Case Approach in Glomerular Disease

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Asymptomatic
Isolated proteinuria 150 mg to 3 g/day
Hematuria > 2 red blood cells (RBC)/high-power field in spun urine (RBC usually dysmorphic)

**Nephrotic syndrome**
- Proteinuria
  - Adult >3.5 g/day
  - Child > 40 mg/h per m²
- Edema
- Hypoalbuminemia <3.5 g/dl
- Hypercholesterolemia
- Lipiduria

**Nephritic syndrome**
- An abrupt onset of glomerular hematuria (RBC cast or dysmorphic RBCs)
- Proteinuria <3 g/day
- Azotemia
- Edema
- Oliguria
- Recent onset hypertension

**Rapidly progressive glomerulonephritis**
- Glomerular disease characterized by extensive crescents (usually >50%)
- A rapid loss of renal function (usually a 50% decline in GFR within 3 months)

**Chronic glomerulonephritis**
- Slowing developing renal insufficiency
- Proteinuria > 3 g/day and hematuria
- Hypertension
- Shrunken smooth kidneys

Glomerular Disease

- Primary Glomerular Disease
  - Idiopathic
- Secondary Glomerular Disease
  - Systemic disease involving multiple organs
# Secondary glomerular disease

<table>
<thead>
<tr>
<th>Systemic Diseases</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>HIV infection</td>
</tr>
<tr>
<td>SLE/vasculitis</td>
<td>Hepatitis B and C</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Malaria</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Lymphoma and myeloma</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Inherited Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold</td>
<td>Alport syndrome</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Congenital NS</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Nail–patella syndrome</td>
</tr>
<tr>
<td>Penicillamine</td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td></td>
</tr>
</tbody>
</table>
Primary glomerular disease

- Minimal change nephrotic syndrome (MCD)
- Focal segmental glomerulosclerosis (FSGS)
- Membranous nephropathy (MN)
- IgM nephropathy
- IgA nephropathy
- Membranoproliferative glomerulonephritis (MPGN)
Minimal change disease (MCD)

Focal segment glomerulosclerosis (FSGS)

Membranous nephropathy (MN)

Mesangial proliferative GN (IgA or IgM nephropathy)

Membranoproliferative GN (MPGN)
## Manifestation of glomerular diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Nephrotic features</th>
<th>Nephritic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change glomerulopathy</td>
<td>++++</td>
<td>-</td>
</tr>
<tr>
<td>Membranous glomerulopathy</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Fibrillary glomerulonephritis</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Mesangioproliferative glomerulopathy (IgAN, LN)</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis (MPGN)</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Proliferative glomerulonephritis (IgAN, LN)</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Acute diffuse proliferative glomerulonephritis (PSGN)</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Crescentic glomerulonephritis</td>
<td>+</td>
<td>++++</td>
</tr>
</tbody>
</table>

Adapted from Brenner & Rector’s the kidney 10th edition, 2016
## Nephrotic syndrome

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Associations</th>
<th>Serologic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change disease</td>
<td>Allergy, atopy, NSAIDs, Hodgkin disease</td>
<td>–</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>African American, HIV infection, heroin, pamidronate, obesity</td>
<td>HIV antibody</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>Other diabetic microangiopathy</td>
<td>–</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Myeloma Rheumatoid arthritis, bronchiectasis, Crohn disease, Familial Mediterranean fever</td>
<td>Plasma free light chain, Serum protein electrophoresis, urine immunoelectrophoresis</td>
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</tbody>
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Adapted from Johnson RJ, Feehally, J and Floege R. Comprehensive clinical nephrology. 2015, 189.
## Nephritis syndrome

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<tr>
<td>MPGN type I</td>
<td>C4 nephritic factor</td>
<td>Low C3 and C4</td>
</tr>
<tr>
<td>MPGN type II</td>
<td>C3 nephritic factor</td>
<td>Low C3 and normal C4</td>
</tr>
<tr>
<td>Post-streptococcal glomerulonephritis</td>
<td>Pharyngitis, impetigo</td>
<td>ASO titer, streptozyme antibody</td>
</tr>
<tr>
<td>Post-infectious disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Endocarditis</td>
<td>Cardiac murmur</td>
<td>Blood cultures, low C3</td>
</tr>
<tr>
<td>- Shunt</td>
<td>Treated hydrocephalus</td>
<td>Blood cultures, low C3</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Upper respiratory or gastrointestinal infection</td>
<td></td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>Other multi-systemic features of lupus</td>
<td>ANA, anti–ds DNA antibody, low C3 and C4</td>
</tr>
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<td>Cryoglobulinemic glomerulonephritis</td>
<td>Hepatitis C</td>
<td>Anti–hepatitis C virus antibody, rheumatoid factor, cryoglobulinemia, low C3 and C4</td>
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Adapted from Johnson RJ, Feehally, J and Floege R. Comprehensive clinical nephrology. 2015, 189.
History/physical examination

- Family history of CKD, hearing loss
- Perimacular white dot-and-fleck retinopathy, ant lenticonus:
- Alport syndrome
- History of diabetes
  - DR/diabetic neuropathy
  - Diabetic nephropathy

![Anterior lenticonus](image1)
![Dot-and-fleck retinopathy](image2)
![Diabetic retinopathy](image3)
History/physical examination

- Photosensitivity, arthritis, alopecia, oral ulcer, malar rash, Roth spot, discoid lesion:

- Lupus nephritis

- Palpable purpura, vasculitis:
  - Systemic vasculitis/ SLE
  - Cryoglobulinemia
  - Sub acute endocarditis

- Malar rash
- Cytoid body
- Palpable purpura
History/physical examination

- Hepatosplenomegaly, periorbital purpura, macroglossia, carpal tunnel syndrome
- Amyloidosis

Periorbital purpura

Macroglossia
Kidney biopsy

- Secondary glomerular diseases
- High risk for progressive disease (rising SCr, HT, proteinuria)
- Non response with corticosteroids (steroid resistance, steroid dependent, frequency relapse nephrotic syndrome)
- Longterm immunosuppressive agents (cyclophosphamide, cyclosporine)
Risk factors of Progressive Disease

- Male
- Advanced age (>50 years)
- Persistent heavy proteinuria (>3.5 g/d)
- Hypertension
- Impaired GFR
## Grade and Quality of evidence

