Understanding Lab Values in Multiple Myeloma

A reference guide to the common laboratory tests used in the diagnosis and monitoring of multiple myeloma

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Differential Diagnosis

Multiple Myeloma (MM) Is a Plasma Cell Malignancy[1]

MM is characterized by the accumulation of malignant plasma cells within the bone marrow that produce and secrete monoclonal antibodies into the blood and/or urine.[1] The initial evaluation to help confirm a diagnosis of myeloma includes blood and urine tests as well as a bone marrow aspiration and biopsy.[2]

Diagnostic Criteria of MM Disease Spectrum According to the International Myeloma Working Group (IMWG) Consensus Panel[3]

	MGUS	SMOLDERING MYELOMA	MULTIPLE MYELOMA
Monoclonal protein	< 3 g/dL (non IgM)	Serum ≥ 3 g/dL or urinary ≥ 500 mg/24 hr AND/OR 10%-60%	Present
Clonal BM plasma cells	< 10%		≥ 10% OR Biopsy proven bone/extramedullary plasmacytoma
Myeloma Defining Event (MDE)	Absent	Absent	One or more of following: 1. Evidence of **end-organ damage (CRAB symptoms)** attributed to the underlying plasma cell proliferative disorder 2. One or more **biomarkers of malignancy:** • Clonal BM plasma cell ≥ 60% • Involved:uninvolved sFLC ratio ≥ 100 • > 1 focal lesion on MRI

MGUS = monoclonal gammopathy of undetermined significance; IgM = immunoglobulin M; BM = bone marrow; CRAB = serum calcium, renal insufficiency, anemia, bone lesions; sFLC = serum free light chains; MRI = magnetic resonance imaging.

Differential Diagnosis Continued

Myeloma Defining Events (MDEs): SLiM CRAB[3]

A MDE is defined as one or more of the biomarkers of malignancy (SLiM) in addition to serum calcium, renal insufficiency, anemia, and bone lesions (CRAB) features.

	CRITERIA
Clonal BM PlaSma Cell	≥ 60%
Free Light Chain Ratio	Involved:uninvolved sFLC ratio ≥ 100
MRI	> 1 Focal lesion
Calcium Elevation	≥ 11 mg/dL OR > 1 mg/dL higher than ULN
Renal Insufficiency	CrCl < 40 mL/min* OR Serum creatinine > 2 mg/dL
Anemia	Hgb < 10 g/dL OR > 2 g/dL below LLN
Bone Lesions	≥ 1 osteolytic lesions on skeletal radiography, CT, or PET/CT†

*Measured or estimated by validated equations.
†If bone marrow has less than 10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

SLiM = clonal BM plasma cell, free light chain ratio, MRI; CRAB = serum calcium, renal insufficiency, anemia, bone lesions; BM = bone marrow; sFLC = serum free light chains; MRI = magnetic resonance imaging; ULN = upper limit of normal; CrCl = creatinine clearance; Hgb = hemoglobin; LLN = lower limit of normal; CT = computed tomography; PET/CT = positron emission tomography/computed tomography.

For additional resources and information about multiple myeloma, visit the International Myeloma Foundation website

Overview of Lab Tests

Laboratory Tests Used in the Diagnosis and Monitoring of Multiple Myeloma (MM)[2]

LABORATORY TEST		DIAGNOSIS/ WORKUP	MONITORING/ FOLLOW-UP
Blood	CBC + differential	✓	✓
	CMP	✓	✓
	MM-Specific Assays		
	SIFE	✓	✓
	IGs	✓	✓
	β2M	✓	
	SPEP	✓	✓
	sFLC	✓	✓
	LDH	✓	
Urine	24-hour total urine protein	✓	✓
	UPEP	✓	✓
	UIFE	✓	✓
Bone	**Bone Marrow Aspirate/ Biopsy**		
	Karyotyping	✓	
	Plasma cell count	✓	✓
	FISH	✓	✓
	Radiology		
	Skeletal survey	✓	✓
	MRI	✓	✓
	PET/CT	✓	✓

CBC = complete blood count; CMP = comprehensive metabolic panel; SIFE = serum immunofixation electrophoresis; IGs = quantitative immunoglobulins; β2M = serum β_2-microglobulin; SPEP = serum protein electrophoresis; sFLC = serum free light chains; LDH = lactate dehydrogenase; UPEP = urine protein electrophoresis; UIFE = urine immunofixation electrophoresis; FISH = fluorescence in situ hybridization; MRI = magnetic resonance imaging; PET = positron emission tomography; CT = computed tomography.

