Common glomerular disease

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A 56-yr-old woman is found to have normochromic normocytic anemia, renal insufficiency (serum creatinine of 2.6 mg/dl), proteinuria (1+ by dipstick), hypophosphatemia, hypouricemia, and glucosuria. Urine protein excretion was 3.1 g/day. Which ONE of the following is the MOST likely cause of this constellation of findings?

A. Diabetic nephropathy
B. Lead intoxication
C. Aristolochic acid intoxication
D. Multiple myeloma
E. AL amyloidosis

SCOPE

• Isolated proteinuria / hematuria
• Glomerular diseases commonly presented with nephrotic syndrome
• Glomerular diseases commonly presented with nephritic syndrome

Proteinuria

• Overproduction (overflow proteinuria) e.g., multiple myeloma, lymphomas, (amyloidosis)
• Tubular proteinuria e.g., Fanconi syndrome, interstitial disease
• Glomerular proteinuria i.e., glomerular disease
Isolated hematuria

- Lower tract: ureter, bladder, prostate
- Kidney: cystic disease, renal cell carcinoma, hypercalciuria, renal vein thrombosis, interstitial nephritis
- Glomerular disease – dysmorphic RBCs, RBC cast, no clot
  - Thin basement membrane disease
  - Ig A nephropathy
  - Hereditary nephritis (Alport syndrome)

Alport syndrome

- Mutation of COL4A5
- X-linked recessive transmission (majority, 85%)
- Age at presentation: children or young adult (male), any age (female)
- Males: hematuria, proteinuria and HTN, ESRD at age 30 (70%), deafness (30-50%), ocular defect (15-30%) (pathognomonic: anterior lenticonus, “dot and fleck” retinopathy)
- Females: microscopic hematuria without progression, renal impairment (25%)
- Diagnosis: absent of α5-subunit of type IV collagen in epidermal basement membrane (and kidney)

Thin basement membrane disease

- “Benign familial hematuria”
- Mutation of COL4A3 or COL4A4
- Autosomal dominant transmission
- Age at presentation: any age
- Hematuria (persistent or intermittent), no/mild - HTN, proteinuria, renal impairment
  - No deafness, no ocular change
  - Differentiate with carrier state of Alport syndrome in female

Alport syndrome

Ocular manifestations in Alport syndrome

- “Anterior lenticous”
- “Dot and fleck” retinopathy

Secondary causes of nephrotic syndrome

- Autoimmune disease: SLE, RA, MCTD, PSS, HSP (including Ig AN), small vessel vasculitides, cryoglobulinemia
- Infections: HBV, HCV, HIV, malaria, schistosomiasis, syphilis, PSGN, IE, shunt nephritis
- Drugs: NSAIDs, pamidronate, bevacizumab, mercury, gold, penicillamine, heroin, captopril, lithium, interferon-α
- Malignancies: solid tumors (lung, colon, stomach, breast, cervix, kidney, thyroid, ovary, prostate), hematologic tumors (HD, NHL, CLL)
- Metabolic disease: diabetes, amyloidosis
- Miscellaneous: bee sting, preeclampsia, transplant glomerulopathy, renal artery stenosis, morbid obesity, vesicoureteral reflux

Bolds are the common causes of nephrotic syndrome; italics are the causes usually present with nephritic syndrome.

Complements: First test to do

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alternative pathway (C3)</th>
<th>Classical pathway (C4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus nephritis</td>
<td>↓</td>
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</tr>
<tr>
<td>Membranoproliferative GN (type I)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Dense deposit disease (Membranoproliferative GN type II)</td>
<td>↓</td>
<td>↔</td>
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<tr>
<td>Cryoglobulinemia</td>
<td>↔ , ↓</td>
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<tr>
<td>Post-streptococcal GN</td>
<td>↓</td>
<td>↔ , mildly ↓</td>
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<td>Infective endocarditis</td>
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<td>Shunt nephritis</td>
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<tr>
<td>HBV/HCV-associated GN</td>
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<tr>
<td>Atheroembolic disease</td>
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</table>

Minimal change disease

- 10-15% of 1° NS in adults (70-90% in children)
- Clinical features: 100% nephrotic (abrupt onset), mean proteinuria 10 g/d

Hematuria Hypertension Renal impairment

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
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<tbody>
<tr>
<td></td>
<td>Uncommon</td>
<td>20%</td>
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<td></td>
<td>Uncommon</td>
<td>~20% (age &gt;60 y)</td>
</tr>
</tbody>
</table>
- Mechanisms of renal insufficiency: intrarenal hemodynamic or intrarenal edema (nephrosarca)
- Common associated conditions:
  - Drugs: NSAIDs, lithium, interferon-α
  - Malignancies: Hodgkin’s disease, CLL
  - Miscellaneous: viral infection, allergies, bee sting

