MGUS and Multiple Myeloma

Monoclonal Gammopathy of Undetermined Significance (MGUS) and Multiple Myeloma are plasma cell disorders that range from benign to malignant. This pamphlet provides students with a detailed guide to screen, diagnose, treat, and manage these conditions, including MGUS of Clinical Significance (MGCS), with case scenarios to apply the knowledge.

Screening

• When to Screen for MGUS:

- Indications:
  - Asymptomatic patients with unexplained anemia, renal dysfunction, hypercalcemia, bone pain, or incidental finding of elevated total protein or globulin on routine labs.
- Risk Factors:
  - Age >50 (prevalence 3-5% in >70 years), African descent (2-3x higher risk), family history of MGUS/myeloma, exposure to radiation or pesticides.
- Frequency:
  - Not routinely recommended unless symptoms or risk factors are present; if MGUS diagnosed, monitor annually.

• When to Screen for Multiple Myeloma:

- Indications:
  - **Symptoms suggestive of myeloma (CRAB criteria:** hyperCalcemia, Renal impairment, Anemia, Bone lesions), recurrent infections, or incidental findings (e.g., lytic lesions on X-ray, proteinuria).
- Risk Factors:
  - Known MGUS (1% annual risk of progression), smoldering multiple myeloma (SMM, 10% annual risk of progression), obesity, African descent.
- Frequency:
  - Immediate workup if symptomatic; for MGUS/SMM, monitor every 3-6 months initially, then annually if stable.

Diagnosis

• MGUS:

- Definition: Premalignant plasma cell disorder with no end-organ damage.
- Criteria:
  - Monoclonal protein (M-protein) <3 g/dL (serum).
  - Bone marrow plasma cells <10%.
  - No CRAB criteria (hypercalcemia, renal impairment, anemia, bone lesions).
  - Risk of Progression:
    - 1% per year to multiple myeloma, amyloidosis, or lymphoma; higher risk if M-protein >1.5 g/dL, non-IgG subtype (IgA/IgM), abnormal free light chain (FLC) ratio.

• Multiple Myeloma:

- Definition: Malignant plasma cell disorder with end-organ damage.
- Criteria (International Myeloma Working Group, IMWG):
  - Bone marrow plasma cells ≥10% or biopsy-proven plasmacytoma, AND
  - **One or more of:**
    - **CRAB criteria:** Hypercalcemia (Ca >11 mg/dL), Renal impairment (Cr >2 mg/dL or eGFR <40 mL/min), Anemia (Hgb <10 g/dL or >2 g/dL below normal), Bone lesions (lytic lesions on imaging).
    - **Myeloma-defining events:** Bone marrow plasma cells ≥60%, FLC ratio ≥100 (involved/uninvolved), >1 focal lesion on MRI.
- Smoldering Multiple Myeloma (SMM):
  - M-protein ≥3 g/dL or bone marrow plasma cells 10-60%, but no CRAB criteria or myeloma-defining events.
  - **Risk of progression:** 10% per year.

MGUS of Clinical Significance (MGCS)

• Definition:

MGCS refers to a subset of MGUS cases where the monoclonal protein causes clinical symptoms or organ dysfunction, despite not meeting criteria for multiple myeloma or related malignancies (e.g., no CRAB criteria, bone marrow plasma cells <10%). MGCS is distinct from classic MGUS, which is asymptomatic.

• Associated Conditions:

- Neurologic:
  - **Peripheral Neuropathy:** Monoclonal protein (often IgM) acts as an autoantibody against myelin-associated glycoprotein (MAG) or gangliosides, leading to sensory neuropathy (numbness, paresthesias, ataxia). Example: Anti-MAG neuropathy.
  - **Demyelinating Neuropathy:** Similar to chronic inflammatory demyelinating polyneuropathy (CIDP), often IgM-related.
- Renal:
  - **Monoclonal Gammopathy of Renal Significance (MGRS):** Monoclonal protein (usually light chains) causes renal damage (e.g., proximal tubulopathy, glomerulonephritis). Example: Light chain deposition disease (LCDD) with kappa/lambda deposition in glomeruli.
- Dermatologic:
  - **Scleromyxedema:** IgG lambda monoclonal protein associated with skin thickening, waxy papules, and mucin deposition.
  - **Necrobiotic Xanthogranuloma:** Monoclonal protein (often IgG) linked to periorbital xanthomatous lesions.
- Hematologic:
  - **Acquired von Willebrand Syndrome:** Monoclonal protein (IgM) inhibits von Willebrand factor, leading to bleeding (epistaxis, bruising).
  - **Cryoglobulinemia (Type II):** Monoclonal protein (IgM) forms cryoglobulins with polyclonal IgG, causing vasculitis, purpura, arthralgias, and glomerulonephritis.
- Other:
  - **POEMS Syndrome (subset):** Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes; often lambda light chain predominance, associated with osteosclerotic lesions.

