

# Diagnosis and staging

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## Diagnostic criteria

Multiple myeloma (MM) is a plasma cell disorder characterized by a clonal proliferation of cells producing a homogeneous plasma protein of monoclonal character (M-protein or paraprotein), restricted by kappa or lambda light chains, which are detected in the serum and/or urine [1]. In fact, MM is the prototypical malignant monoclonal gammopathy, where the amount of paraprotein produced by the plasma cell proliferation and immunodeficiency gives rise to the clinical and biological features of the disease. Diagnostic criteria from the International Myeloma Working Group include clonal bone marrow plasma cells  $\geq 10\%$ , the presence of serum and/or urinary monoclonal protein (except in patients with non-secretory multiple myeloma), and evidence of end-organ damage, which can be attributed to the underlying plasma cell proliferative disorder [2].

Symptomatic MM is diagnosed on the basis of symptoms and signs derived from organ or tissue impairment due to M-protein or plasma cell proliferation (Table 2.1) [2]. The main clinical manifestations at diagnosis of MM are shown in Table 2.2 [3].

Initial diagnostic workup in patients with MM is summarized in Table 2.3 [4]. Particular attention should be focused on: (1) baseline values (serum and/or urine M-protein, plasma cell infiltration, serum free light chain [FLC], and extramedullary involvement) for follow-up during treatment; (2) presence and degree of end-organ damage, mainly

summarized under the acronym CRAB (Table 2.1), and other clinical myeloma-related manifestations; and (3) risk-stratification.

## Classification

Monoclonal gammopathies are currently classified into two major groups: malignant and benign (Table 2.4).

Increased serum calcium (>11.5 mg/dL)  
 Renal insufficiency (creatinine >2 mg/dL)  
 Anemia: hemoglobin 2 g/dL below the lower normal limit  
 Bone lesions: lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)  
 Other symptoms: symptomatic hyperviscosity (rare), amyloidosis, recurrent bacterial infections (≥2 episodes in 12 months), and extramedullary plasmacytomas

**Table 2.1 Myeloma-related organ or tissue impairment (end-organ damage) due to the plasma cell proliferative process; also known under the acronym ‘CRAB’ (calcium, renal insufficiency, anemia, or bone lesions).** CT, computed tomography; MRI, magnetic resonance imaging. Adapted from © American Society of Hematology, 2011. All rights reserved. Dimopoulos et al [2].

	Characteristic	Frequency (%)
Clinical manifestations	Bone pain	70
	Anemic syndrome	30
	Weight loss	20
	Infections*	10
	Hepatomegaly	15
	Splenomegaly	5
	Extramedullary plasmacytomas	10–22
Laboratory abnormalities	Hemoglobin <90 g/L	30
	Platelets <100 x 10 <sup>9</sup> /L	<10
	Creatinine ≥2 mg/dL	20–25
	Calcium ≥11.5 mg/dL	15–20
	M-spike isotype:	
	• IgG	55
	• IgA	30
• Light chains (Bence Jones)	15	
• IgD, biclonal, non-secretor	1–2 (each)	
• IgE, IgM	Exceedingly rare	

**Table 2.2 Clinical and laboratory findings in multiple myeloma.** \*Non-infectious fever is extremely infrequent (<1%). IgA/D/E/G/M, immunoglobulin A/D/E/G/M. Adapted from © Mayo Foundation for Medical Education and Research, 2003. All rights reserved. Kyle et al [3].

In most cases, if not all, MM evolves from a premalignant stage of clonal proliferation called monoclonal gammopathy of undetermined significance (MGUS) [5]. Thus, asymptomatic gammopathies are mainly MGUS and the so-called asymptomatic or smoldering MM (SMM), classified into these two categories according to tumor burden (Table 2.5) [6,7].

Complete blood count and differential; peripheral blood smear examination  
 Chemistry studies, including calcium, creatinine,  $\beta_2$ -microglobulin, albumin, and LDH  
 Serum protein electrophoresis  
 24-hour urine collection for urine protein quantification and protein electrophoresis  
 Total immunoglobulin quantification (nephelometry)  
 Serum and urine immunofixation  
 Measurement of serum free light chains  
 Radiological skeletal bone survey  
 Bone marrow aspirate and/or biopsy; morphology and immunophenotype  
 Bone marrow plasma cells cytogenetics (FISH)  
 CT-scan and/or MRI if clinically indicated  
 PET-CT investigation; useful if extramedullary plasmacytomas present or suspected

**Table 2.3 Initial studies for patients with multiple myeloma.** CT, computed tomography; FISH, fluorescence in situ hybridization; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography. Adapted from © Informa PLC, 2014. All rights reserved. Fernández de Larrea et al [4].