Foot process effacement

Minimal change disease

- Pathogenesis: abnormal regulation of T cell subset

Hematuria Hypertension Renal impairment

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- Treatment: prednisolone 1 mg/kg/d at a daily single dose (response: children 90-95%, adults 80-85%) (1C), minimum period 4 weeks / maximum period 16 weeks (2C), and tapered slowly over a total period of up to 6 mo (2D)
- CYC or CNIs (cyclosporine and tacrolimus) for patients with relative contraindications or intolerance to steroids (2D)

2012 KDIGO Clinical Practice Guideline for Glomerulonephritis.
**Ig M nephropathy**

- The most common cause of 1° NS in adult Thais???
- Clinical features: the incidence of hematuria, hypertension, or renal impairment is higher than that of in minimal change disease (but how much???, 10-20%?)
- No associated condition reported
- Pathogenesis: abnormal regulation of T cell subset
- Treatment: steroids, 16-20 wk (response ~50?? to 80%)

**Focal segmental glomerulosclerosis**

- Increasing incidence (~1/3 in adults)
- Clinical features: nephrotic 90%
  - Hematuria 60-80%, HTN 80%, renal impairment ~80%
- Pathogenesis: podocyte injury, permeability factor (soluble urokinase-type plasminogen activator receptor, suPAR)

**Membranous nephropathy**

- One of the most common cause of NS in adults (~30%), peak incidence 30-50 years
- Secondary causes (25-30% of cases):
  - Autoimmune diseases e.g., SLE, autoimmune thyroiditis, myasthenia gravis
  - Infection e.g., HBV, HCV, malaria, syphilis, leprosy
  - Drug e.g., penicillamine, gold, mercury
  - Malignancy e.g., lung, prostate, stomach, breast, colon
  - Incidence is significantly higher (9-12 times)
  - 20-30% of patients who are older than 60 years
  - ~50% are asymptomatic
  - Median diagnosis time after MN is 60 mo (usually 12 mo)
Membranous nephropathy

- Clinical features: nephrotic 80%, ↑ risk of thrombosis
  - Hematuria 50%, HTN 50%, renal impairment <10%
- Pathogenesis: subepithelial immune deposits
  - Antigen: M-type phospholipase A2 receptor (PLA2R) — for primary MN, sensitivity 75%, specificity 100%
    - 1/3 each: spontaneous remission, relapsing, renal failure
    - Consider treatment if persistent high-grade proteinuria (>4 g/d) despite at least 6 mo of conservative management
  - Treatment: 6-mo course of alternating monthly cycles of oral and IV steroids and oral CYC (1B) or CNIs monotherapy (1C)
    - Steroid monotherapy not be used

Membranoproliferative GN

- Uncommon in adults
- Clinical features: nephrotic 60%
  - Hematuria (60-80%), HTN (80%), renal impairment (~80%), rapid deterioration in renal function (25%) 
  - 70% hypocomplementemia (C3 in all and C4 in some)
  - 50% developed ESRD at 10 years
- Pathophysiologic classification: subepithelial immune deposits, membrane splitting
  - Immune-complex mediated: chronic infections (hepatitis C and B, endocarditis, shunt nephritis), autoimmune diseases, monoclonal gammopathies
  - Complement mediated: dysregulation of the alternative complement pathway due to mutations or autoantibodies

Hypercoagulable state in NS

- Etiologic factors:
  - Urinary loss of anticoagulants (antithrombin III, protein S) and fibrinolytics (plasminogen)
  - Hepatic overproduction in response to hypoalbuminemia — factor V, factor VIII, fibrinogen
  - Increased synthesis of platelet proaggregants — thromboxane A2
- MN is at the greatest risk — unknown reason
- Risk increased significantly when serum albumin <2.8 g/dl
- Prophylaxis (suggestion???): depends on serum albumin
  - <2.0 g/dl — LMWH or low-dose warfarin
  - 2.0-3.0 g/dl — low dose aspirin

A 68-year-old woman noticed bilateral lower extremity edema. Her past medical history included 50 pack-years of cigarette smoking with ongoing tobacco abuse. Her vital signs (including BP) were normal. Laboratory workup revealed 10 g/d proteinuria, creatinine of 0.7 mg/dl, total cholesterol of 350 mg/dl, and albumin of 2.6 g/dl. The following tests were negative/normal: ANA, C3 and C4, hepatitis B and C. A renal biopsy revealed membranous nephropathy.

What is the most appropriate next step in managing this patient?

