The Newcastle upon Tyne Hospitals NHS Foundation Trust

Guidelines for the Interpretation and Management of immunoglobulins and Paraproteins in Adults

Version No.:	4
Effective From:	1 July 2025
Expiry Date:	1 July 2027
Date Ratified:	1 July 2025
Ratified By:	A McGregor

1 Introduction

Myeloma is a malignancy of plasma cells. The normal role of the plasma cell is to secrete immunoglobulins (mainly immunoglobulin (Ig) A, IgG and IgM) to fight infection. Therefore immunoglobulins will be elevated as a result of infection or inflammation but usually in a polyclonal pattern (*i.e.* lots of different types of immunoglobulin are secreted). This is a normal physiological response to a reactive condition. When a clone of plasma cells turns malignant and expands it produces a single type of immunoglobulin – this is called a paraprotein, monoclonal protein or M protein. When a plasma cell neoplasm is suspected sending a sample for immunoglobulins will provide the clinician with the absolute levels of IgA, IgG and IgM as well as a result from serum protein electrophoresis which allows the identification of a monoclonal immunoglobulin versus polyclonal immunoglobulins. If a monoclonal protein is identified on serum protein electrophoresis immunofixation will be performed.

2 Guideline scope

This guideline applies to adults who have had immunoglobulins and serum protein electrophoresis sent as part of a screen for myeloma. It will also help in the interpretation of immunoglobulins in general. It does not cover indications for immunoglobulin testing outside of the investigation of haematological malignancies.

3 Aim of the guideline

The aim of this document is to advise general practitioners and other hospital staff on the indications for testing immunoglobulins from a haematology perspective, how to monitor patients with a paraprotein and when to refer for haematology assessment.

4 When to send immunoglobulins

There are numerous indications for checking immunoglobulins which are not necessarily related to risk of plasma cell malignancy (for example immunoglobulins

can be part of a screen for liver disease). Therefore different specialties will have different guidelines on when to check immunoglobulins.

From a haematology perspective we usually suggest checking immunoglobulins in the investigation of myeloma or lymphoma. Myeloma is the most common malignancy that produces a monoclonal immunoglobulin. Patients with lymphoma and amyloidosis may also have a monoclonal immunoglobulin. From a haematology perspective we suggest sending immunoglobulins if there is clinical suspicion of a plasma cell disorder or:

- Unexplained hypercalcaemia
- Unexplained renal failure after standard investigations
- Unexplained anaemia (normal ferritin, vitamin B12, folate)
- Unexplained neuropathy
- Unexplained bone pains
- Unexplained elevated total protein or erythrocyte sedimentation rate (ESR)
- Bone lesions suspicious for myeloma on imaging

Screening otherwise healthy patients for a paraprotein is not advised.

5 What does the test include?

When immunoglobulins are requested the result will include the absolute level of IgA, IgG and IgM. A high level of immunoglobulin does not necessarily mean there is a paraprotein as immunoglobulins are most commonly increased because of inflammation or infection. Similarly normal immunoglobulin levels do not exclude a small paraprotein. Therefore in addition to absolute levels of immunoglobulins the laboratory will also perform serum protein electrophoresis to look for a paraprotein.

Serum free light chains (SFLC) have replaced urine protein electrophoresis (also known as urine Bence Jones proteins) for the detection of light chain only myeloma. This is reflexed by the laboratory when there are relevant clinical details or there is a particular pattern on serum protein electrophoresis. If the suspicion of myeloma or plasma cell dyscrasia is high please request both serum protein electrophoresis and SFLC. SFLC are not required when the clinical suspicion is low or if the test is being done for high total protein or high ESR. It would be very unusual to have myeloma with normal immunoglobulin levels and normal serum protein electrophoresis.

6 What causes a paraprotein?

The most common causes of paraprotein are:

1) Monoclonal gammopathy of uncertain significance

- Benign condition that is common in the over 70s (3.9% of people over the age of 50 and 8.9% of people over the age of 85)
- No features of myeloma or other plasma cell dyscrasia
- Paraprotein (***not*** total immunoglobulin) should be less than 30 g/L but mostly it will be less than 15 g/L
- The SFLC ratio is often normal or only mildly abnormal
- All cases of myeloma progress from MGUS but MGUS only rarely progresses to myeloma
- MGUS prognosis can be calculated here: https://qxmd.com/calculate/calculator_148/mgus-prognosis
- The risk of progression varies from 2% at 20 years to 58% at 20 years depending on level and type of immunoglobulin.
- Occasionally paraproteins can be reactive and can therefore disappear when the reactive state has been treated

