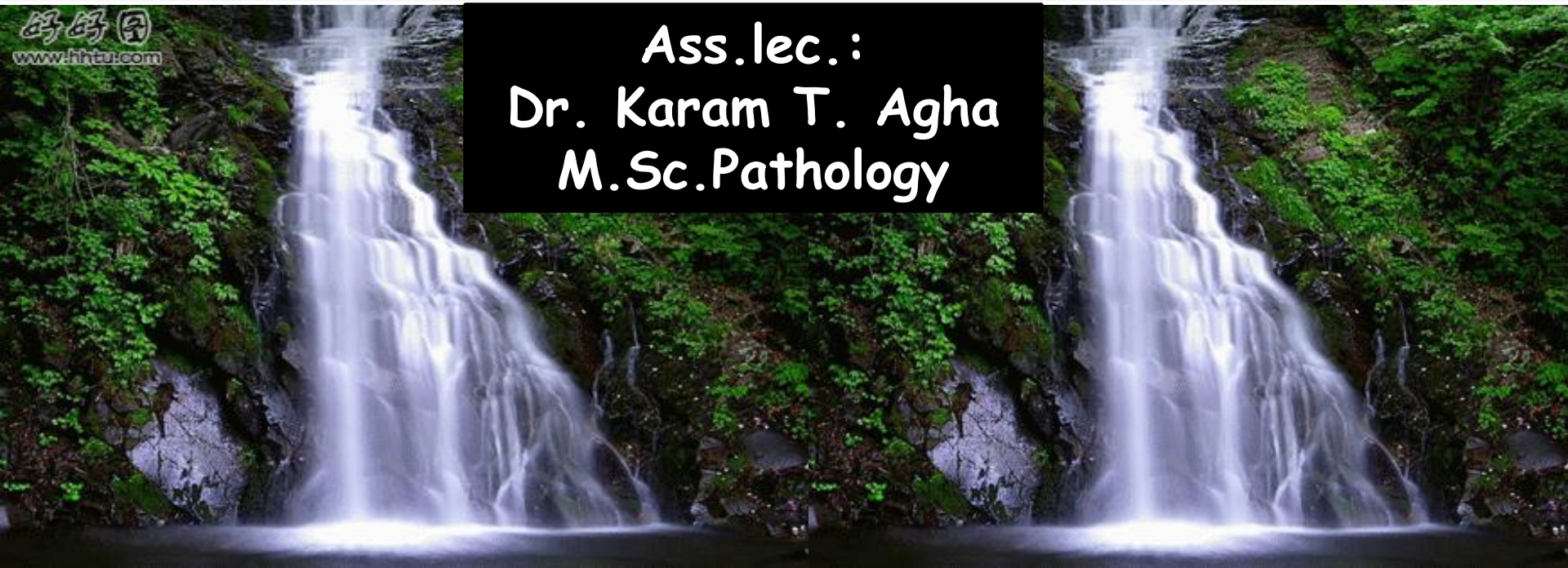
Guidelines for the diagnosis of Multiple Myeloma 2014

By:British Committee for Standards in Haematology (BCSH)



Diagnosis, prognostic factors and disease monitoring

1. Investigation and diagnosis

- ***Investigation*** of a patient with suspected myeloma should include the screening tests indicated , followed by further tests to confirm the diagnosis.
- ***Electrophoresis*** of serum and concentrated urine should be performed, followed by immunofixation to confirm and type any M-protein present.
- Immunofixation and serum-free light chain (***SFLC***) assessment are indicated in patients where there is a strong suspicion of myeloma but in whom routine serum protein electrophoresis is negative (Pratt 2008).

Table 1 - Initial investigations in patients with myeloma

Screening tests	Tests to establish diagnosis	Tests to estimate tumour burden and prognosis	Tests to assess myeloma-related organ impairment (ROTI)	Special tests indicated in some patients
FBC, ESR or plasma viscosity	B. M. aspirate + trephine biopsy with plasma cell phenotyping	FISH analysis	FBC	
Urea, creatinine, calcium, albumin	Immunofixation of serum and urine	Quantification of Monoclonal protein in serum and urine	Serum urea and creatinine	SFLC assay in: oligo-secretory, light chain only and non-secretory disease
Electrophoresis of serum and concentrated urine		Albumin B2-microglobulin	Creatinine clearance (measured or calculated)	
Quantification of non-isotypic Immuno-globulins			Calcium ,Albumin ,Plasma viscosity ,Tissue biopsy (or fat pad aspirate) for amyloid (if suspected). Quantification of non-isotypic immunoglobulins	
X-ray of symptomatic areas	Skeletal survey	Skeletal survey	Skeletal survey	MRI, CT scan

- **Quantification of serum M-protein** should be performed by densitometry of the monoclonal peak on electrophoresis; immunochemical measurement of total immunoglobulin (Ig) **isotype level** can also be used and is particularly useful for IgA and IgD M-proteins.
- **Quantification of urinary total protein** and light chain excretion can be performed directly on a 24-h urine collection or calculated on a random urine sample in relation to the urine creatinine.

