MYELOMA FAST FACTS

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

Useful Laboratory Tests in Myeloma

Haematological Test	Reference Values*	
	Male	Female
Red blood cell count [1]	4.5 – 6.5 x 10^{12}/L	3.9 – 5.6 x 10^{12}/L
White blood cell count [1]	4.0 – 11.0 x 10^{9}/L	4.0 – 11.0 x 10^{9}/L
Platelet count [1]	150 – 400 x 10^{9}/L	150 – 400 x 10^{9}/L
White blood cell differential [1]		
• Neutrophils	2.0 – 7.5 x 10^{9}/L (40 – 75%)	2.0 – 7.5 x 10^{9}/L (40 – 75%)
• Lymphocytes	1.3 – 3.5 x 10^{9}/L (20 – 45%)	1.3 – 3.5 x 10^{9}/L (20 – 45%)
• Eosinophils	0.04 – 0.44 x 10^{9}/L (1 – 6%)	0.04 – 0.44 x 10^{9}/L (1 – 6%)
• Monocytes	0.2 – 0.8 x 10^{9}/L (2 – 10%)	0.2 – 0.8 x 10^{9}/L (2 – 10%)
• Basophils	0 (0-1%)	0 (0-1%)
Haematocrit (PCV) [1]	0.40 – 0.52	0.36 – 0.48
Haemoglobin [1]	13.5 – 18.0 g/dL	11.5 – 16.0 g/dL
Erythrocyte sedimentation rate (ESR) [2]	up to 15 mm/hour	up to 20 mm/hour
Plasma viscosity [1]	1.50 – 1.70 cP	1.50 – 1.70 cP

** Reference values may vary slightly from laboratory to laboratory. These figures are provided for guidance only. Please contact your local laboratory for your hospital-specific ranges*

1. *General Practice Notebook (www.gpnotebook.co.uk). Accessed 1st December 2010.*
2. *Medical Encyclopedia. National Library of Medicine. http://www.nlm.nih.gov/medlineplus/encyclopedia.html. Accessed 1st December 2010*

Useful Laboratory Tests (cont.)

Serum Test	Normal Values
Blood urea nitrogen (BUN)* [1]	7 – 20 mg/dL
Serum creatinine [1]	0.8 – 1.4 mg/dL
Creatinine clearance* [1]	Male: 97 - 137 ml/min Female: 88 - 128 ml/min
Serum calcium [1]	8.5 – 10.2 mg/dL
Serum albumin [1]	3.4 – 5.4 g/dL
Electrophoresis of serum & concentrated urine [1]	Absence of monoclonal band
Quantitation of non-isotypic immunoglobulins [2]	Not applicable
Serum immunofixation [1]	Absence of monoclonal band
• IgG [3] • IgA [3] • IgM [3] • IgD [3] • IgE [3] • Free light chain κ [4] • Free light chain λ [4]	85 – 385 mg/dL 565 – 1765 mg/dL 55 – 375 mg/dL 5 – 30 µg/L 10 – 1421 µg/L 3.3 – 19.4 mg/L 5.71 – 26.3 mg/L
Urine Tests [2]	
Urine protein Urine electrophoresis: absence of monoclonal peak Urine immunofixation: absence of monoclonal band	

**Serum creatinine offers an alternative measure of renal function, although the glomerular filtration rate (GFR) or creatinine clearance are preferred whenever renal disease is suspected or careful dosing of nephrotoxic drugs is required. The creatinine clearance can be estimated using the Cockgroft-Gault formula:*

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [\,0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

1. *Medical Encyclopedia. National Library of Medicine. http://www.nlm.nih.gov/medlineplus/encyclopedia.html. Accessed 1st December 2010*
2. *UK Myeloma Forum Guidelines Working Group. Guidelines on the diagnosis and management of multiple myeloma. Br J Haematol 2005; 132: 410-415*
3. *WebMd. Immunoglobulins. http://www.webmd.com/a-to-z-guides/immunoglobulins?page=2. Accessed 1st December 2010*
4. *Katzmann et al. (2002) Serum reference intervals and diagnostic ranges for free κ and free λ immunoglobulin light chains: relative sensitivity for detection of monoclonal light chains. Clin Chem; 48(9): 1437-1444*