2) Myeloma

- Malignant disorder of plasma cells resulting in production of monoclonal immunoglobulin
- Patients are often symptomatic with anaemia, hypercalcaemia, renal failure, or bone disease
- The paraprotein is usually IgG or IgA
- Treated with chemotherapy and immunomodulatory agents

3) Plasmacytoma

- A collection of malignant plasma cells in one area – usually a bone or soft tissue mass. Causes pain, swelling or fracture.
- Treated with radiotherapy

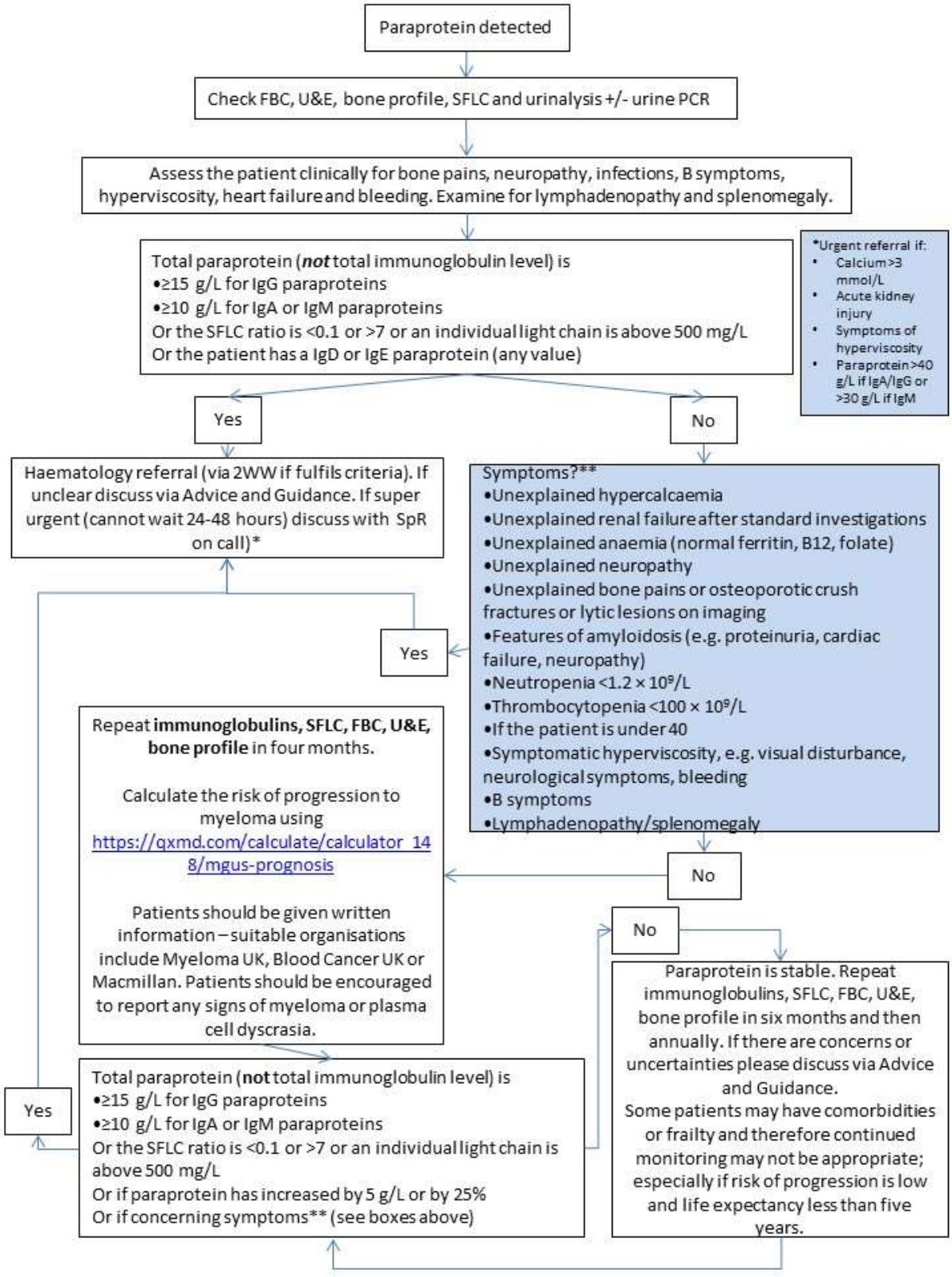
4) Lymphoma – especially lymphoplasmacytic lymphoma (Waldenström macroglobulinaemia)

