UK Myeloma Forum (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)

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1. Introduction

The objective of this guideline is to provide healthcare professionals with clear guidance for the effective clinical investigation of patients with newly detected M-proteins and the practical management of patients with monoclonal gammopathy of undetermined significance (MGUS). The guidance may not be appropriate to all patients and individual patient circumstances may dictate an alternative approach.

2. Methodology

The members of the joint guideline group of the UK Myeloma Forum (UKMF) and the Nordic Myeloma Study Group (NMSG) were selected to be representative of UK-based and Nordic based medical experts and patient representatives. MEDLINE and EMBASE were searched systematically for publications in English from 1950 to October 2008. The writing group produced the draft guideline, which was subsequently revised by consensus by the UK Myeloma Forum Executive, regional coordinators of the NMSG and members of the Haemato-Oncology Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was then reviewed by a sounding board of approximately 100 UK haematologists, the BCSH, the British Society for Haematology Committee and the comments incorporated where appropriate.

Criteria used to quote levels and grades of evidence where specified are as outlined in Appendix III of the Procedure for Guidelines Commissioned by the BCSH (http://www.bcshguidelines.com/process1.asp#appendix7). However, as these levels and grades of evidence usually relate to patient treatment that, by definition, is not required in these patients, levels and grades of evidence are not quoted for most of the recommendations made in this guideline. Clinical trials have provided very little evidence to inform these guidelines. Most of the recommendations which follow are based on the outcomes of large observational studies and evidence from expert committee reports and/or the clinical experiences of respected authorities and are therefore grade C, level IV.

3. Background

Monoclonal gammopathy of undetermined significance (MGUS) is a term originally coined by the Mayo Clinic group (Kyle, 1978) and is defined as the presence of a monoclonal protein in the serum or urine of an individual with no evidence of multiple myeloma, AL amyloidosis, Waldenström macroglobulinaemia (WM) or other related disorders. Monoclonal immunoglobulins (M-proteins or paraproteins) can be detected in the serum of about 1% of the population overall (Axelsson *et al*, 1966) and most will be classified as MGUS

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(reviewed in detail in Rajkumar *et al*, 2007 and Kyle & Rajkumar, 2006) following the exclusion of other conditions associated with monoclonal immunoglobulins.

M-proteins are frequently identified during investigation of unrelated symptoms or during health screening and their identification presents clinicians with the challenge of whom and how far to investigate. Clinicians need to be able to identify and treat promptly those patients with multiple myeloma, other lymphoproliferative disease and conditions in which the monoclonal immunoglobulin itself directly causes tissue damage, such as AL amyloidosis. It is also important to identify those patients at highest risk of progression to significant disease. Conversely, it is important to have a strategy to identify and manage patients with MGUS so as to avoid unnecessarily over-investigating patients with a low risk of current or future significant disease.

3.1. What is an M-protein?

An M-protein (also referred to as paraprotein or M-component) is a monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells in an amount that can be visualised by immunofixation of serum and/or urine. M-proteins can be whole (heavy and light chain) immunoglobulin (Ig) or just immunoglobulin free light chain (FLC).

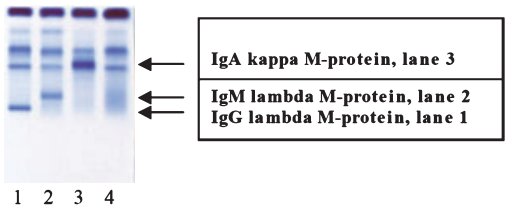
3.2. When should testing for M-proteins be carried out?

Serum protein electrophoresis (SPEP) should be performed if there is clinical suspicion of an M-protein related disorder or when the results of other tests raise the possibility of the presence of an M-protein. Abnormal test results include:

- raised erythrocyte sedimentation rate (ESR) or plasma viscosity;
- unexplained anaemia, hypercalcaemia or renal failure;
- raised total protein/globulin or immunoglobulins, particularly if one or more immunoglobulin classes (IgG, IgA, IgM) are reduced. It should be noted that raised levels of polyclonal immunoglobulins are commonly seen in disorders such as liver disease, infection, rheumatological and other autoimmune conditions;
- reduction of one or more immunoglobulin class (IgG, IgA and IgM) levels.

3.3. Identification and laboratory investigation of M-proteins

3.3.1. Laboratory methods. Identification of M-proteins is usually carried out by SPEP but some M-proteins are not visible by electrophoresis alone and so, when there is a high index of suspicion of B-cell malignancy, the more sensitive method of immunofixation should be requested. Figures 1 and 2 show examples of SPEP and immunofixation of samples from a normal individual and from a variety of patients.



Lane 1 shows an IgG lambda M-protein of 7 g/l

Lane 2 shows an IgM lambda M-protein of 8 g/l

Lane 3 shows an IgA kappa M-protein of 28 g/l

Lane 4 shows normal polyclonal immunoglobulins

Fig 1. Serum protein electrophoresis showing a range of different patient samples.

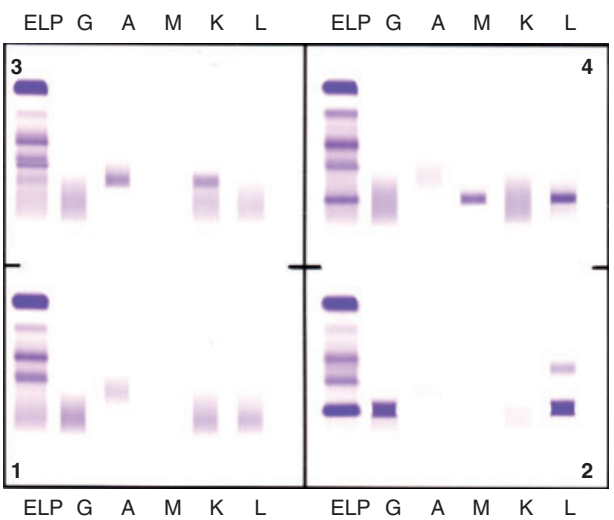


Fig 2. Four serum samples have been processed by immunofixation. In each of the four panels the same serum has migrated along six tracks, which have then been stained for protein (ELP) or for IgG (G), IgA (A) or IgM (M) heavy chains or kappa (K) or lambda (L) light chains. Panel 1 is normal serum with polyclonal immunoglobulins. Panel 2 is serum containing a high level of IgG lambda monoclonal immunoglobulin with monoclonal lambda free light chains and little polyclonal immunoglobulin; the patient had myeloma with renal failure. Panel 3 is serum containing a low concentration IgA kappa M-protein. Panel 4 is serum containing an IgM lambda M-protein.

Monoclonal serum FLCs are usually only detectable by immunofixation when removal of FLC from blood by glomerular filtration is compromised. The limit of immunofixation sensitivity is >10× normal serum FLC levels. Consequently, plasma cell dyscrasias secreting only FLC are usually not detectable by immunofixation of serum alone; urine must be assessed as well. FLC are detectable in urine only when their level in the glomerular filtrate exceeds renal tubular capacity to reabsorb them. Consequently, some plasma cell disorders secreting only FLC are still not detected even when urine is examined as well as serum.

The introduction of methods to measure low levels of FLC in serum (SFLC) (Bradwell *et al*, 2003) has confirmed that both normal and neoplastic plasma cells secrete FLC as well as whole immunoglobulin and that an abnormal kappa/lambda SFLC ratio can be used as a surrogate marker for the secretion of monoclonal FLC. This SFLC ratio is often abnormal even when the renal threshold for reabsorption of FLC has not been exceeded and so no monoclonal FLC can be detected by immunofixation of urine. Thus 'non-secretory' myeloma and some cases of oligosecretory myeloma or AL amyloidosis may not be detected unless SFLC levels are measured. However abnormal SFLC ratios also occur when there is dysregulation of immunoglobulin production e.g. in patients with systemic lupus erythematosus (SLE) or human immunodeficiency virus (HIV) infection and during immune reconstitution following stem cell transplantation. It should also be noted that polyclonal FLC may be detected in urine when their production is greatly increased (usually in association with hypergammaglobulinaemia) and/or renal reabsorption is reduced by renal tubular damage e.g. in SLE. Polyclonal FLC in urine are not indicative of plasma cell dyscrasia.

When SPEP demonstrates a narrow band in the beta or gamma region, immunofixation should always be performed to confirm an M-protein and identify its class and light chain type. Further investigation should include quantification of the M-protein. Urine should be examined for secretion of monoclonal FLC by urinary protein electrophoresis, immunofixation and quantification of monoclonal FLC. Alternatively, if no urine is available, serum FLC levels can be measured and urine only requested for immunofixation if the serum FLC ratio is abnormal. For details of recommended laboratory methods and references, see Appendix I.

