Information for Clinicians

Blood Sciences Department

Monoclonal Gammopathy of Undetermined Significance (MGUS) – a guide for GPs

Introduction

Monoclonal Gammopathy of Undetermined Significance (MGUS) describes an abnormal population of plasma cells in the bone marrow that produce redundant immunoglobulins known as paraproteins (aka M-protein, monoclonal protein, monoclonal band, monoclonal peak). Paraproteins (PP) may be whole immunoglobulins and/or abnormal ratio of free light chains (FLC), detected in serum.

Definition of MGUS: Presence of serum PP of <30 g/L and <10% bone marrow plasma cells in the absence of myeloma defining events (SLiM**CRAB**) or other related lymphoproliferative malignancies (Table 1). Light-chain MGUS is when only light-chain PP is produced and results in an abnormal FLC ratio (outside age and CKD-related reference ranges), in the absence of myeloma defining events or other related lymphoproliferative malignancies (Table 1).

Table 1: Features of non-MGUS paraproteins

Myeloma defining events (SLiMCRAB):	**Other lymphoproliferative malignancies (predominantly IgM paraproteins):**
○ S: ≥60% clonal plasma cells ○ Li: Serum free light chain (FLC) ratio >100 or <0.01 ○ M: MRI >1 focal lesion ○ **C:** hypercalcaemia ○ **R:** renal insufficiency ○ **A:** anaemia ○ **B:** bone disease	○ Waldenström's macroglobulinemia (WM) ○ Chronic lymphocytic leukaemia (CLL) ○ B-cell lymphomas ○ Light-chain amyloidosis (AL)

Prevalence of MGUS: Incidence of MGUS increases with age, affecting approximately 3.5% of adults over the age of 50 and 5% 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: MGUS is a precursor to malignancy (e.g. myeloma or lymphoma), for this reason MGUS usually requires long term follow up once detected.

Initial referral criteria: Refer patients to haematology if any of the following are detected:

- **IgG PP ≥15 g/L**
- **IgA or IgM PP ≥10 g/L**
- **IgE or IgD PP at any level** (extremely rare)
- **FLC ratio <0.1 OR >7.0**
- **PP + other laboratory OR clinical red flags** (Table 2)

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Table 2: Red flags for myeloma or related lymphoproliferative disease

Laboratory red flags	Clinical red flags
Unexplained: ○ Hypercalcaemia ○ Renal insufficiency ○ Anaemia or other cytopenia Paraprotein trend: ○ PP increased ≥50% (+ absolute PP increase ≥5 g/L) ○ Involved FLC increase ≥50% (+ involved FLC ≥100 mg/L)	○ Bone pain (especially back, rib, hips) ○ Unintentional weight loss ○ Recurrent infections ○ Neurological symptoms (numbness and weakness in legs and feet, peripheral neuropathy, headache, dizziness, loss of vision/hearing) ○ Abnormal bleeding ○ Fever, drenching night sweats ○ Lymphadenopathy, hepatomegaly, splenomegaly ○ Suspicion of amyloidosis (e.g. macroglossia, periorbital purpura, nephrotic range proteinuria, restrictive cardiomyopathy)

Myeloma is highly unlikely if the PP is <10 g/L and the FLC ratio is in the range 0.1–7.0. Using a PP threshold of >10 g/L and FLC ratio range (<0.1 or >7.0) provides 98% sensitivity for the detection of myeloma.

MGUS monitoring: The risk of progression of MGUS to myeloma or related disorder can be predicted by presence of the three risk factors (PP ≥15 g/L, non-IgG PP, FLC ratio <0.1 or >7.0), using these risk factors, patients should be stratified for monitoring frequency (Table 3).