• Diagnostic Considerations:

- Workup:
  - If MGUS is diagnosed (M-protein <3 g/dL, bone marrow plasma cells <10%), evaluate for MGCS if symptoms are present (e.g., neuropathy, renal dysfunction, skin lesions).
- Tests:
  - Nerve conduction studies (neuropathy), anti-MAG antibodies (IgM neuropathy), renal biopsy (MGRS), cryoglobulin levels (vasculitis), von Willebrand factor activity (bleeding), VEGF levels (POEMS syndrome).

- Differentiate:
  - MGCS requires a causal link between the monoclonal protein and symptoms (e.g., IgM anti-MAG antibodies causing neuropathy); rule out other causes (e.g., diabetes for neuropathy, infection for renal dysfunction).

• Management:

- Treat Underlying Cause:
  - Therapy targets the monoclonal protein production, even though MGUS itself is not malignant.
  - **Neuropathy:** Rituximab 375 mg/m² IV weekly x 4 (if IgM-related, e.g., anti-MAG neuropathy); IVIG 0.4 g/kg IV daily x 5 days (if CIDP-like).
  - **MGRS:** Treat as myeloma (e.g., bortezomib-based regimen: bortezomib 1.3 mg/m² SC days 1, 4, 8, 11, 21-day cycles) to reduce light chain production.
  - **Scleromyxedema:** IVIG 2 g/kg IV monthly; consider thalidomide 100 mg PO daily (if refractory).
  - **Cryoglobulinemia:** Rituximab 375 mg/m² IV weekly x 4; plasmapheresis (if severe vasculitis).
- Monitoring:
  - More frequent than classic MGUS (every 3-6 months) due to symptomatic nature; monitor SPEP, FLC, and organ-specific tests (e.g., renal function, nerve conduction).
- Referral: Immediate hematology referral for suspected MGCS to guide therapy and prevent organ damage.

Diagnostic Tests

• Initial Labs:

- CBC:
  - Anemia (Hgb <10 g/dL in myeloma), leukopenia/thrombocytopenia (marrow infiltration).
- Metabolic Panel:
  - Calcium (hypercalcemia), Cr (renal impairment), albumin (low in myeloma), total protein (elevated).
  - Serum Protein Electrophoresis (SPEP):
  - Monoclonal spike (M-protein) in gamma region.
  - Urine Protein Electrophoresis (UPEP): (only needed if MM is diagnosed to guide treatment)
    - Bence Jones proteins (light chains in urine); primarily used in treatment monitoring for myeloma (see Pathophysiology section).

    - Serum Free Light Chains (FLC):
        - Kappa/lambda ratio (normal 0.26-1.65); abnormal if >100 (myeloma).
- Beta-2 Microglobulin: Prognostic marker (elevated in myeloma, poor prognosis if >5.5 mg/L).
- LDH: Elevated in aggressive disease (myeloma).

• Bone Marrow Biopsy:

- Indication: Confirm plasma cell percentage, clonality (CD138+ plasma cells), cytogenetics (FISH for t(4;14), del(17p), high-risk).
- MGUS/MGCS: **<10% plasma cells; Myeloma:** ≥10% plasma cells.

• Imaging:

- Skeletal Survey:
    - **X-rays (lytic lesions in myeloma:** “punched-out” appearance in skull, spine, long bones).
- MRI/CT/PET-CT:
    - Focal lesions (>5 mm in myeloma), bone marrow involvement, extramedullary disease; osteosclerotic lesions in POEMS (MGCS).
- Low-Dose Whole-Body CT:
    - Preferred for initial myeloma workup (higher sensitivity for lytic lesions).

