Information for Clinicians

Haematology Department

Monoclonal Gammopathy of Undetermined Significance (MGUS)

Amendment History

Issue	Status	Date	Reason for Change	Authorised
1.0	Obsolete	16.01.2014	First Issue	W. Hubbard
2.0	Approved	07.10.2021	Updated Guideline	B. Harris

Introduction

Monoclonal Gammopathy of Undetermined Significance (MGUS) describes an abnormal population of plasma cells in the bone marrow that produce redundant immunoglubulins. It is one of the most common pre-malignant disorders, affecting approximately 3.5% of adults over the age of 50. MGUS is a precursor to other conditions, Multiple Myeloma (MM) is most common and clinically significant, and for this reason MGUS requires long term follow up once detected.

DEFINITION OF MGUS: Presence of serum monoclonal immunoglobulin (aka M-protein, monoclonal protein or paraprotein) of up to 30 g/L and <10% bone marrow plasma cells in the absence of:

- Myeloma defining events (SLiMCRAB):
  - S: ≥60% clonal plasma cells
  - Li: Serum free light chain (sFLC) ratio >100 or <0.01
  - M: MRI >1 focal lesion
  - C: hypercalcaemia
  - R: renal insufficiency
  - A: anaemia
  - B: bone disease

- Other lymphoproliferative malignancies such as (predominantly IgM paraproteins):
  - Waldenström's macroglobulinemia (WM),
  - Chronic lymphocytic leukaemia (CLL),
  - B-cell lymphomas.

PREVALANCE OF MGUS: 5% in those aged >70 years, but higher in African/Caribbean individuals than Caucasians. The most common paraprotein isotype is IgG, followed by IgM, then IgA.

PROGRESSION OF MGUS TO MYELOMA: The risk of progression of MGUS to MM or related disorder is around 1% per year. The most important predictors of progression to MM are:

- Non-IgG isotype (predominately IgA)
- Paraprotein ≥15 g/L
- Abnormal sFLC ratio

Where all 3 factors are present, the risk of progression is 20 fold higher than when no risk factors are present. Patients with no risk factors are termed “low-risk MGUS” with a 0.1% annual risk of progression. To further guide clinicians and GPs, as a rough rule of thumb, the paraprotein level (g/L) is equivalent to the risk of progression for that patient at 10 years following detection.

Level of Paraprotein	Risk of Progression over 10 years
5 g/L	5%
20 g/L	20%

OTHER CONDITIONS ASSOCIATED WITH MGUS:
Whilst the majority of MGUS patients have no clinical symptoms, a small number can be associated with other clinical conditions. The referring clinician should be aware that any MGUS has the potential to develop into systemic AL amyloidosis with the most common symptoms being:

- Weight loss
- Neuropathy
- Ankle oedema/proteinuria

Other associations to be aware of are:

- Peripheral neuropathy
- Bleeding abnormalities
- Skin lesions
- Renal impairment (Monoclonal Gammopathy of Renal Significance (MGRS))

Clinical Findings/Investigations

Once a paraprotein has been detected all of the following investigations should also be completed:

- FBC
- Creatinine and electrolytes
- LFT
- Calcium
- Immunoglobulins
- sFLC

Note: Using "myeloma screen" profile on ICE when requesting serum electrophoresis ensures all relevant tests are performed. The laboratory will automatically perform sFLC and immunoglobulins on all samples where a new paraprotein or urine Bence Jones Protein (BJP) has been detected.

Although abnormal sFLC have been shown to be a risk factor for progression, studies support community monitoring where there is a sFLC ratio between 0.1 – 7.0 and there are no other haematological, biochemical or clinical signs suggestive of MM, other lymphoproliferative disorder or AL amyloidosis.

SYMPTOMS:
Exclude or otherwise explain any symptoms or laboratory findings suggestive of MM, other lymphoproliferative disorder or AL amyloidosis prior to classifying as MGUS e.g.

- Hypercalcaemia **(C)**
- Renal impairment **(R)**
- Anaemia or other cytopenias **(A)**
- Bone pain; especially in back, rib or hips **(B)**
- Spinal cord compression symptoms; numbness and weakness in legs and feet
- Recurrent infections
- Weight loss
- Lymphadenopathy/hepatosplenomegaly (associated with IgM paraprotein, in such cases consider CT scan)

Even if a patient is reviewed frequently, symptoms may rapidly develop. The patient is the best person to be aware of these symptoms and is **essential** they report these outside of an appointment if they occur. Provision of a **patient information leaflet is recommended,** see: Macmillan Patient Information (MGUS).

