

# IgA Nephropathy: From Pathogenesis to Precision Medicine

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## IgA Nephropathy: From Pathogenesis to Precision Medicine

### Learning Objectives

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

1. **Explain** the four-hit pathogenesis model and identify therapeutic targets at each stage
2. **Recognize** clinical presentations and risk stratify for treatment intensity
3. **Compare** current and emerging therapeutic options with efficacy data
4. **Apply** risk-based treatment decisions to patient scenarios
5. **Understand** pregnancy considerations in reproductive-age patients

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### What Makes IgA Nephropathy Unique?

**Global Epidemiology:** - Most common primary kidney disease worldwide - Prevalence varies: ~45% of primary GN in Asia, ~20% in Europe, ~10% in North America - Predominates in young adults (peak 20-40 years) - Male:female ratio approximately 2:1

**Natural History:** - 30-40% progress to kidney failure over 20 years without intervention - Highly variable course: some remain stable, others progress rapidly - Characterized by episodic gross hematuria often following respiratory infections

**Pathophysiology:** IgA-containing immune complexes deposit in glomerular mesangium, triggering inflammatory cascades leading to progressive scarring.

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### The Four-Hit Pathogenesis Model: Therapeutic Framework

Understanding disease mechanisms enables rational therapeutic selection targeting specific pathogenic steps.

#### Hit 1: Abnormal Antibody Production (Gut-Associated)

**Location:** Gut-associated lymphoid tissue, particularly Peyer's patches in small intestine

**What Goes Wrong:** - Environmental triggers, genetic factors, or infections stimulate production of galactose-deficient IgA1 (Gd-IgA1) - These abnormal IgA antibodies lack important sugar modifications - Altered glycosylation promotes aggregation and immune complex formation

**Therapeutic Target:** - **TARPEYO (targeted-release budesonide):** Delivers steroid specifically to Peyer's patches - **APRIL inhibitors:** Block A Proliferation-Inducing Ligand controlling IgA class switching in gut

### **Hit 2: Autoimmune Response (Anti-Glycan Antibodies)**

**What Develops:** - Immune system recognizes abnormal IgA as "foreign" - Produces anti-glycan autoantibodies targeting galactose-deficient regions - Creates autoimmune attack against body's own antibodies

**Cascade Effect:** - IgA1-specific glycan modifications become immunogenic - Antibodies bind to the abnormal IgA, forming pathogenic complexes

**No Direct Therapeutic Target Yet:** - Future approaches may involve tolerizing autoimmune responses - Current therapy focuses on downstream steps

### **Hit 3: Immune Complex Formation**

**Result:** Formation of circulating immune complexes with: - Altered size properties (too small for normal clearance) - Altered charge properties - Enhanced propensity for glomerular deposition

**Therapeutic Target:** - Complementary strategies reducing circulating complex load - SGLT2 inhibitors may help prevent progression

### **Hit 4: Kidney Deposition and Inflammation**

**Pathology:** - Complexes deposit in glomerular mesangium - Complement activation triggered - Inflammatory cell infiltration - Fibroblast proliferation □ progressive scarring

**Therapeutic Targets:** - **Sparsentan:** Dual endothelin A + angiotensin receptor blockade - **Ip-tacopan:** Factor B inhibitor blocking alternative complement pathway - **Conventional therapy:** ACE-I/ARB, corticosteroids

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## **Clinical Presentation Patterns**

### **Classic Presentation (40% of Cases)**

**Presentation:** Gross hematuria within 1-3 days of upper respiratory infection

**Key Features:** - "Tea-colored" or "cola-colored" urine - Peak in young adults - Often misattributed to urinary tract infection initially - Represents acute glomerular inflammation triggered by respiratory pathogen

**Typical Labs:** Normal kidney function, proteinuria 1-3 g/day initially

### **Asymptomatic Urinary Abnormalities (30% of Cases)**

**Presentation:** Microhematuria and proteinuria found on routine screening

**Key Features:** - No gross hematuria - May have slowly progressive disease without obvious symptoms - Often in older patients or with incidental screening

