



Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smouldering Multiple Myeloma (SMM): A Practical Guide to Management

Journal:	<i>Hematological Oncology</i>
Manuscript ID	HON-16-0091.R1
Wiley - Manuscript type:	Original Research Article
Date Submitted by the Author:	08-Jul-2016
Complete List of Authors:	Maciocia, Nicola; University College London Hospital, Haematology Wechalekar, Ashutosh; Royal Free Hospital, National Amyloidosis Centre Yong, Kwee; University College London Hospital, Haematology
Keywords:	plasma cells, paraprotein, gammopathy, myeloma, smouldering

SCHOLARONE™
Manuscripts

Only

1
2 1 **Monoclonal Gammopathy of Undetermined Significance (MGUS) and**
3
4 2 **Smouldering Myeloma (SMM): A Practical Guide to Management**

5
6 3
7 4 **Nicola Maciocia¹, Ashutosh Wechalekar², Kwee Yong³**

8
9 5
10 6 ¹Department of Haematology, University College London Hospitals, 250 Euston Road,
11 7 London NW1 2PG, UK

12 8
13 9 ²National Amyloidosis Centre, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14 10
15 11 ³Department of Haematology, Cancer Institute, University College London, 72 Huntley
16 12 Street, London WC1E 6BT, UK

17 13
18 14
19 15
20 16 Corresponding Author:

21 17 Kwee L Yong,

22 18 UCL Cancer Institute

23 19 72 Huntley Street

24 20 London WC1E 6BT

25 21 Email: kwee.yong@ucl.ac.uk

26 22 Tel: +44 207 6796139

27 23 Fax: +44 207 6796222

24 **Abstract**

25 Monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple
26 myeloma (SMM) are precursor conditions of symptomatic multiple myeloma (MM).
27 Diagnostic principles are aimed at excluding MM requiring therapy, other conditions
28 associated with paraproteins that may require different management, and risk stratifying
29 patients for the purposes of tailored follow up and investigation. The IMWG have recently
30 published a revised definition of MM, that singles out a small group of patients with SMM
31 who are at very high risk of progression and organ damage; such patients are now included
32 under the definition of MM, and recommended to start anti-myeloma treatment.
33 Furthermore, **the recently published NICE guideline recommends cross sectional imaging**
34 **techniques in place of skeletal survey. These recent recommendations are discussed, and**
35 practical guidance for investigation and management presented.

37 **Introduction**

38 Monoclonal gammopathy of undetermined significance (MGUS) describes the presence of a
39 serum monoclonal protein (paraprotein) without other evidence of multiple myeloma
40 (MM), Waldentrom's macroglobulinaemia (WM), amyloidosis or other lymphoproliferative
41 disorder[1]. MGUS is thought to consistently precede the development of MM[2], but not
42 all patients with MGUS have the same risk of progression to MM. Many paraproteins are
43 picked up incidentally and the challenge is how best to manage these patients whilst
44 avoiding over investigation and/or incurring undue anxiety[3]. Risk models for progression
45 can be incorporated into management algorithms for these patients.

47 Smouldering myeloma (SMM) is an intermediate stage between MGUS and symptomatic
48 MM[4]. Patients with SMM have a higher initial risk of progression compared to MGUS
49 patients but risk reverts to MGUS levels after 10 years. Median time to progression is
50 around 4.8 years[5]. SMM patients lack evidence of end organ damage, but a small
51 proportion may warrant treatment on the basis of high risk biomarkers[6].

52 **Epidemiology and pathophysiology**

53 The overall risk of progression of MGUS is approximately 1% per year[7], and remains
54 unchanged over many years although many are elderly and will die from unrelated
55 conditions[8]. Prevalence increases with age (3.2% over 50years), is higher in males and in
56 Africans[9][10]. IgG is the commonest subtype (68.9%)[11]. MGUS is associated with
57 diverse conditions including autoimmune and inflammatory conditions, liver disease, bone

1
2 58 marrow and organ transplantation[12][13]. The aetiology is unclear, suggested
3
4 59 predisposing factors include family history of haematological malignancy,
5
6 60 immunosuppression, radiation exposure and pesticides[14, 15]. SMM has a similar age of
7
8 61 presentation as MGUS and symptomatic MM (60-70years), and is most commonly IgG
9
10 62 (74%) or IgA (22.5%) [5][16].

11
12 63
13 64 Founder genetic events in MM such as chromosomal translocation into the IgH gene loci
14 65 and hyperdiploidy are present in MGUS. Secondary genetic lesions occurring in sub-clones
15 66 that compete for dominance may lead ultimately to clonal progression and expansion of
16 67 certain “fitter” sub clones. Common secondary events that are associated with the
17 68 progression to symptomatic MM include point mutations in oncogenes (eg. N-RAS, K-RAS,
18 69 TRAF3, p53), MYC up regulation by a variety of mechanisms, and chromosome 1 imbalance
19 70 (1q gain or 1p loss). A progressive increase in the incidence of copy number abnormalities
20 71 and epigenetic modifications may occur [17] [18].