Diagnostic Criteria in Myeloma UKMF Criteria[1]

	Myeloma*	MGUS**
Marrow plasma cells	>10% on aspirate	<10% on aspirate
Serum paraprotein	Variable serum concentration; no specific diagnostic levels	IgG usually <20 g/L IgA usually <10 g/L
Bence – Jones proteinuria	>50% cases	Rare
Lytic bone lesions	Often present	Absent
Symptoms	Frequent	Absent
Anaemia	Frequent	Absent
Hypercalcaemia	May be present	Absent
Abnormal renal function	May be present	Absent

** Myeloma diagnosed if >10% plasma cells in marrow aspirate and serum monoclonal protein or lytic bone lesions on X-ray*

*** MGUS – monoclonal gammopathy of undetermined significance.*

Diagnostic criteria for multiple myeloma requiring systemic therapy[2]

Presence of an M-component in serum and/or urine plus clonal plasma cells in the bone marrow and/or a documented clonal plasmacytoma.

PLUS one or more of the following (CRAB Criteria):

Calcium elevation (>11.5mg/dl) [>2.65mmol/L]

Renal insufficiency (creatinine >2mg/dl) [177µmol/L or more]

Anaemia (haemoglobin <10g/dl or 2mg<normal) (haemoglobin <12.5mmol/L or 1.25mmol/L<normal)

Bone disease (lytic lesion or osteopenia)

1. *UK Myeloma Forum. British Committee for Standards in Haematology. (2001) Diagnosis and management of multiple myeloma. British Journal of Haematology 115: 522-40.*
2. *Durie, BGM et al. (2006) International uniform response criteria for multiple myeloma. Leukemia 20 (10): 1467-1473*

IMWG Criteria [1]

MGUS	Smouldering myeloma (asymptomatic myeloma)	Multiple myeloma
All 3 criteria must be met	*Both criteria must be met*	*All 3 criteria must be met except as noted*
Serum monoclonal protein <3 g/100 ml	Serum monoclonal protein (IgG or IgA) ≥3 g/100 ml and/or clonal bone marrow plasma cells ≥10%	Clonal bone marrow plasma cells ≥ 10%
Clonal bone marrow plasma cells <10%	Absence of end-organ damage such as lytic bone lesions, anaemia, hypocalcaemia or renal failure that can be attributed to a plasma cell proliferative disorder	Presence of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma)
Absence of end-organ damage such as hypocalcaemia, renal insufficiency, anaemia and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder		Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: • Hypocalcaemia: serum calcium ≥ 11.5 mg/100 ml or • Renal insufficiency: serum creatinine >1.73 mmol/l) • Anaemia: normochromic, normocytic with a haemoglobin value of >2 g/100 ml below the lower limit of normal or a haemoglobin value <10 g/100 ml • Bone lesions: lytic lesions, severe osteopenia or pathologic fractures

1. *Kyle, R. A.; Rajkumar, S. V. (2009) Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia; 23(1): 3-9*

Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) 2.0. Classification of active myeloma [1]

High Risk	Intermediate Risk [a]	Standard Risk [ab]
FISH • Del 17p • t(14;16) • t(14;20) GEP • High risk signature	FISH • t(4;14)[c] Cytogenetic deletion 13 or hypodiploidy PCLI ≥ 3%	All others including: • Hyperdiploid • t(11;14)[d] • t(6;14)

a Note that a subset of patients with these factors will be classified as high-risk by GEP

b LDH > upper limit of normal and β_2M > 5.5 may indicate worse prognosis

c Prognosis is worse when associated with high β_2M and anaemia

d t(11;14) may be associated with plasma cell leukaemia

Durie and Salmon Staging System [2]