**Clinical Significance:** May represent slowly progressive IgA nephropathy requiring monitoring even without symptoms

### **Nephrotic/Nephritic Syndrome (20% of Cases)**

**Presentation:** Significant proteinuria >3.5 g/day with hypoalbuminemia and edema

**Key Features:** - More aggressive disease phenotype - Combined nephrotic and nephritic features - Requires intensive intervention

**Prognosis:** Worse short-term outlook; requires maximum therapeutic intervention

### **Acute Kidney Injury (10% of Cases)**

**Presentation:** Rapid decline in kidney function

**Pathology:** Often associated with crescentic glomerulonephritis

**Clinical Significance:** Most severe form; requires emergent aggressive treatment

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## **Risk Stratification for Treatment Planning**

### **Low-Risk Patients**

**Definition:** - Proteinuria <1 g/day - Normal kidney function (eGFR >90) - Minimal histologic changes on biopsy

**Management:** - ACE inhibitor or ARB optimization (primary therapy) - Blood pressure target <130/80 mmHg - Lifestyle modification (salt restriction, protein moderation) - Close monitoring with 3-6 month urinalysis

**Monitoring:** Annual assessment adequate

### **Moderate-Risk Patients**

**Definition:** - Proteinuria 1-3 g/day - Stable kidney function - Moderate histologic changes

**Management:** - **TARPEYO** indicated for risk reduction - Combined with optimized ACE-I/ARB - Close monitoring for progression

**Monitoring:** 3-6 month intervals

## High-Risk Patients

**Definition:** - Proteinuria >3 g/day - Declining kidney function - Severe histologic changes including crescents

**Management:** - **Sparsentan** or combination therapy - More intensive monitoring - May require specialist referral

**Monitoring:** Monthly initially with clinic/lab assessment

## Very High-Risk Patients

**Definition:** - Proteinuria >5 g/day plus declining eGFR - Crescentic disease with rapidly declining function - Multiple organ systems involved

**Management:** - Combination therapy (endothelin antagonist + complement inhibitor + supportive care) - Specialist (nephrologist) co-management - Weekly monitoring initially

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## Current Therapeutic Armamentarium

### Foundation Therapy: RAAS Blockade

**First-line for ALL patients:** - ACE inhibitor or angiotensin receptor blocker - Dual therapy (ACEi + ARB) not recommended - Maximize dose to highest tolerated level - **Target:** ≥30% proteinuria reduction

**Mechanism:** - Reduces glomerular hyperfiltration - Provides anti-inflammatory and anti-fibrotic effects - Lowers blood pressure

### TARPEYO (Targeted-Release Budesonide)

**Mechanism:** Delivers budesonide specifically to Peyer's patches in intestine, targeting presumed site of abnormal IgA production while minimizing systemic steroid exposure

**Clinical Evidence - NefIgArd Trial:** - 27% proteinuria reduction at 9 months - 50% reduction in eGFR decline rate over 2 years - Sustained benefits at 15-month follow-up

**Optimal Patient Selection:** - Moderate-risk patients with proteinuria 1-3 g/day - Desire to avoid systemic immunosuppression - Need for intervention beyond supportive care

**Practical Use:** - Oral capsule administration for 9 months - Common side effects: peripheral edema (17%), hypertension (12%) - **Advantage:** Avoids serious complications of systemic steroids

### Sparsentan (FILSPARI)

**Mechanism:** First-in-class dual endothelin A receptor and angiotensin II type 1 receptor antagonist in single molecule

**Clinical Evidence - PROTECT Trial:** - 49.8% proteinuria reduction with sparsentan vs. 15.1% with maximum-dose irbesartan - Slower eGFR decline: 1.2 mL/min/1.73m<sup>2</sup>/year treatment effect - Two-year data shows sustained benefit

**Optimal Patient Selection:** - High-risk patients with proteinuria >1 g/day - Need for maximum efficacy intervention - Patients requiring combined anti-proteinuric and nephroprotective effects

