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# Globulins

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## Basic science

Globulins are a group of proteins within the blood. They are produced by the liver and the immune system. Albumin makes up more than half of the total protein within the blood, and globulins make up the remainder. Globulins have multiple different functions; the group includes immunoglobulins, enzymes, carrier proteins and complement.

There are four groups of globulins. Serum protein electrophoresis is the test used to distinguish one from another and establish levels of each within the bloodstream.

### Alpha 1 globulins

- Mainly alpha-1 antitrypsin.

### Alpha 2 globulins

- Alpha 2 macroglobulin.
- Haptoglobin.

### Beta globulins

- Transferrin.
- Complement components C3, C4, C5.

### Gamma globulins

Mostly immunoglobulins (antibodies):

- IgG: majority of the immunoglobulin component. Many antibodies to bacteria and viruses are IgG.
- IgE: involved in allergic response. Triggers histamine release. Also protects against parasites.
- IgM: largest antibodies and first type produced in response to infection.
- IgD: exists in very small quantities in blood. Function not very well understood.
- IgA: found in mucous membranes, blood, saliva and tears. Protect body surfaces which are exposed to foreign substances.

## Tests and their clinical significance

### Globulin level

Total protein is routinely done as part of the LFTs. Subtracting albumin from serum protein leaves the total globulin level.

- Decreased total globulin level:
  - Malnutrition (due to decreased synthesis).
  - Congenital immune deficiency (due to decreased synthesis).
  - Nephrotic syndrome (due to protein loss through the kidneys).
  - Increased albumin level causing decreased globulin fraction - eg, acute dehydration.
- Increased total globulin level:
  - Acute infection.
  - Chronic inflammatory disease - eg, rheumatoid arthritis, systemic lupus erythematosus (SLE).
  - Multiple myeloma.
  - Waldenström's macroglobulinaemia.
  - Hyperimmunisation.
  - Low albumin level causing increased globulin fraction - cirrhosis, nephrotic syndrome.

Globulin ratio may also be used, which is the ratio of albumin to globulin, and is usually between 1.7-2.2, ie there is normally around twice as much albumin as globulin.

### Serum protein electrophoresis (SPEP)

Electrophoresis divides serum proteins in order to determine if any group of protein is present in abnormal levels. Serum is exposed to an electrical current which causes the different proteins to migrate in bands. It thus divides globulins into the alpha-1, alpha-2, beta and gamma fractions. It is more sensitive than the quantitative immunoglobulin tests (below).

Alpha-1 abnormalities are usually due to alpha-1 antitrypsin changes.

- Decreased levels in congenital [alpha-1-antitrypsin deficiency](#).

- Increases are found in acute inflammatory disorders (it is an acute phase reactant).

Alpha-2 abnormalities mainly involve alpha-2 macroglobulin and haptoglobin.

- Alpha-2 macroglobulin rises in nephrotic syndrome.
- Haptoglobin levels increase in stress, infection, inflammation and tissue necrosis. Levels decrease with haemolytic reactions.

The beta fraction consists mostly of transferrin. This is elevated in severe **iron deficiency**.

Where the gamma fraction is increased, it can then be further established whether this is a narrow spike-like increase of a single immunoglobulin (a monoclonal rise) or a broader-based increase (polyclonal rise.) Monoclonal rises are then further evaluated with immunoelectrophoresis or immunofixation electrophoresis (see below.) Monoclonal spikes are more likely to have a malignant cause, with multiple myeloma being the most common of these. However, the most common cause of a monoclonal rise is monoclonal gammopathy of uncertain significance (MGUS) which is usually a benign condition. Abnormal immunoglobulins produced in excess monoclonally are also known as paraproteins.

To establish a diagnosis of myeloma or Waldenström's macroglobulinaemia, urine electrophoresis is also carried out to look for monoclonal immunoglobulin bands within urine. The finding of Bence Jones' protein is suggestive of myeloma or Waldenström's macroglobulinaemia.

SPEP can be further used to monitor response to treatment in myeloma.

### **Immunoelectrophoresis or immunofixation electrophoresis**

Immunoelectrophoresis or immunofixation electrophoresis is usually performed when SPEP has found the presence of increased gammaglobulin levels in order to further establish the nature of the abnormality. It identifies the type of gammaglobulin. This is commonly used in the diagnosis of myeloma.

### **Quantitative immunoglobulin levels**

These test the levels of the three major immunoglobulin groups (IgG, IgM and IgA).

