TEST

Febrile (warm) and cold agglutinins

This blood test looks for antibodies that clump selected bacteria or red blood cells under specific conditions.

WHAT IT MEASURES
Antibodies that clump selected bacteria or red cells at set temperatures

SAMPLE
Blood serum

FASTING NEEDED?
No

HOW LONG IT TAKES
Usually less than 10 minutes

RESULTS IN
Usually several days; timing varies by laboratory

USED FOR
Supporting diagnosis of selected infections or cold-antibody hemolysis

MAIN LIMITATION
Different assays share this name and are not interchangeable

Overview

Agglutinins are antibodies that make cells or particles clump together. "Febrile," "warm," and "cold" agglutinin tests do not always refer to the same type of antibody, so the exact test name matters.

A febrile agglutinin panel looks for antibodies that react with selected bacteria. Depending on the laboratory, these may include types of Salmonella , Brucella , Francisella , or certain Proteus strains. These older tests may help investigate particular infections, but they can cross-react with unrelated antibodies and often cannot prove that an infection is active.

A cold agglutinin test looks for antibodies that bind to red blood cells more strongly at lower temperatures. These antibodies may occur temporarily with infections. Less commonly, they are associated with ongoing red blood cell destruction, called hemolysis.

"Warm autoantibody" testing is different again. Warm autoantibodies react near body temperature and are usually investigated with a direct antiglobulin test, also called a direct Coombs test. A febrile agglutinin panel does not diagnose warm autoimmune hemolytic

anemia.

Why the test is ordered

A febrile agglutinin panel may be ordered when your symptoms, travel, animal exposure, food or water exposure, and local infection patterns suggest a specific bacterial infection. It is now used less often because cultures, molecular tests such as PCR, and more specific antibody tests may give clearer answers.

A cold agglutinin test may be ordered if blood tests suggest that red blood cells are being destroyed. Possible findings include anemia, increased bilirubin, or red blood cells clumping in a blood sample. It may also be considered if you have symptoms that become worse in the cold, such as painful or bluish fingers and toes.

The test name alone does not show which antibodies were measured. Your result should identify the individual assay or organisms tested.

Who should have the test

These tests are generally used for a focused investigation rather than routine screening.

You may have a febrile agglutinin test if a particular infection is suspected and the result could add useful information. Exposure history and the timing of your illness are important because antibodies often take time to develop.

Cold agglutinin testing may be useful if other results suggest hemolysis or if a blood sample repeatedly shows unexplained red cell clumping. It is not usually helpful for nonspecific tiredness alone.

If warm autoimmune hemolytic anemia is being considered, other tests are usually more appropriate. These include a direct antiglobulin test, a complete blood count, a blood film, bilirubin, lactate dehydrogenase, and haptoglobin.

How to prepare

You normally do not need to fast. You can usually eat, drink water, and take your regular medicines.

Tell the healthcare professional arranging the test about:

Cold agglutinin samples may need special temperature-controlled handling. This is the

laboratory's responsibility; you do not need to warm yourself or the sample unless you receive specific instructions.

- Recent infections, vaccinations, travel, and animal exposures
- Antibiotics or medicines that affect the immune system
- Intravenous immunoglobulin treatment
- A recent blood transfusion
- Any past diagnosis involving anemia or abnormal antibodies

What happens during the test

A healthcare professional places a needle into a vein, usually in your arm, and collects a small tube of blood. The blood draw usually takes less than 10 minutes.

The sample is allowed to clot, and the liquid part, called serum, is tested. For cold agglutinins, the tube may need to stay warm until the serum has been separated from the blood cells.

In an agglutination test, the laboratory mixes diluted serum with selected bacteria, bacterial particles, or red blood cells. It then checks whether visible clumping occurs.

Understanding your results

Results may be reported as negative, positive, or as a titer. A titer shows how far the serum could be diluted while clumping was still detected. For example, a result written as 1:64 is a dilution, not a count of antibodies.

There is no single reference range that applies to every febrile or cold agglutinin test. Ranges and interpretation vary by laboratory, method, age, sex, pregnancy status, medicines, and clinical context.

A positive febrile agglutinin result means that an antibody reacted with one of the test antigens. It does not necessarily mean that you currently have that infection. Past exposure, vaccination, or cross-reaction with another antibody may produce a positive result.

A rising antibody level in blood samples taken at different stages of an illness may be more informative than one result. Even then, the result must fit your symptoms and exposure history.