**Key Advantage:** No fluid retention or heart failure observed (distinguishes from other endothelin blockers)

**Monitoring:** Liver function tests required through REMS program

### **Iptacopan (FABHALTA)**

**Mechanism:** Selective factor B inhibitor blocking alternative complement pathway amplification while preserving classical and lectin pathway function

**Clinical Evidence - APPLAUSE-IgAN:** - 38.3% proteinuria reduction at 9 months - Composite kidney outcome improvement (NNT = 14)

**Optimal Patient Selection:** - Patients with evidence of active complement activation - Non-immunosuppressive therapy preference - Requires meningococcal vaccination

**Practical Considerations:** - Prescribing limited to certified providers through REMS - Infection monitoring required - Continued approval depends on eGFR benefit demonstration

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## **Emerging Therapies: The Future Pipeline**

### **APRIL Inhibitors (Next-Generation Therapy)**

**Target:** A Proliferation-Inducing Ligand (APRIL) controls IgA class switching in gut lymphoid tissue

**Clinical Data - Sibeprenlimab (VISIONARY Trial):** - 51.2% proteinuria reduction (highest efficacy to date) - Excellent safety profile - Subcutaneous injection every 4 weeks - Disease-modifying potential (addresses pathogenic source)

**Significance:** Represents highest efficacy demonstrated and most direct hit on pathogenic mechanism

### **Combination Strategies**

**Rationale:** Multiple pathogenic pathways present opportunity for synergistic targeting

**Investigational Approaches:** - APRIL inhibitor + complement inhibitor (upstream + downstream) - Endothelin antagonist + SGLT2 inhibitor (anti-proteinuric + anti-fibrotic) - Triple therapy for very high-risk patients

**Future Direction:** Biomarker-guided combination selection based on individual pathway activation

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## **Treatment Decision Framework**

Risk Level	Proteinuria	Recommended Approach	Monitoring
<b>Low</b>	<1 g/day	ACE-I/ARB optimization	Annual
<b>Moderate</b>	1-3 g/day	TARPEYO + ACE-I/ARB	3-6 months
<b>High</b>	>3 g/day	Sparsentan or combination	Monthly initially
<b>Very High</b>	>5 g/day + declining eGFR	Combination therapy + specialist	Weekly initially

## Special Populations: Case-Based Learning

### Case 1: Reproductive-Age Female

**Scenario:** 26-year-old planning pregnancy with stable IgA nephropathy

**Challenge:** Most novel therapies (sparsentan, complement inhibitors, APRIL inhibitors) contraindicated in pregnancy due to teratogenic potential

**Management Approach:** 1. Optimize supportive care with pregnancy-compatible agents 2. Continue ACE-I until pregnancy confirmed, then discontinue 3. Plan for multidisciplinary obstetric-nephrology collaboration 4. Close monitoring during pregnancy and postpartum period

**Learning Point:** Reproductive health planning essential for young adults with IgA nephropathy

### Case 2: Aggressive Disease with Crescents

**Scenario:** 32-year-old male with 4.2 g/day proteinuria, eGFR decline 90  $\square$  65 over 6 months, crescentic lesions on biopsy

**Assessment:** High-risk disease requiring maximum intervention

**Treatment Strategy:** - Initiate sparsentan for dual mechanism benefit - Plan combination therapy if inadequate response at 3-6 months - Close monitoring with monthly clinic and lab assessment - Consider rheumatology/nephrology co-management

**Learning Point:** Rapidly progressive disease requires immediate intensive intervention

## Monitoring and Assessment Strategies

### Proteinuria Monitoring

- Check spot UPCR every 3-6 months during treatment
- Look for  $\geq 30\%$  reduction as meaningful response
- Response may take 3-6 months to become apparent
- Monitor for proteinuria rebound with therapy discontinuation

### Kidney Function Assessment

- Monitor eGFR trends rather than absolute values
- Stable or slowing decline rate indicates therapeutic benefit

- Assess for premature GFR decline suggesting treatment failure

### Safety Monitoring

- **TARPEYO:** Hypertension, glucose monitoring
  - **Sparsentan:** Liver function tests, blood pressure
  - **Iptacopan:** Infection surveillance, meningococcal vaccination verification
  - All agents: Serum creatinine for acute kidney injury
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### Practice Questions

**Question 1:** A 28-year-old woman with IgA nephropathy and 2.8 g/day proteinuria plans pregnancy in 6 months. Which therapeutic approach is most appropriate?