Recommendations

1 **Screening normal populations for M-proteins for clinical purposes is not recommended.**
2 **Electrophoresis of serum and urine should always be requested where there is clinical suspicion of plasma cell dyscrasia/B-cell malignancy. If the clinical suspicion of an underlying plasma cell dyscrasia is strong despite the absence of a detectable M-protein, then immunofixation should be performed. SFLC measurement is required to detect non-secretory myeloma and some cases of AL amyloidosis and light chain only myeloma when urine is not available.**
3 **Electrophoresis of serum and urine should be requested in all patients with a persistent elevation of ESR above 30 mm/h, anaemia, renal failure or hypercalcaemia with no other obvious explanation.**
4 **The laboratory should perform serum protein electrophoresis when there are abnormally high or low serum levels of total immunoglobulin or individual Ig classes. In cases with low serum immunoglobulin levels and no detectable serum M-protein, the laboratory should measure SFLC levels or request urine for immunofixation.**

4. Epidemiology

4.1. Prevalence of M-proteins in normal populations and hospitalised patients

The frequency of detection of M-proteins depends on the extent to which SPEP is used in the investigation of patients, the sensitivity of the SPEP methods and the extent to which laboratories direct or suggest further investigations. There are a large number of population-based studies in Europe and North America describing the prevalence of M-proteins in the general population and in patients in community/general practise and in hospitals. The incidence of M-proteins in these studies is generally similar but some variation does occur due to differences in the composition of the patient population and also in the frequency of performing SPEP.

In a health survey in a county in Sweden, which included 79% of people above 25 years of age, 0·9% of the population were found to have an M-protein detected by paper protein electrophoresis (Axelsson *et al*, 1966); this percentage was 1·1% in a French study of 30 279 members of a health care programme (Saleun *et al*, 1982). Later reports have used the more sensitive technique of agarose gel electrophoresis. In screening a normal Minnesota population of 21 463 people aged over 50 years, MGUS was found in 694 individuals (3·2%) (Kyle *et al*, 2006). Of these, 68·9% had an IgG M-protein, 17·2% IgM and 10·8% IgA. The light chain was kappa in 62% and lambda in 38% and monoclonal light chains were detected in the urine in 21·5% (Kyle *et al*, 2006).

Similar figures are obtained in hospitalised patients. M-proteins were found in 0·7% and 1·2% of hospitalised patients screened in studies in Italy and North America respectively (Malacrida *et al*, 1987; Vladutiu, 1987).

4.2. Distribution of M-proteins by age and race

Monoclonal gammopathy of undetermined significance is uncommon below the age of 50 years and the prevalence increases with advancing age (Axelsson *et al*, 1966; Fine *et al*, 1972; Saleun *et al*, 1982; Kyle *et al*, 2006). In the Minnesota population study, MGUS was present in 1–2% of people in their sixth decade, 2–4% in their seventh decade, rising to 4–5% in their eighth decade (Kyle *et al*, 2006). In one study of 111 residents of a retirement home in Carolina, monoclonal bands were found in 14% over the age of 90 years (Crawford *et al*, 1987). Thus, the majority of patients being investigated for a newly detected M-protein will be elderly.

There are racial differences in the prevalence of M-proteins, with black people more than twice as likely as white people to

have an M-protein, as demonstrated in a community-based study in North Carolina of 1732 subjects over 70 years of age (Cohen *et al*, 1998).

4.3. Distribution by diagnosis of newly diagnosed M-proteins

Several studies have reported the percentages of different diagnoses identified in patients presenting with an M-protein in studies in Sweden, Italy and America. Differences between the studies are likely to reflect the different referral population of secondary and tertiary centres.

In 930 cases of newly detected M-proteins among residents of the City of Malmö (1975–89) the distribution of subsequent diagnoses was: MGUS 72%, macroglobulinaemia 2%, myeloma 19%, other lymphoproliferative disease/disorder (LPD) 6%, AL-amyloidosis 1% (I. Turesson, Department of Medicine, Malmö University Hospital, Malmö, Sweden, personal communication). In a study of 375 newly detected M-proteins in a general district hospital in Italy, 69·6% were classified as MGUS, 26·6% as myeloma and 4·8% as other lympho-proliferative diseases (Malacrida *et al*, 1987). A study from the Mayo clinic, a tertiary referral centre, of 1510 patients with new M-proteins in 2005 reported 51% to be MGUS, 18% myeloma, 6% smouldering myeloma, 1% plasmacytoma, 3% WM, 4% other LPDs, 11% AL-amyloidosis and 6% other diseases (Kyle & Rajkumar, 2006). These results are summarised in Table I.

A serum M-protein is detectable by electrophoresis in approximately 80% of patients with myeloma but in only a small proportion of patients with, for example, low grade B-cell non-Hodgkin lymphoma (NHL). M-proteins of IgM subclass are more commonly associated with WM and lymphoplasmacytoid lymphoma than myeloma.

5. Diagnostic criteria and differential diagnosis of M-proteins

Monoclonal gammopathies include the following conditions:

- MGUS
- Multiple myeloma
- Solitary plasmacytoma (skeletal or extra-medullary)
- AL amyloidosis
- WM
- Low grade B-lineage non-Hodgkin's lymphoma and other B-lineage LPD
- Other M-protein related disorders.

It is clearly very important not to miss any of the clinically significant diseases associated with an M-protein that require treatment. However, the majority of individuals found to have an M-protein will have MGUS (see *Epidemiology* section above).

5.1. Differentiation of MGUS from myeloma and other plasma cell disorders

An International Working Group has recently recommended a new classification of monoclonal gammopathies, based on the level/concentration of serum M-protein, percentage of bone marrow plasma cells and the presence or absence of myeloma-related organ or tissue impairment (ROTI) (The International Myeloma Working Group, 2003).

The classification defines criteria for MGUS, asymptomatic myeloma and symptomatic myeloma (see Table II). To exclude myeloma, the serum M-protein concentration should be <30 g/l, plasma cells in the marrow <10% and there must be no evidence of myeloma-ROTI (see Table II).

The distinction between symptomatic and asymptomatic myeloma depends on the presence or absence of myeloma-ROTI and the relevant criteria are shown in Table III.

Low level M-proteins are common and will be most commonly accounted for by MGUS but it is very important to recognise that within this group there will be some patients with clinically important disease, such as AL amyloidosis, light chain myeloma or solitary plasmacytoma. The investigation and diagnosis of AL amyloidosis and of solitary plasmacytoma have been reviewed in recent UKMF/BCSH guidelines (Bird *et al*, 2004; Soutar *et al*, 2004).

5.2. Differentiation of MGUS from M-proteins associated with Waldenström macroglobulinaemia

Waldenström macroglobulinaemia is characterised by bone marrow infiltration by lymphoplasmacytoid lymphoma and IgM monoclonal gammopathy (reviewed by Fonseca & Hayman, 2007). The presenting features are heterogeneous and are caused both by infiltration of the neoplastic cells in the bone marrow and peripheral lymphoid tissues and by biological effects of the M-protein. These latter include hyperviscosity,

Table I. Summary of subsequent diagnosis in series of patients.

	Population studied	MGUS	Myeloma	Other LPD	WM	AL amyloidosis	Others
Malmo (1975–89) (I. Turesson, personal communication)	Patients in primary and secondary care	72	19	6	2	1	
Italy (Malacrida *et al*, 1987)	All patients in large DGH	69·6	26·6	4·8			
Mayo clinic (Kyle & Rajkumar, 2006)	Tertiary referral population	51	24	4	3	11	6

MGUS, monoclonal gammopathy of undetermined significance; LPD, lymphoprolifreative disease/disorder; WM, Waldenström macroglobulinaemia.

Table II. Diagnostic criteria for MGUS, asymptomatic myeloma and symptomatic myeloma.

MGUS	Asymptomatic myeloma	Symptomatic myeloma*
M-protein in serum <30 g/l	M-protein in serum >30 g/l	M-protein in serum and or urine†
Bone marrow clonal plasma cells <10% and low level of plasma cell infiltration in a trephine biopsy (if done)	*and/or* Bone marrow clonal plasma cells >10%	Bone marrow (clonal) plasma cells
No myeloma-related organ or tissue impairment (including bone lesions or symptoms)	No myeloma-related organ or tissue impairment (including bone lesions or symptoms)	Myeloma-related organ or tissue impairment (including bone lesions or symptoms)
No evidence of other B-cell LPD or light chain associated amyloidosis or other light chain, heavy chain or immunoglobulin-associated tissue damage‡		

Adapted from International Myeloma Working Group. (2003) Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *British Journal of Haematology*, **121**, 749–757, with permission of Wiley-Blackwell.
*Patients without symptoms but with significant myeloma-ROTI are grouped with symptomatic myeloma because of the need for treatment.
†No specific level required for diagnosis. A small percentage of patients have no detectable M-protein in serum or urine but do have myeloma-related organ or tissue impairment (ROTI) and increased bone marrow plasma cells (non-secretory myeloma).
‡AL amyloid and the IgM paraprotein-related neurological syndromes would be instances of monoclonal gammopathy associated with specific syndromes.

Table III. Myeloma-related organ or tissue impairment (ROTI)*.