<table>
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<th>Implications</th>
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<tr>
<td><strong>Level 1</strong></td>
<td><em>We recommend</em></td>
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<tr>
<td>Patients</td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not.</td>
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<tr>
<td>Clinicians</td>
<td>Most patients should receive the recommended course of action.</td>
</tr>
<tr>
<td>Policy</td>
<td>The recommendation can be evaluated as a candidate for developing a policy or a performance measure.</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td><em>We suggest</em></td>
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<tr>
<td>Patients</td>
<td>The majority of people in your situation would want the recommended course of action, but many would not.</td>
</tr>
<tr>
<td>Clinicians</td>
<td>Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.</td>
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<td>Policy</td>
<td>The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.</td>
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*The additional category “Not Graded” was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

### Grade, Quality of evidence, Meaning

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<th>Meaning</th>
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<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td>Very Low</td>
<td>The estimate of effect is very uncertain, and often will be far from the truth.</td>
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### An Analysis of 1,135 Cases of Kidney Biopsy: Thailand Glomerular Research Network (TGRN)

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IgA nephropathy
IgA nephropathy: Pathology

- Immunohistology is the clue of diagnosis
- Mesangial cell proliferation with IgA deposit predominate

Aberrant IgA1 antibody

Kidney Int 2012:81:833
Abnormality in mucosal immune system or Abnormal systemic response to mucosal antigens

Decreased clearance of IgA1 immune complexes

Increased production of IgA1 in bone marrow

Liver

ASGP-Receptor

Liver

ASGP-Receptor

Liver

ASGP-Receptor

Circulation:
Aberrant IgA1 immune complexes

Glomerulus:
Aberrant IgA1 immune complex deposits on Mesangial Transferrin receptor (TfR)

-IgA1 on FcγR associated transmembrane FcεRI

Activated Monocytes

-Cytokines
-Chemokines
-Complement activation

Fibrosis

Mesangial IgA nephropathy and Renal interstitial inflammation

Chemotaxis

Inflammation

Multi-hit pathogenesis model of IgA nephropathy

### IgA nephropathy and associated disorders

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<tr>
<th>IgA vasculitis</th>
<th>Neoplasia: Mycosis fungoides, CA lung</th>
</tr>
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<tbody>
<tr>
<td>HIV infection</td>
<td>Cyclic neutropenia</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Immunothrombocytopenia</td>
</tr>
<tr>
<td>Seronegative spondyloarthropathy</td>
<td>Gluten-sensitive enteropathy</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Scleritis</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>Sicca syndrome</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>Mastitis</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>Pulmonary hemosiderosis</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Berger’s disease</td>
</tr>
<tr>
<td>Reiter’s syndrome</td>
<td>Leprosy</td>
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Adapted from Brenner & Rector’s the kidney 10th edition, 2016
IgA nephropathy

Clinical presentation
- Asymptomatic hematuria/proteinuria
- Acute nephritic/Nephrotic syndrome
- Rapidly progressive Glomerulonephritis
- Chronic Glomerulonephritis

Renal pathology
- Normal glomeruli
- Mesangial proliferative
- Membranoproliferative or Necrotizing
- Crescentic glomerulonephritis
- Sclerosing
- Rapidly progressive Glomerulonephritis
Clinical presentations relation to age

Adapted from Johnson RJ, Feehally, J and Floege R. Comprehensive clinical nephrology. 2015.
IgA (Henoch–Schönlein) vasculitis

- Anaphylactoid purpura
- Male > Female, predominant in Children
- Severity in Adult > children
  - 1. Palpable purpura
  - 2. Arthritis
  - 3. Abdominal pain due to mesenteric angina
  - 4. Renal involvement vary 20–100%
IgA nephropathy: Clinical feature

- Wide spectrum of clinical presentations
- Recurrent macroscopic hematuria provoke by mucosal infection (synpharyngitis) (40–50%)
- Microscopic hematuria with or without proteinuria (30–40%)
- Nephrotic syndrome (5%)
- RPGN (<10%)
Treatment of IgA Nephropathy

- Long-term ACE-I or ARB treatment: proteinuria >1 g/d, with up-titration of the drug depending on blood pressure (1B)

- ACE-I or ARB be titrated upwards to achieve proteinuria <1 g/d (2C)

- Fish oil: Persistent proteinuria >1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and BP control) (2D)

Meta-analysis
Subgroup analysis for the effect of corticosteroid on composite renal endpoint

- High-dose and short-term steroid therapy (prednisone > 30 mg/d or high-dose IVMP with duration < 1 year) produced significant renal protection.

- Low-dose and long-term steroid therapy did not benefit.

- Steroid therapy was associated with a 55% higher risk for adverse events.

Corticosteroids in IgA nephropathy

- Persistent proteinuria >1 g/d, despite 3–6 months of optimized supportive care, and GFR >50 ml/min per 1.73m²

- A 6-month course of corticosteroid therapy (2C)

- Pozzi C et al.
  - IV 1 g methylprednisolone for 3 days each at months 1, 3, and 5, followed by oral steroid 0.5 mg/kg prednisone on alternate days for 6 months

- Manno C et al.; Lv J et al.
  - 6-month regimen of oral prednisone starting with 0.8–1 mg/kg/d for 2 months and then reduced by 0.2 mg/kg/d per month for the next 4 months

Variants of IgA nephropathy

- **MCD with mesangial IgA deposits**
  - Treatment as for MCD in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy (2B)

- **Crescentic IgA Nephropathy**
  - Steroids and cyclophosphamide, analogous to the treatment of ANCA vasculitis (2D)
Immunosuppressive agents

❖ No treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients except crescentic IgAN (2D)

❖ No using immunosuppressive therapy in patients with GFR <30 ml/min per 1.73m$^2$ except crescentic IgAN (2C)

❖ No using MMF in IgAN (2C)
Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study

Vladimir Tesar,* Stéphan Trojanov,† Shubha Bellur,‡ Jacobien C. Verhave,†
H. Terence Cook,§ John Feehally,‖ Ian S.D. Roberts,‡ Daniel Cattrran,¶ Rosanna Coppo,**
and on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group

*Department of Nephrology, First Faculty of Medicine and General University Hospital, Prague, Czech Republic;
†Sacré-Cœur Hospital of Montreal, Montreal, Quebec, Canada; ‡Oxford University Hospitals, Oxford, United
Kingdom; §Imperial College, Hammersmith Hospital, London, United Kingdom; ‖University Hospitals of Leicester,
Leicester, United Kingdom; ¶University Health Network, Toronto General Hospital, Toronto, Canada; and **Regina
Margherita Children’s Hospital, Turin, Italy

VALIGA-Consortium: Corticosteroids in IgAN

Response to CS and RASB compared with RASB alone in propensity-matched individuals. (A) Entire propensity-matched cohort. (B) Stratified by initial eGFR.

