Monoclonal Gammopathy and Kidney Disease — Module 24

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Monoclonal Gammopathy and Kidney Disease

Advanced Nephrology Module 24 — Student Handout

Learning Objectives

By the end of this module, you will be able to:

1. **Distinguish between MGUS, MGRS, and MM** with renal involvement based on diagnostic criteria
2. **Recognize clinical and pathologic features** of cast nephropathy (myeloma kidney)
3. **Diagnose and manage light chain deposition disease (LCDD)** and heavy chain deposition disease
4. **Understand renal manifestations of AL amyloidosis** including biopsy findings and treatment principles
5. **Identify fibrillary and immunotactoid glomerulonephritis** and their association with lymphoproliferation
6. **Diagnose proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID)**
7. **Perform appropriate serologic and tissue workup** for suspected monoclonal gammopathy-related kidney disease
8. **Apply clone-directed therapy principles** including proteasome inhibitors, IMiDs, and monoclonal antibodies

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Part I: Framework—MGUS, MGRS, and Multiple Myeloma with Renal Involvement

Definitions & Diagnostic Criteria

MGUS (Monoclonal Gammopathy of Undetermined Significance) - Serum monoclonal protein <3 g/dL AND - Bone marrow clonal cells <10% AND - Absent end-organ damage (CRAB criteria: hypercalcemia, renal insufficiency, anemia, bone lesions) or MDE (myeloma defining events: ≥60% clonal cells, ≥100 ratio involved:uninvolved FLC, ≥2 focal lesions on MRI)

MGRS (Monoclonal Gammopathy of Renal Significance) - Clonal bone marrow or plasma cell proliferation (any size) with evidence that clonal protein is directly causative of kidney disease (monoclonal deposits on kidney biopsy confirmed by kappa/lambda restriction) - Kidney disease attributable to monoclonal protein - MGRS does NOT require systemic myeloma burden or M-spike

Multiple Myeloma (MM) - ≥10% clonal bone marrow plasma cells OR - Biopsy-proven bone plasmacytoma AND - Evidence of end-organ damage (CRAB) or myeloma defining events (MDE)

Key Point: MGRS is defined by kidney pathology showing monoclonal deposits, regardless of systemic burden. Many MGRS patients have <10% bone marrow involvement and would be classified as MGUS by hematologic criteria alone.

Epidemiology & Risk of Progression

MGUS Prevalence: - 3–4% of population >50 years - Only 1–2% progress to MM or related disorders per year - Cumulative progression risk: ~5% at 10 years (but varies by risk category)

MGRS Prevalence: - Less common than MGUS; exact prevalence unknown - Estimated 2–10% of serum paraprotein carriers have MGRS - Earlier intervention may prevent progression to symptomatic MM

Risk Stratification for MGUS: - **Low-risk MGUS:** M-spike <1.5 g/dL, non-IgA isotype, normal FLC ratio ☐ 5% progression at 10 years - **Intermediate-risk:** M-spike 1.5–2.5 g/dL OR abnormal FLC ratio ☐ 10% progression at 10 years - **High-risk MGUS:** M-spike ≥2.5 g/dL AND abnormal FLC ratio ☐ 30% progression at 10 years - **Very high-risk MGUS:** ≥60% clonal BMC or ≥100 FLC ratio OR 2+ focal lesions on MRI ☐ risk of myeloma-defining event very high

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Part II: Cast Nephropathy (Myeloma Kidney)

Definition & Pathophysiology

- Most common form of kidney disease in MM (caused by ~40% of myeloma kidneys)
- Caused by **filtered free light chains** (FLC) precipitating in collecting ducts and distal tubules
- Kappa chains more likely to precipitate than lambda (kappa is smaller, more hydrophobic)

Mechanism of FLC-Induced Injury

1. **Glomerular filtration:** Small FLC (22–25 kDa) readily pass GBM; normal kidneys reabsorb and catabolize FLC
2. **Tubular reabsorption saturation:** High FLC concentrations overwhelm reabsorptive capacity
3. **FLC aggregation:** FLC precipitate in acidic environment of distal tubule/collecting duct
4. **Cast formation:** FLC + Tamm-Horsfall protein (uromodulin) form casts
5. **Tubular obstruction:** Casts cause mechanical obstruction and tubular epithelial injury
6. **Additional injury:** Direct toxic effects of FLC on tubular epithelium and podocytes

