

Treatment of Glomerular Diseases: Evidence-Based Immunosuppressive Strategies

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Learning Objectives

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

1. **Apply** KDIGO guidelines for first-line therapy in specific glomerular diseases
2. **Understand** mechanisms of action for major immunosuppressive drug classes
3. **Recognize** steroid-resistant presentations and appropriate salvage strategies
4. **Navigate** drug selection for special populations (pregnancy, renal impairment)
5. **Monitor** for treatment response and toxicity

Foundational Principles of Glomerular Disease Treatment

Universal Supportive Care (All Diseases)

Blood Pressure Control: - Target <130/80 mmHg for all patients with glomerular disease - More aggressive targets for significant proteinuria - Use RAAS blockers (ACE inhibitors or ARBs) as foundation

RAAS Blockade (Angiotensin System Inhibition): - First-line for virtually all glomerular diseases - Reduces proteinuria 30-50% through hemodynamic and anti-inflammatory mechanisms - Provides kidney protection through non-immunologic pathways - Maximize dose to highest tolerated level

Lifestyle Modifications: - Sodium restriction (<2 g/day) reduces edema and blood pressure - Protein restriction (0.8 g/kg/day) in CKD, modest reduction in primary GN - Lipid management with statins - Weight loss when overweight

Anticoagulation in Nephrotic Syndrome: - Risk of venous/arterial thromboembolism elevated - Membranous nephropathy and FSGS highest risk - Screen for clinical indicators; anticoagulate if risk substantial

Disease-Specific Treatment Algorithms

Minimal Change Disease (MCD)

First-Line Therapy: - Corticosteroids (all patients) - Prednisone 1 mg/kg/day (maximum 80 mg) or 2 mg/kg every other day - Maintain high dose minimum 4 weeks, maximum 16 weeks - Taper slowly over 6+ months after complete remission achieved - **Expected response:** 85-95% complete remission rate

Frequently Relapsing/Steroid-Dependent MCD: - Cyclophosphamide (KDIGO first-line) - Oral 1-2 mg/kg/day for 8-12 weeks - Remission rate 80% with <10% relapse at 1 year - Alternative: CNI monotherapy often requires long-term therapy

- **Calcineurin Inhibitors**
 - Cyclosporine or tacrolimus as alternative to cyclophosphamide
 - Remission rates 70-80%
 - Relapse frequent during tapering
- **Mycophenolate Mofetil (MMF)**
 - Emerging option for patients with cyclophosphamide failure
 - 1,200 mg/m²/day divided doses
 - Effective even in cyclophosphamide-refractory disease
- **Rituximab**
 - Anti-B cell antibody
 - Steroid-sparing benefit in pediatric population
 - Increasingly used in adults

Focal Segmental Glomerulosclerosis (FSGS)

Primary FSGS - Initial Treatment: - Corticosteroids (first-line) - Prednisone 1 mg/kg/day (maximum 80 mg) - Duration 8-16 weeks to determine response - 40-50% achieve remission with steroids

Steroid-Resistant FSGS (KDIGO 2021):

- **Calcineurin Inhibitors (first-line)**
 - **Cyclosporine:** 5-10 mg/kg/day targeting trough 125-175 ng/mL
 - **Tacrolimus:** 0.1-0.2 mg/kg/day divided doses
 - **Tacrolimus particularly effective:** 81% complete remission in SRNS
 - CNI + low-dose steroid reduces corticosteroid exposure
- **Mycophenolate Mofetil**
 - Alternative for CNI-intolerant patients
 - Complete/partial remission reduction 67% in SRNS
 - Less effective than CNI monotherapy
- **Sirolimus**
 - mTOR inhibitor
 - Reduces proteinuria and glomerular pore size in SRNS
 - Limited experience; reserve for specific scenarios
- **Rituximab**
 - Emerging data for steroid-resistant FSGS
 - May be particularly effective for certain FSGS subtypes

Secondary FSGS: - Treat underlying cause (HIV, obesity, remove nephrotoxin) - Immunosuppression generally ineffective - RAAS blockade foundation of therapy

Membranous Nephropathy

Diagnosis and Risk Stratification: - **Anti-PLA2R antibody testing:** Positive in 70-80% of primary MN - **Risk categories determine treatment intensity**

Low-Risk Patients: - Normal eGFR, proteinuria <3.5 g/dL, albumin >30 g/L - **Conservative therapy:** RAAS blockade, lipid management - Monitor; 30% achieve spontaneous remission

Moderate-Risk Patients: - Can receive symptomatic therapy (RAAS blockade, edema control) - OR rituximab OR calcineurin inhibitors