Steroids reduced proteinuria and the rate of renal function decline and increased renal survival extended to those with an eGFR < 50 ml/min per 1.73 m²

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*

Stop IgAN study

Stop IgAN study

Comprehensive supportive care: RAS blocker, keep BP < 125/75 mmHg

High risk patients

Supportive care group

EGR > 60 ml/min/1.73m²
Glucocorticoid monotherapy
IVMP 1 g/d x3 day of months 1, 3, and 5)
prednisolone 0.5 mg/kg AD on the other days

Immunosuppression group

EGR 30–59 ml/min/1.73m²
Cyclophosphamide 1.5 mg/kg/d for 3 months,
followed by azathioprine 1.5 mg/kg/d during months 4 through 36,
plus oral prednisolone

Persistent proteinuria
> 0.75 g/day, but < 3.5 g/day

After 3 years, 4 patients (5%) in the supportive-care group, as compared with 14 (17%) in the immunosuppression group, had a full clinical remission (P=0.01).

Addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgA nephropathy did not significantly improve the outcome.

- Full clinical remission (UPCR <0.2)
- Stable renal function (decrease in the eGFR of <5 ml/min/1.73m² from baseline eGFR at the end of the 3-year trial phase)
Secondary End Points on the Basis of the Analysis of Available Cases at the End of the Trial Phase

<table>
<thead>
<tr>
<th>Secondary End Point</th>
<th>Supportive Care (N = 80)</th>
<th>Supportive Care plus Immunosuppression (N = 82)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Available Data</td>
<td>no.</td>
<td>mean ±SD or no. (%)</td>
<td>no.</td>
<td>mean ±SD or no. (%)</td>
</tr>
<tr>
<td>Absolute eGFR change at 36 mo — ml/min/1.73 m²</td>
<td>71</td>
<td>-4.7±12.3</td>
<td>72</td>
<td>-4.2±14.1</td>
</tr>
<tr>
<td>Mean annual change in the slope of the reciprocal of serum creatinine concentration — mg/dl</td>
<td>77</td>
<td>-0.02±0.06</td>
<td>74</td>
<td>-0.01±0.06</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>67</td>
<td>0.80±0.67</td>
<td>59</td>
<td>0.57±0.53</td>
</tr>
<tr>
<td>At 36 mo</td>
<td>64</td>
<td>0.85±0.66</td>
<td>59</td>
<td>0.76±0.90</td>
</tr>
<tr>
<td>eGFR decrease ≥30 ml/min/1.73 m²</td>
<td>76</td>
<td>7 (9)</td>
<td>78</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Onset of end-stage renal disease</td>
<td>76</td>
<td>6 (8)</td>
<td>78</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Disappearance of microhematuria</td>
<td>55†</td>
<td>9 (16)</td>
<td>57†</td>
<td>24 (42)</td>
</tr>
</tbody>
</table>
Patients with AKI associated with macroscopic hematuria

AKI and macroscopic hematuria

Renal biopsy

Causes other than IgAN:
(Crescentic GN, vasculitis, LN, postinfectious GN)

IgAN
(Dominant with IgA in glomeruli by immunohistology)

ATN and intratubular erythrocytic casts
Supportive treatment as in other types of ATN.

Crescentic IgAN
Steroids and cyclophosphamide as in crescentic ANCA vasculitis

Repeated episodes of AKI accompanying macroscopic hematuria:
Consider a kidney biopsy when no improvement of kidney function is observed after at least 5 days from the onset of kidney function worsening

IgA nephropathy: Poor prognosis

- Older age
- Increase BMI
- Severity of proteinuria
- Persistent microscopic hematuria
- Hypertension
- Renal impairment

- Diffuse proliferative lesion with crescents
- Glomerulosclerosis
- Tubular atrophy, interstitial fibrosis
- Vascular wall thickening
- Capillary loop IgA deposit

An Analysis of 1,135 Cases of Kidney Biopsy: Thailand Glomerular Research Network (TGRN)

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<tr>
<td>6. Membranoproliferative GN</td>
<td>18 (3.6)</td>
</tr>
</tbody>
</table>
Membranoproliferative GN
MPGN: Pathology

Endocapillary proliferation with GBM thickening/double contour

Granular deposition of IgG and C3 in the mesangium and capillary wall
Electron microscope: MPGN

MPGN Type 1
Immune deposits in the mesangium and subendothelial space

MPGN Type 2
Continuous, dense ribbon-like deposits along the GBM

MPGN Type 3
Complex disruption of the GBM with large lucent areas
Newer classification based on immunopathology

IgG and/or C3 component
MPGN pattern
(Double contour and mesangial expansion)

- C3 and Ig staining
  - Dense deposit disease
  - GN with isolated C3
    - C3 nephritic factor (C3 NeF) and Circulating IgG resulting in persistent C3 breakdown
    - Infection (sub acute IE)
    - Monoclonal gammopathy
    - Autoimmune disease (SLE)

- C3 staining

- No staining
  - Thrombotic microangiopathy

Immune complex: classical pathway, low C3/C4 or alternative pathway: low C3
MPGN: Clinical manifestation

- Focal glomerulonephritis (dysmorphic RBC, occasionally red cell casts, and proteinuria)
  - Hypertension: 50–80%
  - Nephritic syndrome/RPGN: 25%
  - Non nephrotic range proteinuria: 25%
  - Nephrotic syndrome: 50%
  - Spontaneous improvement < 10%