A. Request serologic testing for anti-M-type phospholipase receptor (anti-PLA2R) antibodies  
B. Request IF staining of the biopsy for anti-PLA2R antibodies  
C. Start prophylactic anticoagulation with warfarin  
D. Arrange age- and risk factor-appropriate cancer screening  
E. Recommend first-line immunosuppressive therapy of steroids+alkylating agent

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**HBV-associated GN**

- Membranous nephropathy (followed by MPGN)
  - Proteinuria (non-nephrotic or nephrotic), normal renal function, hematuria (uncommon)
  - Low complement levels (~20%)
  - Chronic HBV (positive HBsAg)
  - Mildly elevated AST and ALT (~100-200 IU/L)
  - Treatment: interferon-\(\alpha\) or nucleoside analogues (1C)

- HBV-associated polyarteritis nodosa
  - Renal artery aneurysms or renal infarction
  - ACR criteria: “Presence of HBsAg or Ab in serum”

**HCV-associated GN**

- MPGN with/without mixed cryoglobulinemia (type II) (followed by membranous nephropathy)
- Nephrotic syndrome, hematuria (common), impaired renal function (common)
- Low complement levels (50-90%) and positive cryoglobulinemia (~60-70%)
- Transaminitis in most patients
- 50% showed extrarenal manifestations: vasculitic purpura, arthralgia, and neuropathy
- Treatment: pegylated interferon + ribavirin (2C)
- Cryoglobulinemia: plasmapheresis, rituximab, or CYC, in conjunction with IV methylprednisolone (2D)

**Renal amyloidosis**

- Positive Congo red, “apple green appearance”: kidney or liver (90%), abdominal fat (70%)
- Primary (AL, light chains): lambda 75%, MM 10-20%, age >50
  - Kidney (50%): proteinuria (80%), nephrotic syndrome (30%), renal impairment (20%), rare hematuria, pRTA
  - Heart (40%): restrictive cardiomyopathy
  - Neuromuscular (≤25%): neuropathy, orthostatic hypotension
  - Hepatomegaly (25%), macroglossia (10%), purpura (15%)
  - Treatment: melphalan + pred (30% effectiveness) ± HSCT
- Secondary (AA, serum amyloid A): chronic infection/inflammation – RA (40%), AS and psoriatic arthritis (10%)
- Rare cardiac involvement, NS (common), ESRD 40-60%
- Treatment: treat underlying disease

DDD, dense deposit disease; MPGN membranoproliferative GN
A 50-year-old obese woman with a 5-year history of hypertension controlled by enalapril is being evaluated because of proteinuria. Physical examination disclosed obese woman, BP 130/80 mmHg, and trace pedal edema. Laboratory: creatinine 1.4 mg/dl, BUN 18 mg/dl; urinalysis: pH 5.0, protein 3+, no glucose, RBC 10-20/hpf. Urine protein 5.9 gm/day. A renal biopsy demonstrates that 60% of the glomeruli have segmental scarring.

The most likely diagnosis is:
A. Hypertensive nephrosclerosis
B. Primary focal and segmental sclerosis
C. Secondary focal and segmental sclerosis
D. Membranous nephropathy
E. Crescentic glomerulonephritis

A 20-year-old female in excellent health suddenly develops periorbital and pretibial edema. Three weeks ago, she went to Loi Krathong Festival and developed a respiratory tract infection, from which she has now recovered. On PE, BP is 150/100 mmHg. There are crackles in both lung bases and bilateral tibial pitting edema. Laboratory studies reveal low C3 and normal C4, BUN 30 mg/dl, serum creatinine 1.5 mg/dl, serum albumin 3.8 mg/dl. Urinalysis reveals no protein, RBC casts, and dysmorphic RBCs.

Which ONE of the following is the MOST likely diagnosis?
A. Ig A nephropathy
B. Goodpasture’s syndrome
C. ANCA-associated small vessel vasculitis
D. Post-infectious glomerulonephritis
E. Systemic lupus erythematosus nephritis

Glomerular diseases with predominant nephritic syndrome

- Poststreptococcal glomerulonephritis
- Infective endocarditis
- Ig A nephropathy
- Lupus nephritis
- Goodpasture disease/anti-GBM disease
- Small vessel vasculitides:
  - Wegener’s granulomatosis (granulomatosis with polyangiitis, GPA)
  - Microscopic polyangiitis (MPA)
  - Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis, EGPA)
  - Henoch-Schonlein purpura (Ig A vasculitis)
  - Cryoglobulinemic vasculitis

Post-streptococcal GN

- Streptococcus group A (nephritogenic strains) particularly M type 12
  - Superepithelial hump

Antigen:
- Streptococcal pyrogenic exotoxin B (SPEB) generated by proteolysis of a zymogen precursor (zSPEB)
- Nephritis-associated plasmin receptor (NAPlr)