Clinical Presentation

- **AKI** (most common): Acute rise in creatinine, often reversible with volume repletion and FLC reduction
- **Proteinuria:** Usually <1 g/day (tubular proteinuria, minimal glomerular involvement)
- **Absence of hematuria:** No dysmorphic RBC or casts in urine (distinguishes from glomerulonephritis)
- **Normal UA sediment:** Key diagnostic feature
- **FLC in urine:** Positive urine FLC (kappa or lambda monoclonal)

Biopsy Findings (Light Microscopy)

Characteristic LM Pattern: - **Intraluminal casts in distal tubules and collecting ducts** - Casts are **eosinophilic, crystalline, wavy, fractured** ("fracture lines") - Casts stain weakly with PAS (proteinaceous, not carbohydrate-rich) - Tubular epithelial cells show necrosis and flattening - Minimal or absent glomerular involvement (no proliferation, no inflammation) - Interstitial inflammation variable (can be mild to severe) - **No crescents** (hallmark distinguishing from GN)

Special Stains: - Crystal violet: Highlights wavy crystalline fracture pattern - Immunofluorescence: Shows monoclonal light chain (kappa or lambda) in casts and tubular epithelium - Toluidine blue: Enhances visualization of crystalline casts

Immunofluorescence Pattern

Diagnostic IF: - **Monoclonal light chain (kappa OR lambda, not both) in casts and tubular epithelium** - No immunoglobulins or complement (distinguishes from immune complex GN) - May show some degree of light chain reactivity in glomeruli if concurrent glomerular disease (e.g., light chain deposition disease)

Electron Microscopy

- **Crystalline deposits in tubular lumen** (appearance depends on FLC type)
- Kappa chains: Often form **lattice-like or angular crystalline structures**
- Lambda chains: May appear more fibrillar or rod-like
- Foot process effacement: Usually absent (unless concurrent LCDD or other podocytopathy)

Differential Diagnosis

Condition	UA Pattern	Casts on Biopsy	IF Pattern	Glomeruli
Cast Nephropathy	Proteinuria <1 g/day, no RBC	Monoclonal FLC casts	Monoclonal light chain in casts	Normal/minimal change
Acute Glomerulonephritis	Hematuria, RBC casts	No monoclonal casts	Granular Ig/C3 or pauci-immune	Proliferative inflammation
Contrast Nephropathy	Pigmented casts	No monoclonal deposits	Usually negative	Acute tubular necrosis

Condition	UA Pattern	Casts on Biopsy	IF Pattern	Glomeruli
Myoglobinuria	Brown urine, no RBC	Pigmented casts	Usually negative	Normal

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Management of Cast Nephropathy

Acute Management: 1. **Volume repletion:** IV hydration to maintain urine output (goal: 200 mL/hr) 2. **FLC reduction:** - Proteasome inhibitor (bortezomib) or lenalidomide for rapid FLC lowering - Aim to reduce involved FLC by 50% within 1–2 weeks 3. **Loop diuretics:** If necessary to maintain urine output (caution: avoid under-hydration) 4. **Avoid nephrotoxins:** NSAIDs, ACE inhibitors initially (may worsen renal function)

Chronic Management: - **Chemotherapy induction:** Bortezomib + dexamethasone or bortezomib + lenalidomide + dexamethasone - **Goal:** Complete hematologic response (normal serum/urine protein, normal FLC ratio) - **Maintenance therapy:** Lenalidomide ± dexamethasone to prevent relapse - **Dialysis:** May be needed if ESRD develops before FLC control achieved

Prognosis: - **Reversible if FLC rapidly reduced:** 50% of AKI reversible with early aggressive therapy - **Poor if delayed treatment:** Prolonged elevation of FLC ☐ tubular atrophy, interstitial fibrosis, irreversible AKI - **Outcome depends on rapidity of FLC reduction:** Early intervention critical

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Part III: Light Chain Deposition Disease (LCDD)

Definition & Mechanism

- **Nonamyloid light chain deposition disease**
- Caused by misfolded monoclonal light chains depositing in **glomerular and tubular basement membranes**
- NOT amyloid (Congo red negative, no beta-pleated sheet)
- Predominantly in kidneys; can affect heart, lung, liver