Stage	Features

Stage I - Low tumour mass (<0.6 x 10^{12}cells/m^2)	All of the following:
	• Haemoglobin > 10 g/dL
	• Low paraprotein
	  • *Serum IgG < 5 g/dL; serum IgA < 3 g/dL*
	  • *Urine κ or λ light chains < 4 g/24 hours*
	• Normal serum calcium
	• Normal bone structure or only one lytic bone lesion

Stage II - Intermediate tumour mass (0.6–1.2 x 10^{12} cells/m^2)	Features intermediate between Stage I and Stage III

Stage III - High tumour mass (>1.2 x 10^{12} cells/m^2)	One or more of the following:
	• Haemoglobin < 8.5 g/dL
	• High paraprotein
	  • *Serum IgG > 7 g/dL; serum IgA > 5 g/dL,*
	  • *Urine κ or λ light chains > 12 g/24 hours*
	  • *Serum calcium > 12.0 mg/dL*
	  • *Advanced lytic bone lesions (scale 3)*

Sub classification of stages: A. Creatinine < 2.0 mg/dL; B. Creatinine ≥ 2.0 mg/dL

1. *mSMART guidelines for newly diagnosed myeloma. www.msmart.org (accessed 3rd Dec 2010)*

2. *Durie BG, Salmon SE. (1975) A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. Cancer; 36, 842-854.*

International Staging System [1]

Stage	Features
Stage 1	β_2M < 3.5 mg/L; albumin ≥ 3.5 g/dL
Stage 2	β_2M < 3.5 mg/L; albumin < 3.5 g/dL or β_2M 3.5 – 5.5 mg/L
Stage 3	β_2M ≥ 5.5 mg/L

β_2M – serum β_2 Microglobulin level; albumin – serum albumin level

Age is the only other factor that significantly affects outcome: survival > 5 years is associated with age <60 years and for < 2 years with age > 60 years. Other correlations include platelet count <130 x 10^9/L and/or serum LDH above normal. Cytogenetics also influence outcome. However, chr13 deletion and complex chromosome abnormalities do not add to the impact of age, β_2M and albumin.

International Myeloma Working Group uniform response criteria [2]

Response Category	Response Criteria
Complete Response (CR) *	Negative immunofixation of serum and urine and Disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow
Stringent complete response (sCR)	CR as defined above plus Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR)*	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h

**Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.*

1. *Greipp PR, San Miguel J, Durie BG, et al. (2005) International staging system for multiple myeloma. Journal of Clinical Oncology 20;23(15):3412-20.*
2. *Kyle, R. A.; Rajkumar, S. V. (2009) Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia; 23(1): 3-9*

International Myeloma Working Group uniform response criteria [1]

Response Category	Response Criteria
Partial response (PR)	≥50% reduction of serum M protein and reduction in 24-h urinary M protein by ≥90% or to <200 mg per 24h If the serum and urine M protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M protein criteria. If serum and urine M protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥30% In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease (PD)†	Increase of 25% from lowest response value in any one or more of the following: • Serum M-component (absolute increase must be ≥0.5 g/100 ml)† and/or • Urine M-component (absolute increase must be ≥200 mg per 24 h) and/or • Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/l) • Bone marrow plasma cell percentage (absolute % must be ≥10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcaemia (corrected serum calcium >11.5 mg/100 ml) that can be attributed solely to the plasma cell proliferative disorder

All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; complete, PR and SD categories also require e no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

†For progressive disease, serum M-component increases of ≥1 gm/100 ml are sufficient to define relapse if starting M-component is ≥5 gm/100 ml.