Latent period:
- Pharyngitis (1-3 weeks)
- Impetigo (2-6 weeks)
Post-streptococcal GN

- Wide spectrum of severity: abrupt onset of edema (>90%), proteinuria and hematuria (100%)
- Gross hematuria (30%), nephrotic-range proteinuria (20%)
- Hypertension (>75%)
- Transient oliguria (50%), creatinine >2 mg/dl (20%, 60% in patients >55 years), RPGN (<5%)
- Clinical manifestations typically resolve within 1-2 wk
- In children, complete resolution of hematuria and proteinuria in 3-6 weeks, ESRD (~1%)
- In adults, may not have complete recovery and high incidence ESRD in elderly
- Treatment: supportive
- No evidence that early treatment of streptococcal disease will alter the risk of glomerulonephritis

Endocarditis-associated GN

- Renal complications in IE: embolic infarcts, renal abscesses, and GN
- ~20% of IE patients developed GN
- Acute kidney injury (80%)
- Hematuria (97%), proteinuria 80-90% (nephrotic 5%)
- Low C3 (50%), C4 (20%)
- Positive ANCA (30%)
- Organisms: S. aureus (53%), Streptococcus species (23%)
- Treatment: appropriate antibiotics

A 36-year-old woman is found to have intermittent hematuria and proteinuria (2+ by dipstick). There is no family history of renal disease. Her BP is 150/92 mmHg, and serum creatinine is 1.4 mg/dl. A urine protein-to-creatinine ratio is 1.2 g/g. Serum albumin and C3 complement are normal; ANA level is 1:40.

Which ONE of the following is the MOST likely to be present on further study?

A. Elevated serum levels of C-reactive protein
B. Elevated serum levels of undergalactosylated Ig A1
C. Reduced serum levels of C4
D. Decreased ratio of Ig A to C3 in serum
E. Elevated serum levels of Ig A

Post-streptococcal GN

- Positive throat/skin cultures: inconsistently present (10-70%)
- Positive antistreptolysin O (30%), anti-DNAse B (70%), or antihyaluronidase (40%)
- Positive rheumatoid factor (30-40%), cryoglobulins and circulating immune complexes (60-70%), and MPO-ANCA (10%)
- Reduced C3 and CH50 (>90%) which returns to normal within 6-8 wk, normal or mildly reduced C4
- Persistent hypocomplementemia: MPGN, IE, LN, occult infection, atheroembolic disease

Ig A nephropathy

- One of, if not the, most common glomerular disease (30% in Asia Pacific, 20% in southern Europe)
- Male preponderance, a peak incidence in the 2nd and 3rd decades of life, and rare familial clustering
- Associated disease: SNSA especially AS, cirrhosis, HIV, dermatitis herpetiformis, Crohn’s disease, celiac disease, mycosis fungoides, leprosy, relapsing polychondritis, and Sjögren’s syndrome
- Serum Ig A levels do not correlate with disease: increased in 20-50% of patient

Ig A nephropathy: Clinical features

- Diagnosis: serum Ig A?, Ig A-fibronectin?, increased Ig A to C3 ratio, abnormally glycosylated Ig A1

Ig A nephropathy: Poor prognostic factors

- Pathology: Oxford-MEST classification (Mesangial hypercellularity, Endocapillary proliferation, Segmental sclerosis, Tubular atrophy/interstitial fibrosis)
- Persistent microscopic hematuria (compared to recurrent gross hematuria)
- AKI associated with macroscopic hematuria does not affect long term prognosis
- Older age at disease onset
- Sustained hypertension
- Persistent proteinuria (>1 g/d) or nephrotic syndrome
- Impaired renal function
Ig A nephropathy: Treatment

- Macroscopic hematuria with normal renal function
- Aggressive hydration (no role of antibiotics or tonsillecctomy)

Low risk
- Microscopic hematuria ± proteinuria ≥0.5 g/day, GFR normal, no HTN
- Annual or Bi-annual screening for at least 10 years
- GFR >50 ml/min/1.73 m²

Intermediate risk
- Proteinuria >0.5-1 g/day ± reduced GFR ± HTN
- Optimized supportive therapy For 3-6 months
- GFR 30-50 ml/min/1.73 m²

High risk
- Acute or rapid loss of GFR
- Proteinuria >1 g/day and GFR stable
- GFR <30 ml/min/1.73 m²
- Nephrotic syndrome or crescentic GN with RPGN course
- AKI due to macroscopic hematuria
- Nephrotic-range proteinuria, hematuria, or both
- Continue supportive therapy
- ↓ 6-mo course of steroids ± fish oil??

