Classification of Renal Glomerular Diseases

• Morphological
• Immunological
• Etiological
• Clinical

Vulnerability of Glomerulus to IC Injury

1. 20% Cardiac Output
2. High glomerular capillary pressure
3. Fenestrated endothelium
4. Concentration (sieving effect)

Mechanisms of Immunologic Injury to the Glomerulus

1. Glomerular deposition of circulating Ag-Ab complexes
2. Binding of Circulating Ab to fixed glomerular Ag (i.e. anti-GBM Ab)
3. In situ immune complex formation
Glomerular Proliferation

1. Endocapillary
2. Extracapillary (crescentic)

Patterns of Glomerular Disease

1. Focal Vs Diffuse
2. Segmental Vs Global

Signs of Glomerular Disease

Erythrocyte Casts
Deformed-Crenated Urinary RBC’s
Large amounts Albuminuria ( >3g/D )
• 7 yo W M c/o x several days bad sore throat + low grade temperature; he is given acetaminophen, and recovers uneventfully. 2 wks later develops dark, coca-cola colored urine and notes urinating less. On Px pedal edema and an elevated blood pressure.

• Labs:
  – U/A rbc’s, rbc casts, 2+ prot.
  – Creatinine 2.4 mg/dl
  – Complement 22 (normal 50-150)
  – C3 level low
  – ASLO 1250 (normal < 250)
Nephritic Syndrome

- Decreased GFR
- Oliguria
- Edema
- Hypertension
- Active urinary sediment
Post-Streptococcal GN

- Follows certain serotype streptococcal infections – sore throats, impetigo, etc.
- Children more common than adults
- Time lag between infection & kidney disease
- Nephritic picture common
- Serologic tests for strept infections +
- Low complement and C3 levels
- Excellent prognosis children, +/- in adults

Serum Complement in GN

- Low Levels
  - Post-infectious GN
  - SLE
  - Cryoglobulinemia
  - Idiopathic MPGN

- Normal Levels
  - MCD, FSGS, Memb Neph, Amyloidosis, IgA, DM, ANCA + RPGN, Goodpastre’s, HSP, etc.

- A 16 y o high school junior notices dark brown urine after playing basketball. Urinary sediment has rbc’s and rbc casts.

- Labs:
  - Creatinine 1.1 mg/dl
  - Creatinine clearance 128 cc/min
  - 660 mg proteinuria/day
  - Serologic tests are normal or negative
Demographics of IgA Nephropathy

<table>
<thead>
<tr>
<th>Ages</th>
<th>4 – 80 (mean 25) years</th>
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<tbody>
<tr>
<td>M/F</td>
<td>2/1</td>
</tr>
<tr>
<td>Incidence</td>
<td>(% primary glomerulopathies)</td>
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<tr>
<td>5-10%</td>
<td>N. America</td>
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<tr>
<td></td>
<td>U.K.</td>
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<tr>
<td>20-30%</td>
<td>Scandinavia</td>
</tr>
<tr>
<td>25-45%</td>
<td>Australia</td>
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Pathogenesis

1. Defective hepatic clearance
   - Liver cirrhosis
2. Increased IgA production
   - Association with elevated serum IgA
   - Onset may follow URI or Gastroenteritis
3. Defect of antigen exclusion at the mucosal surface
   - URI
   - Gastroenteritis
   - Celiac disease
**IgA Nephropathy**

- Most common idiopathic GN world
- Defined by IgA deposition in mesangium
- Presents: Young – gross hematuria
  - Adults – Proteinuria +
  - Not benign hematuria (Berger’s Dis)
- 20-30% progress to ESRD over 20 years
- Rx – ACE inhib. + Stds, F.O., MMF

**Corticosteroids in IgAN: a controlled trial**

- 86 Pts
  - Uprot 1-3.5g/D
  - Pcreat < 1.5 mg/dl
  - Rx cyclic Pulse SM + QOD Stds vs PBO x 6 mo.
  - Endpoint 50% rise in Pcreat.  Follow 6 yrs

  - Endpoint 9/43 Rx vs. 14/43 PBO (p<.05)
  - High risk Pts: vascular sclerosis, males,
  - no Steroid Rx
  - No major side effects