Blood Tests

COMPLETE BLOOD COUNT	REFERENCE RANGE	RELEVANCE IN MM
Red Blood Cells (RBC)	Male: 4.32–5.72 x 10^{12} cells/L[4] Female: 3.90–5.03 x 10^{12} cells/L[4]	• Anemia, defined by Hgb < 10 g/dL, or > 2 g/dL below LLN, is considered a MDE and suggests symptomatic MM[3]
Hematocrit (Hct)	Male: 39%-50%[4] Female: 35%-45%[4]	
Hemoglobin (Hgb)	Male: 13.5–17.5 g/dL[4] Female: 12.0–15.5 g/dL[4]	
Platelets (Plts)	150–450 x 10^9 cells/L[4]	• Thrombocytopenia is defined as Plt < 150 x 10^9 cells/L and may also occur secondary to MM therapies[5]
White Blood Cells (WBC)	3.5–10.5 x 10^9 cells/L[4] Absolute Neutrophil Count (ANC): Male: 1.78–5.38 x 10^9 cells/L[6] Female: 1.56–6.13 x 10^9 cells/L[6]	• An ANC < 500 cells/µL is associated with increased risk of infection[7]

MM = multiple myeloma; LLN = lower limit of normal; MDE = myeloma defining event.

CTCAE 4.03 Grade 1–4 Anemia Definitions[8]

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Hgb < LLN-10.0 g/dL	Hgb < 10.0–8.0 g/dL	Hgb < 8.0 g/dL; transfusion indicated	Life-threatening consequences; urgent intervention indicated

CTCAE 4.03 Grade 1–4 Plt Count Decreased Definitions[8,*]

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Plt < LLN–75000/mm^3; < LLN–75.0 x 10^9/L	Plt < 75000–50000/mm^3; < 75.0–50.0 x 10^9/L	Plt < 50000–25000/mm^3; < 50.0–25.0 x 10^9/L	Plt < 25000/mm^3; < 25.0 x 10^9/L

CTCAE 4.03 Grade 1–4 Decreased Neutrophil Count Definitions[8,†]

GRADE 1	GRADE 2	GRADE 3	GRADE 4
< LLN–1500/mm^3; < LLN–1.5 x 10^9/L	< 1500–1000/mm^3; < 1.5–1.0 x 10^9/L	< 1000–500/mm^3; < 1.0–0.5 x 10^9/L	< 500/mm^3; < 0.5 x 10^9/L

*A finding based on laboratory test results that indicates a decrease in number of platelets in a blood specimen.
†A finding based on laboratory test results that indicates a decrease in number of neutrophils in a blood specimen.

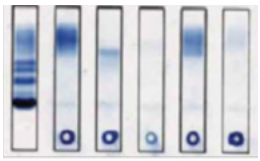
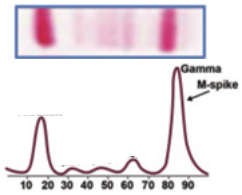
CTCAE = Common Terminology Criteria for Adverse Events; Hgb = hemoglobin; Plt = platelet; LLN = lower limit of normal.