A cold agglutinin titer shows whether cold-reacting antibodies were detected and at what dilution. The titer alone does not show whether they are harming your red blood cells. How

close to body temperature the antibody remains active-its "thermal amplitude"-may matter more than the titer.

What affects the results

The timing of the sample is especially important. Testing early in an infection may give a negative result because your body has not yet made enough antibodies. A later sample may be needed.

Several other factors can affect interpretation:

For cold agglutinin testing, allowing the sample to cool before serum separation can cause antibodies to attach to red cells inside the tube. This may reduce the amount left in the serum and produce an inaccurately low result.

Ordinary food, coffee, time of day, and routine exercise have little direct effect on these antibodies.

- Past infection or vaccination may leave detectable antibodies
- Related bacteria may cause cross-reactions and false-positive results
- Immune-suppressing medicines or immune disorders may weaken antibody production
- Intravenous immunoglobulin can introduce passively transferred antibodies
- Antibiotic treatment may affect related cultures and the overall diagnostic picture
- A recent transfusion can complicate red cell antibody and hemolysis testing
- Pregnancy and age can change the clinical meaning of some findings
- Poor temperature control may make a cold agglutinin result misleading

Accuracy and limitations

Febrile agglutinin panels have important limits. They may say "positive" because of past exposure or cross-reaction when the suspected infection is not present. They may also miss an infection when testing is done too early or when antibody production is weak.

For active typhoid or paratyphoid fever, blood culture is generally more useful than a Widal-type agglutinin test. Culture, PCR, or a more specific antibody assay may also be preferable for other infections, depending on the organism and stage of illness.

Cold agglutinin testing can detect an antibody without showing that it causes disease.

Low-level cold-reacting antibodies may be found in people without hemolysis. Conversely, a sample handled at the wrong temperature can miss or underestimate a clinically important antibody.

When cold-antibody hemolysis is suspected, the result is interpreted with a direct antiglobulin test and evidence of red cell destruction. A cold agglutinin titer by itself cannot establish the cause of anemia.

Risks and complications

The risks are those of an ordinary blood draw. You may have brief discomfort, a small bruise, or feel light-headed.

Serious complications are uncommon. Pressure on the puncture site usually stops minor bleeding.

What happens next

A negative result may end the investigation if the chance of the suspected condition was already low. If the sample was taken early, repeat testing or a different test may be appropriate.

A positive febrile agglutinin result may lead to a culture, PCR test, or more specific antibody test. Treatment is not usually based on a nonspecific agglutinin result alone.

If cold agglutinins are found, further blood tests may check whether red cells are being destroyed and whether anemia is present. Routine follow-up is appropriate when you feel well and the result was an incidental finding.

Seek urgent medical advice for rapidly worsening weakness, marked yellowing of the skin or eyes, or dark urine accompanied by feeling unwell. Call emergency services for severe trouble breathing, chest pain, fainting, or confusion. These symptoms require assessment rather than interpretation of the agglutinin result alone.

Common questions

Can I drink coffee before the test?

Yes. Coffee does not usually affect agglutinin antibodies. Follow separate fasting instructions if other blood tests are being collected at the same time.

Does the time of day matter?

Usually not. The number of days since symptoms began matters more, especially when testing for antibodies to an infection.

Can I exercise beforehand?

Routine exercise is unlikely to change the result. Avoiding exercise is not normally required unless another test being collected has different instructions.

Do I need to keep warm before a cold agglutinin test?

No special preparation is usually needed. Correct handling of the blood tube after collection is more important than your body temperature before the test.

Why might I need a second blood sample?

Antibody levels can change during an infection. Comparing an early sample with a later one may show whether the antibody response is rising.

Is this the same as a Coombs test?

No. A direct Coombs test checks whether antibodies or complement proteins are attached to your red blood cells. It is often used alongside other tests when immune-related hemolysis is suspected.

Sources

- ARUP Laboratories Test Directory: Febrile Agglutinins Panel
- ARUP Consult: Cold Agglutinin Disease
- Mayo Clinic Laboratories: Cold Agglutinin Titer, Serum
- CDC: Clinical Guidance for Typhoid Fever and Paratyphoid Fever
- CDC: Clinical Testing and Diagnosis for Tularemia
- Berentsen S. How I treat cold agglutinin disease. Blood . 2021;137(10):1295-1303