**Controlled Trial of Fish Oils in IgAN**

- 106 Pts
  - 78M/28F
  - age 36yo
  - Uprot > 1 g/D
  - HBP 60%
  - Rx Max EPA 12g/D vs Olive oil
  - Rx 2yr follow 5yr

  - Endpoint 50% increase in Pcreat.
    - 6% Rx EPA vs 33% PBO
    - Change Pcreat .03 mg/dl vs .14 mg/dl
    - DDT 10% vs 40%


**IgA Nephropathy: A Controlled Trial of Steroids (Pozzi, et al)**

- 86 Pts
  - Uprot 1-3.5g/D
  - Pcreat < 1.5 mg/dl
  - Rx cyclic Pulse SM + QOD Stds vs PBO x 6 mo.
  - Endpoint 50% rise in Pcreat.  Follow 6 yrs

- Endpoint 9/43 Rx vs. 14/43 PBO (p<.05)
- High risk Pts: vascular sclerosis, males,
  - no Steroid Rx
- No major side effects

Immunosuppressive Rx for IgAN

Change in Proteinuria

- A 29 y o saleswoman develops arthritis of multiple joints, fever, lymphadenopathy, and a malar rash.

- Labs:
  - Urinalysis 3+ protein, crenated rbc’s
  - Creatinine 1.2 mg/dl
  - 24 hr. protein 1.8 g/dl
  - Complement 18% (normal 50-150%)
  - ANA positive, Anti-DNA antibody positive
Lupus Nephritis Class IV
Lupus Nephritis WHO Classification

CLASSES
I Normal
II Mesangial Proliferative
III Focal Segmental Proliferative
IV Diffuse Proliferative
V Membranous

Lupus Nephritis Class II

Treatment of Lupus Nephritis by Class
- Class I and II – Treat extra-renal findings
- Class III -FPLN – Vigorous Rx if necrotizing features, crescents, extensive proliferation.
- Class IV – DPLN – Vigorous Rx immunosuppressives
- Class V – Memb LN – Treat to induce remit proteinuria – Nephrotic syndrome
Predictors of Progression of Lupus Nephritis in Three Ethnic Groups

New York City Cohort:
- 129 pts - 51 H, 22 AA, 55 C Class III-IV LN
- Predictors (age-adjusted hazard ratio)
  - Hispanic ethnicity (3.7)
  - African American race (3.1)
  - Living in neighborhood with high poverty (2.9)
  - Government insurance – Medicare (3.2)
  - Elevated creatinine (4.3)
  - Proteinuria (3.8)
  - Hypertension (3.2)
  - WHO Class IV (3.3)  
  Barr...Appel et al, 2003

Impact of Race on Renal Prognosis – NYC  n= 129

Impact of Poverty on Renal Prognosis- NYC

Probability of Developing End-Stage Renal Disease: Comparison Among Lupus Nephritis Treatment Regimens

CYC = cyclophosphamide; AZA = azathioprine.
Steinberg AD, Steinberg SC. Arthritis Rheum. 1991;34:945-950.
Multicenter Trial of MMF vs IVCyc for Induction Therapy of Severe LN

- Multicenter, randomized, nonblinded trial of induction RX for severe active LN
- Designed as equivalence trial
  - Calculated sample size: 64/ Rx arm
- Hypothesis: MMF has equivalent efficacy with superior toxicity/tolerability profile vs. IVC
  