- RAAS blockade titrated as far as tolerated to achieve proteinuria <1 g/d (2IC)
- BP <130/80 mmHg if proteinuria <1 g/d and <125/75 mmHg if proteinuria >1 g/d (Not graded)

Supportive therapy
- Continue supportive therapy
- No immunosuppression (except if RPGN)
- Supportive therapy
- Renal biopsy is mandatory if AKI persists >5 days

Supportive Care
- Supportive Care plus Immunosuppression

AKI: Acute Kidney Injury
GFR: Glomerular Filtration Rate
RPGN: Rapid Progessive Glomerulonephritis
VS: Value of Supportive Therapy

STOP-Ig A nephropathy trials

In Full Clinical Remission (UPCI <0.2 + i eGFR <5 ml/min/1.73 m²)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Supportive Care</th>
<th>Supportive Care plus Immunosuppression</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-analysis set</td>
<td>4/80</td>
<td>14/82</td>
<td></td>
<td>4.82 (1.43–16.30)</td>
</tr>
<tr>
<td>Available-case analysis</td>
<td>4/72</td>
<td>14/71</td>
<td></td>
<td>5.38 (1.53–18.66)</td>
</tr>
</tbody>
</table>

Lower BP <125/75 mmHg
- ~30% on both ACEIs + ARBs

Supportive Care
- Supportive Care plus Immunosuppression

Supportive Care Better
- Supportive Care plus Immunosuppression Better

Lupus nephritis: 2004 ISN/RPS classification

### Lupus nephritis

- 30-50% of SLE patients have renal disease at the time of diagnosis
- 60% of adults and 80% of children develop renal disease at some point of their diseases
- Risk for severe nephritis: children, males, non-Caucasian
- Anti-dsDNA correlates best with renal disease
- ~5-10% positive for MPO-ANCA
- Monitoring: anti-dsDNA, complement, ESR, dysmorphic RBCs
- Dialysis and transplantation

### Class

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Clinical</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Minimal mesangial LN</td>
<td>Minimal renal manifestation, rare nephrotic-range proteinuria, and normal creatinine</td>
</tr>
<tr>
<td>II</td>
<td>Mesangial proliferative LN</td>
<td>Varied course: HTN, active sediments, nephrotic-range proteinuria (25-33%) and ↑creatinine (25%)</td>
</tr>
<tr>
<td>III (A, A/C, C)</td>
<td>Focal proliferative LN (&lt;50% of glomeruli)</td>
<td>↑Anti-dsDNA Ab, ↑ complement levels, HTN, active sediments, nephrotic-range proteinuria (50%), and ↑creatinine</td>
</tr>
<tr>
<td>IV (A, A/C, C)</td>
<td>Diffuse proliferative LN (≥50% of glomeruli) – segmental (IV-S) or global (IV-G)</td>
<td>Uncommon HTN and renal dysfunction, nephrotic-range proteinuria (60%)</td>
</tr>
<tr>
<td>V</td>
<td>Membranous LN</td>
<td>Uncommon HTN and renal dysfunction, nephrotic-range proteinuria (60%)</td>
</tr>
<tr>
<td>VI</td>
<td>Sclerotic nephritis</td>
<td>↑Creatinine</td>
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Active lesions: endocapillary hypercellularity with or without leucocyte infiltration; karyorrhexis; fibrinoid necrosis, rupture of GBM; crescents, cellular or fibrocellular; subendothelial deposits (wireloops); intraluminal immune aggregates (hyaline thrombi)

Chronic lesions: glomerular sclerosis (segmental, global); fibrous adhesions; fibrous crescents
**Treatment schema for lupus nephritis**

**Class III, IV, (V) without crescents/without impaired renal function**
- Oral prednisolone 0.5-1 mg/kg/d, WITH
  1) MMF (1.5-2 g/day) x 6 mo, OR
  2) Pulse cyclophosphamide 0.5-1 g/m² monthly (NIH) x 6 mo OR
  Pulse cyclophosphamide 500 mg q 2 wk (EuroLupus) x 6 doses ±
  3) Pulse methylprednisolone 0.5-1 g x 1-3 d at the start of therapy
  4) Cyclosporine/Tacrolimus may be used in class V

**Class IV with crescents/with impaired renal function**
- Oral prednisolone 0.5-1 mg/kg/d, WITH
  1) MMF (1.5-2 g/day) x 6 mo, OR
  2) Pulse cyclophosphamide 0.5-1 g/m² monthly (NIH) x 6 mo OR
  3) Pulse methylprednisolone 0.5-1 g x 1-3 d at the start of therapy
  4) Cyclosporine/Tacrolimus may be used in class V

**Induction protocol**
- Pulse methylprednisolone 1 g x 3 d followed by oral prednisolone 0.5-1 mg/kg/d WITH
  Pulse cyclophosphamide 0.5-1 g/m² monthly x 6 mo