Calcium levels increased: corrected serum calcium >0·25 mmol/l above the upper limit of normal or >2·75 mmol/l
Renal insufficiency attributable to myeloma
Anaemia: haemoglobin 20 g/l below the lower limit of normal or haemoglobin <100 g/l
Bone lesions: lytic lesions or osteoporosis with compression fractures: (MRI or CT may clarify)
Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

Adapted from International Myeloma Working Group (2003) Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *British Journal of Haematology*, **121**, 749–757, with permission of Wiley-Blackwell.
*Where there is uncertainty as to whether or not organ or tissue impairment is attributable to myeloma the percentage of bone marrow plasma cells should be >30%.

Table IV. Diagnostic criteria for the diagnosis of WM.

IgM monoclonal gammopathy of any concentration
Bone marrow infiltration by small lymphocytes, plasmacytoid cells and plasma cells
Diffuse, interstitial or nodular pattern of bone marrow infiltration
Surface Ig^+ $CD5^-$ $CD10^-$ $CD19^+$ $CD20^+$ $CD23^-$ immunophenotype

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cryoglobulinaemia, peripheral neuropathy, cold agglutinin disease and bleeding diathesis. Diagnostic criteria and a description of the clinical features, cytomorphology, pattern of bone marrow infiltration and immunophenotype have been published and are summarised in Table IV (Owen *et al*, 2003).

5.3. MGUS and other LPDs

Numerous reports have made the association between a monoclonal gammopathy and B-lineage LPDs (Azar *et al*, 1957; Kyle *et al*, 1960; Alexanian, 1975; Kyle & Gahrton, 1987; Lin *et al*, 2005) including chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), marginal zone lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma and angioimmunoblastic T-cell lymphoma. The M-protein in these disorders is usually of the IgM class.

The serum M-protein level is not a reliable discriminator in differential diagnosis and there is no apparent difference in clinico-pathological features and clinical outcome in CLL/SLL between M-protein-associated cases and those without an M-protein (Yin *et al*, 2005).

6. M-proteins and associated disorders

There are a number of recognised associations between the presence of an M-protein and other conditions and in some of these a causal relationship has been established. The M-protein secreted in any monoclonal gammopathy can sometimes be damaging and cause serious symptoms. Aggregation and deposition of monoclonal immunoglobulins or monoclonal light chains with subsequent organ damage is the cardinal feature of AL-amyloidosis, light chain deposition disease, adult Fanconi syndrome and type I cryoglobulinaemia. On the other hand, it is the antibody activity of the M-protein that leads to organ damage in monoclonal cold agglutinin disease, mixed cryoglobulinaemia and M-protein-related neuropathy (Merlini

Table V. M-protein-related disorders.

Diseases caused by M-protein aggregation
Light chain-cast nephropathy
AL amyloidosis
Light chain-deposition disease
Crystal-storing histiocytosis: adult Fanconi syndrome
Cryoglobulinemia type I
Diseases caused by M-protein antibody activity
Mixed cryoglobulinemia type II
Monoclonal cold agglutinins
Polyneuropathies

This research was originally published in *Blood*. Merlini G, Stone MJ. Dangerous small B-cell clones. *Blood*. 2006; 108: 2520–2530. © American Society of Hematology.

& Stone, 2006). All these conditions may be seen within the setting of myeloma, WM and other LPD but also in association with M-protein-producing clones that behave biologically as MGUS. For these latter cases the term M-protein-related disorders has been introduced (Table V) (Merlini & Stone, 2006). As these diseases are uncommon and the clinical manifestations protean, the diagnosis is often delayed. The finding of an M-protein may be an important clue to establishing a correct diagnosis and instigating early treatment. It is however beyond the scope of these guidelines to give detailed recommendations on the diagnosis and management of these disorders.

M-proteins and neurological disorders

Polyneuropathies (PNs) form an important group of clinical disorders that are frequent in patients with a monoclonal gammopathy (Dispenzieri & Kyle, 2005). Their importance stems from the potentially damaging clinical course that may occur, raising the need for therapeutic intervention. They are more common in the presence of an IgM gammopathy than either IgA or IgG (Nobile-Orazio *et al*, 1992), and in some cases, anti-neuronal antibody activity of the M-protein against carbohydrate antigenic targets has been identified and associated with distinct clinical presentations. However, in many cases, the association is less clear; patients with IgM gammopathy may present with typical sensory symptoms, such as parasthesiae, dysasthesiae or neuropathic pain associated with ataxia and gait disturbance, but on investigation, may not possess a specific antibody to confirm the causal association between the monoclonal gammopathy and the PN. It is thus important to consider the possibility of other PNs, such as chronic inflammatory demyelinating polyneuropathy (CIDP), paraneoplastic, metabolic and toxic neuropathies, which may co-exist with a monoclonal protein, and arrange for appropriate management (Hughes *et al*, 2006). Guidelines for the management of M-protein-associated neuropathies have recently been published (Hadden *et al*, 2006).

M-proteins and other diseases

An increased prevalence of M-proteins has also been reported in various systemic conditions without clear evidence for a pathogenetic role of the M-protein. Owing to its increasing prevalence in older age groups, MGUS frequently co-exists with other conditions, many of which also have increasing prevalence with age and the finding of an M-protein is only coincidental. In the following section some of these associations will be addressed and recommendations made on how to manage MGUS within the stated clinical context.

Monoclonal gammopathy of undetermined significance has also been described in the setting of numerous other clinical situations. MGUS has been reported in patients with connective tissue disorders such as rheumatoid arthritis (RA) (Hardiman *et al*, 1994), SLE, scleroderma, polymyositis and ankylosing spondylitis. A number of skin disorders have been described in association with plasma cell dyscrasias and neoplasms, (Daoud *et al*, 1999). The prevalence of monoclonal gammopathies in patients with hepatitis C virus (HCV)-related chronic liver disease is striking, may be accompanied by mixed cryoglobulinaemia (Idilman *et al*, 2004) and has been reported to be more prevalent in the context of HIV infection than would be expected in HIV-negative individuals (Amara *et al*, 2006). Infection by *Helicobacter pylori* has been linked to MGUS and eradication of the former has been associated with resolution of the latter in a proportion of cases (Malik *et al*, 2002). MGUS is frequent after autologous stem cell transplantation (Zent *et al*, 1998) and a higher prevalence of MGUS has been noted also following solid organ transplantation (Radl *et al*, 1985; Renoult *et al*, 1988; Caforio *et al*, 2001). Haematological associations of MGUS include acquired von Willebrand disease, lupus anticoagulant, pernicious anaemia, refractory anaemia, pure red cell aplasia, polycythaemia vera, myelofibrosis, congenital dyserythropoietic anaemia type III and Gaucher disease (Kyle & Rajkumar, 2006). There is little evidence that the occurrence of an M-protein in these disorders influences the natural history or treatment outcome of the disease. A detailed review of M-protein-associated disorders has been published (Kyle & Rajkumar, 2006).

Recommendations

1 **The finding of an M-protein in any patient with polyneuropathy, signs of systemic vasculitis or evidence of cardiac, renal or hepatic abnormalities and no other explanation should alert the physician to look for an M-protein-related disorder. For the diagnosis and treatment of these disorders the reader is referred to specific clinical practise guidelines.**
2 **There is no evidence that MGUS in patients with RA and other connective disorders, dermatological disorders, infections, primary hyperparathyroidism, or following autologous or allogeneic transplantation should be managed differently to patients with isolated MGUS.**

7. Clinical course of MGUS

7.1. Characteristics of MGUS

The M-protein level is usually low in MGUS. In 1065 consecutive cases of MGUS diagnosed in inhabitants of the City of Malmö, Sweden the level was <10 g/l in 754 (70·8%) (I. Turesson, Department of Medicine, Malmö University Hospital, Malmö, Sweden, personal communication) (Figure 3 and Table VI). This is in contrast to 329 and 109 consecutive cases of IgG and IgA myeloma among inhabitants of Malmo in which the proportion of cases with M-protein level <10 g/l was 6·4% and 11%, respectively (Figure 4 and Table VII).

Of 2836 patients entered into UK Medical Research Council myeloma trials, one-third of IgG and IgA M-proteins were <30 g/l at diagnosis 5% were <10 g/l (Drayson *et al*, 2006 and M. Drayson, Division of Immunity and Infection, University of Birmingham, personal communication). Nineteen per cent of all patients in these trials had no serum M-protein.

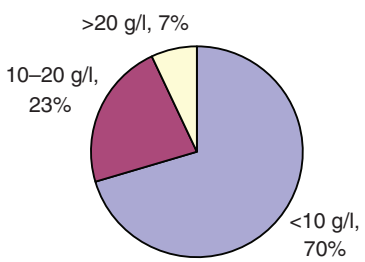

Fig 3. M-protein concentration in individuals with MGUS (I. Turesson, personal communication).

Table VI. M-protein concentration in individuals with MGUS by immunoglobulin class (I. Turesson, personal communication).