- A) Start sparsentan for maximum efficacy now
- B) Initiate TARPEYO before pregnancy
- C) Maximize ACE-I therapy; discuss transitioning to pregnancy-compatible management
- D) Defer all therapy until postpartum period

**Correct Answer: C** — ACE inhibitors provide maximum nephroprotection but must be discontinued once pregnancy is confirmed due to teratogenicity. Early optimization before pregnancy then transition to alternative agents represents appropriate approach. Most novel therapies contraindicated in pregnancy.

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**Question 2:** Which mechanism best explains sparsentan's superior proteinuria reduction compared to standard ACE inhibitors alone?

- A) More potent angiotensin receptor blockade
- B) Dual pathway targeting with synergistic effects
- C) Selective complement inhibition
- D) Direct anti-inflammatory properties

**Correct Answer: B** — Sparsentan combines endothelin A receptor antagonism with angiotensin receptor antagonism in a single molecule, providing synergistic renoprotection through dual pathway inhibition.

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**Question 3:** A 35-year-old with IgA nephropathy starts iptacopan (FABHALTA) but develops recurrent sinusitis and otitis within 2 months. What is the most likely explanation?

- A) Drug intolerance requiring immediate discontinuation
- B) Complement inhibition increases infection risk; enhance monitoring and verify meningococcal vaccination
- C) Unrelated coincidence; continue therapy
- D) Indication for combination with prophylactic antibiotics

**Correct Answer: B** — Selective complement pathway inhibition increases infection risk by 2-3 fold. Meningococcal vaccination mandatory before therapy. Enhanced infection surveillance

required. This is an expected risk, not indication for discontinuation, but requires active management.

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## Clinical Pearls

1. **Risk stratification drives therapy** – not all IgA patients need same treatment intensity
  2. **ACE-I/ARB optimization is foundation** – all patients require maximal RAAS blockade
  3. **TARPEYO targets disease source** – delivers therapy to Peyer’s patches
  4. **Sparsentan dual mechanism** – superior efficacy for high-risk patients
  5. **Fertility planning essential** – most novel therapies contraindicated in pregnancy
  6. **Proteinuria decline takes time** – expect 3-6 months for therapeutic effect
  7. **Monitoring strategy depends on therapy** – different agents require different surveillance
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## Related Topics

### See Also

### Related Student Handouts

- Nephritic and Nephrotic Syndromes
- Vasculitis and Complement-Mediated Diseases
- Glomerular Treatment Principles
- Kidney Biopsy Essentials
- Immunosuppressive Therapy in Nephrology

## Clinical Content (01-Clinical-Medicine/Nephrology)

- Glomerular Diseases Hub
- Essential Renal Laboratory Tests

## Butler-COM Resources

- Butler COM - Nephrology Deep Dive
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- Clinical Recognition and Differential Diagnosis
  - General Immunosuppressive Principles
  - Other Causes of Hematuria and Proteinuria
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## Summary

IgA nephropathy represents a paradigm shift in nephrology from empiric immunosuppression to mechanism-based precision medicine. Understanding the four-hit pathogenesis model enables

rational therapeutic selection targeting specific disease mechanisms. Risk stratification guides appropriate therapy intensity from supportive care to combination approaches. Novel agents including TARPEYO, sparsentan, and iptacopan expand therapeutic options with improved efficacy and safety profiles. The robust development pipeline promises continued advancement with APRIL inhibitors demonstrating highest efficacy to date. Future directions include biomarker-guided combination therapy tailored to individual pathway activation patterns. For medical students and residents, IgA nephropathy provides an excellent model of translating mechanistic understanding into effective therapies and demonstrates the power of precision medicine approaches in modern nephrology.