Blood Tests Continued

COMPREHENSIVE METABOLIC PANEL	REFERENCE RANGE	RELEVANCE IN MM
Serum Calcium	8.6–10.0 mg/dL[9]	• Serum calcium > 11 mg/dL or > 1 mg/dL higher than ULN suggests evidence of organ damage and symptomatic MM[3]
Serum Creatinine (SCr)	Male: 0.7–1.3 mg/dL[9] Female: 0.6–1.1 mg/dL[9]	• SCr > 2 mg/dL is considered a MDE and suggests symptomatic MM[3] • Abnormal levels of SCr and BUN may indicate renal disease or disorder[10]
Blood Urea Nitrogen (BUN)	6–20 mg/dL[9]	
Serum Albumin	Adult: 3.5–5.2 g/dL[9] > 60 years: 3.2–4.6 g/dL[9]	• Albumin is a key criterion used in the International Staging System (ISS) in MM[2]
Total Serum Protein	6.4–8.3 g/dL[9]	• Measures the total amount of albumin and globulins present in the blood[11] • Elevated levels may indicate MM[11]
Serum Glucose	70–140 mg/dL[12]	• Concomitant MM and diabetes is a major challenge in MM, and serum glucose levels should be monitored[13]

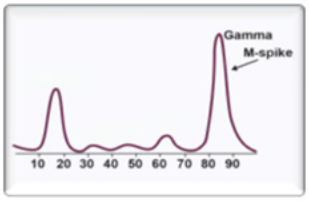
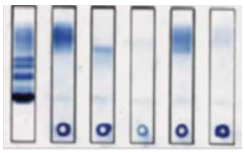
MM = multiple myeloma; ULN = upper limit of normal; MDE = myeloma defining event.

Blood Tests Continued

MM-SPECIFIC BLOOD TESTS	REFERENCE RANGE	RELEVANCE IN MM
Serum Immunofixation Electrophoresis (SIFE)	SP G A M κ λ  Reproduced with permission from ASH Image Bank. 2014. ©The American Society of Hematology.[14]	• SIFE is the "gold standard" method to confirm the presence and type of monoclonal protein (M-protein) in the blood[15] • Each type is associated with slightly different patterns of disease[1]
Quantitative Immunoglobulins (IGs)	IgG: 767–1590 mg/dL[16,*] IgA: 61–356 mg/dL[16,*] IgD: ≤ 10 mg/dL[17,*] IgE: ≤ 214 kU/L[18,*] IgM: 37–286 mg/dL[16,*] *Adults ≥ 18 years old.	• The type of M-protein produced varies from patient to patient. The most common is IgG (52% incidence in MM), and the least common is IgE (< 0.01% incidence in MM)[1]
Serum β_2-Microglobulin (β2M)	1.21–2.70 µg/mL[19]	• Elevated β2M was a factor considered for ISS staging in MM[15] • β2M related to ISS staging as follows: stage I: serum β2M < 3.5 mg/L, serum albumin ≥ 3.5 g/dL; stage II: not ISS stage I or III; stage III: serum β2M ≥ 5.5 mg/L[20]
Serum Protein Electrophoresis (SPEP)	Not detected in the serum or urine in healthy individuals[1] Abnormal SPEP Showing M-spike of Myeloma[21] 	• M-protein is identified as a "spike" on SPEP[21,22] • An increase of ≥ 25% from baseline of serum M-protein suggests progressive disease[23,†] †Absolute increase must be ≥ 0.5 g/dL.
Serum Free Light Chains (sFLC)	FLCk: 3.3–19.4 mg/L[24] FLCλ: 5.7–26.3 mg/L[24] k:λ ratio: 0.3–1.2[24]	• An involved:uninvolved sFLC ratio ≥ 100 is considered a MDE[3] • A ≥ 25% increase from baseline in the difference between involved and uninvolved FLC levels suggests progressive disease. The absolute increase must be > 10 mg/dL[23,‡] ‡Only in patients without measurable serum and urine M-protein levels.
Lactate Dehydrogenase (LDH)	Adult ≤ 60 years: 100–190 U/L[9] Adult > 60 years: 110–210 U/L[9]	• Elevated LDH is predictive of poor prognosis in MM[15]

MM = multiple myeloma; MDE = myeloma defining event; κ = kappa; λ = lambda; β = beta; ISS = International Staging System; Ig = immunoglobulin.