MPGN: treatment

- Optimal therapy of idiopathic MPGN remains uncertain
- Nephrotic syndrome and progressive decline of kidney function
  - Oral cyclophosphamide or MMF plus low-dose alternate day or daily corticosteroids with initial therapy <6 mo (2D)

Evaluate patients with the histological (light-microscopic) pattern of MPGN for underlying diseases before considering a specific treatment regimen (Not Graded)

# Secondary Causes of MPGN

<table>
<thead>
<tr>
<th>Associated with infection</th>
<th>Associated with Rheumatologic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B and C</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Visceral abscesses</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>Mixed essential cryoglobulinemia with or without hepatitis C infection</td>
</tr>
<tr>
<td>Shunt nephritis</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Quartan malaria</td>
<td>Anti–smooth muscle syndrome</td>
</tr>
<tr>
<td>Schistosoma nephropathy</td>
<td>Sjögren’s syndrome</td>
</tr>
<tr>
<td>Mycoplasma infection</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Associated with Malignancy</th>
<th>Associated with an Inherited Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>α1–Antitrypsin deficiency</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Complement deficiency (C2 or C3), with or without partial lipodystrophy</td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Brenner & Rector’s the kidney 10th edition, 2016
Pathogenesis of systemic lupus erythematosus (SLE)

1. Genes
   - C1q, C2, C4
   - HLA-D2, 3, 8
   - MBL
   - FcR 2A, 3A, 2B
   - IL-10
   - MCP-1
   - PTPN22

Environment

2. Abnormal Immune Response
   - DC
   - Ag
   - T cell
   - B cell
   - C3
   - C3a

3. Autoantibodies
   - Immune Complexes

4. Inflammation
   - Rash
   - Nephritis
   - Arthritis
   - Leukopenia
   - CNS dz
   - Carditis
   - Clotting
   - Etc.

5. Damage
   - Renal Failure
   - Artherosclerosis
   - Pulm fibrosis
   - Stroke
   - Damage from Rx
   - Etc.

EPIGENETIC CHANGES
- DNA hypomethylation, miRNA
- UV Light
- EBV
- ?Infection
- Others

GENGER
- Female predisposes

Harrison’s Principle of Internal Medicine 19th edition
SLE: Pathogenesis

- Apoptosis defect
- Defect clearance of apoptosis cells
- Complement deficiency
- Clearance hypothesis

- Loss of tolerance of apoptosis self
- Hyperactivation of self-reactive B cells
- Tolerance hypothesis

- Apoptosis cells
- Immune complex
- Kidney
- Neutrophil
- Macrophage

- B cell and T cell co-operation
- T cell
- TCR
- Lymphoid compartment
- C1
- C2b
- C4b
- C3
- C3a
- C3b
## Organ Involvement in the Course of SLE

- Systemic (fatigue, malaise, fever) **95%**
- Musculoskeletal **95%**
- Cutaneous **80%**
- Hematologic **85%**
- Neurological **60%**
- Cardiopulmonary **60%**
- Kidney **30-50%**
- Gastrointestinal **40%**
- Thrombosis **15%**
- Ocular **15%**
- Vasculitis **5%**

Adapted from Harrison’s Principle of Internal Medicine 19th edition
2012 American College of Rheumatology criteria for lupus nephritis

- Spot urine protein/creatinine ratio >0.5
- “Active urinary sediment” (5 RBCs/HPF, 5 WBCs/HPF in the absence of infection, or cellular casts limited to RBC or WBC casts)
Systemic Lupus International Collaborating Clinics Classification Criteria for SLE

> 4 criterion OR Biopsy–proven lupus nephritis and ANA or anti–dsDNA Ab

At least one Clinical criteria
- Acute cutaneous lupus
- Chronic cutaneous lupus
- Oral ulcers
- Non–scarring alopecia
- Synovitis
- Serositis
- Renal
- Neurologic

At least one Immunologic criteria
- ANA level
- Anti–dsDNA antibody
- Anti–Sm antibody
- Antiphospholipid antibody
- Low complement
- Direct Coombs’ test in the absence of hemolytic anemia

Sensitivity 94% and specificity 92%, 4 item

### Clinical Manifestation Related Renal Pathological Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Urine sediment active</th>
<th>Proteinuria</th>
<th>Nephrotic syndrome</th>
<th>Renal insuff</th>
<th>5-year renal survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>II</td>
<td>&lt;25%</td>
<td>25–50%</td>
<td>0</td>
<td>&lt;15%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>III</td>
<td>50%</td>
<td>67%</td>
<td>25–33%</td>
<td>10–25%</td>
<td>70–80%</td>
</tr>
<tr>
<td>IV</td>
<td>75%</td>
<td>&gt;95%</td>
<td>50%</td>
<td>&gt;50%</td>
<td>60–80%</td>
</tr>
<tr>
<td>V</td>
<td>30%</td>
<td>&gt;95%</td>
<td>90%</td>
<td>10%</td>
<td>80–90%</td>
</tr>
</tbody>
</table>
Renal Pathology Classification
Lupus nephritis biopsy ISN/RPS Classification

No endocapillary hypercellularity
- Mesangial deposits only class I
- Mesangial hypercellularity class II
- Subepithelial deposits class V

Endocapillary hypercellularity
- Involving <50% glom Class III*
- Involving >50% Glom

Segmental distribution Class IV S*
- Global distribution Class IV G*

*Give the proportion of glomeruli with active and chronic lesions, necrosis, and crescents
# ISN/RPS 2003 classification

<table>
<thead>
<tr>
<th>Class</th>
<th>% involved glomeruli</th>
<th>Pathology of each glomerulus</th>
<th>Activity and chronicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Minimal mesangial LN (normal LM and immune-complex deposit in IF)</td>
<td>S=segment, G=global</td>
<td>A=active, C=chronic</td>
</tr>
<tr>
<td>II</td>
<td>Mesangial proliferation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III – focal</td>
<td>&lt; 50% of total glom</td>
<td>S=segment, G=global</td>
<td>A=active, C=chronic</td>
</tr>
<tr>
<td>IV – diffuse</td>
<td>&gt; 50% of total glom</td>
<td>S=segment, G=global</td>
<td>A=active, C=chronic</td>
</tr>
<tr>
<td>V</td>
<td>Membranous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Diffuse glomerulosclerosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Minimum 10 glomeruli. Diagnosis of LN dominant IgG, C3 and C1q deposits are absolutely required.