High/Very High-Risk Patients: - Proteinuria >4 g/day, declining eGFR, high anti-PLA2R titers - **Require immunosuppressive treatment**

Treatment Options:

- **Rituximab (KDIGO first-line)**
 - Superior in maintaining remission (60% vs. 20% with cyclophosphamide at 24 months)
 - Fewer adverse events
 - Re-treatment if failing to attain immunological remission at 3 months
- **Modified Ponticelli Regimen (Cyclophosphamide + Steroids)**
 - Alternating months of IV methylprednisolone + oral cyclophosphamide
 - Proven effective over decades
 - Immunological response faster at 6 months but comparable by 24 months
- **Calcineurin Inhibitors**
 - Cyclosporine 3-5 mg/kg/day targeting trough 125-175 ng/mL
 - Higher relapse rates compared to other treatments

IgA Nephropathy

Proteinuria <0.5 g/day: - RAAS blockade alone

Proteinuria 0.5-1 g/day: - RAAS blockade + consider steroids

Proteinuria >1 g/day Despite RAAS Blockade: - **TARPEYO (targeted-release budesonide)** indicated - Delivers therapy to Peyer's patches - 27% proteinuria reduction, 50% eGFR decline reduction

Progressive Disease or High-Risk Features: - **Sparsentan (dual endothelin/ARB antagonist)** - 49.8% vs. 15.1% proteinuria reduction vs. irbesartan - Indicated for high-risk patients

- Mycophenolate mofetil for rapid progression
- Cyclophosphamide reserved for rapidly progressive disease

ANCA-Associated Vasculitis (AAV)

Induction Therapy (Remission Induction):

Non-Severe Disease: - Rituximab or mycophenolate mofetil + corticosteroids

Severe/Organ-Threatening Disease: - Cyclophosphamide or rituximab + high-dose corticosteroids - IV methylprednisolone 0.5-1 g/day × 3 days - Oral prednisone 1 mg/kg/day tapered

Life-Threatening Disease (Pulmonary Hemorrhage): - Above therapy PLUS plasma exchange (7-14 days) - Cyclophosphamide dosing: IV 15 mg/kg every 2 weeks or daily oral 1.5-2 mg/kg

Avacopan (C5a Receptor Antagonist): - FDA approved 2021 for severe active ANCA-associated vasculitis - Complement C5a receptor antagonist - Used as adjunctive therapy with standard immunosuppression

Maintenance Therapy (≥18-24 months): - Azathioprine 2 mg/kg/day OR - Mycophenolate mofetil 1 g twice daily OR - Rituximab 500 mg every 6 months - Low-dose prednisone (goal <7.5 mg/day)

Lupus Nephritis

Class I-II: - Conservative management - Hydroxychloroquine (all patients)

Class III-IV (Proliferative):

Induction Therapy (3-6 months): - Option A (MMF-preferred): - Mycophenolate mofetil 1-3 g/day - Corticosteroids (tapered to lowest effective dose) - 50-60% remission rate

- **Option B (Cyclophosphamide):**

- IV 500-1000 mg/m² × 6 pulses monthly
- Indicated for crescentic or rapidly progressive disease
- Proven effective but more toxicity than MMF

- **Belimumab (Anti-BLyS):**

- Added to standard induction
- First biologic approved for lupus nephritis

- **Obinutuzumab (Anti-CD20):**

- Potent B-cell depletion
- FDA approval pending; shows benefit especially in high-proteinuria patients

Maintenance (≥2-3 years): - Mycophenolate mofetil or azathioprine - Low-dose prednisone (goal <7.5 mg/day)

All patients: - Hydroxychloroquine 200-400 mg daily (reduces flares, mortality benefit)

Class V (Membranous): - Calcineurin inhibitors or mycophenolate mofetil - Low-dose steroids

Anti-GBM Disease (Goodpasture Syndrome)

Urgent Treatment (Medical Emergency):

- **Plasma Exchange:** 7-14 days or until anti-GBM antibodies undetectable
 - Essential for antibody removal
 - Most effective if initiated before serum Cr >5.7 mg/dL
- **Immunosuppression:**
 - IV methylprednisolone 1 g daily × 3 days
 - Oral prednisone 1 mg/kg/day
 - Cyclophosphamide 2 mg/kg/day (oral)

Prognosis: 90% patient survival with treatment; renal recovery depends on initial severity

Major Drug Classes: Mechanisms and Monitoring

Corticosteroids

Mechanism: - Glucocorticoid receptor-mediated gene transcription - Induces apoptosis through BIM expression - NF- κ B inhibition - Anti-inflammatory cytokine effects