  ACR Ginzler et al 2003,  ASN Appel et al 2003

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>MMF (n=71)</th>
<th>IVC (n=69)</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>32.5 ± 10.9</td>
<td>31.0 ± 9.0</td>
</tr>
<tr>
<td>Female</td>
<td>61 (86%)</td>
<td>65 (94%)</td>
</tr>
<tr>
<td>Black</td>
<td>43 (61%)</td>
<td>36 (52%)</td>
</tr>
<tr>
<td>Duration of SLE, mo.</td>
<td>43.7 ± 66.88</td>
<td>58.7 ± 80.64</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.06 ± 0.52</td>
<td>1.08 ± 0.49</td>
</tr>
<tr>
<td>Urine protein, g/24 hr</td>
<td>4.06 ± 3.14</td>
<td>4.41 ± 3.51</td>
</tr>
<tr>
<td>Urine sediment RBC/hpf</td>
<td>24.1 ± 50.3</td>
<td>33.2 ± 115.5</td>
</tr>
<tr>
<td>WBC/hpf</td>
<td>12.6 ± 23.5</td>
<td>10.3 ± 17.3</td>
</tr>
<tr>
<td>Salbumin, g/L</td>
<td>2.81 ± 0.95</td>
<td>2.69 ± 0.56</td>
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### WHO Renal Biopsy Classification of Study Population

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<th>MMF (n=71)</th>
<th>IVC (n=69)</th>
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<tbody>
<tr>
<td>Proliferative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>Class III</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Membranous (V)</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Mixed</td>
<td>7</td>
<td>8</td>
</tr>
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### Change in Serum Creatinine and Urine Protein Excretion

<table>
<thead>
<tr>
<th></th>
<th>Serum Creatinine (mg/dL)</th>
<th>Urine Protein (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMF</td>
<td>![Graph]</td>
<td>![Graph]</td>
</tr>
<tr>
<td>IVC</td>
<td>![Graph]</td>
<td>![Graph]</td>
</tr>
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</table>

### Remission Rates: MMF vs. IVC

**Intent-to-Treat Analysis**

- Complete Remission: MMF 16/71 vs. IVC 4/69
- Partial Remission: MMF 21/71 vs. IVC 17/69
- Complete + Partial Remission: MMF 37/71 vs. IVC 21/69

P-value (Complete Remission): 0.005
P-value (Partial Remission): NS
P-value (Complete + Partial Remission): 0.009

### Change in Urine Sediment

- RBC: ![Graph]
- WBC: ![Graph]

### Change in Prednisone Dose

- Prednisone (mg/day): ![Graph]

P-value: 0.004

### Change in Complement Components

- C3: ![Graph]
- C4: ![Graph]
• A 58 y o insurance salesman develops sinusitis, weight loss, malaise and a dry cough over three weeks. His sinus films show opacification of the left maxillary sinus, and he is found to have a cavitary lesion on his chest X-ray.

• Labs:
  – Urinalysis: rbc’s, wbc’s, and rbc casts
  – Creatinine 2.7 mg/dl
  – Serum complement is normal
  – Anti-GBM antibodies are absent
  – ANCA is positive
Pulmonary-Renal Vasculitic Syndrome

- Pauci-immune (usually ANCA associated)
  - Wegener's granulomatosis
  - Microscopic Polyangiitis
- Immune Complex Deposits (granular)
  - SLE
  - Cryoglobulinemic vasculitis
- Anti-Glomerular Basement Membrane Antibody Deposits (linear)
  - Goodpasture's Syndrome
Rapidly Progressive Glomerulonephritis

A severe form of GN leading to RF in days to months
RPGN = Crescentic GN
Secondary RPGN (SLE, HSP, Post-infectious, etc.)
Primary RPGN
- anti-GBM disease
- immune complex GN
- pauci-immune GN
Rx and Course depend on etiology and stage

Treatment of RPGN

- Anti-GBM disease – Steroids, cytotoxics, and plasmapheresis
- Immune Complex GN – Treat underlying disease
- Pauci-immune RPGN (ANCA +) – Cytotoxics (IV or P.O.)

Anti-Neutrophil Cytoplasmic Antibodies

- C-ANCA cytoplasmic against serine proteinase 3 (PR3)
- P-ANCA perinuclear against myeloperoxidase (MPO)
- P-ANCA is an artifact of alcohol fixation

ANCA is to RPGN as Anti-DNA is to SLE
Renal Pulmonary Syndromes

- Goodpasture's Synd.       Anti GBM Abs
- SLE lung dis. + LN        aDNA + CH50
- RPGN, Weg.G., PAN         ANCA
- Pulmonary emboli          RVT ( memb NS )
- Pneumonia                 Immune complex GN
- Uremic Lung               CHF + Renal failure