- Causes anaemia, lymphadenopathy and B symptoms
- The paraprotein is usually IgM

5) Amyloidosis

- Systemic disorder which can result in neuropathy, cardiac failure, bleeding, gastro-intestinal problems, autonomic dysfunction, renal failure, nephrotic syndrome, arrhythmia, carpal tunnel syndrome, liver failure and macroglossia.
- The paraprotein can be small

7 Flow chart if find a paraprotein



8 No paraprotein found but results abnormal

Hypogammaglobulinaemia
One or more immunoglobulin class reduced below the reference range. In adults, please check SFLC for light chain only myeloma. If SFLC ratio is normal then look for clinical signs of lymphoma and check for lymphocytosis. If none, then please consider other causes of low immunoglobulin levels such as HIV, immunosuppressant medications, chemotherapy or gastrointestinal/renal protein loss. If there is no obvious cause, and if recurrent infections are a feature, then please discuss with/refer to immunology. Please note that mild decreases in IgM are common in elderly patients and that selective IgA deficiency is seen in 1 in 600 people and is generally an asymptomatic condition. In children, this test would only usually be requested by a specialist haematologist or immunologist, but please seek advice if there are concerns.

Hypergammaglobulinaemia
One or more immunoglobulin class increased above the reference range. The report may say 'increased gamma zone' or the serum protein electrophoresis will be normal. This means there is a polyclonal rise in immunoglobulins which can be seen in reactive cases e.g. infection, inflammation, malignancy or liver disease. Isolated rises in IgA are common in the elderly. Investigation of the underlying cause may be warranted depending on symptoms and clinical suspicion. This sort of result is not indicative of myeloma and does not warrant a haematology referral.

Multiple banding
This is often seen in inflammatory conditions. Repeating the result in four to six months to ensure no larger band appears is recommended. If multiple banding is still present investigate for inflammatory condition.

Possible band
Repeating the result in four to six months to ensure no larger band appears is recommended. If a possible band is persistent then follow MGUS flow chart.

9 Interpretation of SFLC when there is no paraprotein

It is normal to have more serum kappa light chains than lambda. Light chains increase in the serum in renal failure due to under excretion and in inflammation due to overproduction. Although the individual values are important the ratio between the kappa and lambda light chains is more important because if the individual light chains are proportionally increased then the ratio will be normal.

The normal ratio is 0.26 -1.65 if the eGFR is ≥60 mL/min and 0.37-3.1 if the eGFR <60 mL/min. If it is outside of these ranges and the:

- Ratio is <0.1 or >7 or an individual light chain is above 500 mg/L – refer to haematology as per paraprotein flow chart
- Ratio 0.1-0.2 or 5-7 – probable light chain MGUS – follow paraprotein flow chart for monitoring
- Abnormal but between 0.2 and 5 – minor abnormality of SFLC. In presence of normal immunoglobulin levels myeloma very unlikely. Likely causes include

inflammation or abnormal renal function. Can discuss via haematology Advice and Guidance if concerns.

10 Further advice

If further advice is needed then please contact a haematologist via the Advice and Guidance system. If the patient is known to a haematologist please write to the clinician directly. In an emergency please discuss with the on call specialist registrar for haematology. Please don't phone the on call specialist registrar for day-to-day routine queries. If the patient has hypogammaglobulinaemia and recurrent infections discuss with an immunologist. Patients with no paraprotein and hypergammaglobulinaemia should be investigated in a similar fashion to an elevated ESR.

11 Evidence Review and Evaluation

The evidence was reviewed and evaluated by Dr Andrew McGregor, consultant haematologist. The guideline was written by Dr Andrew McGregor and was reviewed and amended by Dr Brigit Greystoke, consultant haematologist, Dr Suzanne Elcombe, consultant immunologist, Dr Ashleigh Rainey, healthcare scientist and Dr Jennifer Young, consultant haematologist.

13. Document changes

Any document changes must be updated in:

- NCCC Q Pulse
- Laboratory medicine Q Pulse
- Trust website (haematology departmental website and Newcastle Laboratories)
- Intranet
- GP TeamNet