<b>Malignant gammopathies</b>	Multiple myeloma
	Symptomatic myeloma
	Smoldering myeloma
	Plasma cell leukemia
	POEMS syndrome (osteosclerotic myeloma)
	Located plasmacytoma
	Solitary bone plasmacytoma
	Extramedullary plasmacytoma
	Waldenström's macroglobulinemia
	Diseases of the heavy chains
	AL (light chains) amyloidosis
<b>Benign gammopathies</b>	Monoclonal gammopathy of undetermined significance
	Transient monoclonal gammopathies associated with immunosuppression or infection (ie, HIV infection, bone marrow transplantation, and solid organ transplantation)

**Table 2.4 Classification of monoclonal gammopathies.** HIV, human immunodeficiency virus; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

Progression to MM and related disease is constant during MGUS evolution (1% per year), being the actuarial and actual probability of malignant transformation at 20 years from diagnosis of 25% and 11%, respectively [8]. IgM MGUS has a predilection for developing into Waldenström's macroglobulinemia or other lymphoproliferative disorders; other isotypes progress mainly to MM [9]. However, in SMM the risk of progression is higher in the first 5 years of follow-up (10% per year), changing to a MGUS-like progression profile beyond the first 5 years from diagnosis [10].

Plasma cell leukemia (PCL) is a rare and aggressive variant of myeloma characterized by the presence of circulating plasma cells. Present diagnostic criteria include more than 20% and/or an absolute count greater than

<b>IgG or IgA gammopathies*</b>		
<b>MGUS</b>	<b>Smoldering myeloma</b>	<b>Multiple myeloma</b>
Serum monoclonal protein <30 g/L, and	Serum monoclonal protein $\geq 30$ g/L, and/or	Serum and/or urinary monoclonal protein*, and
Clonal bone marrow plasma cells <10%, and	Clonal bone marrow plasma cells $\geq 10\%$ , and	Clonal bone marrow plasma cells $\geq 10\%$ , and
Absence of end-organ damage	Absence of end-organ damage	Evidence of end-organ damage attributed to plasma cell proliferative disorder
<b>IgM gammopathies**</b>		
<b>IgM MGUS</b>	<b>Smoldering Waldenström's macroglobulinemia</b>	<b>Waldenström's macroglobulinemia</b>
Serum monoclonal protein <30 g/L, and	Serum IgM monoclonal protein $\geq 3$ g/dL and/or	IgM monoclonal gammopathy, and
Clonal bone marrow lymphoplasmacytic cells <10%, and	Bone marrow lymphoplasmacytic infiltration $\geq 10\%$ , and	$\geq 10\%$ bone marrow lymphoplasmacytic infiltration, and
Absence of end-organ damage	Absence of end-organ damage	Evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly attributed to the lymphoproliferative disorder

**Table 2.5 Classification of asymptomatic gammopathies.** \*Except in patients with true non-secretory multiple myeloma. \*\* For idiopathic Bence Jones (smoldering myeloma) proteinuria all criteria must be met: urinary monoclonal protein on urine protein electrophoresis  $\geq 500$  mg/24 h and/or clonal bone marrow plasma cells  $\geq 10\%$ , no immunoglobulin heavy-chain expression on immunofixation and absence of end-organ damage. IgA/G/M, immunoglobulin A/G/M; MGUS, monoclonal gammopathy of undetermined significance. Adapted from © Nature Publishing Group, 2010. All rights reserved. Kyle et al [6]. Adapted from © American Society of Hematology, 2011. All rights reserved. Korde et al [7].

$2 \times 10^9/L$  circulating plasma cells. The clinical picture is characterized by an aggressive clinical presentation with high tumor burden, extramedullary involvement, marked bone marrow infiltration by immature plasma cells, increased incidence of light-chain only (Bence Jones) type and high lactate dehydrogenase (LDH) serum levels [11].