Epidemiology

- Accounts for 10–15% of monoclonal gammopathy-related kidney disease
- Mean age at presentation: 50–65 years
- Kappa light chains more common than lambda (2:1 ratio)
- Often associated with <10% clonal BMC (MGUS by hematologic criteria)

Pathophysiology

1. **Clonal plasma cell produces monoclonal FLC**
2. **FLC filtered by glomerulus** and reabsorbed by tubular epithelium
3. **Abnormal FLC resists proteolytic degradation** and deposits in basement membranes

4. **Deposition triggers complement activation** (C3 and C1q deposition)
5. **Progressive BM thickening** leads to glomerular and tubular dysfunction

Clinical Presentation

- **Progressive proteinuria:** Often nephrotic range (5–10 g/day)
- **Progressive AKI/CKD:** Gradual decline in GFR over months to years
- **Hematuria:** Usually absent or microscopic (no active sediment)
- **Hypertension:** Often present at presentation
- **NO systemic features of myeloma:** Normal Ca, Hgb, bone imaging

Biopsy Findings

Light Microscopy: - **Nodular expansion of glomerular matrix** (similar to diabetic nodules but in LCDD) - **Capillary wall thickening** (homogeneous, not segmental) - **Membranoproliferative pattern** possible - **Tubular basement membrane thickening** - **Interstitial fibrosis** progressive - Mesangial expansion - **No proliferation, no crescents**

Immunofluorescence (Diagnostic): - **Monoclonal light chain deposits along glomerular and tubular basement membranes** - IF shows **linear or ribbon-like pattern** along BM (may appear similar to anti-GBM but in different distribution) - **C3 and C1q co-deposition** (complement activation) - **No immunoglobulin heavy chains** or only weak staining - This pattern is pathognomonic for LCDD

Electron Microscopy: - **Non-amyloid electron-dense deposits** along inner aspect of GBM and TBM - Deposits appear as linear material on EM (called "ribbon-like" deposits) - **NO Congo-red birefringence** (amyloid shows apple-green birefringence) - Foot process effacement variable (may be absent despite nephrotic syndrome)

Differential Diagnosis: LCDD vs. Light Chain Amyloidosis (AL)

Feature	LCDD	AL Amyloidosis
Congo Red Stain	Negative	Positive (apple-green birefringence)
EM Deposits	Ribbon-like, granular	Fibrillar, 7–12 nm diameter
IF Heavy Chains	Absent/weak	Usually present (may be faint)
BM Distribution	Linear along BM	Granular, mesangial, vessel wall
Systemic Involvement	Usually kidneys only	Heart, nerve, GI, other organs
Prognosis	Better with clone-directed therapy	Poorer; cardiac involvement especially grave
C3/C1q Deposition	Usually present	Usually absent

Management of LCDD

Medical Therapy: 1. **Clone-directed chemotherapy:** - Proteasome inhibitor (bortezomib) + IMiD (lenalidomide) + dexamethasone - Goal: Complete hematologic response (eliminate clonal

plasma cells) 2. **Proteinuria reduction:** - ACE inhibitor or ARB to reduce intraglomerular pressure - Target: <1 g/day if achievable 3. **BP control:** Target <120 mm Hg systolic

Renal Prognosis: - **With chemotherapy:** 50–60% achieve stable renal function or improvement in proteinuria - **Without therapy:** Progressive decline to ESRD over 3–10 years - **Time-sensitive:** Early recognition and treatment critical before irreversible fibrosis

Dialysis/Transplantation: - Dialysis indicated if GFR <15 mL/min - Transplant outcome acceptable if clonal disease controlled (low recurrence if chemotherapy successful)

Part IV: AL Amyloidosis and the Kidney

Definition & Epidemiology

- **Systemic AL amyloidosis:** Misfolded monoclonal immunoglobulin light chains (kappa or lambda) form amyloid fibrils
- **Renal AL:** Kidney involvement in ~70% of AL amyloidosis patients
- Median age at diagnosis: 60–65 years
- Rare but likely under-diagnosed