Initial therapy of SLE

Non-life or organ threatening

- Quality of life: Acceptable
  - Conservative management

- Quality of life: Not-acceptable
  - Conservative treatment plus low dose steroids
  - Consider belimumab

Life or organ threatening

- High dose steroids, usually with addition of second agent
  - Mycofenolate mofetil (or myfortic acid)
  - Cyclophosphamide (Low/high dose)
  - Do not exceed 6 months of Rx

  - After D/C cyclophosphamide; Maintain with MMF or azathioprine
    - Non-response
      - Belimumab, rituximab
      - Calcineurin inhibitors or Experimental therapies

  - Response
    - Taper dose of all agents especially steroids

Harrison’s Principle of Internal Medicine 19th edition
Treatment of lupus nephritis

❖ Class I

❖ Treated as dictated by the extrarenal clinical manifestations of lupus (2D)

❖ Class II

❖ Proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus (2D)

❖ Proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD (2D)
Treatment of Proliferative Lupus Nephritis (Class III–IV)

❖ Induction phase
  ❖ Renal remission at presentation and during follow up

❖ Maintenance phase
  ❖ Prevent relapse and minimizing the side effects of treatment
## Regimens for initial therapy in class III/class IV LN

<table>
<thead>
<tr>
<th>Regimen</th>
<th>A. NIH</th>
<th>B. Euro–Lupus</th>
<th>C. Oral cyclophosphamide</th>
<th>D. MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>i.v. cyclophosphamide 0.5–1 g/m²; monthly for 6 months</td>
<td>i.v. cyclophosphamide 500 mg; every 2 weeks for 3 months</td>
<td>Oral cyclophosphamide 1.0–1.5 mg/kg/d (maximum dose 150 mg/d) for 2–4 months</td>
<td>MMF up to 3 g/d for 6 months</td>
</tr>
<tr>
<td>MMF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefit shown by RCT in proliferative LN</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Benefit shown by RCT in severe proliferative LN</td>
<td>Yes</td>
<td>Untested</td>
<td>Untested</td>
<td>Untested</td>
</tr>
<tr>
<td>Comments</td>
<td>Effective in whites, blacks, Hispanics, Chinese</td>
<td>Effective in whites, blacks, Hispanics, Chinese</td>
<td>Effective in whites, blacks, Chinese; easy to administer and lower cost than i.v. cyclophosphamide</td>
<td>Effective in whites, blacks, Hispanics, Chinese; high cost</td>
</tr>
</tbody>
</table>

IV Pulse Cyclophosphamide: NIH regimen

- **Induction IVCY q 1 mo x 6**
- **Maintenance IVCY q 3 mo x 6**

- Initial IVCY 0.5–1.0 g/m² (0.5 g/m² if GFR 1/3 normal)
- Adjust subsequent IVCY to maximum dose of 1 g/m² unless WBC nadir at 10–14 days after IVCY falls below 1,500/mm³
- Prednisolone 0.5–1 mg/kg/day for 4–8 weeks, which is subsequently tapered to low dose maintenance therapy

KDIGO guideline: Class III–IV: initial therapy

- Corticosteroids (1A), combined with
  - Cyclophosphamide (1B)
  - OR
- Corticosteroids (1A), combined with MMF (1B)
ACR Guidelines for induction Rx in LN class III–IV

**MMF 2–3 gm a day for 6 mo (preferred to CYC in AA and Hispanics)**
PLUS
GC IV pulse x 3 days then prednisone 0.5–1.0
MKD tapered after a few weeks to lowest effective dose (1 MKD if crescents seen)

**CYC**
PLUS
GC IV pulse x 3 days then prednisone 0.5–1.0
MKD tapered after a few weeks to lowest effective dose (1 MKD if crescents seen)

**High dose CYC**
500–1000 mg/m2 BSA IV q 1 mo x 6

**Low dose CYC**
500 mg IV q 2 wks x 6 followed by maintenance with oral MMF or AZA (regimen for white with European background)

Adapted from ACR Guidelines for Lupus Nephritis. Arthritis Care & Research; 2012, 797–808
KDIGO guideline: Class III–IV: maintenance therapy

- AZA (1.5–2.5 mg/kg/d) or MMF (1–2 g/d in divided doses), and low-dose prednisolone (<10 mg/d) (1B)

- Maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression (2D)
Beyond Disease Activity: Hydroxychloroquine

- Reduced damage accrual (renal, skin)
- Decrease in flares
- Improved survival
- Improved lipid profiles (TC, LDL)
- Less neonatal lupus
- Less the risk of clotting events in SLE

LUMINA (Multiethnic longitudinal cohort, n=635)
Guillermo J Arthritis Care Res 2010
Alarcon GS Ann Rheum Dis 2007
General treatment of LN

❖ All patients with any class LN

❖ Hydroxychloroquine (maximum daily dose of 6–6.5 mg/kg ideal body weight) (2C) or Level C

ACR Guidelines for Lupus Nephritis. Arthritis Care & Research; 2012, 797–808
Further investigation and Monitoring

- Clinical monitoring:
  - Systemic symptoms and signs
  - BUN, serum creatinine
  - CBC
  - Urinalysis
  - Spot or 24 hr urine protein
  - Serum albumin, cholesterol
  - Infections: CXR, stool examination

- Immunologic monitoring:
  - Complements: CH50, C3, C4
  - Anti-ds DNA antibody titer
  - Kidney biopsy
### An Analysis of 1,135 Cases of Kidney Biopsy: Thailand Glomerular Research Network (TGRN)

<table>
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</tbody>
</table>
Minimal-change disease in adults
MCD: Pathology

- Normal light microscopy and IF
- Effacement of GEC foot processes by electron microscopy
MCD: Pathogenesis

❖ Systemic T cell dysfunction results in the production of a glomerular permeability factor
❖ Associated with HD or allergy

❖ Diminishes the heparin sulfate negative-charge barrier (anionic) properties of the GBM

MCD: clinical feature

- Nil (Nothing-In-Light microscopy) disease
- Children > adult (Male > female)
- 70% of children <10 years
- 10-15% of adults
- Bimodal with peak incidences in young children and older adults

