Test Definition: C1INF

C1 Esterase Inhibitor, Functional, Serum

Overview

Useful For

Diagnosing hereditary angioedema

Monitoring response to C1 esterase inhibitor replacement therapy

Method Name

Enzyme Immunoassay (EIA)

NY State Available

Yes

Specimen

Specimen Type

Serum Red

Specimen Required

Patient Preparation:

Fasting: 8 hours, preferred but not required

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)

Collection Container/Tube:

Preferred: Red top

Acceptable: Serum gel

Submission Container/Tube: Plastic vial

Specimen Volume: 1 mL

Collection Instructions:

1. Immediately after specimen collection, place the tube on wet ice.
2. After sample has clotted on wet ice, centrifuge at 4 degrees C and aliquot serum into a plastic vial.
3. Freeze specimen within 30 minutes of centrifugation. Sample must be placed on dry ice if not frozen immediately.

NOTE: If a refrigerated centrifuge is not available, it is acceptable to use a room temperature centrifuge, provided the specimen is kept on ice before centrifugation, and immediately afterward, the serum aliquoted and frozen.

Specimen Minimum Volume

0.4 mL

Reject Due To

Gross hemolysis	OK
Gross lipemia	OK

Gross icterus	Reject
Heat-inactivated samples	Reject

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum Red	Frozen	28 days	

Clinical & Interpretive

Clinical Information

C1 esterase inhibitor (C1-INH) is a multispecific protease inhibitor that is present in normal human plasma and serum and regulates enzymes of the complement, coagulation, fibrinolytic, and kinin-forming systems. The enzymes (proteases) regulated by this protein include the C1r and C1s subunits of the activated first component of complement (the C1qrs complex), activated Hageman factor (factor XIa), kallikrein (Fletcher factor), and plasmin.

A deficiency of functionally active C1-INH may lead to life-threatening angioedema. Two major forms of C1- INH deficiency have been reported: the congenital form, termed hereditary angioedema (HAE), and the acquired form, which is associated with a variety of diseases, acquired angioedema (AAE).

In HAE, there is insufficient C1-INH to negatively regulate bradykinin release and stop angioedema attacks from occurring. The mechanism of HAE attacks is distinct from an allergic angioedema as it is not mediated by histamine release via mast cell activation. Therefore, HAE patients are unresponsive to antihistamines or corticosteroids.

There are 2 main types of HAE that are attributed to C1-INH deficiency (type I) or dysfunction (type II), resulting in C1-INH activity ranging from less than 20% to 50% of normal. Type I HAEs, representing approximately 85% of patients, are associated with low circulating concentrations of C1-INH, leading to a concomitant decrease in C1-INH function. In type II HAEs, normal or elevated concentrations of functionally inactive C1-INH are produced. The relative proportion of type I and type II HAE may differ based on geographical location.

A third HAE subtype with unknown prevalence termed "HAE with normal C1-INH" has been described. Although poorly characterized, a minority of these patients is known to harbor a variant in Factor XII; the disease origin for the remainder of patients remains unknown. Factor XII is the zymogen form of Factor XIIa and plays a key role in bradykinin production as part of the contact system.

Angioedema due to C1-INH deficiency can also be acquired during adulthood in the fifth decade of life or later. The prevalence of AAE is extremely low and is estimated at 10% of HAE. AAE is frequently associated with monoclonal gammopathies or lymphoproliferative disease as well as different types of cancer and autoimmune diseases. AAE may be caused by development of anti-C1-INH autoantibodies, which act to reduce the functional activity or increase the catabolism of C1-INH.

For patients exhibiting symptoms associated with HAE, evaluation of pertinent family history in combination with laboratory results for C1-INH function and concentration, C4 concentration, and C1q concentration can assist in HAE

diagnosis and determination of HAE type. Identification of low C1-INH function and low C4 concentration support the diagnosis of HAE and was found to have 98% specificity towards C1-INH deficiency and a negative predictive value of 95%. C4 is decreased owing to excessive consumption through the classical pathway in the absence of inhibition by C1-INH. Due to low disease prevalence, false-positive results are common and therefore, repeated testing is recommended to confirm findings.

