MAYO CLINIC LABORATORIES

Test Definition: C4FX

C4 Complement, Functional, Serum

Overview

Useful For

Diagnosis of C4 deficiency

Investigation of a patient with an undetectable total complement level

Method Name

Automated Liposome Lysis Assay

NY State Available

Yes

Specimen

Specimen Type

Serum Red

Ordering Guidance

The total complement assay (COM / Complement, Total, Serum) should be used as a screen for suspected complement deficiencies before ordering individual complement component assays. A deficiency of an individual component of the complement cascade will result in an undetectable total complement level.

Specimen Required

Patient Preparation: Fasting preferred

Supplies: Sarstedt 5 mL Aliquot Tube (T914)

Collection Container/Tube: Red top

Submission Container/Tube: Plastic vial

Specimen Volume: 1 mL

Collection Instructions:

1. Immediately after specimen collection, place the tube on wet ice.
2. Centrifuge and aliquot serum into plastic vial.
3. Immediately freeze specimen.

Specimen Minimum Volume

0.5 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	Reject

Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum Red	Frozen	14 days	

Clinical & Interpretive

Clinical Information

Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classical pathway, 2) the alternative (or properdin) pathway, and 3) the lectin (or mannan-binding lectin) pathway. The classical pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. A single IgM molecule or 2 IgG molecules are sufficient to trigger activation of the recognition complex initiated by C1q. The activation process triggers a cascade that includes an amplification loop. The amplification loop is mediated by C3, with cleavage of a series of proteins, and results in 3 main end products: 1) anaphylatoxins that promote inflammation (C3a, C5a), 2) opsonization peptides that are chemotactic for neutrophils (C3b) and facilitate phagocytosis, and 3) the membrane attack complex, which promotes cell lysis.

The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate the peptides that are necessary clear immune complexes and to attract neutrophils or to generate to lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease, of which complement deficiency may be an etiologic factor.

Approximately 30 cases of homozygous C4 deficiency have been reported. Most of these patients have systemic lupus erythematosus (SLE) or glomerulonephritis, IgA nephropathy. Patients with C4 deficiency may also have frequent bacterial infections and may present with autoimmune diseases such as SLE and SLE-like syndromes or rheumatoid arthritis. C4 is coded by two different genes in the major histocompatibility complex on human chromosome 6. Seventy-five percent of the population has two *C4A* and two *C4B* genes. However, the total sum of *C4A* and *C4B* genes in an individual can range from zero to 8 or more copies, giving this protein a wide range of concentrations and an even wider range of function in the general population. Most of the partial C4 deficiencies are without consequence, although deficiency of C4A is associated with a 15% incidence of SLE.

Complement levels can be detected by antigen assays that quantitate the amount of the protein (C4 / Complement C4, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Reference Values

22-45 U/mL

Interpretation

Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes).

Absent C4 levels in the presence of normal C3 and C2 values are consistent with a C4 deficiency.

Normal results indicate both normal C4 protein levels and normal functional activity.

In hereditary angioedema, a disorder caused by C1 esterase inhibitor deficiency, absent or low C4 and C2 values are seen in the presence of normal C3 (due to activation and consumption of C4 and C2).

Cautions

Absent (or low) C4 functional levels in the presence of normal C4 antigen levels should be replicated with a new serum specimen to confirm that C4 inactivation did not occur during shipping.

Clinical Reference

1. Davis ML, Austin C, Messmer BL, et al: IFCC-standardization pediatric reference intervals for 10 serum proteins using the Beckman Array 360 system. Clin Biochem. 1996;29(5):489-492
2. Gaither TA, Frank MM: Complement. In: Henry JB, ed. Clinical Diagnosis and Management by Laboratory Methods. 17th ed. WB Saunders Company; 1984:879-892
3. O'Neil KM: Complement deficiency. Clin Rev in Allergy Immunol. 2000;19:83-108
4. Frank MM: Complement deficiencies. Pediatr Clin North Am. 2000;47:1339-1354
5. Brodszki N, Frazer-Abel A, Grumach AS, et al: European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, Diagnosis, and Management. J Clin Immunol. 2020 May;40(4):576-591
6. Willrich MAV, Braun KMP, Moyer AM, Jeffrey DH, Frazer-Abel A. Complement testing in the clinical laboratory. Crit Rev Clin Lab Sci. 2021 Nov;58(7):447-478. doi: 10.1080/10408363.2021.1907297

Performance

Method Description

C4 activity is measured by mixing patient serum with a C4-deficient serum. The lytic activity of the serum mixture is tested against sensitized, labeled liposomes. If lysis occurs, the patient serum must be the source of the C4. The target liposomes are a commercial reagent (WAKO total complement CH50), and the assay is performed on an Advia XPT.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday through Friday

Report Available

1 to 3 days

Specimen Retention Time

14 days

Performing Laboratory Location
Rochester

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

86161

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
C4FX	C4 Complement, Functional, S	93978-5

Result ID	Test Result Name	Result LOINC® Value
C4FX	C4 Complement, Functional, S	93978-5