• Additional Tests:

- Peripheral Smear:
    - Rouleaux formation (stacked RBCs) in myeloma.
- Quantitative Immunoglobulins:
    - Reduced IgG/IgA/IgM (immune paresis in myeloma).
- 24-Hour Urine Protein:
    - Quantify proteinuria (light chains, albumin in renal impairment).
- MGCS-Specific Tests:
    - Anti-MAG antibodies, cryoglobulins, renal biopsy, nerve conduction studies, VEGF (POEMS).

Pathophysiology: Free Light Chains, SPEP, and UPEP

• Free Light Chains (FLC):

- Pathophysiology:
  - Plasma cells produce immunoglobulins (Ig) consisting of heavy chains (IgG, IgA, IgM) and light chains (kappa or lambda). In normal conditions, light chains are produced in slight excess and excreted as free light chains (FLC) in the urine. In plasma cell disorders like MGUS and myeloma, clonal plasma cells overproduce a single type of light chain (monoclonal, either kappa or lambda), leading to an imbalance in the kappa/lambda ratio. This overproduction can cause renal damage (light chain cast nephropathy) in myeloma due to filtration and deposition in the renal tubules. In MGCS, FLC may contribute to organ damage (e.g., MGRS).
- Clinical Utility:
  - Serum FLC assay measures kappa and lambda light chains and their ratio (normal 0.26-1.65). An abnormal ratio (e.g., >100 or <0.01) indicates monoclonal production and is a myeloma-defining event if ≥100. FLC is more sensitive than UPEP for detecting light chain disease and is used for diagnosis and monitoring response to treatment.

• Serum Protein Electrophoresis (SPEP):

- Pathophysiology:
  - SPEP separates serum proteins based on their charge and size, producing a graph with distinct bands (albumin, alpha, beta, gamma regions). In plasma cell disorders, clonal plasma cells produce a single immunoglobulin (monoclonal protein or M-protein), which appears as a sharp spike (M-spike) in the gamma region. This spike represents the monoclonal gammopathy in MGUS, MGCS, SMM, or myeloma.
- Clinical Utility:
  - SPEP quantifies the M-protein (e.g., 1.2 g/dL in MGUS, >3 g/dL in myeloma) and is essential for diagnosis, risk stratification (MGUS progression risk if >1.5 g/dL), and monitoring treatment response (e.g., decrease in M-spike indicates response).

• Urine Protein Electrophoresis (UPEP):

- Pathophysiology:
  - In plasma cell disorders, excess free light chains (Bence Jones proteins) are filtered by the kidneys and excreted in the urine. UPEP separates urine proteins and identifies a monoclonal light chain spike, confirming the

presence of Bence Jones proteins. These proteins are nephrotoxic and contribute to renal impairment in myeloma (cast nephropathy) or MGCS (MGRS).

- Clinical Utility:
  - Historically, UPEP was critical for detecting light chain disease, especially in light chain-only myeloma (20% of cases, where no heavy chain is produced). However, with the advent of the serum FLC assay, which is more sensitive and less invasive (no 24-hour urine collection needed), UPEP is now primarily used in the treatment phase of multiple myeloma to monitor light chain excretion and assess renal response to therapy (e.g., decrease in Bence Jones proteins post-treatment). UPEP is not typically needed for initial diagnosis of MGUS, MGCS, or SMM since FLC testing is sufficient.

• Why UPEP is Primarily for Myeloma Treatment:

The serum FLC assay has largely replaced UPEP for initial diagnosis due to its sensitivity, ease of use (serum vs. urine), and ability to detect light chain disease early (e.g., in MGUS, MGCS, or SMM). However, in active multiple myeloma, UPEP remains valuable during treatment to quantify Bence Jones proteinuria, assess renal recovery (e.g., decrease in light chain excretion), and monitor for relapse (e.g., reappearance of Bence Jones proteins). UPEP also helps in cases where FLC assays may be less reliable (e.g., renal impairment affecting FLC clearance).