Ig class	<5 g/l (%)	5–10 g/l (%)	10–20 g/l (%)	>20 g/l (%)	Total
IgG	46·6	26·7	20·7	6·0	697
IgA	14·0	56·1	24·0	5·8	171
IgM	25·9	36·7	28·9	8·6	197

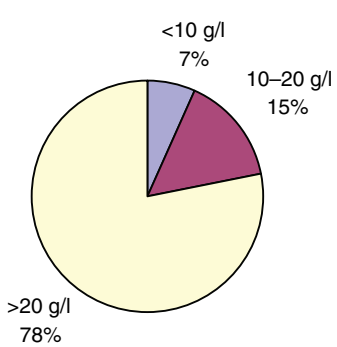

Fig 4. M-protein concentration in myeloma patients (I. Turesson, personal communication).

Table VII. M-protein concentration in myeloma patients by immunoglobulin class (I. Turesson, personal communication).

	Concentration				
Ig class	<5 g/l (%)	5–10 g/l (%)	10–20 g/l (%)	>20 g/l (%)	Number
IgG	2·4	4·0	11·5	82·1	329
IgA	4·6	6·4	18·3	70·7	109

Immune paresis. Between 30% and 40% of patients with MGUS have a reduction in polyclonal immunoglobulins (Blade *et al*, 1992; Baldini *et al*, 1996; Kyle *et al*, 2002) whereas a reduction of one or more polyclonal immunoglobulins is seen in more than 90% of patients with myeloma (Kyle *et al*, 2003).

Presence of urinary Bence-Jones protein (BJP). In a study of 1384 individuals diagnosed with MGUS in south-eastern Minnesota between 1960 and 1994, monoclonal light chain was detected in the urine in 31% patients (10% lambda; 21% kappa) by immunofixation (Kyle *et al*, 2002). Sixty-nine per cent were negative for monoclonal light chain and only 17% had a urinary monoclonal protein value >150 mg/24 h.

7.2. Cytogenetic abnormalities in MGUS

Because of the low proliferation rate of MGUS, plasma cells with abnormal karyotypes are rarely detected in MGUS by conventional cytogenetic techniques. However the introduction of fluorescence *in situ* hybridization (FISH), a technique not dependent upon the presence of dividing cells, has demonstrated that cytogenetic abnormalities typical in multiple myeloma can also be found in a high proportion of patients with MGUS. This applies to translocations involving the IgH locus (*IGH@*, 14q32), to other structural changes and also to the numerical changes which usually result in hyperdiploidy. Hence there are no unequivocal genetic markers that distinguish MGUS from myeloma.

It has been suggested that 14q translocations and monosomy 13 observed in MGUS delineate a multi-step process for the oncogenesis of multiple myeloma. Bone marrow plasma cells from myeloma patients and other monoclonal gammopathies display an aberrant phenotype by flow cytometry and restricted immunoglobulin light chain expression at the cytoplasmic level. Based on these features, unequivocal identification and enumeration of aberrant and normal plasma cells co-existing in a bone marrow sample can be performed. There is correlation between neoplastic plasma cell phenotype and cytogenetic abnormalities but it is not possible to distinguish between myeloma and MGUS on the basis of phenotype.

8. The prognosis of MGUS and risk factors for malignant transformation

Monoclonal gammopathy of undetermined significance is a clinical diagnosis based on the exclusion of B cell/plasma cell malignancy and made after finding an M-protein in blood and/or urine. The decision on which patients should be referred and how far to investigate a patient who has been found to have an M-protein also requires a knowledge of the evolution of MGUS (see below).

8.1. The prognosis of MGUS

People with MGUS have an increased risk of developing malignant disorders, most often multiple myeloma from IgG and IgA MGUS, and other malignant LPDs from IgM MGUS. A large study from the Mayo Clinic of 1384 patients with MGUS who resided in SE Minnesota detected 115 cases of malignant transformation during 11 009 person-years of follow-up (median 15·4 years) (Kyle *et al*, 2002). The cumulative risk of progression to myeloma or other LPDs was 10% at 10 years; 21% at 20 years and 26% at 25 years. The overall risk of progression was 1% per year and the risk remained even after 25 years or more. Because of the high median age at detection of the M-protein and the existence of diseases not associated with the M-protein, the risk that a patient with MGUS in his/her lifetime will develop myeloma or related disorders is considerably lower (Rajkumar *et al*, 2005).

Another population-based study of 1324 Danish patients with MGUS found similar risks of malignant transformation, with 107 observed cases versus 6·0 expected yielding a standardised incidence ratio of 17·9 (95% confidence interval, 14·7–21·7) (Gregersen *et al*, 2001a).

The few studies that have compared the survival of MGUS patients with the general population have indicated a reduced life expectancy for MGUS. (Kyle *et al*, 2004; Gregersen *et al*, 2001b; Van de Poel *et al*, 1995). Although malignant transformation is an important cause of death in MGUS it only explained 20% of an excess mortality in a Danish cohort of MGUS patients (Fig 5, Gregersen *et al*, 2001b). In reality, given the limited life expectancy in this elderly population, a greater proportion of patients will die from causes other than transformation.

The cumulative risks of malignant transformation in the two studies were, in general, lower than the risks reported from studies of MGUS patients from haematological centres (Giraldo *et al*, 1991; Blade *et al*, 1992; Van de Poel *et al*, 1995; Baldini *et al*, 1996; Pasqualetti *et al*, 1997; Cesana *et al*, 2002). The difference in risk between studies is most likely to reflect differences in referral patterns.

Patients with MGUS are at increased risk of certain other clinical events other than malignant transformation. Recent published studies found lower bone mineral density measurements in MGUS patients than in patients without MGUS (Pepe *et al*, 2006; Dizdar *et al*, 2008). This might explain an increased risk of fractures in patients with MGUS (Melton *et al*, 2004; Gregersen *et al*, 2006). In addition, two uncontrolled studies have indicated that the risk of venous thromboembolism is increased in MGUS (Sallah *et al*, 2004; Srkalovic *et al*, 2004). The clinical implications of these findings are yet to be clarified in terms of the risk-benefit of therapeutic intervention.

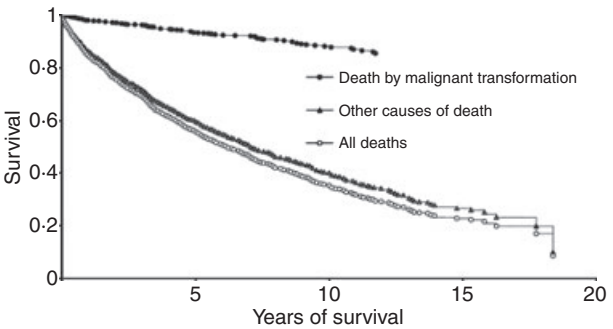

Fig 5. The probability of survival in a cohort of 1324 Danish patients with monoclonal gammopathy of undetermined significance. The probability of survival in the entire cohort, the subgroup of patients dying of malignant transformation and the subgroup of patients dying of other causes (Reproduced from Gregersen, H., Ibsen, J.S., Mellemkjær, L., Dahlerup, J.F., Olsen, J.H. & Sørensen, H.T. (2001b) Mortality and causes of death in patients with monoclonal gammopathy of undetermined significance. *British Journal of Haematology*, **112**, 353–357. With permission of Wiley-Blackwell.).

8.2. Risk factors for malignant transformation of MGUS

Risk factors for transformation of MGUS to malignant conditions have been addressed in several studies. A major shortcoming of most of these studies has been their relative small size and the inclusion of patients who today would be classified as asymptomatic multiple myeloma. The data are conflicting but the initial concentration of M-protein and type of M-protein are consistent risk factors for progression.

8.2.1. Type of M-protein. In the Mayo Clinic study, M-proteins of IgA and IgM class were associated with an increased risk of progression (Kyle *et al*, 2002). The higher risk of non-IgG MGUS was also found in an Italian study (Cesana *et al*, 2002). Other studies have confirmed that IgA MGUS carries a higher risk of transformation than the other types of MGUS (Blade *et al*, 1992; Gregersen *et al*, 2001a; Rosiñol *et al*, 2007).

8.2.2. Level of M-protein. The Mayo Clinic study also found a strong association between the level of M-protein and risk of progression (Kyle *et al*, 2002) – see Table VIII.

The impact of initial M-protein concentration on the risk of malignant transformation has been confirmed in a number of other studies (Van de Poel *et al*, 1995; Baldini *et al*, 1996;

Table VIII. Association between the level of M-protein and risk of progression at 20 years.

M-protein level (g/l)	Risk of progression (%)
<5	14
<10	16
<15	25
<20	41
<25	49
<30	64

Gregersen *et al*, 2001a; Van De Donk *et al*, 2001; Rosiñol *et al*, 2007).