## Prognosis

Prognostic factors may be related to the patient, the tumor clone and/or related to tumor mass:

- Patient: advanced age and poor performance status (ECOG) are two independent prognostic factors. Survival, particularly those under 60 years, has increased significantly during the last 10 years [12]. Renal function is also consistently associated with a shortened survival [13].

Disease	Aneuploidies	Balanced translocations	Deletions	Other abnormalities
Multiple myeloma	70% normal karyotype	t(4;14)(p16;q32) (15%)	Monosomy/deletion 13 chromosome (40%)	1q 21 amplification (30%)
	Hyperdiploidy (50%): odd chromosomes 3, 5, 7, 9, 11, 15, 19, and 21	t(14;16)(q32;q23) (15%)	17p13 deletion (5–10%)	
	No hyperdiploidy: hypodiploidy (20%), pseudodiploidy, and tetraploidy	t(11;14)(q13;q32) (5%)	1p21 deletion (15%)	
Plasma cell leukemia	Hipodiploidy (40%)	t(11;14)(q13;q32) (50%)	Monosomy/deletion 13 chromosome (50–80%)	1q 21 amplification (60%)
	Complex karyotype (40%)	chg	17p13 deletion (50%)	
AL amyloidosis	Hyperdiploidy (50%)	t(11;14)(q13;q32) (50%)	Monosomy/deletion 13 chromosome (30%)	1q 21 amplification (20%)
		t(14;16)(q32;q23) (2%)		

**Table 2.6 Cytogenetic abnormalities identified in malignant gammopathies.** Adapted from © Nature Publishing Group, 2009. All rights reserved. Fonseca et al [14].

- Tumor clone: a number of features, such as immature or plasmablastic morphology of plasma cells, proliferative index (S phase) or less than 5% plasma cells that are phenotypically normal in the bone marrow at the time of diagnosis, are associated with worse prognosis [2]. However, the most important prognostic factor is the cytogenetic status, mainly detected by fluorescence in situ hybridization (FISH) (Table 2.6) in isolated CD138 plasma cells. High-risk abnormalities include t(4,14) (p16,q32), t(14,16) (q32, q23), deletion of 17p13, abnormalities of chromosome 1 (1q gains, 1p losses), deletion of chromosome 22, and hypodiploidy. By contrast, the presence of the t(11,14) (q13, q32) or 9, 11 and 17 trisomies, and hyperdiploidy are associated with good or average prognosis [14–16].
- Tumor mass: the staging system published in 1975 by Durie and Salmon established a relationship between tumor mass and M-protein through mathematical models and has been widely used (Table 2.7) [17]. However, the International Staging System (ISS), validated in 10,750 patients, is the most reproducible and easy

Stage	Criteria	Tumor burden (cells × 10 <sup>12</sup> /m <sup>2</sup> )
I	All the following: <ul style="list-style-type: none"> <li>• Hb &gt;100 g/L</li> <li>• Normal calcium</li> <li>• Normal skeletal survey, single plasmacytoma or osteoporosis</li> <li>• Serum paraprotein level</li> <li>• IgG &lt;50 g/L</li> <li>• IgA &lt;30 g/L</li> <li>• Urine light chain excretion &lt;4 g/24 h</li> </ul>	<0.6
II	Fulfilling the criteria of neither I nor III	0.6–1.2
III	One or more of the following: <ul style="list-style-type: none"> <li>• Hb &lt;85 g/L</li> <li>• Calcium &gt;12 mg/dL</li> <li>• Skeletal survey: advanced lytic bone lesions;</li> <li>• Serum paraprotein</li> <li>• IgG &gt;70 g/L</li> <li>• IgA &gt;50 g/L</li> <li>• Urine light chain excretion &gt;12 g/24 h</li> </ul>	>1.2

**Table 2.7 Durie and Salmon prognostic staging system.** Stages can be divided depending on serum creatinine: (A) serum creatinine <2 mg/dL; and (B) serum creatinine ≥2 mg/dL. Hb, hemoglobin; IgA/G, immunoglobulin A/G. Adapted from © John Wiley & Sons, Inc, 1975. All rights reserved. Durie and Salmon [17].

classification for MM at diagnosis, only requiring two biochemical values: albumin and  $\beta_2$ -microglobulin (Table 2.8) [18].