Mechanism of Renal Injury

1. **Monoclonal FLC misfolding** ☐ amyloid fibril formation
2. **Fibril deposition in glomeruli** (primarily mesangium and walls)
3. **Triggers innate immunity:** SAP (serum amyloid P) binding, complement activation
4. **Progressive podocyte and GBM injury** ☐ proteinuria, declining GFR
5. **Vascular involvement:** Amyloid deposition in vessel walls ☐ ischemia and sclerosis

Clinical Presentation

Renal Manifestations: - **Heavy proteinuria:** Often nephrotic (10–15 g/day common) - **Nephrotic syndrome:** Edema, hypoalbuminemia, hyperlipidemia - **AKI/CKD:** Can develop rapidly or insidiously - **Normal complement:** C3, C4 typically normal (distinguishes from post-infectious GN) - **Hematuria:** Absent or minimal

Systemic Features: - **Cardiac:** Heart failure, arrhythmias, sudden death (most common cause of death in AL) - **Neurologic:** Peripheral neuropathy, carpal tunnel syndrome, autonomic dysfunction - **GI:** Diarrhea, malabsorption, bleeding - **Hepatic:** Hepatomegaly, elevated transaminases - **Macroglossia:** Diagnostic clue (enlargement of tongue due to amyloid)

Biopsy Findings

Light Microscopy: - **Glomerular infiltrate:** Deposits in glomeruli appearing as homogeneous, pale, waxy material - **Mesangial expansion:** Usually prominent - **Capillary wall thickening:** May see "collapsed" or "moth-eaten" appearance - **Congo red stain (CRITICAL): Pink/red material that shows apple-green birefringence under polarized light** — pathognomonic for amyloid - **Vessel wall involvement:** Amyloid in afferent arterioles and small arteries

Immunofluorescence: - **Monoclonal light chain (kappa or lambda) in deposits** - Usually **weak or negative** for heavy chains (lambda chains especially may show minimal heavy chain staining) - **Weak or absent C3/C1q** (unlike LCDD or post-infectious)

Electron Microscopy: - **Fibrillar deposits:** 7–12 nm diameter straight fibrils (characteristic appearance) - **Mesangial and glomerular wall deposition** - **No Congo-red birefringence on EM** but Congo-red positive on LM (confirms amyloid) - Foot process effacement variable

Staging & Prognosis

Risk Stratification (Mayo Clinic System): - Uses **cardiac biomarkers:** NT-proBNP, troponin I (cTnI) - **Stage I:** Both normal - **Stage II:** Either NT-proBNP or cTnI elevated - **Stage III:** Both elevated - **Stage IV:** Severe elevations

Median Survival: - Stage I: ~26 months - Stage II: ~10 months - Stage III: ~4 months - Presence of renal involvement (nephrotic syndrome) = poor prognostic factor

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Management of AL Amyloidosis

Diagnostic Confirmation: - Kidney or fat-pad biopsy with Congo-red staining (MUST confirm amyloid before treating) - Typing of amyloid protein (mass spectrometry) — confirms AL vs. other amyloid types - SPEP, UPEP, free light chain assay - Cardiac evaluation (echo, troponin, NT-proBNP, ECG) - Genetic testing if familial amyloidosis suspected

Induction Chemotherapy: - **Bortezomib-based regimen:** Bortezomib + dexamethasone ± lenalidomide (CyBorD or DBd) - Advantages: Rapid FLC reduction; subcutaneous dosing option; cardiac improvements - Goal: ≥90% reduction in involved FLC or complete response - **Alternative:** Melphalan + dexamethasone (if bortezomib contraindicated) - **Stem cell transplant:** May be considered in young, fit patients after achieving hematologic response (controversial, may improve outcomes)

Management of Organ Complications: - **Cardiac:** ACE inhibitors, beta-blockers, diuretics; cardiac device therapy if indicated - **Renal:** ACE inhibitor/ARB for proteinuria reduction; dialysis if GFR <15 mL/min - **Nutritional:** Nutritional support; vitamin D and fat-soluble vitamin replacement if GI involvement

Prognosis: - **Hematologic response rate:** 60–70% with modern therapy - **Organ response:** 30–50% achieve organ response (improvement in cardiac or renal parameters) - **Median overall survival:** ~5–7 years with modern therapy (vs. <2 years without treatment) - **Renal prognosis:** Depends on degree of glomerulosclerosis at baseline; advanced fibrosis = poorer prognosis