Urine Tests

URINE TESTS	REFERENCE RANGE	RELEVANCE IN MM
24-Hour Total Urine Protein	50–80 mg/24h (at rest)[9]	• A 24-hour urine collection should be completed for all patients with suspected or established MM to calculate the amount of proteinuria[15]
Urine Protein Electrophoresis (UPEP)	Abnormal UPEP Showing M-spike of Myeloma[1] 	• The presence of M-protein in the urine will present as an M-spike on electrophoresis[22] • An increase of ≥ 25% from baseline in urine M-protein suggests progressive disease[23,*] *Absolute increase must be ≥ 200 mg/24h.
Urine Immunofixation Electrophoresis (UIFE)	SP G A M κ λ  Reproduced with permission from ASH Image Bank. 2014. ©The American Society of Hematology.[14]	• If the UPEP demonstrates the presence of an M-protein, UIFE should be done to determine what subtype of M-protein is present[22]

MM = multiple myeloma; κ = kappa; λ = lambda.

Bone Tests

BONE MARROW ASPIRATION AND BIOPSY	REFERENCE RANGE	RELEVANCE IN MM
Plasma Cell Count	Plasma cell percentage: < 5%[25]	• A diagnosis of MM is confirmed with clonal BM plasma cells ≥ 10%[3] • Clonal BM plasma cells ≥ 60% is considered a MDE[3]
Metaphase Karyotyping (Test used only in the diagnosis of MM, not for monitoring/follow-up.)	Photographic representation of the chromosomes of a single cell, cut and arranged in pairs based on banding pattern and size[26]	• Genomic abnormalities influence risk and prognosis
Fluorescence in Situ Hybridization (FISH)	Determines presence of specific chromosome abnormalities associated with MM [eg, del17p, t(14;20), and t(14;16)][27]	• FISH is an important factor in the mSMART 2.0 risk stratification system[27] • Del17p, t(14;20), and t(14;16) myeloma are considered high-risk disease indicators[27] • Prognosis and treatment plans may differ depending on specific genetic mutations present and level of disease risk[27]

MM = multiple myeloma; BM = bone marrow; MDE = myeloma defining event.

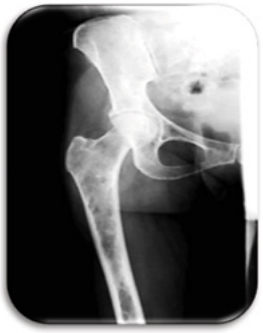
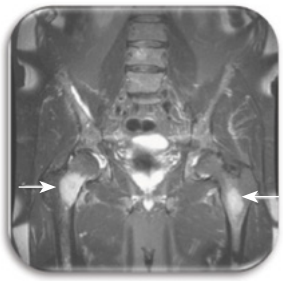
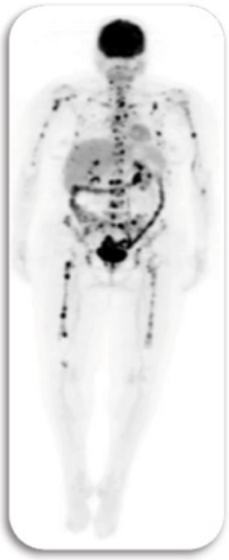
Risk Stratification of Active MM: mSMART 2.0[27,28]

MM risk stratification by mSMART 2.0 is defined by cytogenetic features. A risk-adapted approach provides optimal therapy to patients, ensuring intense therapy for aggressive disease and providing sufficient but less intense therapy for low-risk disease to minimize toxic effects.