Reference Values

>67% normal (normal)
41-67% normal (equivocal)
<41% normal (abnormal)

Interpretation

The C1 esterase inhibitor (C1-INH) concentration assay can be used to distinguish type I hereditary angioedema (HAE), with low C1-INH concentration, from type II HAE characterized by normal or elevated concentration. Furthermore, serum C1q concentrations can be used to differentiate HAE from acquired angioedema (AAE) forms of angioedema as the latter is characterized by decreased C1q antigen concentration and autoantibodies against C1-INH. Genetic analysis for *SERPING1* variants status may also help exclude HAE.
-Nonfunctional C1-INH results are consistent with HAE
-Patients with current attacks may also have low C2 and C4 concentrations due to C1 activation and complement activation of the classical pathway (consumption).
-Patients with acquired C1-INH deficiency have a low C1q concentration and/or function in addition to low C1-INH.

Table. Laboratory Features Consistent with Hereditary and Acquired Angioedema Subtypes

	Type I hereditary angioedema	**Type II hereditary angioedema**	**Acquired angioedema**

C1 esterase inhibitor (C1-INH) concentration	Low	Normal/high	Low
C1-INH function	Low	Low	Low/normal
C	L	L	Low

4 concentration	ow	ow	
C1q concentration	Normal	Normal	Low
Anti-C1-INH antibodies	Absent	Absent	Present
C3	No	No	Normal

concentration	rmal	rmal	
Family history	Yes	Yes	No

Cautions

This assay is a functional test and is dependent on correct sampling, storage, and shipping conditions.

Absent (or low) C1 esterase inhibitor function should be confirmed with a new serum specimen to confirm that inactivation has not occurred during shipping.

Clinical Reference

1. Stoppa-Lyonnet D, Tosi M, Laurent J, Sobel A, Lagrue G, Meo T. Altered C1 inhibitor genes in type I hereditary angioedema. N Engl J Med. 1987;317(1):1-6. doi:10.1056/NEJM198707023170101
2. Frigas E. Angioedema with acquired deficiency of the C1 inhibitor: a constellation of syndromes. Mayo Clin Proc. 1989;64(10):1269-1275. doi:10.1016/s0025-6196(12)61290-7
3. Frazer-Abel A, Sepiashvili L, Mbughuni MM, Willrich MA. Overview of laboratory testing and clinical presentations of complement deficiencies and dysregulation. Adv Clin Chem. 2016;77:1-75. doi:10.1016/bs.acc.2016.06.001

Performance

Method Description

The Quidel C1 inhibitor enzyme immunoassay for the quantitation of functional C1 inhibitor protein in human serum or plasma is a four-step procedure. In the first step, standards, controls, and test specimens are incubated with C1 esterase inhibitor (C1-INH) reactant (biotinylated, activated C1s). During this incubation, functionally active C1-INH present in the standards, controls, and test samples will bind to the biotinylated C1-INH reactant to form complexes. In the second

step, an aliquot of the incubation mixtures containing biotinylated C1-INH reactant is added to microtiter wells pre-coated with avidin. C1-INH reactant: C1-INH complexes present in the standards, controls, or specimens will bind to the avidin-coated microassay wells. After incubation, a wash cycle removes unbound material. In the third step, horseradish peroxidase (HRP)-conjugated goat anti-C1-INH is added to each test well. During this step, the HRP-conjugated anti-C1-INH binds to the C1-INH reactant: C1-INH complexes, which were captured on the surface of the avidin-coated microassay wells. After incubation, a wash cycle removes excess conjugate. In the fourth step, a chromogenic enzyme substrate is added to each microassay well. The bound HRP-conjugate reacts with the substrate forming a blue color. After incubation, the enzyme reaction is stopped chemically, forming a yellow color and the color intensity is measured spectrophotometrically at 450 nm. The color intensity of the reaction mixture is proportional to the concentration of functional C1-INH protein present in the test specimens, standards, and controls.(Package insert: C1-Inhibitor Enzyme Immunoassay. Quidel; 09/2021)

PDF Report
No

Day(s) Performed
Varies

Report Available
3 to 5 days

Specimen Retention Time
14 days

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

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 has been cleared, approved, or is exempt by the US Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

CPT Code Information
83520

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value

C1INF	C1 Esterase Inhib, Functional, S	48494-9

Result ID	Test Result Name	Result LOINC® Value
C1INF	C1 Esterase Inhib, Functional, S	48494-9