8.2.3. Other factors associated with risk of progression. Other studies have demonstrated that the level of bone marrow plasmacytosis is correlated with an increased risk of progression (Van De Donk *et al*, 2001; Baldini *et al*, 1996; Cesana *et al*, 2002). Patients with 6–9% of bone marrow plasma cells had twice the risk of those with 0–5% bone marrow plasma cells (Cesana *et al*, 2002).

A number of other variables have been shown to be predictors of malignant transformation in single studies but the results need confirmation in other studies. These include the presence of circulating peripheral blood plasma cells (Kumar *et al*, 2005) and increased bone marrow angiogenesis (Rajkumar *et al*, 2002). The proportion of phenotypically aberrant plasma cells detected by multi-parametric flow cytometry is also considered a possible risk factor for malignant transformation (Pérez-Persona *et al*, 2007).

Although these findings are unlikely to translate into routine clinical practise as they rely on repeated marrow sampling, or on specialised techniques, they could be useful to predict subgroups in which preventive strategies are justified.

8.2.4. The significance of an abnormal serum free kappa: lambda light chain ratio. The levels of free light chains in serum samples of 1148 of 1384 MGUS patients in the SE Minnesota study were analysed (Rajkumar *et al*, 2005). An abnormal ratio of kappa and lambda light chain levels was detected in 379 (33%) of the patients. At a median follow-up of 15 years malignant transformation occurred in 87 patients (7·6%). The risk of progression in patients with an abnormal free light chain ratio was significantly higher than in patients with a normal ratio (hazard ratio, 3·5; 95% confidence interval, 2·3–5·5) and was independent of the size and type of serum M-protein.

The authors proposed a risk-stratification model based on concentration of the serum M-protein, the type of immunoglobulin and the presence of an abnormal free light chain ratio (Table IX). Patients with risk factors consisting of an abnormal serum free light chain ratio, non-IgG MGUS and an elevated serum M-protein value (≥15 g/l) had a risk of malignant progression at 20 years of 58%, compared with 37% with any two risk factors present, 21% with one risk factor present, and 5% when none of the risk factors was present.

This risk-stratification model may prove very useful in identifying MGUS patients with a high risk of progression as candidates for closer supervision and possible testing of preventive strategies. On the other hand, it might also prove useful in identifying patients with a very low risk of malignant transformation and no need for follow-up. However, these findings need to be confirmed by other studies before this model can be recommended for all patients.

8.2.5. Factors not associated with risk of progression. Importantly, variables such as the presence of Bence-Jones proteinuria, immuno-suppression, age and sex have not been found to have predictive value (Kyle *et al*, 2006). In addition, there are no cytogenetic factors that have been found to have prognostic value with regard to progression of MGUS to myeloma. Conventional cytogenetic analysis is not useful in predicting progression of MGUS to myeloma as abnormal karyotypes are rarely seen in MGUS because of the low percentage of plasma cells and low proliferative rate. Similar cytogenetic changes are seen in both MGUS and myeloma when FISH is used (Avet-Loiseau *et al*, 1999; Fonseca *et al*, 2002). The presence of particular abnormalities does not have predictive value and its routine use is not recommended.

Table IX. Proposed risk stratification model.

Risk group	No. patients	Relative risk 95% CI	20 year risk of progression %	20 year risk accounting for death %
Low risk (serum M-protein <15 g/l, IgG subtype, normal FLC ratio (normal range 0·26–0·65)	449	1	5	2
Low-intermediate risk (any one factor abnormal)	420	5·4	21	10
High-intermediate risk (any two factors abnormal)	226	10·1	37	18
High risk (all three factors abnormal)	53	20·8	58	27

This research was originally published in *Blood*. Rajkumar, S.V., Kyle, R.A., Therneau, T.M., Melton, L.J. 3rd, Bradwell, A.R., Clark, R.J., Larson, D.R., Plevak, M.F., Dispenzieri, A. & Katzmann, J.A. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood*. 2005; 106: 812–817. © American Society of Hematology.

9. Recommendations for the investigation of M-proteins and the management of patients with MGUS

9.1. Investigation of a patient with a newly diagnosed M-protein and referral guidelines

The majority of patients in whom an M-protein is detected will initially be under the care of a general practitioner or clinician other than a haematologist. The initial evaluation following the detection of an M-protein (before referral to a haematologist) requires the following:

a) Definition of the immunoglobulin class of the M-protein. This may direct future investigations. Myeloma is associated with M-proteins of IgG and IgA type, rarely IgD or IgE. IgM M-proteins are more commonly associated with LPDs, such as WM or low grade lymphoma.

b) Detailed history and examination. This should focus on the possibility that the patient has a plasma cell or lymphoproliferative malignant disorder. Symptoms and signs and test results commonly associated with myeloma, lymphoma or AL amyloid are shown in Table X and must be actively looked for: the finding of an M-protein may be associated with his/her presenting symptoms, or have no relevance to them.

The combination of an M-protein (any concentration) and the presence of any of the signs described above or an M-protein >30 g/l should lead to immediate referral to a haematologist.

A low concentration of M-protein makes MGUS more likely, whereas a high concentration is more commonly associated with myeloma or WM. However it is essential to be aware of the fact that AL amyloidosis is commonly associated with a low level M-protein and that myeloma can also occur with low levels of M-proteins. It is for this reason that it is imperative that symptoms and signs commonly associated with myeloma and amyloid should be actively looked for in patients with M-proteins at any level. Both myeloma and amyloid are commonly missed diagnoses (Soutar *et al*, 2004 and Smith *et al*, 2006).

Table X. Symptoms and signs and test results commonly associated with myeloma, lymphoma or AL amyloidosis.

Myeloma	Lymphoma/LPD	AL amyloidosis
Hypercalcaemia	Lymphadenopathy	Macroglossia
Renal failure	Hepatosplenomegaly	Unexplained heart failure
Anaemia	Hyperviscosity (especially if IgM) M-protein	Peripheral neuropathy
Bone pain/lesions	Pancytopenia	Carpal tunnel syndrome
Hyperviscosity	Symptoms e.g. night sweats, fever, weight loss	Nephrotic syndrome

c) Further investigations. All patients in whom an M-protein has been found should undergo routine blood and urine testing as follows:

- serum immunoglobulin levels;
- spot urine for urinary protein excretion and urinary protein electrophoresis;
- full blood count;
- serum creatinine;
- urea and electrolytes;
- serum calcium.

9.2. Guidelines for referral to a Haematology Consultant/ Specialist

The following recommendations aim to assist clinicians in how they should respond once an M-protein has been found. It is to be noted that, although specific levels of M-protein have been suggested to trigger referral or continued monitoring, the risk of transformation is related to the concentration and type of the M-protein and, for any given individual, to the numbers of years they will live with MGUS. Thus, an individual with an IgG M-protein of 14 g/l is at significantly greater risk of progression than a person with an IgG M-protein level of 2 g/l. Similarly, the risk of progression for a person with any level of M-protein is greater if that individual is aged 40 or 50 than one whose actuarial life expectancy may only be perhaps 2–3 years. IgA and IgM M-proteins are also associated with a greater risk of progression. Thus, all patients should be assessed individually and younger patients with higher levels of M-proteins require closer follow up than the very elderly with very low levels of M-proteins.

Recommendations

The following groups of patients should be referred to a Haematology Specialist for further investigation:

- **Those**
  - **with symptoms or physical signs suggestive of underlying myeloma, other LPD or AL amyloidosis (see Table X);**
  - **without symptoms but with unexplained incidental abnormal investigation results (laboratory or imaging) e.g. anaemia, renal impairment, hypercalcaemia, lytic lesions or osteoporosis on X-rays.**
- **Those with**
  - **significant Bence-Jones proteinuria (e.g. >500 mg/l);**
  - **IgD or E M-proteins irrespective of concentration;**
  - **IgG M-proteins >15 g/l;**
  - **IgA or IgM M-proteins >10 g/l.**

A patient with a low level M-protein who is asymptomatic does not necessarily require referral to a Consultant Haematologist but will require continued monitoring (see section 11). The above recommendations have been summarised in an algorithm (Appendix II) intended as an easy reference guide for GPs and other clinicians to use when deciding whether referral to a Consultant Haematologist is necessary. This algorithm also includes recommendations for follow-up which are discussed in more detail in the next section.

9.3. Difficult/borderline scenarios

Not all patients are typical and many have co-morbidities that make the decision to refer or not for further investigation more difficult. As the incidence of MGUS rises with age it is likely that this group will include patients with renal failure and bone symptoms from causes other than myeloma and other LPD. It is not entirely possible to avoid including some of these patients in more detailed investigations of a newly detected M-protein in the search for patients with myeloma or other treatable causes of an M-protein. It is acknowledged that there are certain common clinical scenarios which will present clinicians with difficulties and some of these are described below:

9.3.1. Low level M-protein i.e. <10 g/l plus renal impairment without clear cause. There is a need for robust renal investigation to try and establish a renal diagnosis prior to a request for further investigation including examination of the bone marrow and skeletal survey unless myeloma is strongly clinically suspected on other grounds e.g. bone pain or hypercalcaemia.