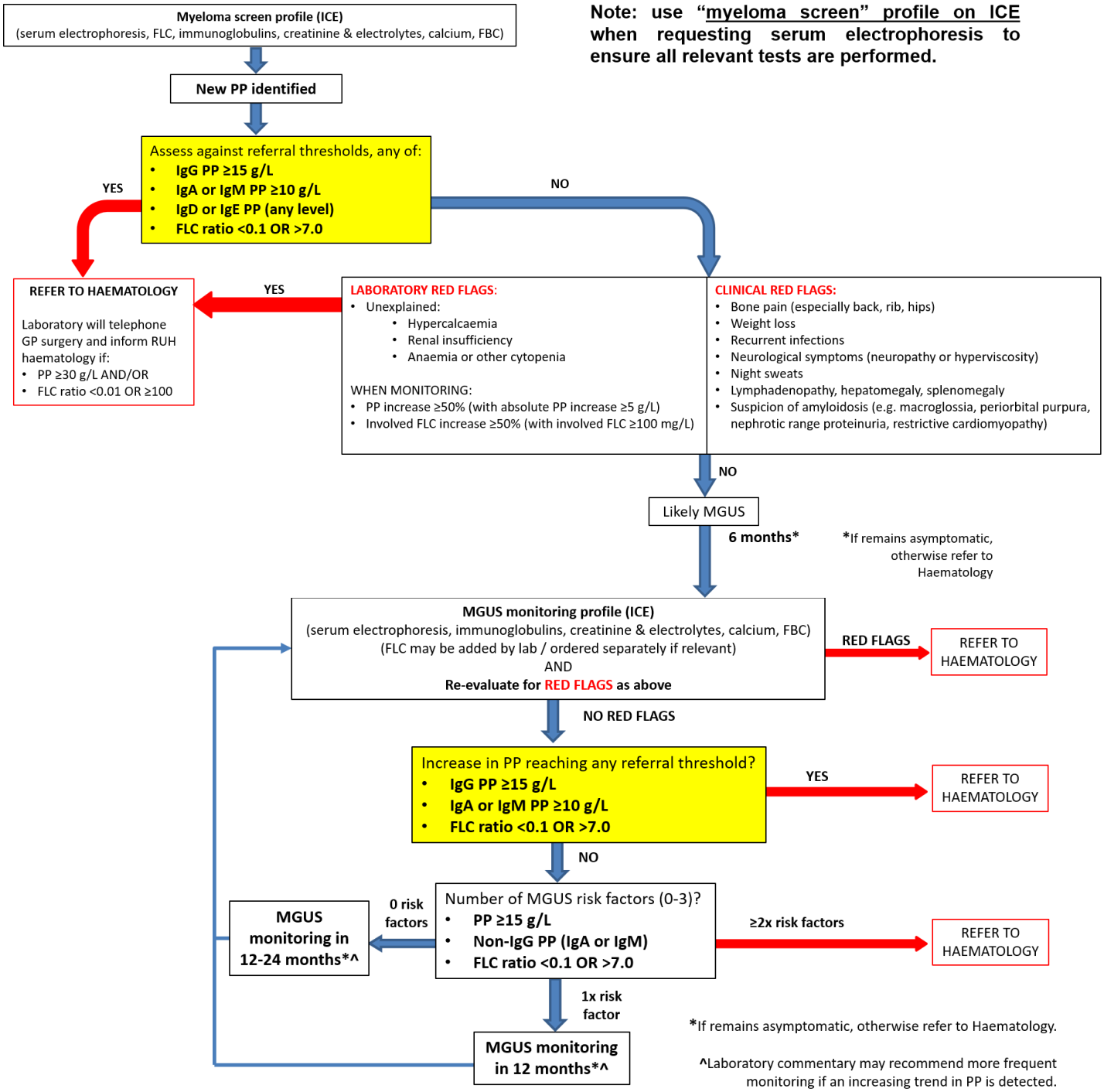
However, consider life expectancy and other comorbidities: <u>monitoring may not be appropriate or may be reduced if life expectancy is short.</u>

Table 3 Risk stratification for MGUS monitoring (based on the Mayo Clinic Risk Stratification Model)

Number of risk factors - PP ≥15 g/L - Non-IgG MGUS (IgA or IgM) - Abnormal FLC ratio	**Risk of disease progression over 20 years**	**Risk of disease progression when accounting for death as a competing risk**	**Definition**	**Management**
Three	58%	27%	High-risk	Refer to Haematology
Two	37%	18%	High-intermediate risk	
One	21%	10%	Intermediate risk	MGUS-monitoring bloods at 6-months then **annually** if stable
No risk factors	5%	2%	Low-risk	MGUS-monitoring bloods at 6-months then **1-2 yearly** if stable

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Summary flowchart



NOTES:

Signposting patients to information that explain MGUS is recommended, the patient is the best person to be aware of symptoms that could indicate progression, and is **essential** they report these promptly if they occur. See **MGUS: Macmillan Webpage**

Inter-laboratory variation in quantitation of PP can be as high as 25%. Monitoring over time should be performed by the same methodology in the same laboratory, where possible.

Paraproteins may be transient, reactive findings due to inflammation or infection and may resolve. If PP previously categorised as MGUS is no longer present, on-going MGUS monitoring is not required.

Polyclonal gammopathy (aka hypergammaglobulinaemia) is caused by liver disease, immune dysregulation, or inflammation. Although assessment for a cause may be indicated, this DOES NOT need monitoring as a MGUS

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References

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Heaney JLJ *et al.* Excluding myeloma diagnosis using revised thresholds for serum free light chain ratios and M-protein levels. *Haematologica*, 2020;105(4):169-171

Myeloma UK. Myeloma, MGUS and related conditions – a guide for GPs. Published Aug 2023 Myeloma, MGUS and Related Conditions: A Guide for GPs - Myeloma UK

NICE guideline NG35. Myeloma: diagnosis and management. Published Feb 2016. Last updated 2018 Overview | Myeloma: diagnosis and management | Guidance | NICE

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
3.0	Approved	30.09.2026	Updated guideline	M. O'Doherty

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