Multiple Myeloma

IMWG diagnostic criteria · CRAB and SLiM, R-ISS staging, and the complications that present before the diagnosis does

Suspect it
from the CRAB

DIAGNOSIS *clonal plasma cells PLUS a myeloma-defining event. Both halves are required*

Requirement	What counts
Clonal plasma cells *the first half*	**≥ 10% clonal plasma cells on bone marrow**, *or* a **biopsy-proven bony or extramedullary plasmacytoma**
CRAB *end-organ damage*	**C** alcium **> 11 mg/dL** (or > 1 above the upper limit) · **R** enal: creatinine **> 2 mg/dL** or CrCl **< 40** · **A** nemia: Hb **< 10 g/dL** or > 2 below normal · **B** one: **≥ 1 lytic lesion** on skeletal survey, CT or PET-CT
SLiM *added 2014* treat before damage	**S** ixty: **≥ 60% clonal plasma cells** · **Li** ght chains: involved-to-uninvolved **serum free light chain ratio ≥ 100** (involved FLC must be ≥ 100 mg/L) · **M** RI: **≥ 2 focal lesions**, each at least 5 mm

Why SLiM exists, and why it matters at the bedside. These three biomarkers identify patients whose progression to end-organ damage is near-certain, so **they are treated as active myeloma before the kidney fails or the vertebra collapses**. Waiting for a CRAB feature in a patient with 65% plasma cells is waiting for avoidable harm.

WHERE ON THE SPECTRUM *the same paraprotein, three different decisions*

MGUS

monitor
M-protein **< 3 g/dL**, clonal plasma cells **< 10%**, **no** CRAB or SLiM. Progresses at roughly **1% per year**, and that risk never disappears, so **surveillance is lifelong**.

SMOLDERING MYELOMA

monitor, or trial
M-protein **≥ 3 g/dL** *or* clonal plasma cells **10% to 59%**, and still **no** CRAB or SLiM. Higher progression risk, concentrated in the **first 5 years**.

DO NOT MISS AL AMYLOIDOSIS

A light chain can damage organs **without** meeting myeloma criteria. Red flags: **periorbital purpura, macroglossia, nephrotic-range proteinuria, and heart failure with thick walls but low ECG voltage.** Needs a **Congo red** stain with typing, not just a marrow.

THE WORKUP *order these together, not sequentially*

DEFINE THE PROTEIN

SPEP with immunofixation, UPEP with immunofixation, and serum free light chains. Order all three: roughly 20% secrete light chains only and **2% to 3% are non-secretory**, so an SPEP alone can be falsely reassuring. Quantify with **beta-2 microglobulin, albumin, LDH**.

DEFINE THE MARROW

Bone marrow aspirate and biopsy with flow cytometry and **FISH cytogenetics**. The high-risk set that drives staging: **del(17p), t(4;14), t(14;16)**.

DEFINE THE BONE

Whole-body low-dose CT, PET-CT or whole-body MRI. The plain skeletal survey is obsolete: it needs 30% to 50% bone loss before a lesion is visible, so it understages. **Bone scan is the wrong test**: myeloma lesions are purely lytic with no osteoblastic response.

R-ISS STAGING *three inputs: ISS, cytogenetics, LDH*

Stage	Definition	Median overall survival
R-ISS I	**ISS I** (beta-2 microglobulin **< 3.5** mg/L *and* albumin **≥ 3.5** g/dL), **no** high-risk cytogenetics, **and** normal LDH	**Not reached** at the time of the original report
R-ISS II	Everything that is neither I nor III	**~111 months**
R-ISS III	**ISS III** (beta-2 microglobulin **> 5.5** mg/L) **and** either high-risk cytogenetics **or** raised LDH	**~37 months**

Beta-2 microglobulin rises with renal impairment as well as with tumor burden, so interpret ISS alongside the creatinine rather than reading it as a pure disease-bulk marker.

COMPLICATIONS *these are how the patient actually arrives*

Problem	What to do, and why
Renal failure	Usually **cast nephropathy** from light chains. **Aggressive hydration, stop nephrotoxins and NSAIDs, treat hypercalcemia, start anti-myeloma therapy urgently**, because the fastest way to save the kidney is to stop producing the light chain. **Avoid IV contrast where you can.** Bortezomib-based therapy is preferred: it needs no renal dose adjustment
Hypercalcemia	IV isotonic fluids first, then a **bisphosphonate** (or denosumab if renal function is poor). Reflects osteoclast activation, so it usually signals bulky active disease
Bone disease	**Zoledronic acid or denosumab for all patients with bone disease**, plus calcium and vitamin D. **Denosumab is preferred at low eGFR**. Watch for **osteonecrosis of the jaw**: dental assessment before starting
Cord compression	A neurological emergency. **Urgent MRI of the whole spine plus dexamethasone**, then radiotherapy or surgery. New back pain with any neurological sign in a myeloma patient is cord compression until proven otherwise
Infection	The leading cause of early death. Functional hypogammaglobulinemia plus treatment-related neutropenia. **Vaccinate, and treat fever as an emergency**. Consider PJP and antiviral prophylaxis with steroid- and proteasome-inhibitor-based regimens
Hyperviscosity	Uncommon in myeloma and much more typical of **Waldenstrom**, but consider it with IgA or IgM paraprotein: headache, visual change, mucosal bleeding, confusion. Treatment is **plasmapheresis**

PEARLS & PITFALLS

- **The anion gap points at it.** A **low or negative anion gap** suggests a cationic IgG paraprotein, and unexplained **rouleaux** or a very high ESR are the other incidental tells.
- **Normal calcium does not exclude it.** Only a minority present with hypercalcemia, and **anemia is by far the most common CRAB feature**.
- **Do not give erythropoietin without checking the iron and the kidney first**, and remember that the anemia is usually marrow infiltration rather than a deficiency state.
- **Modern induction is a triplet or quadruplet**, typically an anti-CD38 antibody with a proteasome inhibitor, an immunomodulatory drug and dexamethasone, followed by **autologous stem cell transplant in eligible patients** and lenalidomide maintenance. Refer early: **collect stem cells before prolonged lenalidomide exposure**, which impairs the harvest.

References: International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma (Lancet Oncol 2014) · Revised International Staging System, R-ISS (JCO 2015) · IMWG bone disease and supportive care guidance.