MGUS Monitoring:

Following laboratory investigations and clinical review, patients should fall into one of the two categories below (see Tables 1 & 2):

1. Community monitoring

Blood Results / Symptoms	Action
ALL of the following : Asymptomatic: No CRAB features paraprotein/light chains: IgG <15 g/L IgA or IgM <10 g/L sFLC ratio stable 0.1-7.0	• MM or related disorder is unlikely to be present • Likely MGUS, community monitoring (see Figure 1) • Provide patient with MGUS information (Macmillan leaflet)

Table 1: MGUS criteria for community/primary care monitoring*. Following identification of MGUS, monitoring after 6 months is advisable reducing to annually as long as there are no symptoms and no biochemical or haematological features suggestive of progression. Where there is low risk MGUS (IgG, paraprotein <15 g/L and normal sFLC) and the patient is either > 80 years old or has a life expectancy of less than 5 years, CONSIDER discontinuing follow up.*

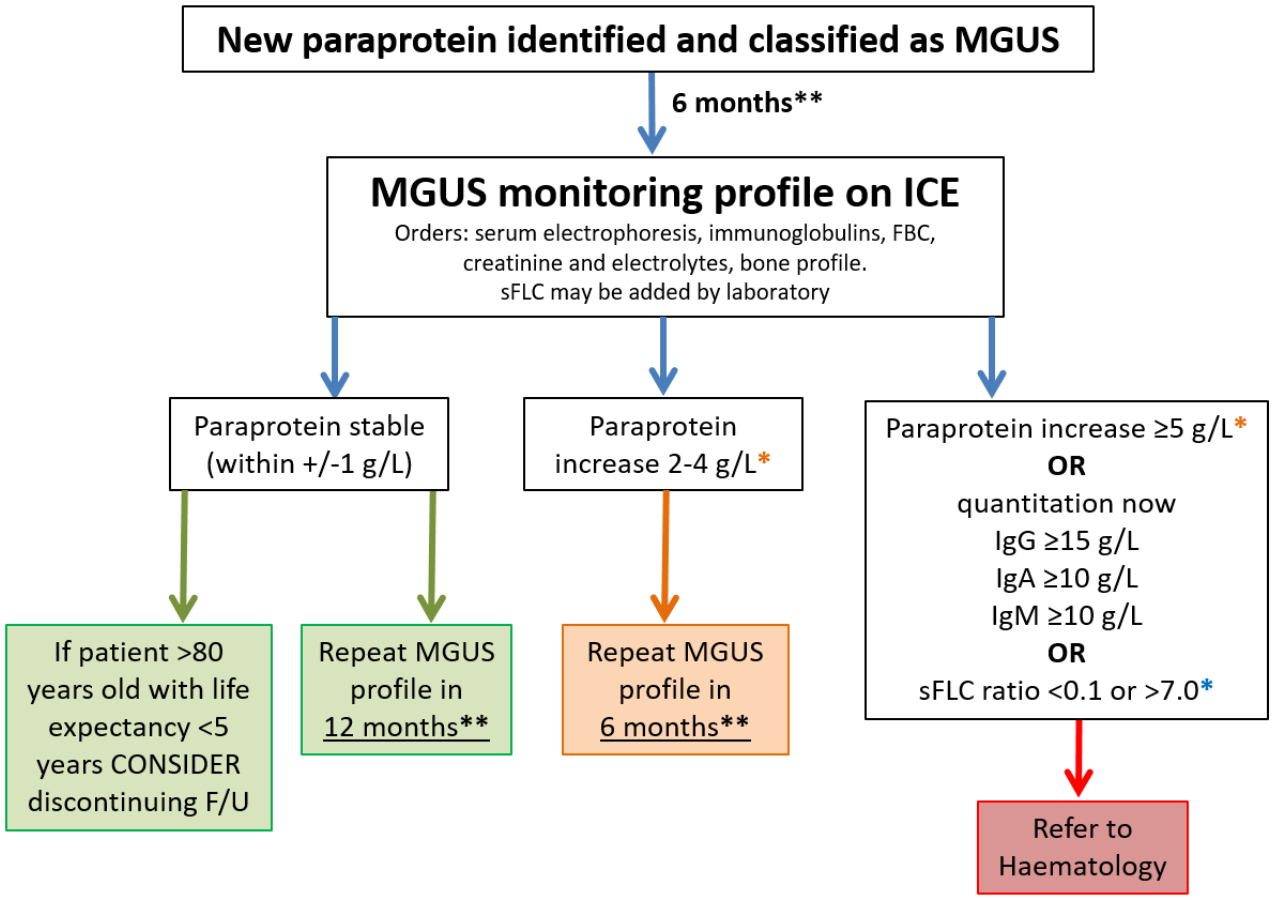
2. Haematology referral

Blood Results / Symptoms	Action
ANY of the following: Symptomatic: Any CRAB features Paraprotein/light chains: IgG ≥15 g/L, IgA or IgM ≥10 g/L IgD/E of any level sFLC ratio <0.1 or >7.0 *Increasing paraprotein: >25% and ≥5g/L **Confirmed sFLC deteriorating trend within 0.1-7.0	• Refer to haematology (2WW)