Diagnostic Criteria Table

Condition	M-Protein	Bone Marrow Plasma Cells	End-Organ Damage	Notes
MGUS	<3 g/dL	<10%	None (no CRAB)	Monitor annually; risk stratification.
Smoldering Myeloma	≥3 g/dL	10-60%	None (no CRAB)	Monitor every 3-6 months initially.
Multiple Myeloma	Any (usually >3 g/dL)	≥10% or plasmacytoma	CRAB or myeloma-defining events	Cytogenetics (FISH) for prognosis.

Treatment

• MGUS:

- Management: Observation only; no treatment required unless progression or MGCS.

- Monitoring:
  - Annual SPEP, FLC, CBC, calcium, Cr; more frequent (every 6 months) if high-risk (M-protein >1.5 g/dL, non-IgG, abnormal FLC ratio).
- Supportive: Vaccinations (pneumococcal, influenza) due to risk of infections.

• MGUS of Clinical Significance (MGCS):

- Management:
  - Treat the underlying condition caused by the monoclonal protein (see MGCS section for specific therapies).
- Monitoring:
  - Every 3-6 months (SPEP, FLC, organ-specific tests like renal function or nerve conduction studies).

• Multiple Myeloma:

- General Principles:
  - Treat if symptomatic (CRAB) or myeloma-defining events (e.g., FLC ratio ≥100).
  - **Assess transplant eligibility:** Age <70, good performance status (ECOG 0-1), no significant comorbidities.
  - Induction Therapy (Transplant-Eligible):
    - **Regimen:** VRd (bortezomib, lenalidomide, dexamethasone):
    - Bortezomib 1.3 mg/m² SC days 1, 4, 8, 11 (cycles 1-4, 21-day cycles).
    - Lenalidomide 25 mg PO daily days 1-14.
    - Dexamethasone 40 mg PO weekly.
      - **Duration:** 4-6 cycles, followed by autologous stem cell transplant (ASCT).
  - Induction Therapy (Transplant-Ineligible):
    - **Regimen:** DRd (daratumumab, lenalidomide, dexamethasone):
    - Daratumumab 16 mg/kg IV weekly (cycles 1-2), then q2 weeks (cycles 3-6), then q4 weeks.
    - Lenalidomide 25 mg PO daily days 1-14 (21-day cycles).
    - Dexamethasone 40 mg PO weekly.
      - **Duration:** Continue until disease progression or intolerance.
  - Autologous Stem Cell Transplant (ASCT):
    - Melphalan 200 mg/m² IV (conditioning), followed by stem cell infusion.
      - Improves progression-free survival (PFS); consider in eligible patients.

        - Maintenance Therapy:
            - Lenalidomide 10 mg PO daily (days 1-21, 28-day cycles) post-ASCT until progression.
            - Bortezomib 1.3 mg/m² SC q2 weeks (if high-risk cytogenetics, e.g., del(17p)).
    - Relapsed/Refractory Myeloma:
        - **Regimen:** Carfilzomib + dexamethasone (Kd):
        - Carfilzomib 20 mg/m² IV days 1-2 (cycle 1), then 56 mg/m² days 8, 9, 15, 16 (28-day cycles).
        - Dexamethasone 20 mg IV/PO days 1, 2, 8, 9, 15, 16.
        - **Alternative:** Daratumumab + pomalidomide + dexamethasone (DPd).

• Supportive Care:

- Bone Disease:
    - Bisphosphonates (zoledronic acid 4 mg IV monthly x 1-2 years), denosumab 120 mg SC monthly (if renal impairment).
- Infections:
    - Prophylaxis (acyclovir 400 mg PO BID if on bortezomib, levofloxacin 500 mg PO daily during neutropenia).
- Anemia:
    - Epoetin alfa 40,000 units SC weekly (if Hgb <10 g/dL, no ESA if prior thrombosis).
- Renal Impairment:
    - Hydration (NS 100 mL/h IV), avoid NSAIDs, treat hypercalcemia; UPEP to monitor light chain excretion.
- Pain:
    - Opioids (morphine 5-10 mg PO q4h PRN), radiation for bone pain (20 Gy in 5 fractions).