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Part V: Fibrillary and Immunotactoid Glomerulonephritis

Fibrillary Glomerulonephritis (FGN)

Definition: - Kidney disease with **non-amyloid fibrils** (≥3 nm diameter) in glomeruli - Can be associated with monoclonal protein (monoclonal FGN) or idiopathic

Prevalence: - Accounts for ~0.5–1% of native kidney biopsies - 20–30% associated with monoclonal protein (need IF and mass spectrometry for typing)

Clinical Presentation: - **Nephrotic or nephritic proteinuria:** 50–80% present with proteinuria >3 g/day - **Hematuria:** Common (often with dysmorphic RBC) - **AKI or CKD:** Progressive renal dysfunction

Biopsy Findings: - **LM:** Glomerulonephritis pattern (proliferative, membranoproliferative, or sclerotic) - **EM (diagnostic): Randomly oriented fibrils (NOT parallel lattice-like as in amyloid)** - Fibril diameter: 15–30 nm (larger than amyloid) - Nonbranching, no specific pattern - **Congo red:** NEGATIVE (distinguishes from amyloid) - **IF:** May be negative/weak or show granular pattern; if monoclonal light chain present ☐ monoclonal FGN

Management: - **If monoclonal:** Clone-directed therapy (proteasome inhibitor, IMiD) - **If idiopathic:** Limited data; proteinuria reduction with ACE inhibitor/ARB; immunosuppression controversial - **Prognosis:** Progressive; 50% develop ESRD by 5–10 years without treatment

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Immunotactoid Glomerulonephritis (ITN)

Definition: - Kidney disease with **hollow microtubules** in electron microscopy - Usually associated with monoclonal immunoglobulin (often IgG, IgM, or IgA) - Rare (accounts for 0.1% of kidney biopsies)

Clinical Presentation: - **Nephrotic syndrome:** 60–80% present with >3 g/day proteinuria - **Hematuria:** Common, often dysmorphic - **Progressive AKI/CKD**

Biopsy Findings: - **LM:** Proliferative or membranoproliferative GN pattern - **EM (diagnostic): Hollow tubular structures (microtubules)** - Diameter: 30–90 nm (larger than fibrils) - Often arranged in parallel arrays or lattice-like structures - May appear like "strings of pearls" or organized lattice - **Congo red:** NEGATIVE - **IF:** Shows **monoclonal immunoglobulin and/or light chain** (often IgG/IgM with kappa restriction)

Management: - **Clone-directed therapy:** Bortezomib, lenalidomide, dexamethasone - **Prognosis:** Highly variable; some progress to ESRD rapidly, others stable for years

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Part VI: Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID)

Definition & Epidemiology

- **Recently recognized entity (2010s)** of GN with glomerular proliferation and monoclonal immunoglobulin deposits
- NOT secondary to recognized systemic disease (SLE, post-infectious, etc.)
- Associated with clonal plasma cell population in bone marrow or circulating B cells
- Accounts for 5–10% of immune complex GN in some series

Clinical Presentation

- **Nephritic presentation:** Hematuria (dysmorphic RBC), proteinuria (1–5 g/day), hypertension
- **Rapidly progressive course:** AKI in some cases (crescentic variant)
- **Age of presentation:** Usually >50 years

Biopsy Findings

Light Microscopy: - **Membranoproliferative GN pattern:** Proliferation + tram-track walls (most common) - **Proliferative GN pattern:** Endocapillary or mesangial proliferation - **Crescentic GN:** Some cases present with segmental crescents

Immunofluorescence (Diagnostic): - **Monoclonal immunoglobulin (heavy chain + light chain monoclonal)** - Most common: IgG-kappa or IgG-lambda - Can also be IgM-monoclonal or IgA-monoclonal - **Deposits in glomeruli** in granular pattern - **Different from typical immune complex GN** which shows polyclonal immunoglobulin deposition

Electron Microscopy: - **Electron-dense deposits** in subendothelial, intramembranous, or mesangial locations - **Pattern similar to membranoproliferative GN or post-infectious GN** - No amyloid fibrils or special structures

Workup

- SPEP/UPEP (may show monoclonal protein, though can be absent)
- Free light chain assay
- Bone marrow biopsy (assess clonal population)
- Exclude other causes of immune complex GN (SLE, post-infectious, hepatitis C, etc.)