STANDARD RISK	INTERMEDIATE RISK	HIGH RISK
All others including • t(11;14) • t(6;14) • Trisomies	• FISH – t(4;14) – 1q amp • High "S" phase	• FISH – Del17p – t(14;16) – t(14;20) • GEP – High-risk signature • Primary refractory disease • Relapse < 12 months from ASCT • Progression within the first year of diagnosis

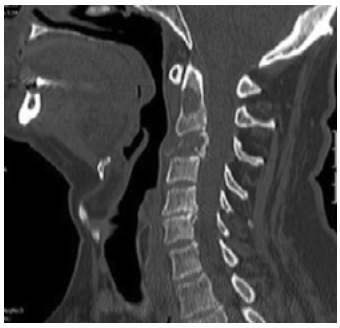
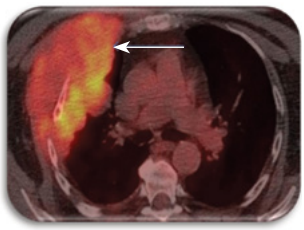
ASCT = autologous stem cell transplant; MM = multiple myeloma; mSMART = Mayo Stratification of Myeloma and Risk-Adapted Therapy; FISH = fluorescence in situ hybridization; GEP = gene expression profiling.

Bone Imaging Tests

RADIOLOGY	RELEVANCE IN MM	EXAMPLE IMAGE
X-ray Skeletal Survey	• Skeletal destruction is a characteristic complication of the uncontrolled growth of myeloma cells[1] • Presence of ≥ 1 osteolytic lesions on skeletal radiography is considered a MDE[3] • Development of definite new or a definite increase in the size of existing bone lesions may suggest PD[23]	 Reproduced with permission from ASH Image Bank. © 2001. American Society of Hematology. Skeletal survey image was originally published in ASH Image Blood bank.[14]
Magnetic Resonance Imaging (MRI)	• MRI is the gold-standard method for the detection of bone marrow involvement in MM[29] • > 1 focal lesion on MRI is a MDE[2,3,*,†] • Development of definite new or a definite increase in the size of existing bone lesions may suggest PD[23] *Additional testing (whole-body MRI or PET/CT scan) recommended to discern active from smoldering myeloma if skeletal survey is negative. †Each focal lesion must be 5 mm or more in size.	T2-Weighted, Fat-Suppressed, Coronal MRI Image of the Pelvis Confirms the Presence of Bilateral Lesions (arrows)[30]  Reprinted from "Imaging Patients With Myeloma," Volume 64, Edition 1. Winterbottom AP and Shaw AS. pages 1-11, © 2009, with permission from Elsevier.[30]
Positron Emission Tomography (PET)	• Active MM is positive on a PET scan[2] • May detect early BM involvement in patients with solitary plasmacytoma[2] • Please see PET/CT Scan on the next page for additional information	PET Image of MM Patient With Focal Lesions[31] 

CT = computed tomography; MM = multiple myeloma; MDE = myeloma defining event; PD = progressive disease; BM = bone marrow.

Bone Imaging Tests Continued

RADIOLOGY	RELEVANCE IN MM	EXAMPLE IMAGE
Computed Tomography (CT)	• Presence of ≥ 1 osteolytic lesions on CT is considered a MDE[3] • CT scans are recommended under certain situations for follow-up of solitary plasmacytomas and smoldering MM[2] • Development of definite new or a definite increase in the size of existing bone lesions may suggest PD[23]	CT Scan of Osteolytic Lesions[32] 
PET/CT Scan	• More sensitive than plain radiographs and indicated when symptomatic areas show no abnormality on routine radiographs[2] • Recommended as follow-up for solitary plasmacytoma or smoldering/asymptomatic MM as clinically indicated[2] • Presence of ≥ 1 osteolytic lesions on PET/CT is considered a MDE[2,3,*,†] *If BM has less than 10% clonal plasma cells, more than 1 bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. †One of the definitions of active/symptomatic MM is bone disease (lytic or osteopenic) with ≥ 1 bone lesions on skeletal radiography, CT, or PET/CT.	Axial Fused PET/CT Thorax at the Level of the Pulmonary Bifurcation With Large Right-Sided Chest Wall Plasmacytoma[33] 

MM = multiple myeloma; MDE = myeloma defining event; PD = progressive disease; PET/CT = positron emission tomography/computed tomography; BM = bone marrow.

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