22 72 **Definition of MGUS**

23 73 All criteria must be met:

- 24 74 1. Serum monoclonal protein <30 g/L
- 25 75 2. Clonal bone marrow (BM) plasma cells (PC) <10%,
- 26 76 3. Absence of end-organ damage (hypercalcemia, renal insufficiency, anaemia, and
27 77 bone lesions) [19].

28 78 **MGUS Related Disorders and associated risks**

29 79 MGUS can be associated with other clinically significant conditions, listed in Table 1 [20],
30 80 including AL amyloidosis, MGUS of renal significance (MGRS), type I and II
31 81 cryoglobulinaemia, cold agglutinin disease and autoimmune neuropathies, the latter
32 82 usually caused by autoantibody activity of an IgM paraprotein. Other rare diseases
33 83 associated with monoclonal gammopathy include POEMS syndrome, scleromyxoedema,
34 84 acquired Fanconi syndrome and Schnitzler syndrome [21, 22]. Individuals with MGUS have
35 85 an increased risk of osteoporosis, venous/arterial thrombosis, infections, as well as an
36 86 increased risk of developing myeloid and non-haematological malignancies [23] [24] [25].

37 87 **Definition of Smouldering MM including recent revisions**

38 88 In 2003 IMWG developed the first international consensus guidelines that classified SMM
39 89 as BMPCs $\geq 10\%$ and/or paraprotein (PP) ≥ 30 g/L) and critically the absence of CRAB

90 features (high calcium, haemoglobin 2g/dL below normal or <10 g/dL, lytic bone lesions or
91 osteoporosis with compression fractures, symptomatic hyperviscosity, amyloidosis, or >2
92 bacterial infections/12 months) [16]. As there was no evidence that treatment of
93 asymptomatic SMM patients altered the natural disease history or improved long term
94 outcomes, treatment was withheld unless progression occurred as defined by end organ
95 damage.

96 **Revised criteria**

97 It became clear that some SMM patients are at very high risk of progression to symptomatic
98 MM[18], moreover, progression was associated with marked morbidity. Hence, work was
99 done to identify patients at ultra high risk (approximately 80%) of progression within 2
100 years. Three markers identify patients at ultra high risk of progression (80% over 2 years)
101 [6]:

102 **Additional new criteria for diagnosis of myeloma (Table 2)**

- 103 • *Bone marrow plasmacytosis*

104 BMPCs of $\geq 60\%$ (present in <5% of patients) carries a very high risk of progression to MM
105 (>80% within 2 years)[26, 27], and is thus now considered a MM defining criterion.

- 107 • *Serum Free Light Chains*

108 High serum free light chains are a risk factor for progression in SMM [28], and SFLC ratio of
109 >100 carries a 2-year progression risk of 72%[29], and is now a MM defining criterion.

- 111 • *Focal lesion/s on MRI*

112 MRI is now recommended for screening in SMM (see below). Patients with >1 focal lesion
113 on MRI had a 70% risk of progression at 2 years)[30], findings subsequently confirmed [31,
114 32]. Thus >1 focal lesion on MRI is now a MM defining criterion. For patients with solitary
115 bone lesions, data are less clear and regular (3-6 monthly) follow up by MRI is
116 recommended.

117

118 Table 2 summarises these new MM defining features, for which anti-MM treatment is
119 recommended. Alongside these recommendations, revised definitions of organ damage
120 have also been produced (Table 3). **The term symptomatic MM should now be dropped, in
121 favour of MM, to include asymptomatic patients who require treatment on the basis of one**

122 or more MM defining criteria. Hence SMM, previously used to refer to “symptomatic MM”
123 should now be used exclusively to refer to smouldering MM, or asymptomatic MM.

124 Risk factors for Progression in MGUS

125 Presenting features and dynamics of the clone during follow up are helpful predictors of
126 progression. Recognised risk factors include:

- 127 a. Level of the monoclonal protein [33].
- 128 b. Level of BMPCs (>5%)[34].
- 129 c. Rise in paraprotein over time [35].
- 130 d. Abnormal SFLC ratio [36].
- 131 e. Biological characteristic of the MGUS clone, higher for IgA/IgM than for IgG. [11,
132 33].

133 Fluorescent-in-situ-hybridisation (FISH) defined abnormalities including recurrent
134 primary IgH translocations and hyperdiploidy are found in MGUS [37], but it is unclear if
135 specific abnormalities eg. del(17p) are predictive of progression to MM.

136 Risk models in MGUS

137 Patients are risk stratified using clinical variables identified in epidemiological studies, and
138 two main prognostic models are the Mayo clinic model, and the PETHEMA group or
139 Spanish model (Table 4). [36] [38].

140 Risk Stratification Models in SMM

141 The main risk models for SMM reflect those in MGUS (Table 4). The Mayo clinic model
142 included abnormal SFLC ratio, paraprotein level and BM plasmacytosis, while the Spanish
143 group used a flow cytometry based model with two independent variables [39].