Table 2: MGUS criteria to prompt secondary care referral. *******In the event of any paraprotein increasing from baseline or within 5 years by >25% (minimum absolute increase 5 g/L), referral should be considered, especially if any symptoms are present. **Where sFLC ratio appears to be worsening within the 0.1-7.0 range repeat to confirm trend prior to referral.*

Note: *Inter-laboratory variation in quantitation of paraprotein can be as high as 25%. Where possible, quantification repeated over time should be performed by the same methodology in the same laboratory.*

MGUS Monitoring Flowchart:



****If remains asymptomatic with no SLiMCRAB, otherwise refer to Haematology**

***Within 5 years**

***Or worsening sFLC ratio within the 0.1-7.0 range (repeat to confirm trend prior to referral)**

Figure 1: Overview of MGUS monitoring. Note: *Clinical biochemists will review serum electrophoresis reports where clinical details are clearly "MGUS", providing interpretative commentary with monitoring frequency or referral recommendations along with serum electrophoresis results.*

Note: *Inter-laboratory variation in quantitation of paraprotein can be as high as 25%. Where possible, quantification repeated over time should be performed by the same methodology in the same laboratory.*

Related documents

Macmillan Patient Information (MGUS)

Myeloma UK MGUS Infosheet

Myeloma Diagnostic Tool: Guidance for Primary Care

References:

UK Myeloma Forum and Nordic Myeloma Study Group: guidelines for the investigation of newly detected M-proteins and the management of MGUS. B J Haem, 147, 22–42.
NICE guidelines [NG12] Suspected Cancer: recognition and referral (2017)
NICE guidelines [NG35] Myeloma: diagnosis and management (25 October 2018)
Myeloma Diagnostic Tool: Guidance for Primary Care; Myeloma UK

APPENDIX: MYELOMA UK – GP GUIDELI

Myeloma Diagnostic Tool: Guidance for Primary Care — MyelomaUK

When to test for myeloma

Any of the following blood test abnormalities:

- Raised Calcium
- Renal impairment
- Anaemia
- Raised ESR

Symptom or finding:

- Bone pain – usually presents as unexplained pain, generalised or localised
- Back pain – persistent or severe/atypical
- Generally unwell – fatigue, weight loss, suspicion of underlying cancer
- Recurrent infections
- Spontaneous fractures including osteoporotic vertebral fractures
- Breathlessness – unexplained

Important factors to consider:

Symptoms and findings persist without explanation or despite initial interventions.

Red flags for myeloma investigation include **unexplained** symptoms and **more than one** symptom.

The **CRAB** criteria for myeloma.

What tests to request

- Serum protein electrophoresis for paraprotein
- Serum free light chain (sFLC) assay
  - If unavailable, urine Bence Jones protein (BJP)
- Serum immunoglobulins (IgG, IgA and IgM)
- Full blood count
- Corrected serum calcium
- Serum creatinine

Response to results

• Any paraprotein/abnormal sFLC ratio **with** significant symptoms indicative of an urgent problem (e.g. spinal cord compression, acute kidney injury)	Recommend **urgent referral** to Clinical Haematology
• Moderate concentration of paraprotein (IgG >15 g/L, IgA or IgM >10g/L) • Identification of an IgD or IgE paraprotein (regardless of concentration) • Significant abnormal sFLC ratio (<0.1 or >7) ◦ Identification of BJP	Recommend **2-week rule referral** to Clinical Haematology
• Minor concentration of paraprotein (IgG <15 g/L, IgA or IgM <10g/L) **without** relevant symptoms • Abnormal sFLC ratio (0.1–7) This pattern is common in elderly patients	Recommend **recheck** serum and urine in 2–3 months to confirm pattern and assess any progression. Patients whose paraprotein concentration increases (25% and >5g/L) or develop symptoms will need a **2-week rule referral**. **Discuss** with your Clinical Haematology Department if results not clear or concerns.
• No serum paraprotein • Normal sFLC ratio ◦ No BJP • Normal immunoglobulin levels	Myeloma very **unlikely** but symptoms may still need to be investigated with other clinical specialties

NICE guideline [NG12] Suspected cancer: recognition and referral (2017) https://www.nice.org.uk/guidance/ng12
NICE guideline [NG35] Myeloma: diagnosis and management (2018) https://www.nice.org.uk/guidance/ng35