## Imaging

Several imaging techniques can be used for the assessment of bone and soft-tissue involvement in MM [2,19]:

- Skeletal survey remains the standard method for imaging screening at diagnosis and is readily available at a modest cost, although its limitations in sensitivity must be noted.
- Magnetic resonance imaging (MRI) or computed tomography (CT) should be performed when extramedullary involvement (EM) is suspected (ie, non-skeletal severe localized pain, palpable masses, or suspected nervous system involvement [spinal cord compression or cranial nerve palsies]). An MRI of the spine and pelvis is mandatory in all patients with a presumed diagnosis of solitary plasmacytoma of the bone, spinal cord compression, and pre-kypho- or vertebroplasty [20].
- [18F]fluorodeoxyglucose positron emission tomography (PET/CT) may be particularly useful in extramedullary disease evaluation, allowing the measurement in size and metabolic activity of soft-tissue masses, similar to the lymphoma setting [20].

## Response criteria

Measurability of the disease is a critical issue in MM that also has an impact on the follow-up of patients in daily clinical practice. Most of the patients, particularly at diagnosis, will have measurable disease in their serum and/or urine, defined by at least 10 g/L and/or light chain urine protein excretion higher than 200 mg in a 24-hour urine specimen. Therefore, paraprotein monitoring is mandatory in patients

Stage	Criteria
I	Serum $\beta_2$ -microglobulin <3.5 mg/L and serum albumin $\geq$ 3.5 g/dL
II	Neither stage I nor stage III
III	Serum $\beta_2$ -microglobulin $\geq$ 5.5 mg/L

**Table 2.8 International Staging System (ISS) for multiple myeloma.** Adapted from © American Society of Clinical Oncology, 2005. All rights reserved. Greipp et al [18].

with a secretory monoclonal gammopathy. Oligosecretory MM are under these thresholds but with positive immunofixation; truly non-secretory myelomas are rare ( $\approx 1\%$ ).

The first modern and still used classification for the assessment of response to treatment in MM is the one developed by the European Society for Blood and Marrow Transplantation (EBMT) group (Table 2.9) [21]. Complete remission (CR) was defined as the disappearance of the M-protein by serum and urine immunofixation, along with the disappearance of plasmacytomas and normal numbers of bone marrow plasma cells. These three elements (serum and urine component, medullary disease, and extramedullary involvement) constitute the basis of MM response evaluation.

A uniform classification by the International Myeloma Working Group (IMWG) has been more recently developed (Table 2.10) [22].

This classification is currently used as standard response criteria worldwide. Complete remission and partial remission categories were defined as per the (EBMT) criteria. One of the major amendments was the incorporation of the definition of ‘stringent complete remission’ (sCR).

Response category*	Criteria
Complete remission	All the following criteria: <ul style="list-style-type: none"> <li>• Negative immunofixation (serum and urine)**</li> <li>• &lt;5% bone marrow plasma cells</li> <li>• Disappearance of soft tissue plasmacytomas</li> </ul>
Partial response	All the following criteria: <ul style="list-style-type: none"> <li>• <math>\geq 50\%</math> serum M-protein <math>\downarrow</math></li> <li>• <math>\geq 90\%</math> urine M-protein <math>\downarrow</math> or &lt; 200 mg/24 h</li> <li>• <math>\geq 50\%</math> <math>\downarrow</math> soft tissue plasmacytomas</li> </ul>
Minimal response	All the following criteria: <ul style="list-style-type: none"> <li>• 25–49% serum M-protein <math>\downarrow</math></li> <li>• 50–89% urine M-protein <math>\downarrow</math></li> <li>• 25–49% <math>\downarrow</math> soft tissue plasmacytomas</li> </ul>
Stable disease	Not meeting criteria for minimal response nor partial response

**Table 2.9 EBMT, IBMTR, ABMTR criteria for definition of response, relapse, and progression in patients with multiple myeloma treated by high-dose therapy and stem cell transplantation.** \*All response categories must be maintained at least 6 weeks. \*\*Excluding oligoclonal bands. ABMTR, Autologous Blood and Marrow Transplant Registry; EBMT, European Society for Blood and Marrow Transplantation; IBMTR, International Bone Marrow Transplant Registry. Adapted from © Blackwell Science Ltd, 1998. All rights reserved. Bladé et al [21].