144 Need for new risk models in SMM

145 Revision of diagnostic criteria for MM that remove the ultra high risk SMM patients
146 requires a re-evaluation of our risk models for SMM. Genetic abnormalities [deletion 17p,
147 t(4;14)] or gene expression signature may be important [31, 40, 41], as may PET-CT
148 findings [42]. The presence of Bence Jones proteinuria (especially >500mg/24 hours) or
149 rising paraprotein (evolving SMM) may also impart greater risk of progression [43].
150 Immunophenotype, circulating plasma cells, a high PC proliferative rate have also been
151 implicated [31]. All these need to be studied in larger patient cohorts to assess their wider
152 applicability.

153 **Diagnosis of MGUS**

154 The major aim of investigating these patients is to distinguish between MGUS, SMM and
155 MM requiring treatment. The commonest reason for assigning a diagnosis of SMM (rather
156 than MGUS) is the presence of $\geq 10\%$ plasma cells in the bone marrow. For IgM and light
157 chain only conditions, the equivalent is called smouldering WM, and idiopathic Bence Jones
158 proteinuria, respectively. It is also important to differentiate MGUS of truly no clinical
159 significance from MGUS associated with amyloidosis, Waldenstrom's macroglobulinaemia
160 (WM) and other lymphoid neoplasms. Symptoms should also be sought for the rarer
161 disorders associated with a paraprotein e.g. POEMS syndrome. (Table 1)

162
163 All patients require history and examination, full blood count, renal function, total protein,
164 serum calcium, serum and urine protein electrophoresis with immunofixation and serum
165 free light chains. A bone marrow aspirate and trephine biopsy (BMAT) should be
166 performed when serum PP $\geq 15\text{g/L}$, if non IgG MGUS, abnormal SFLC ratio (> 10 or < 0.10),
167 or if diagnosis of MGUS is in doubt. All patients with suspected myeloma (paraprotein $>$
168 30g/l or bone marrow plasma cells $>10\%$) need cross-sectional imaging **as per recent NICE**
169 **guidelines: whole body MRI as first line or whole body low dose CT. [50]**

170
171 For high risk MGUS patients (Mayo clinic model), a skeletal survey should be carried out (or
172 a CT chest abdomen and pelvis in IgM MGUS). MRI or PET-CT imaging is not recommended
173 outside the context of a clinical trial [44].

174 **Management of MGUS**

175 Clinical trial results show no benefit for early intervention, and the risk of progression to
176 MM is low, thus current management is 'watch and wait' [45]. As risk of progression does
177 not change over time lifelong follow up is recommended, with monitoring tailored to
178 patient's risk of progression, co-morbidities and life expectancy.

179
180 Risk stratification of patients (Mayo clinic model) into low, intermediate and high risk
181 MGUS aids counselling and follow up [46]. Current practice will vary from centre to centre.
182 Based on currently available evidence and guidelines a reasonable approach is:
183 Low risk: SS and BM not required, monitor every 6 months for 2 years then 1-2yrlly if
184 stable. Monitoring can be done in primary care and should include patient review, blood
185 count, renal function, calcium, and paraprotein level.

186 Intermediate or high risk: SS and BM are mandatory, review and monitor as above every 6
187 months for 2 years then annually for life. Follow up should include history and
188 examination, full blood count, renal function, calcium and paraprotein. Monitoring should
189 be initially in secondary care, but after 5 years, primary care monitoring is reasonable.
190 **Although the risk of progression in patients with light chain only MGUS is relatively low**
191 **(0.3% per year), there is a considerable risk of developing renal disease, hence 6-monthly**
192 **follow up is recommended [11]. Finally, MGUS patients with elevated SFLC should be**
193 **monitored for development of amyloidosis or MGRS, hence measurement of NT-proBNP**
194 **and urine albumin at follow up is recommended [19].**

195
196 A BMAT +/- skeletal survey is always indicated if features suggestive of end organ damage
197 develop or if >25% increase in PP levels occurs over a three month period (minimum
198 5g/L). Diagnostic work up and management plan should be altered according on age and
199 co-morbidities (Figure 1). For example in a person of advanced age with limited life
200 expectancy it may be reasonable to omit SS and BMAT from the work up or not to
201 undertake regular monitoring of the paraprotein level. Whichever risk group a patient falls
202 into, it is important to provide information and counselling as the diagnosis may lead to
203 anxiety and fears for the future. MyelomaUK provide written information and telephone
204 advice:
205 [http://www.myeloma.org.uk/information/myeloma-uk-publications-list/other-related-](http://www.myeloma.org.uk/information/myeloma-uk-publications-list/other-related-conditions/mgus-infosheet/)
206 [conditions/mgus-infosheet/](http://www.myeloma.org.uk/information/myeloma-uk-publications-list/other-related-conditions/mgus-infosheet/)