**Maintenance protocol**
- Low dose prednisolone 0.125-0.5 mg/kg/d, WITH
  1) MMF (1-2 g/d) OR
  2) Azathioprine (1-2 mg/kg/d) OR
  3) Pulse cyclophosphamide 0.5-1 g/m² q 3 mo x 2 yr

**Switch to alternating agents**
- Cyclophosphamide in place of MMF or vice versa OR
  Rituximab OR plasma exchange OR IVIG

**Response**
- Resistance

**Management of lupus nephritis in Asia**

**Mild or moderate disease (e.g., class II)**
- Initial treatment with moderate-dose steroids or in combination with AZA or mycophenolate
- Antimalarial treatment unless contraindicated
- Initial treatment with steroids (PRED 0.8 mg/kg/d) and either mycophenolate or CYC (IV or PO)
- Pulse MP (0.5-1 g/d) for 3 d recommended when renal biopsy shows crescentic involvement >10% or evidence of deteriorating renal function
- Steroid tapering begins after 2 wk except in patients with no sign of improvement, aiming to reach <20 mg/d after 3 mo and ≤7.5 mg/d after 6 mo IV CYC advisable when compliance doubtful
- Mycophenolate dose during induction should be 1.5-2 g/d for at least 24 wk
- CNI (in particular tacrolimus, on which there is more data) to be considered:
  - As induction, in combination with steroids in patients who do not tolerate standard treatment
  - As maintenance, especially in patients with membranous features on biopsy and persistent proteinuria after induction phase
- Immunosuppressive treatment recommended for (pure) class V with proteinuria ≥2 g/d

**Severe disease (Class III/IV±V or class V with significant proteinuria)**
- A 32-yr-old man develops acute kidney injury. PE is unremarkable with BP 130/82 mmHg. His medications include aspirin and omeprazole. Serum creatinine 5.2 mg/dl, and leukocyte and differential count are normal. The kidneys are of normal size as determined by ultrasound. Urinalysis reveals 1+ protein, 3-5 RBCs/hpf, 10-12 WBCs/hpf and a few granular casts, no bacteria or eosinophils found.

**Which ONE of the following is the MOST likely cause of his acute kidney injury?**

A. Acute tubular necrosis  
B. Microscopic polyangiitis  
C. Ig A nephropathy  
D. Acute hypersensitivity interstitial nephritis  
E. Anti-GBM-mediated crescentic nephritis

**Lupus nephritis: Treatment**

- General treatment: all patients of any class are treated with hydroxychloroquine (2C)
- Systemic lupus and thrombotic microangiopathy
  - APS: anticoagulation (target INR 2-3) (2D)
  - TTP: plasma exchange (2D)
- Systemic lupus and pregnancy
  - Delay pregnancy until complete remission (2D)
  - CYC, MMF, ACEI, or ARBs should not be used (1A)
- Hydroxychloroquine can be continued (2B)
- Switch MMF to AZA (1B)
- Steroids or AZA should not be tapered during pregnancy or for at least 3 mo after delivery (2D)
- Low-dose aspirin to decrease the risk of fetal loss (2C)
Rapidly progressive GN (RPGN)

- Acute interstitial nephritis
- Acute tubular necrosis
- Scleroderma
- Malignant hypertension
- Light chain nephropathy
- TTP/HUS
- Renal vein thrombosis
- Renal artery obstruction
- Thromboembolic renal disease

Pseudo-RPGN!!!

- Immune complex:
  - Granular deposit
- Pauci-immune:
  - No deposit

RPGN is just a syndrome

<table>
<thead>
<tr>
<th>Category</th>
<th>Immunopathogenesis</th>
<th>Primary renal disease</th>
<th>Systemic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Anti-GBM</td>
<td>Circulating anti-GBM Ab and glomerular linear Ig G deposit</td>
<td>Anti-GBM Ab disease</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>mediated,</td>
<td></td>
<td>Complicating DN or MN</td>
<td>Henoch-Schonlein purpura</td>
</tr>
<tr>
<td>rare</td>
<td></td>
<td></td>
<td>Cryoglobulinemic vasculitis</td>
</tr>
<tr>
<td>II. Immune complex</td>
<td>Circulating immune complex and granular Ig G deposit</td>
<td>Post-infectious GN IgA nephropathy</td>
<td>Borgasen's disease</td>
</tr>
<tr>
<td>mediated,</td>
<td></td>
<td>Membranous GN MPGN</td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III. Pauci-immune</td>
<td>No glomerular deposit</td>
<td></td>
<td>wegener granulomatosis</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
<td>microscopic polyangiitis</td>
</tr>
<tr>
<td>A. ANCA positive</td>
<td>[30%] ANCA-positive GN (PR3-ANCA, 30%)</td>
<td>[70%]</td>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>(80-90%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. ANCA negative</td>
<td>Idiopathic crescentic GN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10-20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Chronic GN