Another novel concept was the definition of ‘very good partial response’ (VGPR), requiring a 90% reduction of serum M-spike reduction, which was more stringent with urine criteria. Other minor changes included the elimination of the mandatory 6-week wait time to confirm achievement of response required by the EBMT and incorporation of response criteria for the serum FLC assay to enable assessment of response in patients with oligo- and non-secretory disease.

For PCL, no previous specific criteria had been described. Traditionally, EBMT and/or IMWG criteria have been used without distinctive considerations, such as the leukemic nature of the disease, and the relative higher percentage of light-chain only (Bence Jones) and oligosecretory forms. Evaluation of response in primary PCL is based on a combination of acute leukemia and MM response criteria (Table 2.11) [11]. High frequency of extramedullary involvement requires additional evaluation by imaging techniques such as MRI and, particularly, PET/CT.

In the EBMT criteria, progression and relapse were defined according to the previous response achieved in the patients (less than complete remission [partial response, very good partial response] or complete

Response category*	Criteria
Complete remission	All the following criteria: <ul style="list-style-type: none"> <li>• Negative immunofixation (serum and urine)</li> <li>• &lt;5% bone marrow plasma cells</li> <li>• Disappearance of soft tissue plasmacytomas</li> </ul>
Stringent complete remission	As above plus: <ul style="list-style-type: none"> <li>• Normal serum free light-chain ratio</li> <li>• Absence of clonal plasma cells**</li> </ul>
Very good partial response	All the following criteria: <ul style="list-style-type: none"> <li>• <math>\geq 90\%</math> serum M-protein <math>\downarrow</math></li> <li>• Urine M-protein &lt;100 mg/24 h</li> </ul>
Partial response	All the following criteria: <ul style="list-style-type: none"> <li>• <math>\geq 50\%</math> serum M-protein <math>\downarrow</math></li> <li>• <math>\geq 90\%</math> urine M-protein <math>\downarrow</math> or &lt;200 mg/24 h</li> <li>• <math>\geq 50\%</math> <math>\downarrow</math> soft tissue plasmacytomas</li> </ul>

**Table 2.10 IMWG criteria for evaluating response in patients with multiple myeloma.** \*All response categories require two consecutive measurements made at any time. \*\*Bone marrow plasma cells analyzed by immunohistochemistry and/or multiparametric flow cytometry. IMWG, International Myeloma Working Group. Adapted from © Nature Publishing Group, 2006. All rights reserved. Durie et al [22].

remission, respectively) (Table 2.12) [21]. For partial response, it is important to consider the lower M-protein value as nadir or point of comparison to analyze the absolute and relative increase. When evaluating complete remission, the appearance of a serum M-protein that is different from that observed at diagnosis should be taken into account. This oligoclonal phenomenon is almost exclusively restricted to patients in complete remission compared with other degrees of response, and

Category	Bone marrow criteria	Peripheral blood criteria	Serologic criteria
Stringent complete remission	Bone marrow plasma cells <5% No malignant plasma cell by flow cytometry	No plasma cells in peripheral blood by flow cytometry	Negative serum and urine immunofixation Normal serum FLC ratio
Complete remission	Bone marrow plasma cells <5%	No plasma cells in peripheral blood	Negative serum and urine immunofixation
Very good partial response	Bone marrow plasma cells <5%	No plasma cells in peripheral blood	≥90% reduction of serum M-protein, and 24 h urinary M-protein <100 mg per 24 h
Partial response	Bone marrow plasma cells from 5% to 25%	Peripheral plasma cell from 1% to 5%	≥50% reduction of serum M-protein and Reduction in 24 h urinary M-protein by ≥90% and <200 mg per 24 h

**Table 2.11 Response criteria for plasma cell leukemia.** FLC, free light chain. Adapted from © Nature Publishing Group, 2013. All rights reserved. Fernández de Larrea et al [11].