Management & Prognosis

- **Clone-directed therapy:** Bortezomib-based therapy if clonal population identified
- **Immunosuppression:** Prednisolone ± rituximab for induction if crescentic
- **Prognosis:** Variable; some cases remit with therapy, others progress to CKD/ESRD
- **Recent improvement:** Recognition of PGNMID and earlier clone-directed therapy improving outcomes

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Part VII: Diagnostic Workup Algorithm for Suspected MGRS

Step 1: Initial Serologic Testing

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Clinical suspicion of monoclonal gammopathy:
├─ Serum Protein Electrophoresis (SPEP)
├─ Urine Protein Electrophoresis (UPEP)
├─ Serum Free Light Chain Assay (absolute values + kappa/lambda ratio)
├─ Immunofixation Electrophoresis (IFE) if SPEP abnormal
└─ 24-hour urine total protein
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Interpretation: - Monoclonal spike on SPEP = myeloma or MGUS (30–50% of MGRS patients) - Abnormal FLC ratio (>100 or <0.01) = monoclonal population even without spike - Monoclonal protein on UPEP = free light chains or intact immunoglobulin

Step 2: Kidney Biopsy (Diagnostic Test for MGRS)

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If serum or urine monoclonal protein present + kidney disease:
├─ Light Microscopy (LM): Identify morphologic pattern
├─ Immunofluorescence (IF): Check for monoclonal light chain deposits
│   └─ Kappa vs. Lambda restriction indicates monoclonal disease
├─ Electron Microscopy (EM): Characterize deposit structure
└─ Special Stains: Congo red (amyloid), crystal violet (casts)
```

Key IF Findings by MGRS Type: - **Cast Nephropathy:** Monoclonal FLC in tubular casts only - **LCDD:** Linear monoclonal FLC along basement membranes - **AL Amyloidosis:** Monoclonal FLC (± light chain heavy chain), Congo-red positive - **Fibrillary GN:** Non-amyloid fibrils, monoclonal IF - **PGNMID:** Monoclonal Ig deposits in granular pattern

Step 3: Determine Clonal Source (If MGRS Diagnosed)

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Confirmed MGRS on biopsy:
├─ Bone Marrow Biopsy
│   ├─ Morphology: Assess % clonal plasma cells, morphology
│   ├─ Flow Cytometry: Confirm clonal population
│   └─ FISH: Check for high-risk cytogenetics (17p deletion, t(4;14), t(14;16))
├─ Blood Smear: Abnormal cells present?
└─ Circulating Free Light Chains: Measure response to therapy
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Step 4: Assess for Systemic Myeloma

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If MGRS diagnosed and >10% bone marrow involvement:
├─ Calcium, phosphate, albumin (assess CRAB)
├─ CBC: Check for anemia (CRAB criterion)
├─ Skeletal survey or low-dose CT: Assess for bone lesions (CRAB)
└─ If no CRAB criteria met but ≥60% clonal BMC, ≥100 FLC ratio, or ≥2 MRI lesions
    └─ Consider myeloma-defining event (MDE)
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Part VIII: Clone-Directed Therapy Principles

Rationale

- Kidney disease caused by abnormal plasma cell clone
- Elimination of clone = elimination of monoclonal protein = reversal of kidney disease
- **Goal:** Complete hematologic response (negative serum/urine protein, normal FLC ratio)

First-Line Induction Regimens

Bortezomib-Based (Preferred for most MGRS): - **CyBorD:** Cyclophosphamide + Bortezomib (subcutaneous or IV) + Dexamethasone - **DBd:** Dexamethasone + Bortezomib + Daratumumab (anti-CD38 monoclonal antibody) - **PAD:** Bortezomib + Doxorubicin + Dexamethasone - Advantages: Rapid FLC reduction (weeks), subcutaneous dosing, cardiac improvement in AL - Duration: 4–6 months induction, then re-evaluate hematologic and renal response

Lenalidomide-Based (Alternative): - **RVd:** Lenalidomide + Bortezomib + Dexamethasone - **Rd:** Lenalidomide + Dexamethasone (if bortezomib contraindicated) - Slower FLC reduction than proteasome inhibitors - Better for patients with neuropathy (bortezomib can worsen)