207 **Diagnostic Investigations for SMM**

208 Investigations are aimed at differentiating SMM from symptomatic MM requiring
209 treatment. All patients need baseline blood counts, renal function, serum calcium and total
210 protein, serum and urine protein electrophoresis with immunofixation and serum free light
211 chains. Risk stratification of SMM may be useful, eg. the Mayo clinic model. All patients
212 with a paraprotein >30g/L and/or SFLC ratio >8 should be considered for further testing
213 with BM and imaging. **As per NICE guidance, skeletal survey is no longer sufficient and**
214 **cross-sectional imaging is recommended, with the choice of MRI, low-dose whole-body CT**
215 **or PET-CT being made according to local practice [47].**

216 **Treatment for SMM**

217 Historical studies have shown no advantage to initiating treatment for patients with SMM,
218 largely due to lack of efficacy and high toxicity of regimens used.[48] [49][50]. Recently, a

219 randomised trial has indicated, for the first time, that treatment in SMM can improve
220 outcomes. This Phase III trial used flow cytometry to identify high risk patients and
221 prospectively randomised them to receive treatment with lenalidomide and
222 dexamethasone versus observation only. With median follow-up of 40 months, treated
223 patients had significantly longer time to progression (median not reached vs. 21 months)
224 and overall survival (3-year survival 94% vs. 80%) [51]. Drawbacks of the study are the
225 criteria used to risk stratify, and the unexpectedly high rate of death in the control arm.
226 Several trials are currently evaluating new drugs and strategies in high risk SMM, and such
227 patients should be considered for entry into clinical trials otherwise observation still
228 remains standard of care.

229 **Monitoring patients with SMM**

230 The risk of progression in SMM is highest in the first years after diagnosis, maximal in the
231 first two years, and reducing over the next few years. Hence, the monitoring needs to be
232 more frequent soon after diagnosis and can become less frequent 5 years after diagnosis.
233 There are no formal prospective studies of monitoring in SMM. **As per NICE guidelines,**
234 **patients should be monitored every 3 months initially [47].** Pragmatically, a reduced
235 frequency of monitoring may be adopted after 2 years, depending on risk (Figure 2).
236 Monitoring should include assessment of CRAB symptoms, FBC, renal function, bone
237 profile, immunoglobulins, serum protein electrophoresis and SFLC if appropriate [47]. High
238 risk patients, those with a rising paraprotein or new symptoms and those with a single
239 focal lesion on MRI may need repeat imaging or bone marrow examinations.

240 **Conclusion and Future Directions**

241 MGUS is associated with a risk of progression to MM and a variety of other clinically
242 significant conditions. Diagnostic work up of suspected MGUS patients should seek
243 evidence of these. Risk stratification models can help with estimating risk of progression
244 and, together with patient-specific factors, planning follow-up.

245

246 SMM is an area where on-going research is re-defining risk boundaries with implications
247 for monitoring and treatment. As new factors for progression are identified, some patients
248 will now be reclassified as MM requiring treatment, and there is a suggestion that early
249 treatment of high risk SMM may be of benefit. While MM remains incurable, here is
250 insufficient evidence, however, to recommend routine treatment of these asymptomatic
251 patients, or indeed to indicate which treatment is the best. Progression to MM may not the

1
2 252 only important end point for treatment of SMM patients as pre-emptive therapy may
3
4 253 promote the earlier out-growth of resistant disease, making the treatment of truly
5
6 254 symptomatic disease more difficult. Genetics clearly define outcomes in MM, and may also
7
8 255 impact outcomes of therapy in SMM. All these remain important questions to be addressed
9
10 256 in prospective trials to refine our approach to SMM and guide treatment, meanwhile
11
12 257 current guidance is confined to monitoring [47].
13
14 258
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Review Only

260

261 **References**

- 1 Bories C, Jagannath S. Asymptomatic Monoclonal Gammopathies. *Clin. Lymphoma Myeloma Leuk* 2014;14:S78–S86.
- 2 Landgren O, Kyle R, Pfeiffer RA et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood* 2009;113:5412–5417.
- 3 Bird J, Owen RO, D'Sa S et al. Guidelines for the diagnosis and management of multiple myeloma 2011. *Br J Haematol* 2011;154:32–75.
- 4 Kyle RA, Greipp PR. Smoldering multiple myeloma. *N Engl J Med* 1980;302:1347–1349.
- 5 Kyle A, Remstein ED, Therneau TM et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 2007;356:2582–2590.
- 6 Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014:e538–548.
- 7 Kyle A, Therneau T, Rajkumar SV et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med* 2002;346:564–569.
- 8 Engelhardt M, Terpos E, Kleber M et al. European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma. *Haematologica* 2014;99:232–242.
- 9 Kyle R, Therneau T, Rajkumar SV et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med* 2006; 354: 1362–1369.
- 10 Landgren O, Katzmann JA, Hsing AW, et al. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. *Mayo Clin. Proc.* 2007;82:1468–1473.
- 11 Dispenzieri A, Katzmann JA, Kyle RA, et al. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. *Lancet* 2010;375:1721–1728.
- 12 Bida JP, Kyle RA, Thernau TM, et al. Disease associations with monoclonal gammopathy of undetermined significance: a population-based study of 17,398 patients. *Mayo Clin Proc* 2009;84:685–693.
- 13 Leung N, Bridoux F, Hutchinson CA, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. *Blood* 2012;120:4292–429.
- 14 Iwanaga M, Tagawa M, Tsukasaki K, et al. Relationship between monoclonal gammopathy of undetermined significance and radiation exposure in Nagasaki atomic bomb survivors. *Blood* 2009;113:1639–1650.
- 15 Landgren O, Kyle RA, Hoppin JA, et al. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. *Blood* 2009;113:6386–6391.
- 16 International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol* 2003;121:749–757.
- 17 Chng WJ, Glebov O, Bergsagel PL, et al. Genetic events in the pathogenesis of multiple myeloma. *Best Pract. Res Clin Haematol.* 2007;20:571–596.