Cameron JS. Am J Kidney Dis 1987; 10:157
MCD: clinical feature

- Relatively abrupt onset of proteinuria
  - Heavy proteinuria
  - Hypoalbuminemia (<1.5–2.0 g/dL)
  - Hyperlipidemia
  - Rare signs of glomerulonephritis (HT, hematuria, rising Cr)

- Adult MCD
  - HT (40%)
  - Microscopic hematuria (29%)
  - Reversible AKI (18%), ischemic ATN

MCD with AKI

- Acute tubular injury: sloughed epithelial cells, and loss of proximal tubular brush borders

- Risk factors
  - Older age
  - Hypertension
  - Severe nephrotic syndrome
  - Underlying arteriosclerosis of the kidney
  - NSAIDS


Functional renal insufficiency
# Common associations with MCD

<table>
<thead>
<tr>
<th>Infection</th>
<th>Allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>Food, dust</td>
</tr>
<tr>
<td>Parasitic</td>
<td>Bee stings</td>
</tr>
<tr>
<td><strong>Pharmaceutical agents</strong></td>
<td><strong>Pollen</strong></td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Poison ivy and poison oak</td>
</tr>
<tr>
<td>Gold, lithium, interferon</td>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>Ampicillin, rifampin</td>
<td>Disease and other associations</td>
</tr>
<tr>
<td>Trimethadione, tiopronin</td>
<td>SLE</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td><strong>Following allogeneic stem cell transplantation for leukaemia</strong></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td><strong>Following hematopoietic cell transplantation</strong></td>
</tr>
<tr>
<td>Lymphoma, leukemia</td>
<td></td>
</tr>
<tr>
<td>Solid tumors</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Brenner & Rector’s the kidney 10th edition, 2016
Minimal change disease

- Complete remission: 75%
- Prednisolone 1 mg/kg/day or 2 mg/kg/AD

- Duration
  - > 8 wk (remission 60%)
  - 16–20 wk (remission 76–81%)

Treatment of initial episode of adult MCD

- Prednisolone 1 mg/kg/day (maximum 80 mg) OD or 2 mg/kg (maximum 120 mg) AD (2C)
- High dose corticosteroids for a minimum period of 4 weeks, and for a maximum period of 16 weeks if complete remission is not achieved (2C)
- Corticosteroids be tapered slowly (5–10 mg/wk) over a total period of up to 6 months after achieving remission (2D)

Treatment of initial episode of adult MCD

- Relative contraindications or intolerance to high-dose corticosteroids
  - Uncontrolled diabetes, psychiatric conditions, severe osteoporosis
  - Oral cyclophosphamide or cyclosporine (2D)

- Using the same initial dose and duration of corticosteroids for infrequent relapses (2D)

Frequently relapsing and steroid-dependent MCD

- Oral cyclophosphamide 2–2.5 mg/kg/day for 8 wks (2C)

- Oral cyclosporine 3–5mg/kg/day or tacrolimus 0.05–0.1 mg/kg/d in divided doses for 1–2 yrs (2C)

- MMF 500–1000 mg twice daily for 1–2 yrs in pts who are intolerant of corticosteroids, cyclophosphamide, and CNIs (2D)
MCD: prognosis

- Highly remission & relapse rate
  - 50–75% relapse within 6–12 mo
  - 25% frequent relapses
  - 25% steroid dependence
- Good prognosis: 5% turn to ESRD in 25 yr

7 to 12% of adults with steroids resistance

Complication of MCD

- Risk of mortality due to infection (peritonitis)
- Less commonly thromboembolism
- 5% develop ESRD in 9.4 yr
- Related to treatment
  - Side effects of steroids
  - Side effects of cyclophosphamide: infertility, malignancy
  - Side effects of cyclosporine: hypertension, impair renal function
Steroid-resistant MCD

- Re-evaluate other causes of nephrotic syndrome
- Corticosteroid-resistant MCD suggests FSGS
- Steroid resistance may be due to undetected FSGS
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</table>
Focal segmental glomerulosclerosis
Primary FSGS

- Hilar variant
- Tip variant
- Collapsing variant
Primary FSGS

Classic FSGS
FSGS NOS (not otherwise specified)

Cellular variant FSGS

Most common
Primary FSGS

Hilar variant

Tip variant

Collapsing variant

2nd FSGS: obesity

Good respond to steroid

Poor prognosis
Primary FSGS

- Normal IF
- IgM, C1q and C3 at sclerosis area

- EM: foot processes effacement
FSGS: Pathogenesis

- Alterations in T cell function and glomerular permeability factor
- Recurrent FSGS after KT
- Plasmapheresis & anti-IgG columns: absent of proteinuria
- Elevated circulating soluble urokinase receptors (suPAR) levels: 55–84%

Gene mutation causally linked to FSGS

Nephrin: Chromosome 19q13
Congenital nephrotic syndrome of Finnish type

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPHS1</td>
<td>Nephrin</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>NPHS2</td>
<td>Podocin</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>PLCE1</td>
<td>Phospholipase Cε</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>CD2AP</td>
<td>CD2-associated protein</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>TRPC6</td>
<td>Transient receptor potential cation channel, subfamily C, member 6</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>ACTN4</td>
<td>α-Actinin-4</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>MYH9</td>
<td>Nonmuscle myosin heavy chain A (NMMHC-A)</td>
<td>Autosomal dominant,</td>
</tr>
<tr>
<td></td>
<td>de novo mutation</td>
<td></td>
</tr>
<tr>
<td>COQ2</td>
<td>Coenzyme Q3 homolog, prenyl transferase</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>ITGB4</td>
<td>β4 Integrin</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>WT1</td>
<td>Wilms' tumor suppressor protein</td>
<td>Autosomal dominant,</td>
</tr>
<tr>
<td></td>
<td>de novo mutation</td>
<td></td>
</tr>
</tbody>
</table>

Focal Segmental Sclerosis; N Engl J Med 2011;365:2398-411
# Secondary FSGS

## HIV disease
- Other drugs (pamidronate, interferon, anabolic steroids)

## IV drug abuse
- Genetic abnormalities (pdocin, alpha actinin-4, TRPC6)

## Glomerulomegaly
- Morbid obesity
- Sickle cell disease
- Cyanotic congenital heart disease
- Hypoxic pulmonary disease