Older Regimens (If above contraindicated): - **Melphalan + Dexamethasone:** Standard pre-modern era; slower response - **Alkylating agents (Melphalan, Cyclophosphamide):** Acceptable but less rapidly effective

Maintenance Therapy

- **Goal:** Prevent relapse and maintain hematologic response
- **Options:**
  - Lenalidomide monotherapy (Rd maintenance)
  - Bortezomib monotherapy (weekly IV)
  - Observation if complete response achieved

Response Assessment

Hematologic Response Criteria: - **Complete Response (CR):** Negative serum/urine protein on immunofixation, normal FLC ratio - **Very Good Partial Response (VGPR):** ≥90% reduction in monoclonal protein - **Partial Response (PR):** ≥50% reduction in monoclonal protein - **Stable Disease:** <50% reduction - **Progressive Disease:** Increase in monoclonal protein

Renal Response Criteria: - **Complete Renal Response:** Normalization of proteinuria (<0.5 g/day) - **Partial Renal Response:** ≥50% reduction in proteinuria - **No Renal Response:** <50% reduction in proteinuria - **Renal Progression:** Increase in proteinuria or decline in GFR

Timing of Renal Response

- **Hematologic response:** Often achieves within 1–3 months
- **Renal response lag:** Usually 2–6 months after hematologic response
- **Maximum renal improvement:** May take 12–24 months of sustained hematologic remission
- **Clinical Pearl:** Do NOT stop therapy based on lack of immediate renal improvement if hematologic response achieved

Monitoring During Therapy

- **Monthly:** CBC, comprehensive metabolic panel, SPEP/UPEP or FLC assay
- **Every 3 months:** Assess urinalysis, estimate GFR, evaluate proteinuria (24-hr urine or protein/creatinine ratio)
- **Every 4–6 months:** Repeat bone marrow biopsy if diagnosis unclear or to assess response

- **Assess for toxicity:** Neuropathy (bortezomib), cytopenias, infection risk, GI effects

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Clinical Pearls

1. **MGRS is diagnosed on kidney biopsy, not hematology:** A patient with <10% clonal BMC and MGRS-pattern kidney biopsy has MGRS (and would be called MGUS by hematologic criteria alone).
2. **Monoclonal protein doesn't mean monoclonal kidney disease:** Just because a patient has a serum paraprotein doesn't automatically mean the kidney is involved with monoclonal disease; biopsy is diagnostic.
3. **IF monoclonal pattern is key:** Restrictive light chain pattern on IF (kappa-only or lambda-only) is critical for diagnosing MGRS; absence of monoclonal pattern should prompt reconsideration.
4. **Cast nephropathy is reversible early:** AKI from cast nephropathy can reverse if FLC rapidly reduced with early aggressive therapy; delay = irreversible tubular atrophy and fibrosis.
5. **LCDD progresses insidiously:** Light chain deposition disease often presents with 5–10 g/day proteinuria and slowly progressive renal decline; it's often missed if biopsy not done early.
6. **AL amyloidosis is under-diagnosed:** Suspect AL in any patient with unexplained nephrotic syndrome + systemic features (carpal tunnel, neuropathy, cardiac dysfunction, macroglossia).
7. **Congo-red staining is essential:** Always perform Congo-red staining on biopsies with suspected amyloidosis; apple-green birefringence is pathognomonic.
8. **Cardiac involvement is ominous in AL:** Presence of elevated troponin or NT-proBNP in AL amyloidosis patients confers 50% mortality within 4 months if untreated.
9. **FLC ratio >100 = urgent evaluation:** Severe FLC ratio abnormality (>100 involved:uninvolved) warrants aggressive workup for MGRS or myeloma.
10. **Early chemotherapy improves renal outcomes:** Initiating clone-directed therapy before advanced fibrosis develops improves likelihood of renal response and ESRD prevention.
11. **Kappa > lambda in LCDD:** Light chain deposition disease shows 2:1 predominance of kappa over lambda chains; any lambda LCDD warrants careful confirmation.