Response Category	Criteria
Progressive disease*	25% and >5 g/L serum M-protein ↑ 25% and >200 mg/24 h urine M-protein ↑ Bone marrow plasma cells >25% and absolute increase ≥10% New lytic lesions, plasmacytomas or hypercalcemia
Relapse from complete remission*	Paraprotein reappearance (excluding oligoclonal reconstitution) Bone marrow plasma cells >5% New lytic lesions, plasmacytomas, or hypercalcemia

**Table 2.12 EBMT criteria for relapsing/progressing multiple myeloma.** \*Confirmed on at least one repeated sample. EBMT, European Society for Blood and Marrow Transplantation. Adapted from © Blackwell Science Ltd, 1998. All rights reserved. Bladé et al [21].

is associated with a significantly longer progression-free and overall survival [23]. At the time of relapse, the original M-protein reappears.

The IMWG criteria for progression are similar to the EBMT criteria (Table 2.13) [22]. Specific modifications for patients relapsing from complete remission have been proposed as the following: an increase  $\geq 25\%$  plus the absolute number of more than 5 g/L of the serum M-protein and/or  $>200$  mg/24 h in the urine M-protein. Minimal response should be reported separately in clinical trials. When minimal response is reported, the specific rate of minimal response should be distinguished from partial response or better.

## Minimal residual disease

Achievement of immunofixation-negative complete remission is a crucial step forward for long-lasting response and survival in MM, either in the transplantation setting or in elderly patients. Twenty to thirty percent of the patients achieve sustained complete remission without relapse beyond 10 years from autologous transplantation, representing the so-called ‘cure fraction’ or ‘operational cure’ [24]. It is also evident that maintaining complete remission is crucial to achieve a prolonged survival [25].

Response Category	Criteria
Progressive disease*	25% and $>5$ g/L serum M-protein $\uparrow$ 25% and $>200$ mg/24 h urine M-protein $\uparrow$ No measurable disease difference between involved and uninvolved FLC levels must increase $>100$ mg/L Bone marrow plasma cells $>25\%$ and absolute increase $>10\%$ New lytic lesions, plasmacytomas, or hypercalcemia
Relapse from complete remission	Paraprotein reappearance (immunofixation or roteine electrophoresis) (excluding oligoclonal reconstitution) and: $>5$ g/L serum M-protein $\uparrow$ and/or $>200$ mg/24 h urine M-protein $\uparrow$ Bone marrow plasma cells $>5\%$ New lytic lesions, plasmacytomas or hypercalcemia

**Table 2.13 IMWG criteria for relapsing/progressing multiple myeloma.** FLC, free light chain; IMWG, International Myeloma Working Group. Adapted from © Nature Publishing Group, 2006. All rights reserved. Durie et al [22].

Furthermore, with the availability of novel technologies in biomedicine, the achievement of immunofixation-negative complete remission should no longer be the ultimate goal in the treatment of MM and different strategies for minimal residual disease (MRD) have been reported:

- Serological approaches: the impact of sCR (normal serum free light-chain ratio and absence of clonal plasma cells in bone marrow) is under investigation [26].
- Bone marrow response: multiparametric flow cytometry (MFC) has been the first tool for further identification of MRD. It is based on the abnormal expression of surface antigens by malignant plasma cells (Table 2.14) [27]. The presence of malignant plasma cells by MFC after autologous stem cell transplant (ASCT) in bone marrow has been identified as an important prognostic factor in MM, but also in patients receiving non-myeloablative therapy [28,29]. Sensitivity is determined according to the total number of events acquired and the threshold for positive results.
- Molecular biology studies: these techniques can measure the highest level of response; for instance a quantitative PCR using the heavy chain rearrangement in malignant plasma cells as target. Using this technique, a sustained molecular complete remission has been associated with a better prognosis after either ASCT or allogeneic transplantation [30,31]. Molecular studies have the disadvantage of being time- and resource-consuming with a limited applicability to only a subgroup of patients.

Both techniques (molecular and MFC) limit the possibility of patchy infiltration of malignant plasma cells in bone marrow, as well as the presence of isolated extramedullary progression in the absence of medullary disease. Blood-based molecular assays, particularly using NGS approaches, are promising in this regard [32]. In any event, MRD interpretations warrant caution as they are based on limited studies.

#### 8-color markers

Baseline+ MRD	CD45	CD138	CD38	CD56	CD27	CD19	CD117	CD81
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**Table 2.14 Surface markers used during minimal residual disease evaluation in bone marrow by flow cytometry.** MRD, minimal residual disease. Adapted from © John Wiley & Sons, Inc, 2010. All rights reserved. Paiva et al [27].

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