There is however a particular need to diagnose AL amyloidosis in such a patient so a search for evidence of other organ involvement is necessary. This is particularly so in the case of patients with heavy proteinuria and nephrotic syndrome. A renal biopsy should be strongly considered. The investigation and diagnosis of AL amyloidosis has been reviewed in UKMF/BCSH guidelines (Bird *et al*, 2004).

9.3.2. Patients with associated conditions giving rise to the anaemia of chronic disorder and an M-protein. Patients with inflammatory conditions, e.g. RA, present particular difficulties because of the common presence of musculo-skeletal pain, and frequently associated osteoporosis. In such patients there should be a lower threshold to perform a skeletal survey to rule out myeloma bone disease. Osteoporotic collapse should also lead to more intensive investigation including magnetic resonance imaging (MRI), and sometimes evaluation of the bone marrow. Clinicians need to take into account disease status i.e. an active versus quiescent inflammatory disorder, and the concentration of the M-protein.

9.3.3. Osteopenia /isolated vertebral collapse and low level M protein. In such cases there should be a low threshold for MRI and/or bone marrow and skeletal survey to assess for myeloma.

9.4. Informing the patient

The patient should be carefully informed that MGUS is, in most cases, a benign condition with no impact on her/his future health but that in a minority of patients there is progression to myeloma or other disorder requiring treatment. A proposed information leaflet for GPs and other non-haematological clinicians is given in Appendix III.

Patients with MGUS should be provided with suitable, relevant written information and an opportunity given to answer questions. Further guidance is contained within section 13 entitled *Patient information and support*.

10. Specialist investigation and management of patients with M-proteins referred for specialist investigations (Consultant Haematologist level)

All patients referred with a suspicion of a malignant plasma cell/other LPD or AL amyloidosis should undergo a detailed history and examination before proceeding with more detailed investigations. These will be directed by the nature of the symptoms, signs and/or abnormal test results and have been described in detail in other UKMF/BCSH guidelines (Bird *et al*, 2004; Smith *et al*, 2006).

To investigate an M-protein in patients suspected of having a malignant plasma cell disorder, other lympho-proliferative disorder or AL amyloidosis, the following tests are likely to be required:

- full blood count, serum creatinine, corrected calcium, albumin;
- SPEP with measurement of M-protein level and residual immunoglobulins;
- urinary protein electrophoresis with measurement of total protein/albumin and monoclonal free light chain (BJP) excretion;
- serum free light chain assay (if high clinical suspicion of AL amyloidosis or non/low-secretory myeloma);
- bone marrow aspiration for cytological examination, bone marrow trephine biopsy (which may give a more accurate measure of plasma cell infiltrate) and bone marrow immunophenotyping to confirm clonality;
- skeletal survey – details described in UKMF imaging guidelines (D'Sa *et al*, 2007), if necessary supplemented with MRI.

For patients with an IgM M-protein ≥10 g/l, suspected of having WM, initial investigations should include:

- serum and urinary protein electrophoresis with measurement of M-protein level and residual immunoglobulins;
- full blood count, serum creatinine, calcium, albumin and lactate dehydrogenase;
- bone marrow aspiration and trephine for cytological examination, histology and flow cytometry;
- computed tomography (CT) scan of chest, abdomen and pelvis;
- plasma viscosity if hyperviscosity is suspected.

Patients who are referred for a specialist opinion without a strong suspicion of any of the above conditions and who have a low level M-protein do not necessarily need to undergo detailed investigation including examination of the bone marrow or detailed imaging (skeletal survey or CT scan depending on the M-protein type). Further reassurance that these patients fall into a low risk group for progression may be obtained from a normal SFLC assay result.

Routine bone marrow cytogenetic analysis and/or FISH are not recommended in the routine evaluation of patients with MGUS. Although some small studies have indicated that positron emission tomography/CT scanning may be useful in the early detection of bone lesions associated with myeloma, it's routine use in the investigation of patients with a newly diagnosed M-protein cannot be recommended.

If a diagnosis of MGUS is made by excluding conditions that need treatment, follow-up arrangements and monitoring should follow the schema described below.

If the patient falls into a low risk category (see next section) the patient may be referred back to their primary care physician for further follow-up. An example of a proforma that may be used to inform the GP of the results of investigations and to direct further follow-up is enclosed as Appendix IV.

11. Monitoring of patients with MGUS

The purpose of monitoring is to try to identify transformation to a malignant disorder (e.g. myeloma, WM) at an early stage when there is no significant irreversible lytic bone disease, renal failure or other disabling symptoms and at a stage when the patient is fit enough to benefit from increasingly effective treatments. Clinicians responsible for monitoring patients should be aware that the risk of progression to myeloma or other LPD remains lifelong and that risk never disappears even if the M-protein remains stable.

The pattern of disease progression is variable. The Mayo clinic identified four different patterns of progression; in 28 patients, the M-protein was stable, and then it increased either gradually or suddenly; in nine the M-protein increased gradually from diagnosis; in 11 it increased suddenly in concentration and in 10 patients the serum M-protein was essentially stable but lytic lesions, anaemia, renal insufficiency, increase in bone marrow plasma cells or increase in the level of urine M-protein developed (Kyle *et al*, 2004).

Therefore it is essential that patients should be monitored not only by laboratory testing but also clinically. Patients and practitioners should be aware of and report relevant new symptoms and signs, particularly the development of new bone pain, weight loss, fatigue and other symptoms that might indicate progression to myeloma, amyloid or other lymphoproliferative disease.

11.1. Monitoring in primary care

This group can be defined as one in which an M-protein is present at the following levels in whom there are no symptoms, signs or results of initial investigations suggestive of myeloma, other LPD or AL amyloidosis. These patients are considered at low risk of progression, particularly if they have had a normal SFLC ratio:

- IgG M-protein <15 g/l;
- OR IgA or IgM M-protein <10 g/l.

It should be noted that this forms the vast majority of M-proteins detected in routine practise.

There is no published evidence on which to base recommendations for the frequency of follow-up and guidance is, of necessity, pragmatic but should seek to take into account information which is known about risk factors for progression and patterns of progression. It could reasonably be agued that in the people with a very short actuarial life expectancy (perhaps <5 years) and very low level paraproteins (say below 5 g/l) regular follow up is not required once myeloma, AL amyloidosis and LPD have been excluded. However, it would not be unreasonable to measure the M-protein occasionally when the patient has other blood tests.

Conversely, the patient with longer actuarial life expectancy, with higher M-protein concentration and with IgA or IgM isotypes should be monitored more regularly. It is suggested that, in the first year after identification in this group of patients, 3–4 monthly testing for the first year is advisable reducing to 6–12 monthly as long as there are no symptoms suggestive of progression. This advice highlights again the necessity for patients and clinicians to be aware of relevant clinical symptoms.

The blood tests that should be carried at monitoring visits are as follows:

- quantification of the M-protein and immunoglobulin levels;
- full blood count;
- creatinine;
- urea and electrolytes;
- corrected calcium.

11.2. Criteria for re-referral/further investigation

Patients should be re-referred to specialist units under the following circumstances:

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

Even if a patient is seen by the physician at 3-monthly or even more frequent intervals symptoms may rapidly develop in the meantime. The patient is the best person to be aware of the onset

of relevant symptoms. It is essential, therefore, that patients are fully aware of important symptoms and they should be encouraged to report these outside appointment visits if they occur.

11.3. Monitoring in the higher risk group

The high risk group can be defined as one in which an M-protein is present at the following levels and in whom, by definition, there are no symptoms, signs or results of initial investigations suggestive of myeloma, other LPD or AL amyloidosis:

- IgG M-protein >15 g/l;
- IgA or IgM M-protein >10 g/l;
- IgD or IgE M-protein.

Overall, this group of patients requires more frequent follow up, usually under the care of a Consultant Haematologist. Again there is no evidence on which to base recommendations but anything <3–4 monthly may prove ineffective. Clinicians should be aware of the patterns of progression as described above.

Patients with an abnormal SFLC ratio or significant Bence-Jones proteinuria are at increased risk of renal failure and disease progression and should be considered for more frequent monitoring. These patients should be warned of this and advised to maintain high fluid intake. There is no current evidence supporting the use of SFLC in monitoring.

The blood tests that should be carried out at each visit are as follows:

- quantification of the M-protein and immunoglobulin levels;
- full blood count;
- creatinine;
- urea and electrolytes;
- corrected calcium.

There should be a low threshold for proceeding to further investigation to rule out progression if new symptoms/signs develop or if any of the above blood tests show deteriorating values. A greater than a 25% increase in a 3-month period (minimum increase 5 g/l) should be regarded as significant.

When monitoring an individual M-protein level clinicians should be aware that inter-laboratory variation can be as high as 25%. Where possible, M-protein quantification repeated over time should be performed by the same methodology in the same laboratory.

