Monoclonal Gammopathy of Undetermined Significance (MGUS) Haematology Guideline

Definition & Prognosis

The presence of a monoclonal protein (also known as an M-protein or paraprotein) in the serum or urine of an individual with no evidence of multiple myeloma, AL amyloidosis or lymphoproliferative disorder.

Patients with MGUS have no symptoms related to their paraprotein. In many cases the condition is benign, has no impact on the patient's health and does not require any treatment.

The prevalence of MGUS is 3% in patients over the age of 70 and higher in African/Caribbean origin than Caucasians.

Patients with MGUS have an increased risk of developing malignant disorders such as lymphoproliferative disorders (usually IgM) and multiple myeloma (IgG or IgA, or rarely IgD/IgE). This risk is around 1% per year, making it safe for these patients to be monitored in the community. The most important predictors of progression are the level and isotype of the M-protein. The level in grams/litre is roughly equivalent to the risk of progression for that patient at 10 years following detection. Non-IgG MGUS patients are most at risk of progression.

Level of Paraprotein	Risk of progression over 10 years
5 g/l	5%
20 g/l	20%

Terminology of Laboratory Testing

Immunoglobulins (antibodies) are produced in the bone marrow by white blood cells (plasma cells and mature B lymphocytes). Immunoglobulin is made up of two heavy chains (G, A, M, D or E) and two light chains (Kappa or Lambda). A small quantity of light chains circulates in the blood unbound to heavy chains and these are called light chains. The following tests are available:

- **Immunoglobulin profile (g/l)** – A quantitative test of total levels of IgG, IgA and IgM immunoglobulin in the blood. Elevated immunoglobulin levels are found in a wide variety of infective, inflammatory and malignant conditions.
- **Serum protein electrophoresis** – A qualitative test performed to investigate the cause of an abnormally elevated immunoglobulin profile. If an excess of identical (i.e., monoclonal) immunoglobulin is being produced by malignant white cells it will all be of the same molecular weight, and this is seen as a 'M-Band' on the electrophoresis. The detection of a M-Band suggests the presence of clonal white cells.
- **Paraprotein (g/l)** – A quantitative test of the amount of monoclonal immunoglobulin detected on electrophoresis. It may also be called the 'M-protein'. The paraprotein can be used at diagnosis and as a surrogate marker of disease activity over time.
- **Serum free light chains (mg/l)** - A quantitative test of the amount of light chain circulating unbound to heavy chains, reported as Kappa, Lambda and the ratio between the two. Elevation of both kappa and lambda light chains together is seen in renal failure as well as a wide variety of infective and inflammatory conditions. Disproportionate elevation of only one light chain, leading to an abnormal ratio between the two, is suggestive of excess production by clonal white cells.
- **Urine Bence Jones Protein (BJP)** – A urinary test to detect excess light chains that has largely been replaced by serum free light chain testing in most UK laboratories.

What to do with an abnormal result?

If a paraprotein or abnormal serum free light chain ratio has been detected for the first time, the following actions are recommended:

- History and Examination – to assess for the signs and symptoms of a potential haematological malignancy, as listed in Table 1.
- Full blood count, Urea and Electrolytes, Liver Function Tests, Calcium, Protein Electrophoresis and Serum Free Light Chains, again with reference to Table 1. (See Table 3 for additional guidelines of who to refer and frequency of monitoring)
- Based on this to then consider whether the patient requires referral to haematology or can be monitored in the community (see below and Table 3).
- **A urine BJP is not required.**

If a paraprotein or serum free light chain ratio has risen compared to a previous result:

- Review any change in the patient's signs and symptoms (Table 1)
- Assess rate of change and then consider whether the patient requires referral to haematology or can continue to be monitored in the community (see below)

Who to refer to Haematology?

Due to the potential for a diagnosis of haematological malignancy, patients should be referred to the haematology service under any of the following circumstances:

- Symptoms compatible with a diagnosis of myeloma, lymphoma, or amyloidosis (Table 1)
- Unexplained anaemia, other cytopenias, abnormal renal function or hypercalcaemia
- Paraprotein as follows: IgG >15g/l, IgA >10g/l, IgM >10g/l, or IgD / IgE of any quantity.
- Elevated serum free light chains elevated in the absence of a paraprotein (request 'Advice & Guidance')
- M-protein increases by more than 25% (a minimum absolute increase of 5 g/l) compared to previous value.