- Immune complex:
  - No deposit
- Pauci-immune:
  - No deposit

Antibody: Anti-GBM

- Linear deposit

Anti-GBM: Linear deposit

Immune complex: Granular deposit

Pauci-immune: No deposit
Anti-GBM disease

- Abrupt onset of GN, severe oliguria ± pulmonary hemorrhage
- Anti-GBM Ab: positive in 95% of patients
- MPO-ANCA: positive in 10-15% → better prognosis
- Poor prognostic factors: serum creatinine is >5-6 mg/dl, oliguria, and need for dialysis
- Treatment: steroids + CYC + plasmapheresis except those who are dialysis-dependent at presentation and do not have pulmonary hemorrhage (1B)
- No maintenance immunosuppressive therapy (1D)
- Renal survival 60%, patient survival 85%
- Recurrent disease is rare

ANCA-associated GN

- Anti-neutrophilic cytoplasmic autoantibodies: proteinase-3 (PR3), myeloperoxidase (MPO), lysosomal membrane protein-2 (LAMP-2)
- Sensitivity: 81-91%; specificity: 70-90%
- Relapses occur in up to 40% of patients
- High risk of relapse:
  - PR3-ANCA (compared to MPO-ANCA)
  - Upper respiratory tract or lung involvement (compared to ANCA associated GN alone)
**Drug-induced ANCA**

- **MPO-ANCA**
- Strongest association: PTU, hydralazine and minocycline
- Arthralgia/arthritis, cutaneous vasculitis, crescentic GN and pulmonary hemorrhage
- **PTU-induced ANCA**
  - Usually take medication for months or years
  - 27% of patients receiving long-term treatment with PTU developed MPO-ANCA

**Wegener’s granulomatosis**

- Necrotizing granulomatous inflammation primarily involved upper and lower respiratory tracts and GN
- Mean age: 40-60 years
- Upper respiratory tract (>90%): sinusitis, nasal discharge, nasal ulcer, nasal septum perforation
- Lung (75%): nodules (+cavitation), hemorrhage
- Kidney (50-95%): GN, proteinuria (0.5-1 g/d)
- Eye (65%): uveitis, conjunctivitis, retro-bulbar inflammation
- Skin (40%): purpura, nodules, livedo reticularis
- Relapse after achieving remission is more common than the other ANCA-associated vasculitis

**ANCA in small vessel vasculitides**

<table>
<thead>
<tr>
<th>ANCA</th>
<th>Disease</th>
<th>WG</th>
<th>MPA</th>
<th>CSS</th>
<th>Renal-limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR3-ANCA</td>
<td>Wegner granulomatosis</td>
<td>70-80</td>
<td>25-30</td>
<td>30-40</td>
<td>20-30</td>
</tr>
<tr>
<td>MPO-ANCA</td>
<td>Microscopic polyangiitis; Churg-Strauss syndrome</td>
<td>5-10</td>
<td>45-55</td>
<td>40-50</td>
<td>60-70</td>
</tr>
<tr>
<td>Negative ANCA</td>
<td>10-20</td>
<td>20-30</td>
<td>20-40</td>
<td>10-20</td>
<td></td>
</tr>
</tbody>
</table>

- Specificity of PR3-ANCA for WG, 98-99%
- PR3-ANCA is seen in >90% of patients with diffuse WG, but in only ~50% with limited WG (limited = typically no renal involvement)

WG: Wegener’s granulomatosis (granulomatosis with polyangiitis, GPA); MPA, microscopic polyangiitis; CSS, Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis, EGPA).

WG, Wegener’s granulomatosis (granulomatosis with polyangiitis, GPA); MPA, microscopic polyangiitis; CSS, Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis, EGPA).
Microscopic polyangiitis

- Mean age: 50 years
- The most common cause of pulmonary renal syndrome??
- Kidney (80-100%): mostly RPGN, rare nephrotic
- Upper respiratory tract (not typical)
- Lung (60%): alveolar hemorrhage, pulmonary nodules (not typical)
  - CXR: patchy or diffused infiltration
- Biopsy: non-granulomatous inflammation

ANCA-associated GN: Treatment

- Initial therapy: CYC and steroids (1A)
- Rituximab and steroids as an alternatives in patients without severe disease or in whom CYC is contraindicated (1B)
- Plasmapheresis: patients requiring…
  - Dialysis or with rapidly increasing creatinine (1C), or
  - Diffuse pulmonary hemorrhage (2C)
- Maintenance therapy: at least 18 mo (2D)
  - Agents: AZA (1B), or MMF (2C), or MTX (1C)
  - TMP-SMX as an adjunct to maintenance therapy in patients with upper respiratory tract disease (2B)
- Monitoring: not changing immunosuppression based on changes in ANCA titer alone (2D)