Treatment Guidelines Table

Condition	Treatment Agent/ Dose	Notes
MGUS	Observation	Annual SPEP, FLC, CBC Vaccinations (pneumococcal, influenza).
MGCS (Neuropathy)	Rituximab 375 mg/ m² IV weekly x 4	Monitor nerve conduction studies.
Myeloma (Transplant-Eligible)	VRd + ASCT	Bortezomib 1.3 mg/m² SC days 1, 4, 8, 11 Lenalidomide 25 mg PO days 1-14 Maintenance: Lenalidomide 10 mg PO daily.

Condition	Treatment Agent/ Dose	Notes
Myeloma (Transplant-Ineligible)	DRd	Daratumumab 16 mg/kg IV weekly Lenalidomide 25 mg PO days 1-14 Continue until progression; monitor for infections.

When to Refer to Hematology

- **MGUS:**
  - At diagnosis:
    - Confirm diagnosis, risk-stratify (M-protein, FLC ratio), and establish monitoring plan.
  - Progression:
    - If M-protein increases >25% (minimum 0.5 g/dL), new CRAB features, or abnormal FLC ratio develops.
- **MGUS of Clinical Significance (MGCS):**
  - At diagnosis:
    - Immediate referral if symptomatic (e.g., neuropathy, renal dysfunction, skin lesions) to guide therapy and prevent organ damage.
  - Progression:
    - Worsening organ dysfunction or failure to respond to initial therapy.
- **Smoldering Myeloma:**
  - At diagnosis:
    - High-risk SMM (bone marrow plasma cells ≥20%, M-protein ≥2 g/dL, FLC ratio >20) may benefit from early intervention (clinical trials).
  - Progression:
    - Development of CRAB criteria or myeloma-defining events.
- **Multiple Myeloma:**
  - At diagnosis:
    - All patients for treatment planning, transplant evaluation, and cytogenetic risk stratification.
  - Relapse:
    - New regimens, clinical trials, or palliative care discussion.

- Complications:
  - Hypercalcemia, renal failure, infections, or spinal cord compression requiring urgent management.

Complications

• MGUS:

- Progression:
  - 1% annual risk to myeloma, amyloidosis, or lymphoma.
- Infections:
  - Increased risk due to hypogammaglobulinemia (reduced polyclonal Ig).
- Thrombosis:
  - Slightly increased risk (especially IgM MGUS).

• MGUS of Clinical Significance (MGCS):

- Neurologic:
  - Progressive neuropathy (e.g., anti-MAG), leading to disability (e.g., falls, sensory loss).
- Renal:
  - Progressive renal failure (MGRS), potentially requiring dialysis.
- Dermatologic:
  - Disfigurement (scleromyxedema), recurrent lesions (necrobiotic xanthogranuloma).
- Hematologic:
  - Bleeding (acquired von Willebrand syndrome), vasculitis (cryoglobulinemia).

• Multiple Myeloma:

- Bone Disease:
  - Pathologic fractures (spine, ribs), spinal cord compression (5-10% of patients).
- Renal Failure:
  - Light chain cast nephropathy (Bence Jones proteinuria), hypercalcemia, amyloidosis (10-15% of cases).
- Infections:
  - Pneumonia, urinary tract infections (S. pneumoniae, E. coli) due to immune paresis, neutropenia (chemo-related).
- Hypercalcemia:
  - 20-30% of patients at diagnosis; confusion, dehydration, renal impairment.

- Anemia:
  - Normocytic, Hgb <10 g/dL (marrow infiltration, renal failure).
- Hyperviscosity:
  - Rare (IgA myeloma), neurologic symptoms, bleeding (if M-protein >5 g/dL).
- Neuropathy:
  - Peripheral neuropathy (bortezomib, thalidomide), numbness, paresthesias.
- Thrombosis:
  - Increased risk with IMiDs (lenalidomide, pomalidomide); DVT/PE (prophylaxis: aspirin 81 mg PO daily or enoxaparin 40 mg SC daily).

Key Pearls

• **MGUS:** Monitor annually; no treatment unless progression or MGCS.

• **MGCS:** Suspect if MGUS with symptoms (neuropathy, renal dysfunction); treat underlying condition (e.g., rituximab for IgM neuropathy).

• **Myeloma Diagnosis:** CRAB criteria or myeloma-defining events (FLC ratio ≥100, MRI lesions); always check SPEP/FLC.

• **FLC vs. UPEP:** FLC for diagnosis and monitoring; UPEP for treatment phase in myeloma (assess light chain excretion, renal response).