Table 1: Symptoms and biochemical features of malignant disease associated with paraproteinemia.

Myeloma	Lymphoma/ Lymphoproliferative Disorder	AL Amyloidosis
Hypercalcaemia	Lymphadenopathy	Macroglossia
Renal failure	Hepatosplenomegaly	Unexplained heart failure
Anaemia or other features of bone marrow failure	Hyperviscosity (especially if IgM)	Peripheral neuropathy
Bone/back pain (not usually joint pain) or bone lesions	Pancytopenia	Carpal tunnel syndrome
Hyperviscosity	Constitutional 'B' symptoms, i.e., night sweats, fever, weight loss, loss of appetite	Nephrotic syndrome

How should MGUS patients be monitored in primary care?

Patients should only be diagnosed with MGUS after review of the clinical presentation and other laboratory results. New bone symptoms, lymphadenopathy, hepatosplenomegaly or unexplained anaemia, hypercalcaemia or renal failure may need referral to exclude myeloma or lymphoma.

- There is limited evidence that monitoring MGUS for the early detection of haematological malignancy improves outcomes, however it is widely recommended.
- Guidelines recommend considering life expectancy. Patients with life expectancy < 5 years are unlikely to benefit from laboratory monitoring.
- For MGUS patients with long life expectancy (e.g., age < 50 years) consider referral for advice.

Table 2: Criteria for patients likely to have a diagnosis of MGUS rather than a haematological malignancy.

Blood results / symptoms	Action
ALL of the following: Asymptomatic + normal physical examination Normal full blood count, renal function, calcium and immunoglobulins M-proteins: IgG <15 g/l, IgA/M <10 g/l Normal SFLC ratio	Myeloma or related disorder is unlikely to be present. No further investigation necessary, however will need monitoring – see below for guidance,

Patients meeting the criteria in Table 2 should be managed as follows:

- **Patient education** – Patients with MGUS should be fully aware of the important symptoms listed in table 1 and be encouraged to report them outside appointment visits, should they occur in the meantime. PILS available here: https://shop.bloodcancer.org.uk/collections/booklets/products/monoclonal-gammopathy-of-undetermined-significance-mgus
- **Blood monitoring** – FBC, U&E, Calcium, Paraprotein (**and Serum Free Light Chains if this is the abnormal test being monitored)**. Tests should be performed as per Table 3.

Table 3 (taken from the European Myeloma Forum 2014 guidance):

