MEDLAB PATHOLOGY

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COMPLEMENT TESTING: GUIDE TO INTERPRETATION

The complement system consists of a myriad of plasma proteins that work in concert to promote innate defence against common pathogens. There are nine main complement proteins, labelled C1 through to C9. Numerous regulatory proteins, proteolytic enzymes and cell surface receptors also exist to ensure a rigid control of the complement system and prevent inappropriate activation.

There are three known pathways of complement activation - classical, alternative and lectin pathways. These pathways, while initiated differently, merge onto a common path of C3 fragment deposition and membrane attack complex (MAC) formation at the cell surface that ultimately results in cell lysis. The classical pathway is typically triggered by antigen-antibody complexes or by direct binding to the surface of a pathogen. The alternative pathway is activated by direct binding of C3b protein, an opsonin, onto a pathogen surface. The lectin pathway uses pattern recognition molecules instead of antibodies to target activation.

HOW IS COMPLEMENT TESTING USED?

Measurement of complement proteins is available, with the most frequently requested being C3 and C4. Levels of C3 and C4 are interpreted together in order to determine which complement pathway (classical or alternative) is being activated, hence the possible cause of this activation.

Broadly speaking, low C4 alone may reflect activation of the classical pathway and is characteristically seen in hereditary angioedema (HAE) and immune complex diseases. Low C3 alone may reflect activation of the alternative pathway and is seen in infectious diseases. Concurrent low C3 and C4 levels typically indicate classical pathway activation and are often seen in active immune complex diseases.

Measurement of C3 and C4 is also useful in monitoring immune complex diseases (e.g. systemic lupus erythematosus [SLE], cryoglobulinaemia) and infectious diseases (e.g. post streptococcal disease, subacute bacterial endocarditis). Deficiency of one or both complement proteins may have prognostic indications, such as in lupus nephritis. Genetic deficiencies of C3, while exceedingly rare, can result in low C3 levels. Deficiencies in C1-esterase inhibitor (C1-INH), a control protein of the complement pathway, are usually diagnosed following investigation of unexpected low C4 in patients with recurrent swellings (angioedema) in the absence of urticaria.

In addition, CH50/100 and AH50/100 assays may be performed to assess the functional activity of complement pathways. These assays are indicated in the evaluation of complement deficiencies as part of a first-tier screening test, or in the analysis of complement dysregulation. They are not as widely available as C3 and C4 measurements, and specialist's input is recommended in order to aid correct interpretation in concert with clinical findings.

WHEN IS COMPLEMENT TESTING REQUESTED?

Complement testing, in particular C3 and C4 levels, may be requested in following clinical settings:

- When the patient has a history of recurrent microbial (usually bacterial) infections.
- When the patient has recurrent unexplained angioedema without urticaria.
- When monitoring disease activity in patients with immune complex diseases (e.g. SLE, cryoglobulinaemia), or certain glomerulonephritis (e.g. post-streptococcal glomerulonephritis, lupus nephritis).

WHAT DO THE TEST RESULTS MEAN?

Please refer to below (Table 1) for some examples of conditions where you may see evidence of C3 and/or C4 consumption or activation.

Table 1. Examples of clinical entities with various patterns of complement activation

	C3	C4	Examples
Classical pathway activation	Normal	Low	SLE (active) Cryoglobulinaemia (type 2 or 3) C1-INH deficiency
	Low	Low	SLE (active) Lupus nephritis Infective endocarditis
Alternative pathway activation	Low	Normal	Bacterial infection, septicaemia Post-streptococcal glomerulonephritis aHUS C3 glomerulopathy

Abbreviations: SLE, systemic lupus erythematosus; C1-INH, C1-esterase inhibitor; aHUS, atypical haemolytic uraemic syndrome.

Further measurement of individual complement components is possible depending on the clinical context. For example, in suspected hereditary angioedema (HAE), C1-INH level and function are subsequently tested to look for deficiencies. C1-INH level is low in type 1 HAE but is normal or high in type 2 HAE, with the latter also associated with dysfunctional C1-INH.

Degradation of complements can occur due to inappropriate sample handling, storage or delayed processing, thereby leading to falsely low complement levels. Unexpected low C3 and C4 results that are inconsistent with the clinical history or in patients with a low pre-test probability of diseases should be verified with a new blood collection.

Complement proteins are acute phase reactants and elevated levels may be seen during acute or chronic inflammation. Increased C3 and C4 levels are of limited clinical relevance and their measurements should not replace the role of other widely available inflammatory markers such as C-reactive protein (CRP).

TESTING PREPARATION

None required. Sample should be sent to the laboratory as soon as possible for processing.

ORDERING AND COSTS

C3 and C4 levels are available at Medlab Pathology and are bulk billed. If assistance with interpretation is required, please contact Dr Helena Jang or Dr Shane Kelly at Medlab Immunology laboratory on (02) 8745 6500.

Reference: Shih, A.R. and Murali, M.R. (2015), Laboratory tests for disorders of complement and complement regulatory proteins. Am. J. Hematol., 90: 1180-1186. https://-doi.org/10.1002/ajh.24209