- 1
2
3 18 Cherry M, Korde N, Kwok M et al. Modeling progression risk for smoldering multiple
4 myeloma: results from a prospective clinical study. *Leukemia & Lymphoma*
5 2013;54:2215–2218.
6
7 19 Van de Donk NW, Palumbo A, Johnsen HE et al. The clinical relevance and management
8 of monoclonal gammopathy of undetermined significance and related disorders:
9 recommendations from the European Myeloma Network. *Haematologica* 2014;99:984–
10 996.
11
12 20 Merlini G, Stone, MJ. Dangerous small B-cell clones. *Blood* 2006;108:2520–2530.
13 21 Merlini G, Palladini G. Differential diagnosis of monoclonal gammopathy of undetermined
14 significance. *ASH Educ. Program Book* 2012:595–603.
15
16 22 Korde N, Kristinsson SY, Landgren O. Monoclonal gammopathy of undetermined
17 significance (MGUS) and smoldering multiple myeloma (SMM): novel biological insights
18 and development of early treatment strategies. *Blood* 2011;117:5573–5581
19
20 23 Kristinsson SY, Bjorkholm M, Andersson TM, et al. Patterns of survival and causes of
21 death following a diagnosis of monoclonal gammopathy of undetermined significance: a
22 population-based study. *Haematologica* 2009;94:1714–1720.
23
24 24 Kristinsson SY, Tang M, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined
25 significance and risk of skeletal fractures: a population-based study. *Blood*
26 2010;116:2651–2655.
27
28 25 Kristinsson SY, Pfeiffer RM, Bjorkholm M, et al. Arterial and venous thrombosis in
29 monoclonal gammopathy of undetermined significance and multiple myeloma: a
30 population-based study. *Blood* 2010;115:4991–4998.
31
32 26 Rajkumar SV, Larson D, Kyle RA. Diagnosis of smoldering multiple myeloma. *N Engl J Med*
33 2011;365:474–475.
34
35 27 Kastritis E, Terpose E, Mouloupoulos L, et al. Extensive bone marrow infiltration and
36 abnormal free light chain ratio identifies patients with asymptomatic myeloma at high
37 risk for progression to symptomatic disease. *Leukemia* 2013;27:947–953.
38
39 28 Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an
40 independent risk factor for progression of smoldering (asymptomatic) multiple
41 myeloma. *Blood* 2008;111:785–789.
42
43 29 Larsen JT, Kumar SK, Dispenzieri A, et al. Serum free light chain ratio as a biomarker for
44 high-risk smoldering multiple myeloma. *Leukemia* 2013;27:941–946.
45
46 30 Hillengass J, Fechtner K, Weber MA, et al. Prognostic significance of focal lesions in
47 whole-body magnetic resonance imaging in patients with asymptomatic multiple
48 myeloma. *J Clin Oncol* 2010;28:1606–1610.
49
50 31 Dhodapkar MV, Sexton R, Waheed S, et al. Clinical, genomic, and imaging predictors of
51 myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120).
52 *Blood* 2014;123:78–85.
53
54 32 Kastritis E, Mouloupoulos LA, Terpos E, et al. The prognostic importance of the presence of
55 more than one focal lesion in spine MRI of patients with asymptomatic (smoldering)
56 multiple myeloma. *Leukemia* 2014;28:2402–2403.
57
58
59
60

