

## **Guidance for users: Investigation of newly detected Monoclonal proteins and management of monoclonal gammopathy of undetermined significance (MGUS)**

Monoclonal proteins are frequently detected in patients who are under the care of a general practitioner or a non-haematologist. We aim to provide guidance to healthcare professionals who are often uncertain how to appropriately manage these patients in primary care.

*The guidelines summarised below refer only to those patients defined as monoclonal gammopathy of undetermined significance (MGUS) with a newly detected M-protein.*

### **Laboratory procedure at St Helier Hospital for the investigation of suspected M-proteins**

A monoclonal protein (otherwise known as a paraprotein) is a monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells. A monoclonal protein can be whole immunoglobulin or fragments of immunoglobulin e.g. free light chain.

At Epsom & St Helier Hospital screening for suspected monoclonal protein is carried out by the Immunology Laboratory. As a part of the screening procedure for serum monoclonal protein immunoglobulin levels are measured and protein electrophoresis is performed. Upon detection of an abnormal finding the laboratory will perform immunofixation to confirm the presence of a serum monoclonal protein and to determine the immunoglobulin class and light chain type. At this point the laboratory will quantify the monoclonal protein concentration. If a urine sample has been provided electrophoresis will be performed as a screen for free light chains in the urine (Bence-Jones protein-BJP). Identification of the BJP will be determined by immunofixation. It is recommended that the requesting clinician provides the laboratory with both a serum and urine sample.

In all cases in which a new paraprotein is discovered, the patient's serum free light chain level will also be measured as the result has prognostic significance.

If no monoclonal protein is identified as part of the initial screen and there is high clinical suspicion of non-secretory myeloma, light chain (AL) amyloidosis or light chain (LC) myeloma the laboratory will measure serum free light chains (SFLC).

### **Laboratory procedure at St Helier Hospital following identification of a new M-protein**

Immunology will inform the Haematologists of any patients who meet the following criteria:

- IgM & IgA M-protein  $\geq 10\text{g/L}$
- IgG M-protein  $\geq 15\text{g/L}$
- Identification of an IgD or IgE M-protein (regardless of concentration)
- Abnormal SFLC ratio
- Identification of BJP
- Serum M-protein  $< 10\text{g/L}$  where clinical details indicate signs or symptoms suggestive of myeloma related organ or tissue impairment (ROTI)

If patients meet the above criteria the Haematologists will advise the requesting clinician on the initial management of the patient. The advice can vary from suggesting monitoring in primary care to referring the patient to the Haematology clinic.

## **Monoclonal gammopathy of undetermined significance (MGUS)**

MGUS is defined as a serum monoclonal protein <30g/L, <10% clonal plasma cells in the bone marrow and the absence of end organ damage that can be attributed to the plasma cell disorder. End-organ damage is characterised by hypercalcaemia, renal insufficiency, anaemia and bone lesions caused by the plasma cell disorder. Patients will be classified as having MGUS following the exclusion of myeloma, AL amyloidosis, Waldenström's macroglobulinaemia and other conditions associated with monoclonal immunoglobulins. MGUS is uncommon below the age of 50 years but the prevalence increases with age: 1-2% of individuals in their sixth decade have MGUS rising to 4-5% in their eighth decade. Additionally the prevalence is higher in African/Caribbean populations compared to Caucasians.

Consequently, the finding of a low level monoclonal protein is common in the elderly population and the majority will be associated with MGUS. Swedish studies have shown that approximately 70% of MGUS patients have an M-protein <10g/L. However, it is important to note that a proportion of myeloma patients will present at diagnosis with a monoclonal protein <10g/L. In Swedish and UK cohorts this has been estimated at 7% and 5% respectively. Furthermore, other clinically important diseases such as AL amyloidosis, LC myeloma and solitary plasmacytoma can present with a low level monoclonal protein. In fact both myeloma and amyloid are commonly missed diagnoses. Consequently, upon detection of an M-protein, it is important for the requesting clinician to look for signs and symptoms associated with these monoclonal gammopathies regardless of the M-protein concentration identified.

### **Recommendations for the investigation of patients following the detection of an M-protein**

#### ***What further tests will the Immunology laboratory conduct?***

The SFLC ratio at diagnosis can act as an independent prognostic marker for patients with MGUS. At St Helier Hospital SFLC are automatically measured in all patients with a newly detected M-protein.

#### ***What additional investigations should be performed?***

Listed below are a number of additional routine blood and urine tests that the requesting clinician should ensure are performed on all patients with a newly identified M-protein:

- spot urine for urinary protein excretion, Urine Protein:Creatinine ratio and urinary protein electrophoresis (if not already done)
- full blood count
- serum creatinine
- urea and electrolytes
- corrected serum calcium

#### ***Importance of clinical history and examination***

Upon detection of an M-protein a detailed history and examination should be performed to determine the likelihood of a plasma cell disorder or a lymphoproliferative disease. These should focus on symptoms, signs and test results that are commonly associated with myeloma, lymphoma or AL amyloidosis. As discussed previously a low level paraprotein is more likely to be associated with MGUS; however AL amyloidosis is often associated with a low level paraprotein and a low level paraprotein does not exclude myeloma. If the patient has any signs or symptoms suggestive of underlying myeloma, other lymphoproliferative diseases or AL amyloidosis they should be referred to a Haematologist for further investigation. This is also the case in patients without

symptoms but with unexplained abnormal investigations results e.g. anaemia, renal impairment, hypercalcaemia, lytic lesions or osteoporosis on X-ray.

