Immunochemistry

α1-anti-trypsin

Alpha-1-antitrypsin is a slow acute phase reactant; persistent elevations are seen in chronic infection and malignant disease. Quantitation may be indicated in early COPD (chronic obstructive pulmonary disease), and neonatal and adult liver disease where low concentrations may have diagnostic importance. If the level is low, the sample will be tested for A1AT phenotype

β2 Microglobulin

Serum levels of b2-microglobulin are useful indicators of prognosis in myeloma and MGUS, partly reflecting the degree of renal damage (and are raised in other causes of renal failure, malignancies and some autoimmune disorders).

Caeruloplasmin

Caeruloplasmin is an acute phase reactant. Concentrations are age and sex related. Decreased concentrations found in chronic liver disease, or in copper deficiency. Very low values are seen in Wilson's disease.

Haptoglobin

Haptoglobin is an acute phase reactant may be raised in inflammatory conditions. Its main function is in iron conservation as it binds haemoglobin liberated by haemolysis. Low levels are indicative of haemolysis.

Complement Proteins and function

C3 and C4: Raised serum levels of C3 or C4 are associated with inflammation as they are acute phase proteins. Decreased serum levels of **C3** may be seen in sepsis, post-infectious glomerulonephritis, infective endocarditis, mesangiocapillary glomerulonephritis (with C3 nephritic factor) and familial Haemolytic Uraemic Syndrome. Decreased serum levels of **C4** may be found with null alleles (C4 gene mutations), and in C1 inhibitor deficiency (hereditary and acquired angioedema), systemic lupus erythematosus (SLE) and cryoglobulinaemia.

CH100 is a measure of classical complement pathway function and **AP50** is a measure of alternate complement pathway function. Decreased complement activity may be caused by deficiencies of any of the individual complement components, hereditary or acquired.

The **C1-esterase inhibitor (C1-INH)** is a regulatory protein that functions as an inhibitor of several serine proteases in the complement system, the kallikrein-kinin system, the coagulation cascade and in fibrinolysis. C1 esterase inhibitor function is measured for diagnosis of Hereditary Angioedema (HAE).

Low C4 and C1 inhibitor is common in hereditary angioedema. Uncommonly there may be normal C1 INH level with defective function. If C4 is very low without other explanation and C1 INH normal in a patient with angioedema, then C1INH function should be measured.

In autoimmune C1 inhibitor deficiency autoantibodies directed against the C1 INH protein may render it dysfunctional. This is accompanied by either low, normal or raised levels of C1INH depending on the precise influence of the antibody on C1 INH degradation. In any event C4 levels are low and functional C1 INH activity is diminished.

Mannose Binding Lectin

This is a complement protein. Deficiency of MBL may be associated with an increased risk of infections, especially where immunity is already compromised.

Cryoglobulins

Cryoglobulins are immunoglobulins that precipitate at reduced temperature. Cryoglobulins can be placed into three general types based on immunoglobulin composition.
Type I: Monoclonal cryoglobulins associated with haematological neoplasia.
Type II: Mixed polyclonal and monoclonal cryoglobulins with Rheumatoid Factor activity.
Type III: Polyclonal cryoglobulins with Rheumatoid Factor activity.
Types II and III are particularly associated with Hepatitis C infection but may also be found in other chronic infections or connective tissue disease eg Sjogren's Syndrome. Trace amounts of cryoglobulin may be found in people with these conditions, or otherwise healthy individuals, without clinical evidence of cryoglobulinaemia.
The classification of the type of cryoglobulinaemia is far more important than cryoglobulin quantification, which is imprecise and has a weak correlation with clinical disease activity. Cryoglobulin measurement is semi-quantitative with results reported as % cryocrit. Positive cryoglobulins will be assessed for rheumatoid factor and for the presence of paraproteins.

Immunoglobulins and Paraproteins

Serum Protein electrophoresis and Immunofixation

The prime role of these tests is the detection of monoclonal immunoglobulins (paraproteins). These are found in myeloma, lymphoproliferative disease, monoclonal gammopathy of undetermined significance (MGUS) and amyloidosis. If a paraprotein is detected it will quantified and typed by immunofixation.

Urinary Protein Electrophoresis
The presence of free clonal light chains (Bence Jones proteins) in the urine is associated with myeloma and some patients with renal amyloidosis.

Serum Free Light Chains (see also guidance on MGUS / Paraproteins)
This test detects the presence of circulating free immunoglobulin light chains in the serum. These are cleared by the kidneys so renal dysfunction will lead to elevated serum free light chains but with a normal kappa:lambda ratio. Elevated free kappa or lambda chains will lead to an abnormal ratio. Elevated serum free light chains, with an abnormal ratio, is found in myeloma, some B cell tumours and amyloidosis. The test is largely limited to specialist Haematology clinics where it may be used to follow the progress of patients with myeloma, and also to stratify the risk of a patient with MGUS progressing to myeloma.

Immunoglobulins IgG, IgM & IgA
Quantitation of serum concentrations of IgG, IgA and IgM is essential in the diagnosis and monitoring of primary and secondary immunodeficiencies. Serum IgA levels may be raised in IgA nephropathy. Polyclonal elevation in immunoglobulins may be found with chronic liver disease or systemic infection or inflammation, eg CTD, sarcoidosis, HIV.

IgG subclasses
This test has limited utility in patients suspected of immunodeficiency. Functional antibody assessment is a better measure of immune function.

Functional antibodies – Antibodies to Haemophilus, Tetanus and Streptococcus pneumoniae
Antibodies to *Haemophilus influenzae* type B, Tetanus toxoid and Streptococcus pneumoniae polysaccharides should be measured to assess the level of protection and need for further immunisation. Patients with recurrent infections and failed immunisation should be investigated for immunodeficiency and thus inability to respond to specific bacterial antigens.
Ideally functional antibody measurements should be made before and 4 weeks after immunisation.