A possible model of long term follow up has been developed in the UK in which conventional clinic monitoring of patients is replaced by an outreach service, which involves primary care phlebotomy and central haematologist review of laboratory parameters and symptoms identified in a self assessment questionnaire. This has proved popular with primary care physicians as the impact on primary care work load is modest and there is continued review of the parameters by a specialist. Similarly, satisfaction is very high amongst patients principally as a result of the reduced travel and waiting times. Financial modelling has also suggested that this model of care is deliverable at a lower cost than conventional out-patient clinic assessments (Rawstron *et al*, 2007).

12. Preventing progression of MGUS

There are currently no interventions that have been proven to prevent or delay the progression of MGUS to myeloma or other LPD. A number of agents have been identified as candidates for investigation in patients with high risk MGUS or asymptomatic myeloma. The risks associated with such an approach include adverse events, particularly where toxicity is cumulative and also the possibility that despite delaying progression, the intervention has no impact on overall survival.

Agents that have been identified as possibly useful in delaying progression have included bisphosphonates and immunodulatory agents. Most studies, however, have focussed on patients with asymptomatic myeloma rather than MGUS. In this group, a randomised study that compared zoledronic acid with observation showed a reduction in skeletal related events at progression but did not influence the natural history of the disease (Musto *et al*, 2008). Studies carried out in MGUS patients have established that both zoledronic acid and alendronate can increase bone mineral density in patients with bone loss with the theoretical added benefit of reducing fractures (Berenson *et al*, 2008; Pepe *et al*, 2008) but no study has yet demonstrated that progression can be delayed or prevented.

Improved methods to identify MGUS patients at high risk for malignant transformation and the introduction of new drugs for treatment of multiple myeloma, such as thalidomide, bortezomib and lenalidomide, are likely to stimulate new trials aimed at intervening to prevent progression in individuals with high risk MGUS. There is currently ongoing a randomised trial of lenalidomide and dexamethasone versus observation in patients with symptomatic myeloma at high risk of progression but no results are yet available. Vaccination with idiotype protein-pulsed dendritic cells (DCs) has been explored in multiple myeloma with varying sucesss (Yi *et al*, 2002) and may also be possible in MGUS patients in the future.

13. Patient information and support

Provision of information and support for patients and their carers is essential to assist them in coming to terms with and understanding all that a diagnosis brings, as well as helping them to make informed decisions about care options, clinical studies and future treatment. It is important for patients and their families to understand that although MGUS can progress to a malignant condition e.g. myeloma, it doesn't require active treatment, but rather a watch-and-wait approach.

The difficulty for health care professionals is how to provide appropriate information that allows the patient to fully

understand the implications and risks of their diagnosis, but at the same time avoid alarming them unnecessarily about possible progression.

Delivering the appropriate balance of information about MGUS which is asymptomatic and has a small chance of progression should not be underestimated. Many patients living with MGUS often describe it as 'living on a knife edge', not knowing if and when the disease will progress and often question how best to live their life. MGUS patients and their families therefore need appropriate information and support on a wide range of clinical, psychological and social-economic problems which result from a diagnosis of MGUS.

Key recommendations

1 **The diagnosis needs to be communicated honestly with the minimum of delay: uncertainty or vagueness is generally more distressing to a patient and his or her family.**
2 **The diagnosis should be given in the appropriate environment and ideally in the company of a close relative and the presence of a specialist nurse.**
3 **Patients and their carer/family member should be given time to ask relevant questions once they have been given the diagnosis; it may be best to do this after an interval of a few hours or days.**
4 **At the end of the consultation it is recommended that patients and their family/carers are given written information on the condition. They should also be given information and contact details for patient organisations that provide information and support. Examples of these include Myeloma UK and the Leukaemia Research Fund.**
5 **Patients need to be informed of the names of the key members of the specialist team who are in charge of their care and given clear information on how to contact and access advice and support from the team.**
6 **The management/care plan needs to be communicated simply and should be clearly written in the case record so that the information is readily accessible.**
7 **An appropriately trained person, i.e. a specialist nurse, should be available to discuss with/inform patients on information materials including guidance for using the Internet as an information resource. However, patients and their families/carers should be cautioned about accessing information on the internet and should be given contact details of appropriate, well-respected sites.**

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the UK Myeloma Forum the and Nordic Myeloma Group, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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Appendix I. Laboratory considerations

This appendix aims to provide key guidelines for the performance of serum and urine electrophoresis and serum free light chain analysis such that an optimum service can be provided for service users. As in the main document, many of the recommendations come from experience, but key references are provided where available.

M-protein detection

- Serum and urine should both be analysed.
- Serum electrophoresis should be performed using a high-resolution agarose gel (HRAGE) that provides a crisp separation between the beta-1- and beta-2-globulins or by capillary zone electrophoresis (CZE).
- Immunofixation of serum should be performed when
  - there is a band suspicious for an M-protein on electrophoresis;
  - immunoglobulins are increased and out of keeping with the appearance of the electrophoretic pattern;
  - one or more classes of immunoglobulin are below the lower limit of an age-related reference range;
  - Bence-Jones protein (BJP) is found in the urine without an M-protein apparent in the serum;
  - there is a high clinical suspicion of a condition associated with an M-protein.
- Serum immunofixation should be performed with antisera against immunoglobulin heavy chains G, A and M and light chains κ and λ. All patterns that demonstrate monoclonal light chains without an associated heavy chain should be subject to immunofixation with antisera to IgD and IgE.
- Examination of urine for BJP should be performed by agarose gel electrophoresis using urine that is concentrated 50–100-fold or using urine as passed with a highly sensitive protein stain. The criterion for sensitivity is that a band of albumin should be visible in all urines that are examined. A band may not be seen if the urine is very dilute, in which case either further concentration or a fresh, more concentrated, urine sample should be requested. Alternatively, immunofixation may be used as the initial investigation.
- Following urine electrophoresis, immunofixation should be performed whenever a band in addition to albumin is observed even if the pattern is recognisable e.g. that of a glomerular proteinuria.
- Immunochemical quantification of light chains in urine can be used for screening if elevated levels and abnormal ratios are followed by electrophoresis and immunofixation. However, imunofixation of concentrated urine should always be performed if there is a strong clinical suspicion of M-protein-related disease and/or low serum immunoglobulin levels without a detectable M-protein.

M-protein quantification

- Quantification of an M-protein should be made by densitometric measurement or the equivalent for CZE. It should be made clear on the report when a densitometric quantification includes a significant contribution from a co-migrating band like beta-1- or beta-2-globulin.
- Immunochemical measurements by nephelometry or turbidometry using antisera against immunoglobulin heavy and/or light chains are subject to variation due to antigenic differences between individual M-proteins and the measurement will include the polyclonal immunoglobulin component for the immunoglobulin class of the M-protein.
- Immunochemical measurements may be more appropriate than densitometry when the M-protein comigrates with a beta-1- or beta-2-globulin with a total densitometric quantification of <10 g/l or when an IgA or IgM M-protein of <5 g/l appears on a normal polyclonal immunoglobulin background. It can be appropriate to quote the immunochemical quantification of the M-protein immunoglobulin class in addition to the densitometric quantification. In immunochemical quantification of IgG M-proteins the contribution of polyclonal IgG should be estimated and subtracted. For M-proteins of other classes the contribution of polyclonal Ig is usually of minor importance.
- Repeat quantification of an M-protein with time must be made reproducible, whenever possible using the same procedure and laboratory. Correct and consistent delineation of the M-protein peak should be verified on each occasion by referral to archives of previous densitometric patterns for that patient. The laboratory report should make it clear whether or not there has been a significant change in M-protein concentration. Reproducibility with time should be established by each laboratory for a range of M-protein concentrations, classes and electrophoretic mobilities to establish what is a significant change. Failing this, a change of >25% and >5 g/l is the default position and clinicians should be aware that inter-laboratory variation can be as high as 25%.
- Quantification of BJP is made from densitometry of the electrophoretic strip. A problem with densitometry is that it is not unusual that HRAGE demonstrates several spikes and ideally immunofixation is needed to identify the correct band each time densitometry is performed. Urine total protein (or albumin) should be quantified with every examination. Immune assays are associated with other problems that make them less suitable for quantification of

urine monoclonal light chains. At present there is no international reference substance for calibration and both absolute and relative quantities in the same sample differ between laboratories. If immune assays are used the possibility of leakage of proteins due to renal damage must be taken in account since they measure both polyclonal and monoclonal light chains, free or as part of an immunoglobulin molecules.
- By convention, urinary output of light chains is reported as a 24-h output that reflects daily synthetic rate better than the concentration in a random urine sample, but this suffers from potential errors in urine collection. Alternatively light chain output can be expressed as a ratio to creatinine in a random urine sample.