A 42-year-old man has a 3-week history of progressive dyspnea and coughing up blood. He has a long history of chronic rhinitis. On PE, BP is 150/90 and his chest has scattered crackles. BUN 62, creatinine 3.1 mg/dl, hemoglobin 10.5 gm/dl. Urinalysis: 2+ protein, no glucose, 15-20 RBCs/hpf, 5-7 WBCs/hpf. Chest x-ray: diffuse bilateral patchy infiltrates. Renal biopsy demonstrates cellular crescents with negative immunofluorescence.

Which of the following statements is correct?
A. PR3-ANCA is likely to be positive
B. Plasmapheresis should be initiated immediately
C. Anti-GBM antibody is likely to be positive
D. This patient is likely to have a significant eosinophilia
E. Complement levels will be low

Henoch-Schönlein purpura

- Skin purpura from the waist down (almost 100%), GI tract (25-90%: abdominal pain, GI bleeding), joints, and GN (20-100%)
- Young age (<20 years), preceding infection, and abdominal complaints
- More severe renal disease in older children and adults
- Diagnosis: pathology (Ig A positive vasculitis)
- Prognosis: excellent (children), ~10% ESRD (adults)
- Treatment: if persistent proteinuria >1 g/d after ACEIs/ARBs and GFR >50 ml/min/1.73 m², be treated with a 6-month course of steroids (2D)
Cryoglobulinemic vasculitis

- Cryoglobulins: circulating immunoglobulins that precipitate upon cooling and resolubilize on warming
- Type I (10-15%): monoclonal Ig M or Ig G, associated with lymphoproliferative disorders
- Mixed cryoglobulinemia:
  - Type II (50-60%): monoclonal Ig M rheumatoid factor attached polyclonal Ig G, associated with HCV
  - Type III (25-30%): polyclonal Ig M rheumatoid factor and polyclonal Ig G, 1/2 associated with HCV, 1/2 associated with autoimmune disease (e.g., SLE) or lymphoproliferative disorders

Manifestations of nephrotic and nephritic features by glomerular diseases

<table>
<thead>
<tr>
<th>Glomerular Disease</th>
<th>Nephrotic Features</th>
<th>Nephritic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change disease</td>
<td>++++</td>
<td>----</td>
</tr>
<tr>
<td>Ig M nephropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Membranoproliferative GN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Ig A nephropathy</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Postinfectious GN</td>
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<tr>
<td>ANCA-associated GN</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Thin basement membrane disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-GBM disease and Goodpasture syndrome</td>
<td>---</td>
<td>+++</td>
</tr>
<tr>
<td>Endocarditis-associated GN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cryoglobulinemic vasculitis

- Purpuric-vasculitic skin lesions (90-95%) and ulceration (10-25%), hepatosplenomegaly with abnormal LFT (70-75%) and peripheral neuropathy (5-40%)
- Glomerulonephritis (25-50%)
- Laboratory: cryoglobulin, low C3
  - Low C4 level is a characteristic
- Treatment: treat underlying disease, antiviral agents (HCV-associated), corticosteroids ± CYC (idiopathic)

A 23-yr-old woman presents with rapid deterioration of renal function. She was diagnosed as having SLE at age 19. Her serum creatinine and urinalysis were normal at that time. PE reveals a BP of 150/96 mmHg. There are no rashes and her joints are normal. Serum creatinine is 5.4 mg/dl and the urine shows 2+ proteinuria and 2+ blood. Hematocrit 28%, platelet count 80,000 /mm³, and numerous schistocytes are seen in the peripheral blood smear.

Which ONE of the following laboratory tests would be most useful to identify the cause of her disease?

A. Complement levels
B. Anti-nuclear antibody
C. Anti-double strand DNA
D. Anti-phospholipid antibody
E. Direct and indirect Coombs’ test
A 19-year-old man is seen for evaluation of hematuria. He has always been healthy; but yesterday, he developed an upper respiratory infection. Last night, when he urinated, he noted that his urine appeared to be grossly bloody. He has no family history of anyone having any similar problems. His physical examination is entirely normal. BUN 11, creatinine 0.8 mg/dl. Urinalysis: 4+ blood numerous RBCs and occasional RBC casts, and trace protein.

Which of the following is the most appropriate next step in the evaluation and management of this patient?

A. Immediate referral for renal biopsy
B. Referral to urologist
C. Order complement levels
D. Begin prednisolone 60 mg daily
E. Hearing evaluation

Thank you for your attention