Dosing Principles: - Use lowest effective dose - Taper slowly after remission - Prolonged therapy increases infection risk, osteoporosis

Key Monitoring: - Blood glucose (hyperglycemia) - Bone density (osteoporosis prevention) - Infection risk - Psychological effects

Calcineurin Inhibitors (CNI)

Mechanism: - Bind calcineurin phosphatase - Prevent NFAT dephosphorylation - Block T-cell activation and IL-2 production

Specific Agents: - **Cyclosporine:** Monitor trough levels (125-175 ng/mL for GN) - **Tacrolimus:** Monitor trough levels (5-10 ng/mL for GN)

Key Advantages: - Rapid onset of action - Effective for steroid-resistant disease

Key Toxicities: - Nephrotoxicity (can worsen renal function) - Hypertension - Hyperglycemia - Drug interactions (CYP3A4) - Tremor, gingival hyperplasia (cyclosporine)

Antiproliferative Agents

Mycophenolate Mofetil (MMF) Mechanism: - Selective IMPDH type II inhibitor - Blocks T and B lymphocyte proliferation - Non-selective mechanism but selective for lymphocytes

Dosing: - 1-3 g/day divided doses - Dose-dependent effect (more drug, more effect)

Monitoring: - CBC (lymphopenia may indicate overdosing) - Gastrointestinal tolerance - Pregnancy risk (teratogenic)

Azathioprine (AZA) Mechanism: - Purine antimetabolite - Inhibits DNA synthesis - More general immunosuppression

Monitoring: - TPMT enzyme activity (genetic polymorphism affects metabolism) - CBC (myelosuppression) - LFTs

Alkylating Agents

Cyclophosphamide Mechanism: - Nitrogen mustard alkylating agent - Forms DNA crosslinks - Cell cycle arrest and apoptosis

Dosing Variations: - IV pulse: 500-1,000 mg/m² monthly - Oral daily: 1-2 mg/kg/day

Key Toxicities: - Myelosuppression - Hemorrhagic cystitis (rare at GN doses) - Secondary malignancies (with prolonged use) - Infertility

Monitoring: - CBC - Urinalysis (hematuria detection) - Adequate hydration to prevent cystitis

B-Cell Depleting Agents

Rituximab (Anti-CD20) Mechanism: - Monoclonal antibody targeting CD20 on B cells - Multiple killing mechanisms: CDC, ADCC, ADCP, direct apoptosis

Dosing for GN: - 375 mg/m² weekly × 4 weeks OR - 1 g × 2 doses 2 weeks apart

Key Advantages: - Effective for multiple GN types - Good safety profile - Can be used in pregnancy (compatible)

Key Considerations: - Hypogammaglobulinemia with prolonged B-cell depletion - Infection risk - Progressive multifocal leukoencephalopathy (rare)

Complement Inhibitors

Eculizumab (C5 Complement Inhibitor) Mechanism: - Binds C5, prevents terminal complement activation - Preserves C5a-mediated immunity

Indications: - C3 glomerulopathy - Select cases of ANCA vasculitis - Post-infectious GN (limited data)

Iptacopan (Factor B Inhibitor) Mechanism: - Selective alternative pathway inhibition - Preserves classical and lectin pathways

Application: IgA nephropathy (emerging)

Special Populations: Treatment Modifications

Pregnancy

General Principles: - Avoid teratogenic agents: mycophenolate, calcineurin inhibitors (controversial), some biologics - Compatible agents: corticosteroids, azathioprine, rituximab, cyclophosphamide (with caution) - ACE-I/ARB contraindicated; switch at conception

Renal Impairment

Dose Adjustments: - Mycophenolate: Reduce in eGFR <25 - Cyclophosphamide: Reduce in significant renal impairment - CNI: Monitor levels closely, nephrotoxicity concern - Most biologics: No dose adjustment needed

Infection Risk Populations

- Baseline CD4 <200: Avoid intensive immunosuppression if possible
- Prior tuberculosis: Vigilant monitoring during anti-TNF therapy
- Hepatitis B: Risk of reactivation with B-cell depletion

Monitoring Treatment Response

Clinical Response Markers

Complete Remission: - Proteinuria <0.3 g/day (or <300 mg/day) - Normal serum creatinine

Partial Remission: - ≥50% reduction in proteinuria - Stable or improved serum creatinine

No Response: - <50% proteinuria reduction or increasing creatinine

Laboratory Monitoring Timeline

Baseline (Before Therapy): - 24-hour urine protein or UPCR - Serum creatinine, BUN, electrolytes - CBC, LFTs - Serologies as indicated

During Induction (First 3-6 months): - Monthly: Serum creatinine, CBC (if cyclophosphamide/MMF) - 3 months: 24-hour urine protein or UPCR - Drug levels (CNI if used)

Maintenance Phase: - 3-6 months: Creatinine, urine protein - Quarterly: CBC if on mycophenolate - Annual: Comprehensive metabolic panel, lipids

Practice Questions

Question 1: A 35-year-old female with MCD relapses 5 times in 12 months. What is the KDIGO-recommended first-line therapy for frequently relapsing MCD?