## **Prognosis and risk of malignant progression**

Individuals diagnosed with MGUS have an increased risk of progression to malignant disorders including multiple myeloma, Waldenström's macroglobulinaemia, AL amyloidosis and lymphoproliferative disorders. The overall risk of malignant transformation is approximately 1% per year.

## **Monitoring MGUS patients in primary care**

Most patients diagnosed with MGUS will require continuous monitoring as the risk of malignant progression will remain throughout their lifetime. The aim of monitoring is to identify those patients progressing to a malignant disorder prior to development of irreversible lytic bone disease, renal failure and other debilitating symptoms that would negatively impact on the effectiveness of treatment. As the pattern of disease progression is variable it is important to monitor both clinical symptoms and laboratory markers.

### ***How frequently should MGUS patients be followed up?***

No evidence has been published on which to base frequency of follow-up. However it can be argued that younger patients with longer life expectancies and a higher monoclonal protein level should be monitored more frequently than those with a lower monoclonal protein level and shorter life expectancy.

Following identification of a newly detected M-protein it is recommended that MGUS patients should be monitored every 6 months for the first year followed by 12 monthly as long as there are no symptoms suggestive of malignant progression. Both the clinician and the patient should be aware of relevant clinical symptoms; furthermore the patient should be educated and prompted to report these outside appointment visits if necessary.

At each monitoring appointment the patient must be clinically assessed and the following blood tests carried out:

- quantification of the M-protein and serum immunoglobulins
- full blood count
- serum creatinine
- urea and electrolytes
- corrected serum calcium

### ***Further Investigations/Referral to Haematology***

The guidelines recommended that MGUS patients should be referred for specialist advice if any of the criteria below are met:

- concentration of the M-protein increases by more than 25% (a minimum absolute increase of 5g/L)
- development of symptoms compatible with a diagnosis of myeloma or lymphoma
- development of unexplained anaemia, other cytopenias, abnormal renal function or hypercalcaemia

Please refer to our [flow chart](#) for a summary of the recommended algorithm used by Epsom & St Helier Hospital.

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Newly detected serum M-protein

**STEP 1 (Immunology Laboratory)**

Further Immunology investigations performed:

- Identification of serum M-protein isotype
- Quantification of serum M-protein
- Serum immunoglobulin levels
- Screen for serum free light chains (SFLC)
- Screen for Bence-Jones protein (if urine provided)

- IgM & IgA M-protein  $\geq 10\text{g/L}$
- IgG M-protein  $\geq 15\text{g/L}$
- Identification of an IgD or IgE IgE M-protein (regardless of concentration)
- Abnormal SFLC ratio
- Bence-Jones protein identified

Immunology will inform the Haematology Myeloma Team

**STEP 2 (Clinician)**

Ensure the following investigations are carried out:

- Spot urine for urinary protein excretion and urinary protein electrophoresis
- Full blood count
- Serum creatinine
- Urea and electrolytes
- Corrected serum calcium

**STEP 3 (Clinician)**

Are there any symptoms or physical signs suggestive of:

- Myeloma, other lymphoproliferative disorders or light chain amyloidosis

Asymptomatic but unexplained incidental abnormal investigations (laboratory or imaging) such as:

- anaemia, hypercalcaemia, renal impairment, lytic lesions or osteoporosis on X-rays

Refer to Haematology for further investigation and management

Lifelong monitoring of the patient is required:

- Follow up patient every 6 months for the 1<sup>st</sup> year
- Extend follow up to every 12 months if patient is asymptomatic and laboratory markers are stable

Follow up appointment:

- Examine the patient for symptoms or physical signs suggestive of underlying plasma cell or lymphoproliferative disorder
- Ensure the following laboratory markers are measured:
  - Quantification of M-protein and serum immunoglobulins
  - Full blood count
  - Serum creatinine
  - Urea and electrolytes

Are any of the following criteria met?

- M-protein concentration has increased by  $\geq 25\%$  (min absolute increase of  $5\text{g/L}$ )
- Development of symptoms compatible with an underlying plasma cell or lymphoproliferative disorder
- Development of unexplained anaemia, other cytopenias, abnormal renal function or hypercalcaemia

## Guidance Notes

- It is the responsibility of the patient's Clinician to ensure that steps 2 and 3 are carried out
- For more detailed information please refer to our guidance for users: [Investigation of newly detected M-proteins and management of monoclonal gammopathy of undetermined significance \(MGUS\)](#)
- For blood sample requirements please refer to the [pathology test directory](#)

## References

- Bird J, Behrens J, Westin J, Turesson I, Drayson M, Beetham R, et al. UK Myeloma (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). *British Journal of Haematology*. 2009; 147: 22-42.
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