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
-
- ³³ Katzmann J, Clark R, Kyle RA, et al. Suppression of uninvolved immunoglobulins defined by heavy/light chain pair suppression is a risk factor for progression of MGUS. *Leukemia* 2013;27:208–212.
- ³⁴ Cesana C, Klersy C, Barbarano L, et al. Prognostic factors for malignant transformation in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. *J Clin Oncol* 2002;20:1625–1634.
- ³⁵ Rosiñol L, Cibeira MT, Montoto S, et al. Monoclonal gammopathy of undetermined significance: predictors of malignant transformation and recognition of an evolving type characterized by a progressive increase in M protein size. *Mayo Clin Proc* 2007;82:428–434
- ³⁶ Rajkumar SV, Kyle RA, Thernau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood* 2005;106:812–817.
- ³⁷ Kuehl WM, Bergsagel PL. Multiple myeloma: evolving genetic events and host interactions. *Nat Rev Cancer* 2002;2:175–187.
- ³⁸ Pérez-Persona E, Vidriales MB, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood* 2007;110:2586–2592.
- ³⁹ Perez-Persona E, Mateo G, Garcia-Sanz R, et al. Risk of progression in smouldering myeloma and monoclonal gammopathies of unknown significance: comparative analysis of the evolution of monoclonal component and multiparameter flow cytometry of bone marrow plasma cells: Short Report. *Br J Haematol* 2010;148:110–114.
- ⁴⁰ Rajkumar SV, Gupta V, Fonseca R, et al. Impact of primary molecular cytogenetic abnormalities and risk of progression in smoldering multiple myeloma. *Leukemia* 2013;27:1738–1744.
- ⁴¹ Neben K, Jauch A, Hielscher T et al. Progression in Smoldering Myeloma Is Independently Determined by the Chromosomal Abnormalities del(17p), t(4;14), Gain 1q, Hyperdiploidy, and Tumor Load. *J Clin Oncol* 2012;248:4923
- ⁴² Zamagni E, Nanni C, Gay F, et al. 18F-FDG PET/CT focal, but not osteolytic, lesions predict the progression of smoldering myeloma to active disease. *Leukemia* 2016;30:417–422
- ⁴³ González-Calle, V., J. Dávila, F. Escalante, A. G. de Coca, C. Aguilera, R. López, A. Báñez, et al. ‘Bence Jones Proteinuria in Smoldering Multiple Myeloma as a Predictor Marker of Progression to Symptomatic Multiple Myeloma’. *Leukemia*, 27 May 2016. doi:10.1038/leu.2016.123.
- ⁴⁴ Dimopoulos M, Terpos E, Comenzo RL, et al. International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. *Leukemia* 2009;23:1545–1556.
- ⁴⁵ Blade J, Dimopoulos M, Rosinol L, et al. Smoldering (Asymptomatic) Multiple Myeloma: Current Diagnostic Criteria, New Predictors of Outcome, and Follow-Up Recommendations. *J Clin Oncol* 2010;28:690–697.
- ⁴⁶ Kyle RA, Durie BG, Rajkumar SV, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG

consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia* 2010;24:1121–1127.

- ⁴⁷ National Institute for Health and Care Excellence (2016) Myeloma: diagnosis and management. NICE guideline [NG35]
- ⁴⁸ Hjorth M, Kellquist L, Holmberg E, et al. Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I--a randomized study. Myeloma Group of Western Sweden. *Eur J Haematol* 1993;50:95–102.
- ⁴⁹ Barlogie B, van Rhee F, Shaughnessy JD Jr, et al. Seven-year median time to progression with thalidomide for smoldering myeloma: partial response identifies subset requiring earlier salvage therapy for symptomatic disease. *Blood* 2008;112:3122–3125.
- ⁵⁰ Musto P, Petrucci MT, Brinchen S, et al. A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma. *Cancer* 2008;113:1588–1595.
- ⁵¹ Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med* 2013;369:438–447.

Tables
Table 1. M-protein related disorders (other than AL amyloidosis) adapted ²¹

Disorder	Clinical features and diagnostic tests
Light chain deposition disease (LCDD)	Usually kappa light chain, presenting with albuminuria and nephrotic syndrome
POEMS syndrome	Majority IgG lambda Peripheral neuropathy Organomegaly (liver, spleen, lymphadenopathy) Skin changes (cherry angiomas, changes in texture and pigmentation, alterations in body hair) Endocrinopathy (pancreatic, adrenal, gonadal, parathyroid, pituitary) Ascites, pleural effusions, peripheral oedema Pappilodema Sclerotic bone lesions Thrombocytosis, polycythaemia, thrombotic diathesis Elevated circulating vascular endothelial growth factor
Acquired Fanconi syndrome	Tubular proteinuria, glycosuria, amino aciduria, acidosis, hypophosphatemia Renal failure, osteomalacia Almost all kappa light chain
Cryoglobulinaemia	Vasculitis, peripheral neuropathy, fatigue, renal failure, purpuric rashes, Raynaud's phenomenon, leg ulcers, acrocyanosis
Scleromyxoedema	Diffuse skin thickening, obstructive lung disease, pulmonary hypertension Usually IgG lambda
Schnitzler Syndrome	Chronic neutrophilic urticarial dermatosis Arthralgia, bone pain, lymph nodes, liver, spleen enlarged Usually IgM kappa
Xanthomatosis	Cutaneous xanthoma lesions (yellow papules) Usually IgG
Cold agglutinin disease	Haemolysis, Raynaud's phenomenon, acrocyanosis

Table 2: Definition of multiple myeloma, incorporating recent revisions⁶

Clonal bone marrow plasma cells **≥10% or biopsy-proven bony or extramedullary plasmacytoma*** and any one or more of the following myeloma defining events or any one or more of the following biomarkers of malignancy.