- A) Rituximab
- B) Cyclophosphamide
- C) Calcineurin inhibitors
- D) Higher-dose prednisone

Correct Answer: B — KDIGO recommends cyclophosphamide for frequently relapsing (≥2 relapses in 6 months) or steroid-dependent MCD. Oral cyclophosphamide 1-2 mg/kg/day for 8-12 weeks achieves 80% remission with <10% relapse at 1 year.

Question 2: A 28-year-old with Class IV lupus nephritis and activity index 15/24 is steroid-intolerant (severe hyperglycemia, psychosis). Which alternative first-line induction therapy is most appropriate?

- A) High-dose IV cyclophosphamide pulses
- B) Mycophenolate mofetil monotherapy
- C) Calcineurin inhibitor therapy
- D) Rituximab monotherapy

Correct Answer: B — Mycophenolate mofetil is KDIGO first-line alternative for steroid-intolerant patients with proliferative lupus nephritis. MMF 1-3 g/day achieves comparable remission rates to cyclophosphamide with less toxicity. CNI not first-line for Class IV. Cyclophosphamide as alternative if MMF fails.

Question 3: A 52-year-old with IgA nephropathy and 4.2 g/day proteinuria after maximizing ACE inhibitor therapy. Which therapeutic agent directly targets abnormal IgA production?

- A) TARPEYO (targeted-release budesonide)
- B) Sparsentan
- C) Mycophenolate mofetil
- D) Corticosteroids

Correct Answer: A — TARPEYO delivers budesonide specifically to Peyer’s patches in the small intestine, targeting the presumed site of abnormal galactose-deficient IgA production. This mechanism-based approach reduces proteinuria 27% and slows eGFR decline by 50% over 2 years.

Clinical Pearls: Treatment Selection

1. **RAAS blockade foundation** — use ACE-I or ARB for ALL glomerular diseases
 2. **MCD: Steroids work** — 85-95% remission rate with appropriate dosing
 3. **FSGS: CNI > steroids** — 81% remission with tacrolimus vs. 50% with steroids
 4. **MN: Rituximab preferred** — superior remission maintenance vs. cyclophosphamide
 5. **AAV: Rituximab replacing cyclophosphamide** — comparable efficacy, less toxicity
 6. **Lupus: MMF first-line** — preferred over cyclophosphamide; steroid-sparing
 7. **IgAN: TARPEYO targets source** — mechanism-based therapy addressing pathogenic step
 8. **Always use lowest effective dose** — balance efficacy against cumulative toxicity
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See Also

Related Student Handouts

- Nephritic and Nephrotic Syndromes
- Lupus Nephritis
- IgA Nephropathy
- FSGS
- Vasculitis and Complement-Mediated Diseases
- Immunosuppressive Therapy in Nephrology
- Kidney Biopsy Essentials

Clinical Content (01-Clinical-Medicine/Nephrology)

- Glomerular Diseases Hub
- Essential Renal Laboratory Tests

Butler-COM Resources

- Butler COM - Nephrology Deep Dive

Related Topics

- Detailed Supportive Care
 - Updated Evidence-Based Guidelines
 - Therapeutic Drug Level Management
 - Osteoporosis, Infection, Metabolic Complications
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Summary

Modern treatment of glomerular diseases integrates specific immunosuppressive agents with supportive care to achieve remission while minimizing cumulative toxicity. KDIGO guidelines recommend disease-specific algorithms balancing efficacy and safety. RAAS blockade provides universal renoprotection across all glomerular diseases. Corticosteroids remain highly effective for minimal change disease but steroid-resistant presentations require alternative agents (calcineurin inhibitors, mycophenolate mofetil, rituximab). Modern biologics including belimumab, obinutuzumab, and complement inhibitors expand treatment options and improve outcomes. Understanding mechanisms of action enables rational drug selection and risk stratification for special populations. Close monitoring of clinical and laboratory response guides therapy adjustments, enabling most patients with glomerular disease to achieve remission and preserve long-term kidney function.