- The serum tests are particularly useful for diagnosis and monitoring of light chain only.
- In renal impairment the half-life, and thus serum concentration of SFLC, can increase ten-fold and there is often an increased κ/λratio (Hutchison et al, 2008). A diagnosis of myeloma should be confirmed by bone marrow (BM) assessment.
- It is recommended that an adequate trephine **biopsy of at least 20 mm** in length be obtained in all patients as it provides a better assessment of the extent of marrow infiltration than aspirate smears (Al-Quran et al, 2007; Ng et al, 2006).

- It is recommended that a diagnosis of myeloma be confirmed by the demonstration of an aberrant plasma cell phenotype and / or monoclonality by flow cytometry and / or immunohistochemistry on trephine sections.
- The European Myeloma Network have provided practical guidance on the optimal methods for flow cytometry and rapid and cost effective single-tube assays have been developed (Rawstron et al, 2008).
- CD138 immunostaining of trephine sections can be useful to determine the extent of infiltration in selected cases (Al-Quran et al, 2007; Ng et al, 2006).
- All diagnoses should be made or reviewed by an appropriately constituted Multidisciplinary Team (MDT) ([NICE], 2003).

2 . Diagnostic criteria and differential diagnosis

- A diagnosis of myeloma should be made using the criteria proposed in 2003 by the International Myeloma Working Group (IMWG).
- These criteria distinguish between myeloma and MGUS principally on the basis of M-protein concentration, percentage of BM plasma cells and presence or absence of myeloma-related organ and tissue impairment (ROTI).
- Other differential diagnoses in patients with M-proteins include solitary plasmacytoma and other B-cell lymphoproliferative disorders.

Table 2- Diagnostic criteria for MGUS, asymptomatic myeloma and symptomatic myeloma (adapted from International Myeloma Working Group, 2003)

MGUS	Asymptomatic myeloma	Symptomatic myeloma
M-protein in serum <30 g/l	M-protein in serum >30 g/l and/or Bone marrow clonal plasma cells >10 %	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)		Bone marrow (clonal) plasma cells or biopsy proven plasmacytoma
No related organ or tissue impairment (no end organ damage including bone lesions)	No related organ or tissue impairment (no end organ damage including bone lesions) or symptoms	Myeloma-related organ or tissue impairment (including bone lesions)

Table 3 - Myeloma-related organ or tissue impairment (ROTI) (adapted from International Myeloma Working Group, 2003)

Clinical effects due to myeloma (CRAB)	Definition
Calcium levels Increased	Corrected serum calcium >0.25 mmol/l above the upper limit of normal or >2.75 mmol/l
Renal insufficiency	Creatinine>173 µmol/l
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)

3 . Monitoring

- Monitoring of patients with asymptomatic myeloma should include regular (typically 3-monthly) clinical assessment for the emergence of ROTI and measurement of serum and urinary M-protein (and SFLC when indicated).
- Repeat BM examination and skeletal imaging should be considered prior to the start of treatment .

4 .Prognostic factors and staging in symptomatic myeloma

International Staging System (ISS) for multiple myeloma:

Stage	Criteria	Median survival in months
I	Serum ß2 microglobulin < 3.5 mg/l and serum albumin > 3.5 g/dl	62 months
II	Neither I or III	45 months
III	Serum ß2 microglobulin > 5.5 mg/l	29 months

- Certain cytogenetic and molecular genetic abnormalities have been shown to predict outcome in myeloma.
- ***It is now generally accepted that both the immunoglobulin heavy chain gene translocations t(4;14), t(14;16) and t(14;20) as well as the copy number changes 1q gain and 17p deletion, demonstrated by fluorescence in situ hybridization (FISH), confer an adverse outcome in myeloma.***
- It has therefore been proposed that these abnormalities define “high-risk” myeloma and should be specifically sought at diagnosis in all patients (Fonseca, et al 2009, Munshi, et al 2011).
- Recent data suggests that ***chromosome 13 deletion*** is not an independent prognostic marker and the adverse effect relates to its close association with high-risk abnormalities, particularly the t(4;14).

There ***is not yet international consensus*** as to the optimal treatment approach for different risk groups and further studies for high risk myeloma are required.

5 . Measuring Response to Therapy

- The response category ‘sCR’ (for use in the reporting of clinical trials) has been refined recently to incorporate the use of flow cytometry to detect **minimal residual disease** on the basis of the presence of an aberrant immunophenotype (Rajkumar et al, 2011).

- Repeat BM aspirate assessment is required to confirm CR (repeat trephine biopsy is not required under the response criteria but may be needed for accurate assessment) (Durie et al, 2006) and should be performed in all patients at Day 100 following high-dose therapy.
- Flow cytometric assessment of minimal residual disease at this time point also provides prognostic information (Paiva et al, 2008) and may in the future be used to guide maintenance / consolidation therapies.
- The definitions of progressive disease and relapse have also been revised by the IMWG and include a new category of clinical relapse, which reflects the fact that progressive disease (PD) as defined does not necessarily indicate a need for further therapy.

Definitions of measurable disease

Response criteria for all categories and subcategories of response except CR are applicable only to patients who have **'measurable' disease** defined by at least one of the following three measurements:

A. • Serum M-protein : >10 g/l
B. • Urine M-protein: >200 mg/24 h
C. • SFLC assay: Involved FLC level >100 mg/l provided SFLC ratio is abnormal


Thank you