Myeloma defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder as follows:

- Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: **creatinine clearance <40 mL/min† or serum creatinine >177 μmol/L (>2 mg/dL)**
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal or a haemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, **CT, or PET-CT‡**

Biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage* ≥60%
- Involved:uninvolved serum free light chain ratio§ ≥100
- >1 focal lesions on MRI studies¶

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg/24h and/or **clonal bone marrow plasma cells 10–60%**
- Absence of myeloma defining events **including biomarkers of malignancy** or amyloidosis

‡PET-CT=1⁸F-fluorodeoxyglucose PET with CT.

*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

†Measured or estimated by validated equations.

‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.

¶ Each focal lesion must be 5mm or more in size

Table 3. New Definitions of organ damage⁶**Myeloma bone disease**

One of PET-CT, MRI or low-dose whole body CT (depending on local practice) to be used at diagnosis in suspected smouldering myeloma. The detection of one or more sites of osteolytic bone destruction (>5mm) on PET-CT or low-dose whole-body CT meets the criteria for multiple myeloma requiring treatment. Osteoporosis and vertebral compression fractures alone are no longer sufficient for a diagnosis of myeloma. This is to avoid over diagnosing many elderly people with MGUS and osteoporosis.

Definition of renal failure

The 2003 IMWG criteria used a fixed creatinine level (> 173umol/L) to define renal insufficiency. New recommendation is to use measured or estimated GFR of <40ml/min instead for CRAB criteria. Only renal failure caused by light chain cast nephropathy is regarded as a myeloma defining event. A renal biopsy may be needed to exclude other causes of renal failure.

Bone marrow plasmacytosis

Either clonal BMPC $\geq 10\%$ or biopsy proven plasmacytoma required for the diagnosis of MM.

Table 4. Risk models for MGUS, and for SMM

MGUS		
Model and risk factors	Number of factors	Progression risk
<u>Mayo Clinic Model [35]</u>		At 20 years
- non-IgG isotype	0	5%
- M-protein $\geq 15\text{g/L}$	1	21%
- abnormal SFLC ratio	2	37%
	3	58%
<u>PETHEMA model based on flow cytometry of bone marrow [338]</u>		At 5 years
	0	2%
- Abnormal phenotype (aberrant plasma cells)	1	10%
	2	46%
- DNA aneuploidy		
SMM		
<u>Mayo Clinic Model [26]</u>		At 5 years
- abnormal SFLC ratio (<0.125 or > 8)	1	25%
- BM PCs $\geq 10\%$	2	51%
- PP $\geq 30\text{g/L}$	3	76%
<u>PETHEMA model based on flow cytometry [40]</u>		At 5 years
- $\geq 95\%$ abnormal bone PC/total BMPC	0	4%
	1	46%
- Immunoparesis	2	72%