## Causes of low immunoglobulin levels (hypogammaglobulinaemia)

- Congenital immunodeficiency syndromes.
- Conditions causing excess loss of immunoglobulins:
  - Sepsis
  - Nephrotic syndrome
  - Burns
  - Protein-losing enteropathy
- Conditions causing less production of immunoglobulins:
  - Malnutrition
  - Alcoholism
  - Drugs - phenytoin, carbamazepine, immunosuppressants
  - Haematological malignancies - multiple myeloma, chronic lymphocytic leukaemia (CLL), lymphoma
  - Rheumatoid arthritis
  - SLE
  - Viral causes - cytomegalovirus (CMV), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), rubella

## Causes of raised immunoglobulin levels

Electrophoresis will establish if these are polyclonal or monoclonal rises. The most common rise in immunoglobulin levels is polyclonal, and due to immune system activity caused by infection or autoimmune diseases.

- Polyclonal rises in immunoglobulin levels:
  - Infections
  - Autoimmune connective tissue diseases - rheumatoid arthritis, SLE, scleroderma
  - Chronic active autoimmune hepatitis (IgG)
  - Primary biliary cirrhosis (IgM)
  - Chronic liver disease
- Monoclonal rises in one class of immunoglobulin level:
  - Multiple myeloma (IgG or IgA usually)
  - MGUS. The most common cause of monoclonal rise, and usually a benign condition
  - CLL
  - Non-Hodgkin's lymphoma
  - Waldenström's macroglobulinaemia (IgM)
  - Primary systemic amyloidosis

## Allergen-specific IgE tests

Blood tests can be done which measure the amount of IgE antibodies which have been produced in response to specific allergens. These are usually done by the radioallergosorbent testing (RAST) or enzyme-linked immunosorbent assay (ELISA) techniques. Blood allergy tests are more expensive and less sensitive than skin prick testing, but can be useful in certain situations - for example, when there is a risk of anaphylaxis, or severe skin rashes, or when the patient needs to continue taking antihistamines. Hundreds of different allergens can be tested for in this way.

## Common tests done in general practice

Common reasons GPs might order immunoglobulin tests or SPEP might include:

- Excluding myeloma when other blood tests such as FBC or ESR are abnormal.
- Serology tests for allergies.
- Checking for immunodeficiency in patients with recurrent infections.
- Checking responses to immunisations, such as hepatitis B or rubella.
- Checking for immunity to infections, such as chickenpox in pregnant women.
- Screening for coeliac disease.
- Looking for autoimmune diseases.
- Establishing the cause of abnormal protein levels found on LFTs. (Most often a raised globulin fraction will be a polyclonal rise due to infection or inflammation.)

## Investigating the cause of a raised globulin level

A raised globulin level may be a relatively common coincidental finding. The work-up to establish the cause involves history, examination and further investigations to determine which of the conditions listed above may be causing the abnormality. This work-up would include:

### History

- Bone pain (myeloma).
- Night sweats (lymphoproliferative disorders).
- Weight loss (cancers).
- Breathlessness, fatigue (anaemia).
- Unexplained bleeding (lymphoproliferative disorders).
- Symptoms of carpal tunnel syndrome (amyloidosis).
- Fever (infections).

- Joint pains (connective tissue diseases).
- Patients with MGUS are asymptomatic by definition.

### Examination

- Temperature (infections, sepsis).
- Arthropathy (connective tissue disorders).
- Lymphadenopathy, hepatosplenomegaly (lymphoproliferative disorders).
- Anaemia (lymphoproliferative disorders).
- Signs of heart failure (amyloidosis).
- Macroglossia (amyloidosis).
- Signs of carpal tunnel syndrome (amyloidosis).

### Investigations

- FBC (anaemia, lymphocytosis, lymphopenia, thrombocytopenia).
- ESR (raised in myeloma, sepsis, cancers).
- Renal function (impaired renal function).
- Calcium (hypercalcaemia in myeloma).
- LFTs (hepatic diseases).
- Serum protein electrophoresis (monoclonal vs polyclonal rise) and immunofixation electrophoresis (defining immunoglobulin class in monoclonal rises).
- Urine electrophoresis (Bence Jones' protein).
- X-rays if areas of bone pain.
- Further investigations dependent on results of above, and where relevant performed in secondary care.

## Therapeutic uses of globulins

Some of the therapeutic uses of immunoglobulins:

- **Haemolytic disease of the newborn.** IV immunoglobulin is given to the mother in pregnancy to prevent antibody production.
- **Immunodeficiency diseases.**
- **Guillain-Barré syndrome.** IV immunoglobulin counteracts antibodies and slows progression.
- Snake and spider bites - used with antivenom to help the immune system respond.
- **Kawasaki disease.** IV immunoglobulin helps prevent coronary aneurysms.
- **Immune thrombocytopenic purpura (ITP).**
- Immediate short-term protection against **hepatitis A, measles, polio, rubella.**
- Specific immunoglobulin preparations for **hepatitis B, rabies, and varicella-zoster** give short-term immediate protection to a person exposed.

(See also the separate article [Immunoglobulins - Normal and Specific.](#))

## Further reading & references

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