12. **Serial renal biopsies show response:** Repeat kidney biopsy after achieving hematologic response shows decrease in monoclonal deposits and improvement in glomerular/tubular architecture.

Practice Questions

Question 1: A 62-year-old man presents with serum creatinine 2.8 mg/dL and 8 g/day proteinuria. Serum protein electrophoresis shows no monoclonal spike. Free light chain assay: involved kappa 500 mg/L, uninvolved lambda 3 mg/L (ratio 167:1, severely abnormal). Kidney biopsy shows nodular glomerular expansion with monoclonal kappa light chain deposition along glomerular and tubular basement membranes. Congo red stain is negative. What is the most likely diagnosis?

A) AL Amyloidosis
B) Light Chain Deposition Disease (LCDD)
C) Post-Infectious Glomerulonephritis
D) Cast Nephropathy

Answer: B. LCDD. The diagnostic features are: (1) monoclonal light chain (kappa) restricted deposition along basement membranes on IF, (2) nodular glomerular expansion on LM (similar to diabetic nodules), (3) Congo-red negative (excludes amyloidosis), (4) severe FLC ratio abnormality. This patient has monoclonal gammopathy of renal significance (MGRS) with LCDD pattern.

Question 2: A 58-year-old woman with newly diagnosed AL amyloidosis of the kidney is being evaluated for systemic involvement. She has NT-proBNP 2,500 pg/mL (severely elevated, normal <125), troponin I 0.08 ng/mL (elevated, normal <0.04), and EF 38% on echocardiogram. What is her estimated median survival without treatment?

A) 26 months
B) 10 months
C) 4 months
D) <1 month

Answer: C. 4 months. Using the Mayo Clinic staging system for AL amyloidosis, this patient has Stage III disease (both NT-proBNP and troponin severely elevated). Presence of systemic involvement (cardiac with reduced EF) confers very poor prognosis. Median survival for Stage III is ~4 months. This patient requires urgent bortezomib-based induction therapy.

Question 3: A 45-year-old man presents with acute kidney injury (creatinine 3.2 mg/dL, baseline 0.9) and normal urinalysis (no dysmorphic RBC, no casts). Kidney biopsy shows prominent eosinophilic wavy casts in distal tubules and collecting ducts. Immunofluorescence shows monoclonal lambda light chain in casts. Serum FLC: involved lambda 450 mg/L, uninvolved kappa 2 mg/L. Which intervention is most likely to reverse the AKI?

A) Aggressive IV hydration alone
B) Rapid FLC reduction with bortezomib + lenalidomide + dexamethasone
C) ACE inhibitor therapy
D) Dialysis initiation

Answer: B. Rapid FLC reduction with proteasome inhibitor-based chemotherapy. This patient has cast nephropathy (myeloma kidney) with AKI. The AKI is reversible if FLC are rapidly reduced, ideally achieving ≥50% reduction within 1–2 weeks. Bortezomib is preferred for rapid FLC lowering. IV hydration alone is necessary but insufficient; chemotherapy is the critical intervention.

Early aggressive FLC reduction before irreversible tubular atrophy develops is the key to reversing AKI.

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   - Dispenzieri A, et al. Blood. 2012;120:3135–3142. (Mayo Clinic staging system)
   - Gertz MA. Blood Rev. 2019;38:100581. (comprehensive amyloidosis review)
6. **Fibrillary and Immunotactoid GN:**
   - Bridoux F, et al. Kidney Int Rep. 2019;4:1394–1402. (fibrillary GN review)
   - Markowitz GS, et al. J Am Soc Nephrol. 1998;9:1489–1498. (immunotactoid GN characteristics)
7. **PGNMID (Proliferative GN with Monoclonal Deposits):**
   - Zand L, et al. Clin J Am Soc Nephrol. 2016;11:1650–1656. (PGNMID outcomes and treatment)
8. **Proteasome Inhibitor Therapy in MGRS:**
   - Muchtar E, et al. Kidney Int. 2021;99:1341–1354. (bortezomib-based therapy for MGRS)
9. **Monoclonal Light Chain (FLC) Assays:**
   - Dispenzieri A, et al. Am J Clin Pathol. 2005;124:S110–S117. (FLC assay standards and interpretation)
10. **KDIGO References for Glomerulonephritis:**
    - KDIGO Glomerulonephritis Work Group Clinical Practice Guidelines for various GN types (2012–2020)

End of Module 24 *For questions or additional resources, contact your course faculty.*