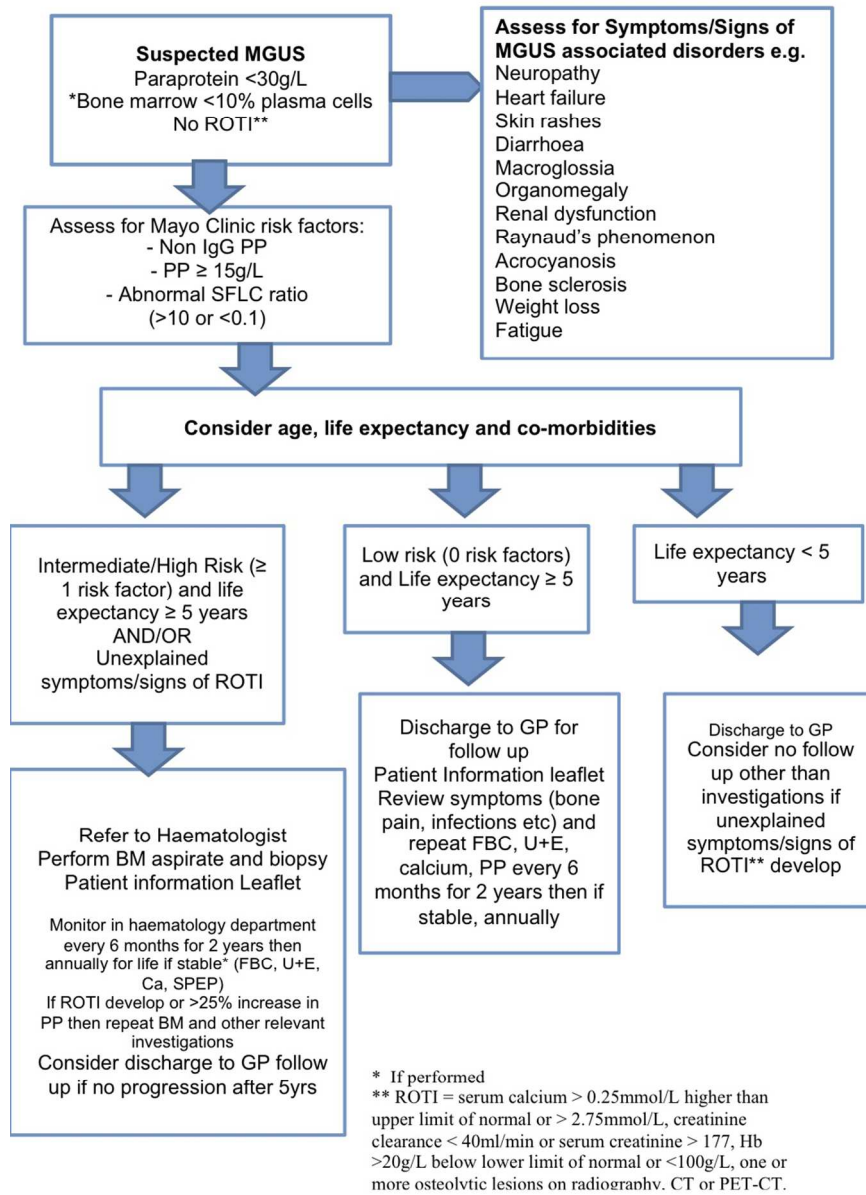
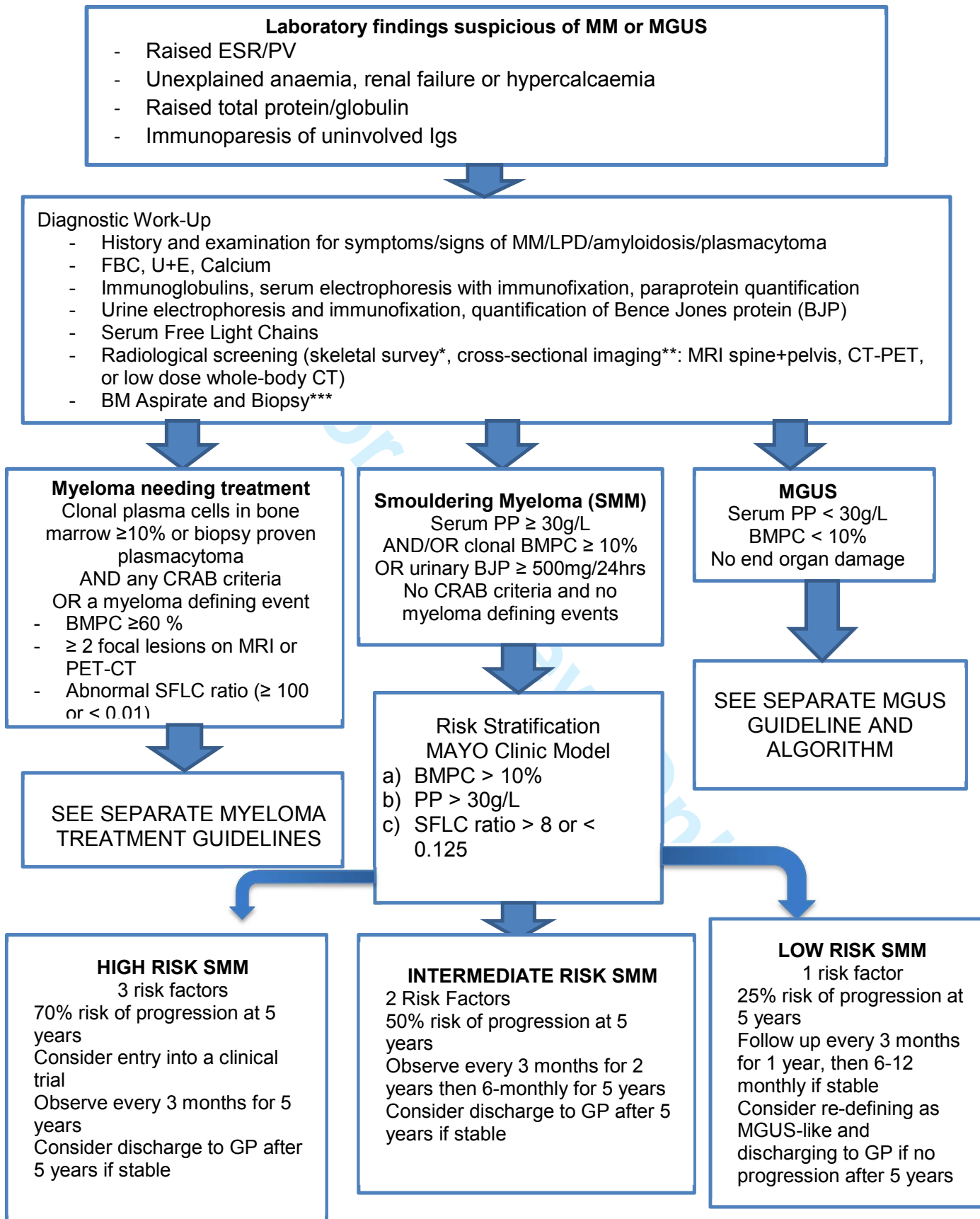


Figure 1. Algorithm for investigation and management of patients with suspected Monoclonal Gammopathy of Undetermined Significance (MGUS)

184x250mm (150 x 150 DPI)



* for high risk MGUS

** if pp>30 or LC ratio >8, choice of technique according to local practice

*** Required if non-IgG MGUS, pp $\geq 15\text{g/L}$