• **Imaging:** Low-dose whole-body CT preferred over skeletal survey for myeloma workup.

• **Treatment:** VRd for transplant-eligible, DRd for transplant-ineligible; bisphosphonates for bone disease.

• **Cytogenetics:** High-risk (t(4;14), del(17p)) impacts prognosis; adjust maintenance (bortezomib).

• **Refer to Hematology:** At diagnosis of MGUS, MGCS, SMM, or myeloma; urgent if CRAB features or complications.

References

• UpToDate: “Monoclonal Gammopathy of Undetermined Significance (MGUS)” (2025).

• NEJM: “Multiple Myeloma: Diagnosis and Treatment” (2023).

• Blood: “Monoclonal Gammopathy of Clinical Significance: Diagnosis and Management” (2024).

• IMWG: “Updated Diagnostic Criteria for Multiple Myeloma” (2024).

Case Scenarios

Case 1: A 55-Year-Old Male with Fatigue

- Presentation: A 55-year-old male presents with fatigue and back pain for 3 months. Exam shows pallor, no organomegaly. No recent infections.
- Labs: Hgb 9.5 g/dL, Ca 12.2 mg/dL, Cr 2.3 mg/dL, total protein 9 g/dL. SPEP: M-protein 3.5 g/dL (IgG). FLC ratio: 120 (kappa-dominant). Bone marrow: 15% plasma cells. Skeletal survey: Lytic lesions in spine, skull.
- Diagnosis: Multiple Myeloma → CRAB criteria (hypercalcemia, renal impairment, anemia, bone lesions), FLC ratio ≥100, bone marrow plasma cells ≥10%.
- Management: Refer to hematology. Start VRd (bortezomib, lenalidomide, dexamethasone); zoledronic acid 4 mg IV monthly for bone disease. UPEP to monitor light chain excretion during treatment. Assess for transplant eligibility. Prophylaxis: Acyclovir 400 mg PO BID, aspirin 81 mg PO daily (thrombosis risk). Monitor calcium, Cr, and Hgb.

Case 2: A 65-Year-Old Female with Numbness

- Presentation: A 65-year-old female presents with numbness and tingling in her hands and feet for 6 months, with difficulty walking. Exam shows sensory loss, ataxia, no organomegaly.
- Labs: **SPEP:** M-protein 1.0 g/dL (IgM), FLC ratio normal, Hgb 12 g/dL, Ca 9.2 mg/dL, Cr 0.8 mg/dL. Bone marrow: 4% plasma cells. Nerve conduction studies: Demyelinating neuropathy. Anti-MAG antibodies: Positive.
- Diagnosis: MGUS of Clinical Significance (MGCS) → MGUS with IgM-related anti-MAG neuropathy (M-protein <3 g/dL, bone marrow <10%, no CRAB, but symptomatic neuropathy).
- Management: Refer to hematology urgently. Start rituximab 375 mg/m² IV weekly x 4 to reduce IgM production. Monitor SPEP, FLC, and nerve conduction studies every 3-6 months. Educate on fall precautions due to ataxia.

Case 3: A 70-Year-Old Male with Renal Impairment

- Presentation: A 70-year-old male with a history of SMM (M-protein 3.2 g/dL, 20% plasma cells, no CRAB) presents with new fatigue and decreased urine output. Exam shows edema, no bone tenderness.
- Labs: Hgb 9.8 g/dL, Ca 10.5 mg/dL, Cr 2.5 mg/dL (baseline 1.2 mg/dL), FLC ratio 150 (kappa-dominant). UPEP: Bence Jones proteins. MRI: 2 focal lesions (>5 mm).

- Diagnosis: Multiple Myeloma → Progression from SMM (new renal impairment, FLC ratio ≥100, MRI lesions as myeloma-defining events).
- Management: Refer to hematology urgently. Start DRd (daratumumab, lenalidomide, dexamethasone) as transplant-ineligible. Hydrate with NS 100 mL/h IV, avoid NSAIDs. Zoledronic acid 4 mg IV monthly (adjust for renal function). Use UPEP to monitor light chain excretion and renal response. Monitor renal function, Hgb, and response (SPEP, FLC).