The Blood Project

UNDERSTANDING CAD

A brief guide for patients with cold agglutinin disease (CAD)

Cold agglutinin disease is a condition in which the immune system reacts to red blood cells at cooler temperatures. In some people, this reaction shortens the lifespan of red blood cells and can lead to **anemia**. Many people live safely with this condition for years, and **treatment is needed only in specific situations or at certain times**.

What is cold agglutinin disease?

Cold agglutinin disease is a type of **autoimmune hemolytic anemia**, meaning the immune system makes antibodies that attach to red blood cells and cause them to be cleared earlier than usual.
The antibodies are most active at **cooler temperatures**, such as in the fingers, toes, ears, or nose. **Not everyone with cold agglutinins develops anemia**. Cold agglutinin disease means the antibodies are causing symptoms or anemia, while cold agglutinin syndrome refers to similar antibodies that appear because of another condition.

Why does it happen?

Cold agglutinin disease occurs when the immune system produces antibodies, most often of the **IgM type**, that recognize red blood cells at lower temperatures. These antibodies can activate **a normal immune process called complement**, which shortens the lifespan of red blood cells.
In many people, the antibody comes from a small, slow-growing group of immune cells in the bone marrow. Doctors sometimes describe this as a **low-grade lymphoproliferative** process. This does not mean an aggressive cancer, and many people remain stable for years.

Does it cause symptoms?

Some people have **no symptoms at all**.
When symptoms occur, they usually include both:

- **anemia-related symptoms**, such as fatigue, shortness of breath, pale or yellowish skin, or dark urine
- **cold-triggered circulation symptoms**, such as temporary pale or bluish color changes, numbness, or discomfort in the fingers or toes

Symptoms often fluctuate and may worsen temporarily during infections or cold weather.

Is it dangerous?

For many people, cold agglutinin disease remains **mild and stable for long periods**.
The condition becomes more concerning when anemia causes symptoms, red blood cells are being broken down more quickly, or symptoms interfere with daily life. Severe complications are uncommon. Some people may occasionally need transfusion, but many are followed safely without active treatment.

How is it evaluated?

- blood counts to assess anemia
- blood tests that show red blood cell breakdown
- tests that detect cold agglutinins or complement activity
- evaluation to determine whether the condition is primary or related to another cause

A **bone marrow biopsy is not needed for everyone**. It is done only in selected situations.

Daily life and self-are

Most people with cold agglutinin disease can live **normal lives**. Dressing warmly, protecting hands and feet in winter, and avoiding very cold drinks if they trigger symptoms are usually sufficient. Brief cold exposure is typically well tolerated.

When should I contact my doctor?

Contact your healthcare team if you notice worsening fatigue, shortness of breath, yellowing of the skin or eyes, dark urine that persists, or symptoms that interfere with daily activities.

What is the usual plan going forward?

Most people are followed with **periodic clinic visits and blood tests**. Long periods of stability are common, and many people have a good long-term outlook with appropriate monitoring.

Key points to remember

- **cold agglutinin disease and cold agglutinin syndrome are not the same**
- **symptoms can involve anemia and cold-triggered circulation changes**
- **bone marrow biopsy is not always required**
- **modern treatments exist**, including anti-complement therapy
- **many people remain stable** with monitoring alone