

Multiple Myeloma, Version 5.2026

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Abstract

The treatment landscape for multiple myeloma (MM) is evolving rapidly and includes several new options. The management must be tailored to the individual. The NCCN Guidelines for MM provide a framework to base decisions regarding diagnosis, workup, treatment, and follow-up of both newly diagnosed and previously treated relapsed/refractory MM. This manuscript outlines the recommendations from NCCN Guidelines for MM specific to newly diagnosed MM (NDMM).

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Overview

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that typically accumulate in bone marrow, leading to bone destruction, elevated blood calcium, and anemia as well as renal damage secondary to the secreted monoclonal protein (M protein). MM is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years.¹ The American Cancer Society has estimated 36,100 new MM cases and an estimated 12,030 deaths in the United States in 2025.² Globally, age-standardized prevalence and mortality rates, as well as disability-adjusted life years have all increased between 1990 and 2021, with the number of MM cases, deaths, and disability-adjusted life-years higher in males than in females.³

Diagnosis and Workup

It is important to distinguish MM from other plasma cell neoplasms/dyscrasias to determine prognosis and provide appropriate treatment.

The initial diagnostic workup in all patients should include a history and physical examination. To differentiate symptomatic from asymptomatic MM the following baseline laboratory studies are needed: a CBC with differential; examination of peripheral

blood smear; blood urea nitrogen; serum creatinine; creatinine clearance (calculated or measured directly) and serum electrolytes; liver function tests; serum calcium; serum uric acid; albumin; lactate dehydrogenase (LDH); and beta-2 microglobulin.

Peripheral smear may show abnormal distribution of RBCs such as the Rouleaux formation (red cells taking on the appearance of a stack of coins) due to elevated serum proteins.⁴ Smear may also show myeloma cells in the circulation. Increased blood urea nitrogen and creatinine indicate decreased kidney function, whereas LDH and beta-2 microglobulin levels reflect tumor burden. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is also recommended, and if N-terminal prohormone of brain natriuretic peptide is not available brain natriuretic peptide can be performed (Figure 1).

Serum and Urine Analysis

Serum analysis includes quantitative immunoglobulin levels (IgG, IgA, and IgM); serum protein electrophoresis (SPEP) for quantitation of M protein; and serum immunofixation electrophoresis to obtain more specific information about the type of M protein present. Assessing changes in levels of various proteins, particularly the M protein, helps track disease progression and

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The full NCCN Guidelines for Multiple Myeloma are not printed in this issue of JNCCN. The complete and most recent version of these guidelines is available free of charge at NCCN.org.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence (≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

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All recommendations are category 2A unless otherwise indicated.

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

PLEASE NOTE

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Preferred: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

Useful in certain: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

response to treatment. Urine analysis as a part of the initial diagnostic workup includes evaluating 24-hour urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis.

Free Light Chain Assay

The serum free light chain (FLC) assay along with serum M protein analyses (SPEP and serum immunofixation electrophoresis) is an important screening tool for MM and related plasma cell disorders.⁵⁻⁷ It is also helpful in prognostication of monoclonal gammopathy of undetermined significance (MGUS), smoldering

myeloma, active MM, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.^{7,8} The serum FLC assay also allows for disease monitoring in patients with light chain amyloidosis and light chain myeloma. In addition to all of the previously stated, the FLC ratio (FLCr) is required for documenting stringent complete response (sCR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria.⁹ The serum FLC assay cannot replace the 24-hour UPEP for monitoring patients with measurable urinary M protein and can also be affected by renal function. Once individuals are found to have an M protein, light chain abnormalities, or both, the same studies

INITIAL DIAGNOSTIC WORKUP^a

- History and physical (H&P) exam
- CBC, differential, and platelet count
- Peripheral blood smear
- Serum BUN/creatinine, electrolytes, liver function tests, albumin,^b calcium, serum uric acid, serum lactate dehydrogenase (LDH),^b and beta-2 microglobulin^b
- Creatinine clearance (calculated or measured directly)^c
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), and serum immunofixation electrophoresis (SIFE)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
- Serum free light chain (FLC) assay
- Whole-body FDG-PET/CT (preferred) or low-dose CT^d
- Unilateral bone marrow aspirate and biopsy, including immunohistochemistry (IHC) and/or multiparameter flow cytometry
- Plasma cell fluorescence in situ hybridization (FISH)^b panel on bone marrow^e [del(13), del(17p13), t(4;14), t(11;14), t(14;16), t(14;20), 1q21 gain/1q21 amplification,^f 1p deletion]
- Next-generation sequencing (NGS) to assess for TP53 mutation
- N-terminal prohormone B-type natriuretic peptide (NT-proBNP)/BNP^g

Useful in Certain Circumstances

- If whole-body low-dose CT or FDG-PET/CT is negative, consider whole-body MRI without contrast to discern smoldering myeloma from multiple myeloma (MM)^d
- Tissue biopsy to confirm suspected plasmacytoma
- Echocardiogram
- Evaluation for light chain amyloidosis, if appropriate (See NCCN Guidelines for Systemic Light Chain Amyloidosis^h)
- Obtain baseline clonotype identification at diagnosis or store an aspirate sample for future clonotype identification to enable minimal residual disease (MRD) testing by NGS
- Serum viscosity
- Hepatitis B and hepatitis C testing and human immunodeficiency virus (HIV) screening as required
- Assess for circulating plasma cells as clinically indicated
- Renal biopsy if albuminuria or abnormal renal function^h

CLINICAL FINDINGS

Solitary plasmacytomaⁱ
(MYEL-2*)

Smoldering myeloma
(asymptomatic)ⁱ
(MYEL-3*)

Multiple myeloma
(symptomatic)ⁱ
(MYEL-4)

Monoclonal gammopathies
of clinical
significance

Polyneuropathy, Organomegaly,
Endocrinopathy, Monoclonal
Protein, Skin Changes
(POEMS-1*)

For Renal
Significance,
see MGRS-1*
• For Monoclonal
Immunoglobulin
Deposition
Disease (MIDD),
see MIDD-1*
For Neurological
Significance,
see MGNS-1*

^a Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology[†].

^b These tests are essential for staging. See Disease Staging and Risk Stratification for Multiple Myeloma (MYEL-B).

^c Management of Renal Disease in Multiple Myeloma (MYEL-L*).

^d Principles of Imaging (MYEL-C*).

^e CD138-positive selected sample is strongly recommended for optimized yield.

^f 1q21 amplification is defined as ≥ 4 copies detected by FISH, and a gain is defined as 3 copies of 1q21.

^g If NT-proBNP is not available, BNP can be performed.

^h Dimopoulos MA, et al. Lancet Oncol 2023;24:e293-e311.

ⁱ Definitions of Myeloma and Related Plasma-Cell Disorders (MYEL-A*).

* Available online, in these guidelines, at NCCN.org. † To view the most recent version of these guidelines, visit NCCN.org.

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MYEL-1

Figure 1. MYEL-1. NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma, Version 5.2026.