## Reduce nephron numbers
- Unilateral renal genesis
- Oligomeganephria
- Reflux interstitial nephritis
- After focal cortical necrosis
- After nephrectomy

Adapted from Brenner & Rector’s the kidney 10th edition, 2016
# Secondary FSGS

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FSGS: Clinical feature

- Acute or insidious onset of proteinuria
- Degree of proteinuria varies from non-nephrotic (1–2 g/day) to massive proteinuria (> 10 g/day)
- Nephrotic syndrome 60–75%
- Associated findings
  - Hypertension 45–65%
  - Microscopic hematuria 30–50%
  - Renal insufficiency 25–50%
# Clinical Features of FSGS

<table>
<thead>
<tr>
<th>Histologic subtype</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOS</td>
<td>Nephrotic syndrome or sub-nephrotic proteinuria</td>
</tr>
<tr>
<td>Perihilar</td>
<td>More likely to present with subnephrotic proteinuria and normal serum albumin levels</td>
</tr>
<tr>
<td>Cellular</td>
<td>Nephrotic syndrome</td>
</tr>
</tbody>
</table>
| Tip                | Abrupt onset of the nephrotic syndrome  
|                    | Best prognosis, with response to glucocorticoids |
| Collapse           | Aggressive variant of primary FSGS with black racial predominance and severe nephrotic syndrome  
|                    | Worst prognosis, with poor response to glucocorticoids |

Perihilar variant FSGS: Massive obesity

- Renal hypertrophy and increase GFR and RBF
- Excessive glomerulomegaly with vascular dilatation and mesangial expansion in five grossly obese individuals

Barisoni L et al. CJASN 2007;2:529–542
Obesity related glomerulomegaly

- **Clinical:** lower incidence of nephrotic syndrome, normal serum albumin and cholesterol
- **Natural history:** more indolent progression
- **Pathology:**
  - Glomerulomegaly
  - Milder foot process effacement
  - Less segmental sclerosis

## Primary VS Secondary FSGS

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<thead>
<tr>
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<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Acute onset of nephrotic syndrome</td>
<td>Slowly increasing proteinuria and renal insufficiency</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>Nephrotic range</td>
<td>Sub-nephrotic range</td>
</tr>
<tr>
<td><strong>Clinical NS</strong></td>
<td>+</td>
<td>+/- Normoalbuminuria</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Diffuse foot process fusion</td>
<td>Focal foot process effacement</td>
</tr>
<tr>
<td><strong>Healed lesion</strong></td>
<td>-</td>
<td>Obsolescent segment of capillary tuft (PAS staining less intensely)</td>
</tr>
</tbody>
</table>

Weight loss in overweight patients with proteinuric nephropathies


Proteinuria decreased by 31.2% in the diet group
Clinical interventions for obesity related glomerulomegaly

- Lifestyle modification
- Weight reduction
- BP-lowering medication (RAAS antagonists)
- Glucose-lowering medication (metformin, thiazolidinediones)
- Lipid-lowering medication

Collapsing FSGS

- Collapse and sclerosis of the entire glomerular tuft
- Marked hypertrophy and hyperplasia of podocytes
- Africa American
- HIV nephropathy
- Pamidonate
- Heroin
Treatment of idiopathic FSGS

❖ Idiopathic FSGS associated with clinical features of the nephrotic syndrome (1C)

❖ Prednisone 1 MKD OD or 2 MKD (maximum 120 mg) AD: Remission 28–74% (2C)

❖ Minimum of 4 wks; continue high-dose corticosteroids up to a maximum of 16 wks (2D)

❖ Corticosteroids be tapered slowly over a period of 6 months after achieving complete remission (2D)

Intolerance to high-dose corticosteroids

- Cyclosporine (CNIs) be considered as first-line therapy for patients with relative contraindications or intolerance to high-dose corticosteroids
- Remission 50 – 60 % (steroid response)
- Remission 20 – 70 % (steroid non response) (2D)
Treatment for steroid-resistant FSGS

- Cyclosporine at 3–5 mg/kg/d (initial target levels 125–175 ng/ml) in divided doses be given for at least 4–6 months (2B)

- Continuing cyclosporine treatment for at least 12 months, followed by a slow taper (2D)

- Combination of MMF and high-dose dexamethasone for not tolerate with cyclosporine (2C)

FSGS: Prognosis

- Relatively poor outcome, with 50% reaching ESRD by 10 years

- Risk factors
  - Massive proteinuria
  - Increase serum creatinine
  - Interstitial fibrosis and tubular atrophy
  - Collapsing variant (ESRD within 15 months)
  - Failure to CR/PR

### An Analysis of 1,135 Cases of Kidney Biopsy: Thailand Glomerular Research Network (TGRN)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary glomerular diseases</td>
<td>507 (46.7)</td>
</tr>
<tr>
<td>1. IgA nephropathy</td>
<td>158 (31.2)</td>
</tr>
<tr>
<td>2. Focal segmental glomerulosclerosis</td>
<td>104 (20.5)</td>
</tr>
<tr>
<td>3. Membranous nephropathy</td>
<td>85 (16.8)</td>
</tr>
<tr>
<td>4. Minimal change disease</td>
<td>63 (12.4)</td>
</tr>
<tr>
<td>5. IgM nephropathy</td>
<td>52 (10.3)</td>
</tr>
<tr>
<td>6. Membranoproliferative GN</td>
<td>18 (3.6)</td>
</tr>
</tbody>
</table>
Idiopathic membranous nephropathy
Membranous nephropathy

Light microscopy:
- GBM thickening
- Spike appearance
Staging of Membranous Nephropathy

Stage I has subepithelial dense deposits (arrow) without adjacent basement membrane reaction.

Stage II has projections of basement membrane adjacent to deposits.

Stage III has deposits surrounded by basement membrane.

