Guidelines for Clinical and Laboratory Evaluation of Patients With Monoclonal Gammopathies

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• **This guideline provides the recommendations of an expert panel for the clinical and laboratory evaluation of patients suspected of having a clinical condition that produces a monoclonal protein in serum or urine. The recommendations describe the clinical conditions in which a monoclonal protein should be sought, the optimal sequence of testing to diagnose and monitor these patients, and the most effective laboratory procedures.**

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Clinical conditions associated with a monoclonal protein (M-protein) in serum or urine may be grouped separately as plasmacytic, lymphocytic, protein infiltrative, or miscellaneous disorders. Incidence data for the most common disorders are listed in Table 1. The clinical features of multiple myeloma are listed in Table 2. A dialogue between the laboratory and the clinician is strongly recommended.

GUIDELINE 1

Serum and urine electrophoresis of high resolution is indicated for all patients suspected of having a plasma cell dyscrasia. The gel should be examined directly by the interpreter. This applies most commonly to clinical disorders that suggest multiple myeloma, Waldenström's macroglobulinemia, or amyloidosis (AL), but also includes less frequent conditions, such as solitary plasmacytoma, POEMS syndrome, heavy-chain diseases, and immunoglobulin deposition disease. The quantitative level of M-protein should be defined precisely by densitometry measurement of the M-protein peak. We discourage the use of electrophoresis of low resolution.

GUIDELINE 2

Immunofixation is indicated to define the abnormal protein type. In addition, even when high-resolution electrophoresis is negative, immunofixation with κ and λ light chain antisera may be useful to detect small M-proteins in cases where there is a suspicion of a plasma cell dyscrasia. Immunofixation is not indicated in cases of obvious polyclonal gammopathies on high-resolution electrophoresis. When there is asymmetry of a polyclonal elevation of gamma globulin, an immunofixation may be useful after contact between the individual interpreting the electrophoresis and the clinician. We discourage the use of immunoelectrophoresis.

GUIDELINE 3

The M-protein should be followed by using densitometric quantitation, unless a low-level M-protein is obscured by other proteins. In such cases, quantitation of immunoglobulins by nephelometry may be more accurate. Immunofixation should not be repeated unless there is a change in the electrophoretic migration, there is an additional spike, or for confirmation of complete remission after treatment.

GUIDELINE 4

For all patients with a plasma cell dyscrasia, direct measurement of immunoglobulins by nephelometry is indicated at diagnosis to define the level of uninvolved immunoglobulins. Nephelometric measurement of immunoglobulins should never be used as the sole means to screen patients for an M-protein. We discourage the use of radial immunodiffusion procedures.

GUIDELINE 5

All patients with multiple myeloma, Waldenström's macroglobulinemia, amyloidosis (AL), and related disorders should be assessed for the presence, type, and daily excretion of monoclonal free light chains. This is best done by the quantitation of 24-hour urine protein excretion, densitometry measurements of the light chain peak in a ≥100× concentrated aliquot, and immunofixation. Screening for monoclonal free light chain by dipstick, sulfosalicylic acid, or acidified heat precipitation tests is not useful.

GUIDELINE 6

Changes in level of a previously identified monoclonal protein in serum or urine should be assayed by high-resolution electrophoresis at regular intervals that vary from every 1 to 2 months for patients being treated for multiple myeloma, Waldenström's macroglobulinemia, or amyloidosis (AL), to every year for patients with low level monoclonal gammopathy of undetermined significance.

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Table 1. Approximate Annual Incidence of Common Monoclonal Gammopathies in the United States

Condition	No. of Cases/y	Median Survival, y
Multiple myeloma	13 000	3
Waldenström's macroglobulinemia	3000	5
Protein infiltrative or deposition diseases		
Amyloidosis (AL)	2500	1
Immunoglobulin deposition disease	Rare	Incomplete data
Heavy-chain disease	Rare	Incomplete data
Monoclonal gammopathy of undetermined significance	>1 000 000	Approaches normal lifespan
Solitary plasmacytoma (bone or extramedullary)	Rare	Approaches normal lifespan

Table 2. Common Clinical Features Associated With Multiple Myeloma

Clinical Feature	Common Cause
Severe bone pain	Pathologic fracture (often of vertebra or rib)
Easy fatigability	Anemia (normochromic, normocytic), possible amyloid
Nausea, confusion, and polyuria	Hypercalcemia
Nausea and fatigue	Renal failure
Recurrent infections	Depression of uninvolved immunoglobulins
Paraplegia	Spinal cord compression
Confusion and blurred vision	Hyperviscosity (rare except when monoclonal protein values > 5.0 g/dL)
Bleeding	Thrombocytopenia
Skin nodules	Plasma cell tumors
Clinical features of amyloidosis	Amyloid (AL) deposition in target organs

GUIDELINE 7

Hyperviscosity syndrome requires emergency plasma exchange with indications based on clinical features. Serum viscosity and serum protein electrophoresis are recommended prior to the first plasma exchange to correlate the level of M-protein with symptoms in that patient. This correlation may be used to anticipate repeat plasma exchanges as the M-protein approaches the level associated with hyperviscosity.

GUIDELINE 8

Cryoglobulins should be assessed in all patients with an M-protein and specific complications due to cold sensitivity, especially in those with monoclonal immunoglobulin M. At least 10 mL of blood should be collected and transported at 37°C, the serum should be separated, and the sample should be kept at 4°C for up to 7 days. After an obvious precipitate is evident that suggests a cryoglobulin, it should be quantified, solubilized, and characterized immunochemically. Screening for cryoglobulinemia is discouraged in patients with vague, nonspecific symptoms.

GUIDELINE 9

Currently recommended techniques for the evaluation of M-proteins consist of high-resolution electrophoresis (either gel- or capillary-based), immunofixation, and immunoselection (to document cases of heavy-chain disease). Immunosubtraction is a promising new technique to characterize M-proteins.

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