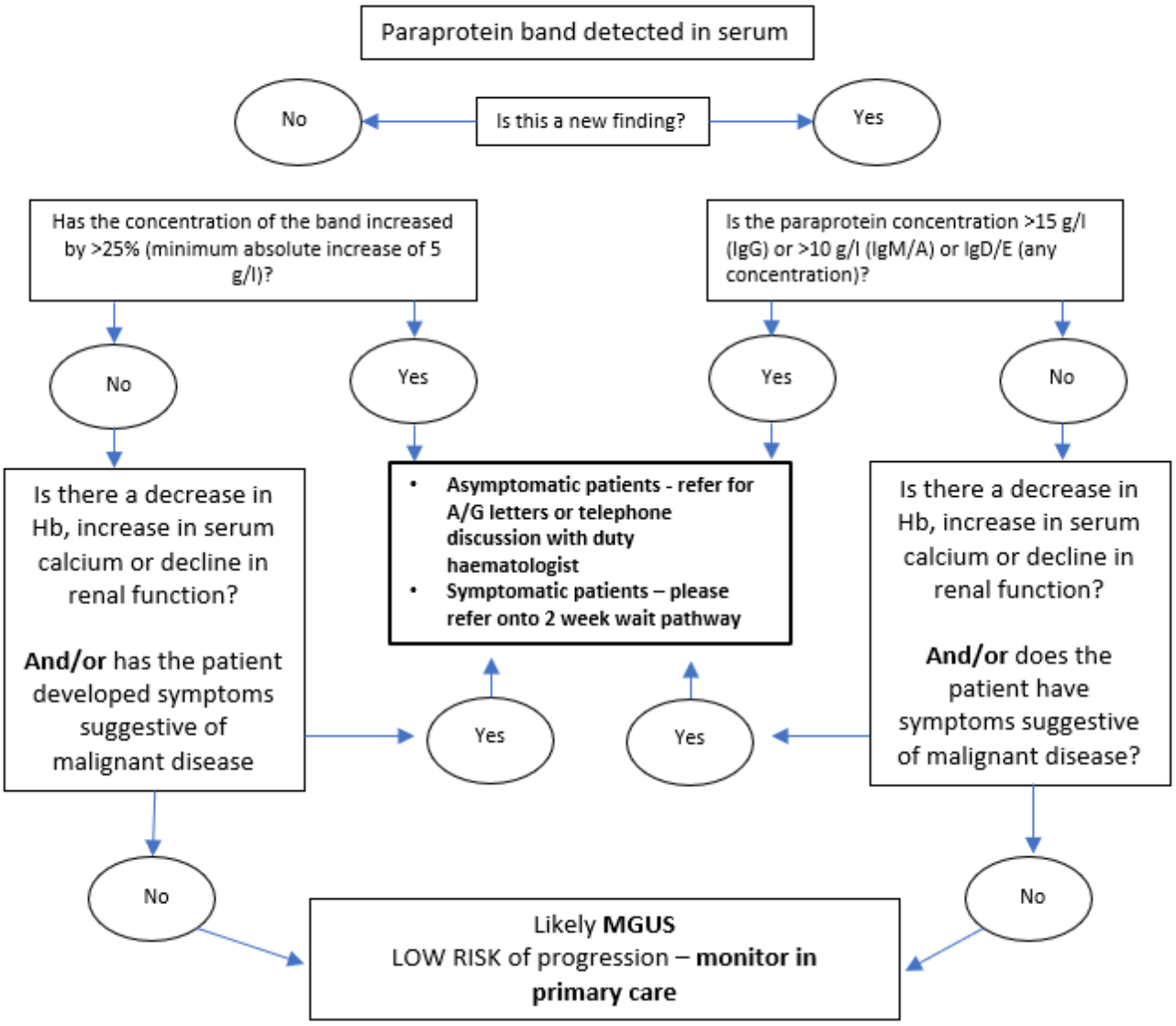
Paraprotein level* /SFLC	Monitoring advice
IgG paraprotein* < 15g/L and normal SFLC ratio (5% absolute risk of progression at 20 years)	**Either:** No further monitoring unless clinical concerns **Or:** Repeat paraprotein (not SFLC) FBC, UE, calcium in 6 months and then every 1-2 years (choice dependent on clinician/patient preference)
IgG paraprotein* < 15g/L and SFLC ratio < normal but > 0.125 or > normal but < 8)	Repeat paraprotein (not SFLC) FBC, UE, calcium in 6 months and then annually. Refer if paraprotein > 15g/L or if new clinical or laboratory concerns for haematological malignancy
IgA paraprotein* < 10g/L, SFLC ratio 0.125 – 8	Repeat paraprotein (not SFLC), FBC, UE, calcium in 6 months and then annually. Refer if paraprotein > 10g/L or if new clinical or laboratory concerns for haematological malignancy
No paraprotein and abnormal SFLC ratio but SFLC ratio 0.125 (i.e., light chain MGUS)	Repeat SFLC, FBC, UE, calcium in 6 months then annually.
IgM paraprotein* < 10g/L	Repeat paraprotein and FBC annually. Refer if > 10gL or if clinical concerns of lymphoma

*NB. It is the total paraprotein result which guides action limits, not the specific immunoglobulin level.

Who does not require further monitoring for haematological malignancy?

Patients with raised immunoglobulin levels in the absence of a monoclonal band on electrophoresis / monoclonal protein on paraprotein quantification. These patients have polyclonal gammopathy which can be seen in a wide variety of infective and inflammatory conditions. It is not indicative of MGUS or haematological malignancy.

Management of Patients with Paraprotein Bands in Primary Care



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