1. *Kyle, R. A.; Rajkumar, S. V. (2009) Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia; 23(1): 3-9*

Assessment of Response in Myeloma EBMT Criteria [1]

Response Category	Definition
Complete remission (CR)	All of the following: • Absence of paraprotein in serum and urine by immunofixation, maintained for six weeks • <5% plasma cells in bone marrow aspirate and trephine bone biopsy, if biopsy performed; if absence of M protein is sustained for six weeks, it is not necessary to repeat the bone marrow biopsy, except in patients with non secretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR • No increase in size or number of lytic bone lesions • Disappearance of soft tissue plasmacytomas
Near – Complete response (nCR)*	Fulfils all of the criteria for CR except that M protein is detectable by immunofixation only.
Partial response (PR)	*All of the following:* • ≥ 50% reduction in serum paraprotein, maintained for six weeks • Reduction in 24 hour urinary light chain excretion either by ≥ 90% or to <200 mg, maintained for six weeks • For patients with non secretory myeloma only, ≥ 50% reduction in plasma cells in bone marrow aspirate and trephine biopsy, if biopsy is performed, maintained for a minimum of six weeks • ≥ 50% reduction in the size of soft tissue plasmacytomas • No increase in size or number of lytic bone lesions
Minimal response (MR)	All of the following: • 25 – 49% reduction in serum paraprotein level maintained for a minimum of six weeks • 50 – 89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24 hours, maintained for a minimum of six weeks • For patients with non secretory myeloma only, 25 – 49% reduction in plasma cells in bone marrow aspirate and trephine biopsy, if biopsy performed, maintained for six weeks • 25 – 49% reduction in size of soft tissue plasmacytomas • No increase in the size or number of lytic bone lesions

** nCR is not a recognised EBMT response category but is included here because of its relevance to practicing physicians and its use in recent myeloma studies.*

1. *Blade J, Samson D, Reece D, et al (1998) Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. British Journal of Haematology, 102, 1115-23*

EBMT Criteria (Cont.)[1]

Response Category	Definition
No change	Not meeting the criteria of either MR or progressive disease
Plateau	Stable values (within ± 25% value at the time response is assessed) maintained for at least three months
Relapse from CR	At least one of the following: • Reappearance of serum or urine paraprotein on immunofixation or electrophoresis, confirmed by at least one other investigation • ≥ 5% plasma cells in marrow aspirate or trephine bone biopsy • Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions • Development of hypercalcaemia not attributable to other cause
Progressive disease	One or more of the following: • > 25% increase in serum paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed by at least one repeated investigation • > 25% increase in 24 hour light chain excretion, which must also be an absolute increase of at least 200 mg/24 hours and confirmed by at least one repeated investigation • > 25% increase in plasma cells in marrow aspirate or trephine biopsy, which must also be an absolute increase of at least 10% • Definite increase in size of existing bone lesions or soft tissue plasmacytomas • Development of new bone lesions or soft tissue plasmacytomas • Development of hypercalcaemia not attributable to other cause

1. *Blade J, Samson D, Reece D, et al (1998) Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. British Journal of Haematology, 102, 1115-23*

NCI Common Terminology Criteria for Adverse Events [1]

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalisation indicated	-
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	≥ 6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalisation indicated	Life-threatening consequences; urgent intervention indicated
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated

1. *Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0 (http://ctep.cancer.gov), Publish Date: May 28, 2009*

NCI Common Terminology Criteria for Adverse Events [1]

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	—
Fever	38.0 - 39.0 ^{o}C (100.4 - 102.2 ^{o}F)	>39.0 - 40.0 ^{o}C (102.3 - 104.0 ^{o}F)	>40.0 ^{o}C (>104.0 ^{o}F) for ≤ 24 hrs	>40.0 ^{o}C (>104.0 ^{o}F) for >24 hrs
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paraesthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalisation indicated	Life-threatening and urgent intervention indicated
Neutrophil count decreased	<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
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9 /L	<25,000/mm^3; <25.0 x 10^9 /L

ADL: Activities of daily living. TPN: Total parenteral nutrition. LLN: Lower limit of normal

1. *Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0 (http://ctep.cancer.gov), Publish Date: May 28, 2009*

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