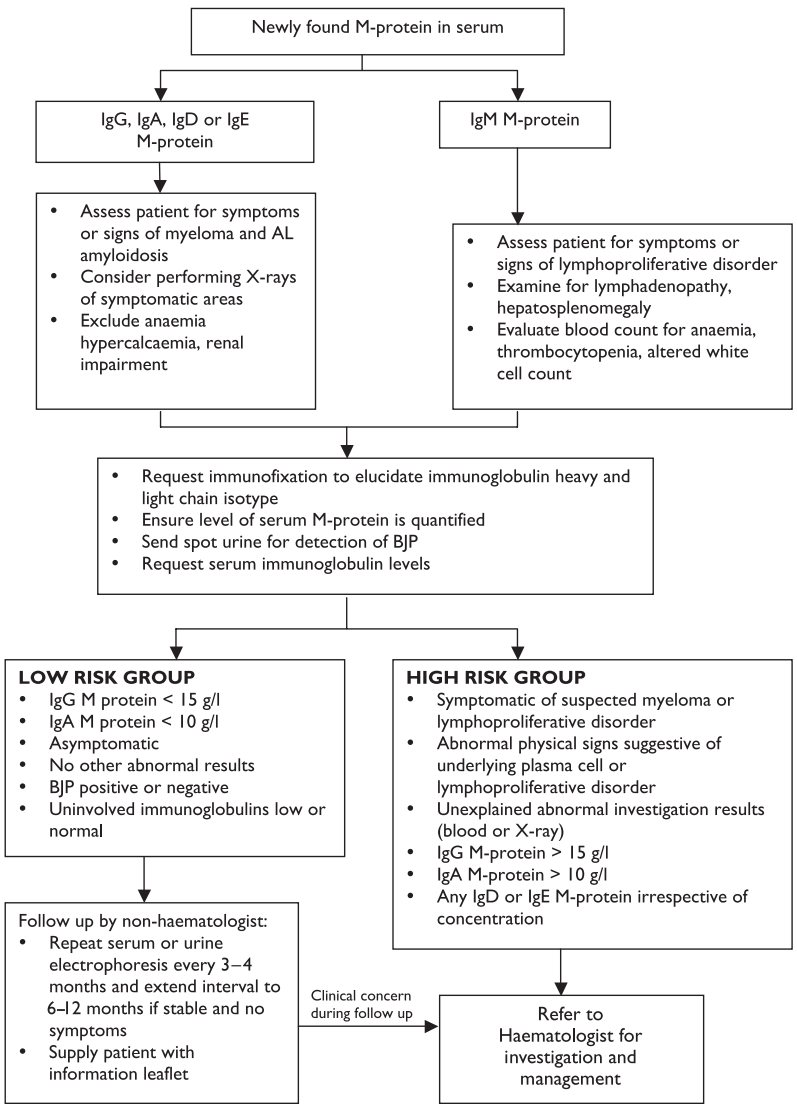
Serum free light chain (FLC) assay

- Monoclonal serum FLC are usually only detectable by immunofixation (limit of sensitivity >150 mg/l), HRAGE or CZE when removal of FLC from blood by glomerular filtration is compromised.
- FLC are detectable in urine only when their level in the glomerular filtrate exceeds renal tubular capacity to reabsorb them.
- An immunochemical assay for FLC (FREELITE) can detect serum FLC to a sensitivity of 1 mg/l. Increasing production of monoclonal FLC from a plasma cell dyscrasia will usually perturb the serum kappa:lambda FLC ratio before FLC production is sufficient to exceed renal tubular absorption and hence be apparent on immunofixation of urine. A common exception to this would be when there is renal tubular damage and normal production of polyclonal FLC as may be found in elderly patients with MGUS. SFLC measurements are the only available test of M-proteins for diagnosis and management of patients with low-secretory myeloma and some light chain amyloid patients in whom no M-protein can be detected by immunofixation of serum and urine. SFLC measurements are a valuable complement to other M-protein tests in Bence Jones myeloma, light chain amyloid and for any patient where urine is not available to the laboratory.
- As for any method for M-protein quantification the FREELITE test gives variable results unless the same platform is used by the same laboratory.
- The importance of between-laboratory variation for determining SFLC kappa:lambda ratios in the context of risk of progression of MGUS is discussed in that section.

Other considerations

The analytical laboratory should establish close links with the clinical service (e.g. Clinical Haematologists) for which the analytical service is provided. It is necessary for the analytical service to determine in conjunction with this clinical service provider responsibility for report formats, appropriate alert procedures for reports that are deemed critical and the degree and nature of any interpretative comments that are added to reports.

Appendix II. Suggested algorithm for the investigation of a newly detected M-protein



Appendix III. Information leaflet for non-haematological physicians: Monoclonal gammopathy of unknown significance (MGUS)

- **Definition:** MGUS is defined by a monoclonal immunoglobulin (M-protein or paraprotein) in the serum of up to 30 g/l in the absence of lytic bone lesions, anaemia, hypercalcaemia and renal insufficiency that is related to the underlying monoclonal plasma cell proliferation and <10% plasma cells in the bone marrow. It is a potential precursor to multiple myeloma (MM) or related disorders and so needs long term clinical follow-up once detected.
- **Prevalence/associations:** The prevalence of MGUS is 3% of persons >70 years, but is higher in persons of African/Caribbean origin than white persons. The commonest type of M-protein (isotype) is IgG, followed by IgM and then IgA. IgM M-proteins are associated with lymphoproliferative conditions such as Waldenstrom Macroglobulinaemia (WM), B cell non-Hodgkin's lymphoma (B-NHL) or chronic lymphocytic leukaemia (CLL), rather than myeloma.
- **Clinical workup/investigations:** Once detected, a series of staging investigations are undertaken, depending on the isotype, age of the patient and results of initial blood profile.
  - The presence of a low-level M-protein (<15 g/l) normal full blood count, renal and bone function, normal uninvolved immunoglobulins and the absence of symptoms, MM or related disorder is unlikely to be present. In such patients, a skeletal survey and bone marrow examination may or may not be carried out at the discretion of the Myeloma Team.

  - In cases where the initial blood profile has features of concern (such as anaemia, renal impairment), or the patient is particularly young (<60 years) or the M-protein level is 10–20 g/l or greater, the complete staging procedure would most likely be carried out, including a skeletal survey and bone marrow examination.
  - In the case of an IgM M-protein, imaging investigations such as a computed tomography (CT) scan may be undertaken to exclude lymphadenopathy/hepatosplenomegaly as evidence of an underlying lymphoproliferative disorder.
  - Detection of urinary Bence-Jones Protein (BJP) is generally performed initially. In MGUS, it may be present at a low level. In the follow up of patients with MGUS, there is no need for serial follow up of BJP levels unless renal impairment supervenes, as this may herald transformation to MM.

- **Risk of progression:** The risk of progression to MM or related disorder is 1% per year, and this risk does not disappear even after long-term follow up. Effort has been put into identifying predictors of progression to MM or related disorder in order to have a targeted strategy for the follow up of patients. The single most discriminatory parameter that is predictive of progression to myeloma is the level of the M-protein. The level in grammes/litre is roughly equivalent to the risk of progression for that patient at 10 years following detection. Thus, a person with an M-protein of 5 g/l has a 5% chance of progression to MM compared to a 20% chance for an individual with an M-protein of 20 g/l. The other risk factor for progression is the M-protein isotype: IgA and IgM MGUS are more likely to progress than IgG. Factors such as the presence of BJP in the urine, suppression of the uninvolved immunoglobulins, age and sex are not predictors for progression.

- **Conclusions:** Once an M-protein is identified, it is important to monitor the clinical and laboratory trends of the patient with MGUS and refer back to the Myeloma Clinic if evidence for progression is found, at which point restaging investigations will be performed and further recommendations made.

Appendix IV. Suggested discharge letter to primary care for patients with MGUS at low risk of progression

Date:

To:

Dear

Stick Hospital Number Label Here	Stick Address Label Here

Your patient has been found to have a serum and/or urine paraprotein. The following investigations were performed as part of their work up in The Myeloma Clinic:

Investigation	**Y/N**	**Result**
Full blood count		
Renal function		
Liver function		
Bone function		
Serum electrophoresis and immunofixation for isotype		
Paraprotein level		
Serum immunoglobulins		
Urine electrophoresis for BJP		
Skeletal survey for myeloma		
Bone marrow biopsy		
CT scan		
Other:		

Owing to the **absence** of any features to suggest multiple myeloma or other underlying lymphoproliferative disorder, your patient has been assigned the diagnosis of **MGUS (see overleaf)** and has received an information leaflet about this.

We are discharging the patient back to your care for follow up and recommend that the following investigations are performed every 3–4 months for 1 year and then 6–12 monthly thereafter if no change is seen:

Full blood count
Renal, liver and bone function tests
Serum electrophoresis and paraprotein quantitation
Serum immunoglobulins

In the event that the paraprotein level rises, the development of abnormal renal or bone function tests or symptoms such as fatigue, recurrent infections, unexplained bleeding, bone pain, weight loss, please refer back to the Myeloma Clinic for re-staging (contact details above).

Signed:

On behalf of the Myeloma Team

