidosis is not a consideration, start acute immunotherapy with high dose corticosteroids (or IVIG or PLEX if steroids are not preferred or contraindicated).*
* *If there is no clinical, radiological, or electrophysiological improvement by the end of the initial treatment cycle, add IVIG or PLEX. Consider IVIG first in agitated patients and in those with bleeding disorders. Consider PLEX first in patients with severe hyponatramia, high thromboembolic (or cancer) risk, and if there is associated brain or spinal demyelination.*
* *Consider starting with a combination therapy of steroids/IVIG or steroids/PLEX from the beginning (as opposed to sequentially) in patients with severe initial presentation (e.g., severe NMDAR-antibody presentation, new-onset refractory status epilepticus, severe dysautonomia, etc.)*
* *If there is no clinical or radiological improvement 2–4 weeks after completion of combined acute therapy, consider starting a second-line agent when the clinical suspicion is high, and/or a clinically relevant antibody is present.*
* *Consider rituximab in known or highly suspected antibody-mediated autoimmunity (e.g., NMDAR-antibody encephalitis) and consider cyclophosphamide in known or highly suspected cell-mediated autoimmunity (e.g., classical paraneoplastic syndrome).*
* *If there is no clear objective or subjective evidence of improvement with conventional second-line therapies, consider novel approaches such as tocilizumab or bortezomib, although there is only minimal evidence to support their use.*
* *Start bridging therapy with gradual oral prednisone taper or monthly intravenous Ig or intravenous methylprednisolone. Avoid steroid taper or implement a shorter taper in vague cases with poor response to initial immunosuppressive therapy or when immunosuppression may impose higher risks than benefits (e.g., patients with cancer or active infection).*

## Differential Diagnosis of Autoimmune Encephalitis

1. Infectious Encephalitis
   * Viral (e.g., herpes simplex virus, varicella-zoster virus)
   * Bacterial, fungal, parasitic infections
2. Primary CNS Inflammatory Diseases
   * Multiple sclerosis
   * CNS vasculitis (large-vessel and small-vessel)
   * Sarcoidosis
3. Systemic Inflammatory Diseases with CNS Involvement
   * Systemic lupus erythematosus (SLE)
   * Other connective tissue diseases
4. Neoplastic Disorders / Paraneoplastic Syndromes
   * CNS tumors (astrocytoma, lymphoma, medulloblastoma)
   * Paraneoplastic limbic encephalitis
5. Metabolic Disorders
   * Mitochondrial encephalomyopathy
   * Thiamine (Vitamin B1) deficiency
   * Vitamin B12 deficiency
6. Toxic Encephalopathies
   * Drug-induced
   * Substance abuse
7. Psychiatric Disorders
   * First-episode psychosis
   * Schizophrenia
   * Mood disorders
8. Neurodegenerative Diseases
   * Alzheimer’s disease
   * Creutzfeldt-Jakob disease
   * Frontotemporal dementia
9. Epileptic Disorders and Postictal States
   * Seizure disorders with postictal confusion
10. Functional Neurological Disorders
    * Non-organic neurological symptoms
11. Infection-Associated Encephalopathy Syndromes
    * Febrile infection-related epilepsy syndrome (FIRES)
    * Acute necrotizing encephalopathy

**EPIDEMIOLOGY**

Epidemiological data on autoimmune encephalitis is under-reported due to its variable presentation and numerous antibodies responsible,Commonly Reported Antibodies. The incidence of encephalitis reported in adults varies between 0.7 to 12.6 per 100,000 and has been reported in adult and pediatric populations.To date, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been commonly reported under AIE, and most studies have been on it. In one large multicentric observational study, 80% of patients with anti-NMDAR encephalitis were female with a median age of disease onset of 21 years. Furthermore, 38% of the population in the study was found to have an underlying neoplasm with a predominance of ovarian teratoma.

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