Stage IV has thickened basement membrane with irregular lucent zones.
Membranous nephropathy

**Immunofluorescence**

Diffuse granular capillary wall staining of IgG and C3

**Electron microscopy**

Electron dense deposits across the GBM in the subepithelial space
Membranous nephropathy: Pathogenesis

Phospholipase A2 receptor (PLA2R)

- In situ deposit through binding of circulating anti-PLA2R autoantibodies to the PLA2R antigen expressed on the surface of podocytes

Membranous associated disorders

Infection:
Hepatitis B and C, syphilis, malaria, schistosomiasis, leprosy

Cancer:
Breast, colon, lung, stomach, kidney, esophagus, ovary, prostate

Drugs:
Gold, mercury, penicillamine, NSAIDS, probenecid, captopil

Autoimmune diseases:
SLE, RA, dermatitis herpetiformis, myasthenia gravis, Sjögren's syndrome

Systemic diseases:
Fanconi's syndrome, Crohn's disease, Sarcoidosis, Guillain–Barré syndrome

Membranous nephropathy: Clinical feature

- Adult > 40 yr (30–50 yr) and men: women = 2–3:1
- > 80% have more than 3 g/d of proteinuria
- Almost always insidious onset
- Bland urine sediment
- Mild microhematuria (30–40%)
- Hypertension (15–55%)
Membranous nephropathy: Clinical feature

- Normal or slightly decreased renal function (impair renal function < 10%)
- Hypoalbuminemia, elevated LDL and VLDL
- Thromboembolic manifestation (RVT, PE, DVT)
- Risk of malignancy increase with age
- Spontaneous remission 30%, stable 30% and progression 30%

Predicting chronic renal insufficiency in idiopathic MN

- Pei and et al.; likelihood of progressing to CKD at 5–6 years
  - 66% in proteinuria > 8g/d for > 6 mo
  - 55% in proteinuria > 6g/d for > 9 mo
  - 44% in proteinuria > 4g/d for > 1 year

- Adequate assessment of proteinuria requires following patients for at least 6 to 12 months

35% spontaneous remission

Patients with nephrotic syndrome with

- Persistent urinary protein >4 g/d and remains at over 50% of the baseline value, during therapy at least 6 months (1B)
- Presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome (1C)
- Serum Cr has risen by 30% within 6 to 12 months (2C)
Initial therapy of membranous nephropathy

- A 6-month course of alternating monthly cycles of oral and i.v. corticosteroids, and oral alkylating agents (1B)
- Cyclophosphamide > chlorambucil for initial therapy (2B)
- At least 6 months before being considered a treatment failure (1C)
- Continuous daily use of oral alkylating agents for 4–6 months may also be effective (2C)
“Ponticelli Regimen”

- Month 1: i.v. methylprednisolone (1 g) daily for three doses, then oral methylprednisolone (0.5 mg/kg/d) for 27 days
- Month 2: Oral chlorambucil (0.15–0.2 mg/kg/d) or oral cyclophosphamide (2.0 mg/kg/d) for 30 days
- Month 3: Repeat Month 1
- Month 4: Repeat Month 2
- Month 5: Repeat Month 1
- Month 6: Repeat Month 2

If total leukocyte count falls to <3500/mm³, then hold chlorambucil or cyclophosphamide until recovery to >4000/mm³
UK Membranous Trial

108 subjects with proteinuria 8.5 g/day and progressive decline in eGFR (>20%) during 2 yrs, serum Cr < 3.4 mg/dL (High risk)

Alternative regimens

- Cyclosporine (3.5–5.0 MKD) or tacrolimus (0.05–0.075 MKD) at least 6 months (1C)

- Discontinued CNI in patients who do not achieve remission after 6 months (2C)
Poor prognosis

- Male
- Advanced age (>50 years)
- Persistent heavy proteinuria (>3.5 g/d)
- Decreased serum albumin
- Hypertension
- Hyperlipidemia
- Impaired GFR
- Poor protein selectivity, or persistent excretion of $\beta_2$ microglobulin or C5b–C9,C3d
- Advanced stage of MN

New Predictors Levels of circulating anti–PLA2R revealed a strong correlation with clinical disease activity

Zuccheli P. Oxford Medical, 1998, 570–612
Coggins CH. Semin Nephrol 2: 264–273, 1982
Management of Complications
Hypertension

❖ Lifestyle modification
❖ Salt restriction, weight normalization, regular exercise, and smoking cessation
❖ ACE-I and ARB to be first-choice therapy
❖ Recommendations <130/80mmHg
Proteinuria

- Toxic to the tubulointerstitium
- ACE-I or ARB may reduce proteinuria by up to 40–50% in a dose dependent manner
- Adequate dietary protein (0.8–1.0 g/kg daily) with a high carbohydrate intake to maximize utilization of protein

Hyperlipidemia

- Follow the guidelines at high risk for the development of cardiovascular disease
- Statins are effective in correcting the lipid profile
Nephrotic edema

- Moderate dietary sodium restriction (1.5–2 g sodium per 24 hours)
- Diuretic-resistant nephrotic syndrome
  - Intestinal-wall edema
  - Oral loop diuretics with once- or twice-daily administration are usually preferred
  - Ease of administration and longer therapeutic effect compared to i.v. therapy

Severe nephrotic edema

- IV diuretic, by bolus injection or infusion
- Combining a loop diuretic with a thiazide diuretic
- IV albumin infusions combined with diuretics, but unproven benefit
- Mechanical ultrafiltration

Hypercoagulability

- Anti-coagulant drugs considered if serum albumin <2.0–2.5 g/dl with one or more of the following
  - Proteinuria >10 g/d
  - BMI > 35 kg/m²
  - Family history of thromboembolism
  - CHF class III or IV
  - Recent abdominal or orthopedic surgery
  - Prolonged immobilization

Risk of infection

- Nephrotic children with ascites
- Fluid should be examined microscopically for SBP
- Parenteral antibiotics should treat as pneumococcal infection
- If repeated infections occur, serum immunoglobulins should be measured
- Serum IgG < 600 mg/dl, monthly administration of i.v. immunoglobulin 10–15 g to keep serum IgG >600 mg/dL
Risk of infection

- Pneumococcal vaccination and annual influenza vaccination
- Live vaccines (measles, mumps, rubella, varicella, rotavirus, yellow fever) is contraindicated while on immunosuppressive or cytotoxic agents
- Deferred until prednisone <20 mg/d and/or immunosuppressive agents have been stopped for at least 1–3 months

Thank you for your attention

Intelligence Dialysis Center
Nephrology Unit
Phramongkutklao Hospital and College of Medicine