CPC: Glomerulonephritis

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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 y o 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
ACUTE GLOMERULONEPHRITIS

Creatinine Clearance
ml/min/1.73 m²
(X ± S.E.)

GLOMERULAR CAPILLARY OBLITERATION
(TOTAL GLOMERULAR DAMAGE)

*BIOPSIES WITHIN 6 WEEKS OF ONSET
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

**Ages**: 4 – 80 (mean 25) years
(65% of patients in 2nd/3rd decade)

**M/F = 2/1**

Rare in blacks

<table>
<thead>
<tr>
<th>Incidence</th>
<th>(% primary glomerulopathies)</th>
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<tbody>
<tr>
<td>5-10%</td>
<td>N. America</td>
</tr>
<tr>
<td></td>
<td>U.K.</td>
</tr>
<tr>
<td></td>
<td>Scandinavia</td>
</tr>
<tr>
<td>20-30%</td>
<td>Europe</td>
</tr>
<tr>
<td></td>
<td>Australia</td>
</tr>
<tr>
<td>25-45%</td>
<td>Asia</td>
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Systemic Disease

Renal Disease

IgA Nephropathy

Henoch Schönlein Purpura
Classification

• Primary
  – IgA Nephropathy
  – Henoch-Schonlein Purpura

• Secondary
  – Liver Cirrhosis
  – Inflammatory Bowel Disease

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 + hematuria
- Not benign hematuria (Berger’s Dis)
- 20-30% progress 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


IgA Nephropathy: A Controlled Trial of Steroids (Pozzi, et al)
Controlled Trial of Fish Oils in IgAN

106 Pts    78M/28F    age 36yo
Uprot > 1 g/D    HBP 60%
Rx Max EPA 12g/D ( 58 ) vs Olive oil ( 51 )
Rx 2yr    follow 5 yr
Endpoint 50% increase Pcreat.

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

**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 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)  

Impact of Race on Renal Prognosis – NYC n= 129

![Probability of not doubling creatinine, % vs Follow-up, months graph]

- White
- Black
- Hispanic

Barr...Appel et al, 2003
Impact of Poverty on Renal Prognosis - NYC

![Graph showing the probability of not doubling creatinine over time for different groups. The graph compares the probability between "Others" and "Poverty" groups.]
Probability of Developing End-Stage Renal Disease:
Comparison Among Lupus Nephritis Treatment Regimens

<table>
<thead>
<tr>
<th>Months</th>
<th>Probability of End-Stage Renal Disease</th>
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<tbody>
<tr>
<td></td>
<td>IV CYC</td>
</tr>
<tr>
<td></td>
<td>Oral CYC + AZA</td>
</tr>
<tr>
<td></td>
<td>Oral CYC</td>
</tr>
<tr>
<td></td>
<td>AZA</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
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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 ± 10.0</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>43.72 ± 66.88</td>
<td>58.70 ± 80.64</td>
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<tr>
<td>Creatinine, mg/dL</td>
<td>1.06 ± 0.52</td>
<td>1.08 ± 0.49</td>
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<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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>MMF (n=71)</th>
<th>IVC (n=69)</th>
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</thead>
<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>
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Remission Rates: MMF vs. IVC

Intent-to-Treat Analysis

<table>
<thead>
<tr>
<th>Remission</th>
<th>MMF</th>
<th>IVC</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>Complete Remission</td>
<td>16/71</td>
<td>4/69</td>
<td>P=0.005</td>
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<tr>
<td>Partial Remission</td>
<td>21/71</td>
<td>17/69</td>
<td>P=NS</td>
</tr>
<tr>
<td>Complete + Partial Remission</td>
<td>37/71</td>
<td>21/69</td>
<td>P=0.009</td>
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Change in Prednisone Dose

Weeks

Prednisone (mg/day)

Change in Serum Creatinine and Urine Protein Excretion

Serum Creatinine

Weeks

Serum Creatinine (mg/dL)

Urine Protein

Weeks

Urine Protein (mg/dL)
Change in Urine Sediment

**RBC**

**WBC**

Change in Complement Components

**C3**

**C4**
Change in Anti-dsDNA and Serum Albumin

**Anti-dsDNA**

**Serum Albumin**

Weeks

0 4 8 12 16 20 24

Anti-dsDNA score

0 0.5 1 1.5 2

Serum Albumin (mg/dL)

2 2.5 3 3.5 4

Weeks

0 4 8 12 16 20 24

- Red square: MMF
- Blue square: IVCY

**MMF vs IVCY Induction - 24 Wk Remission Rates: AA vs Others**

<table>
<thead>
<tr>
<th>Remission Type</th>
<th>Drug 1</th>
<th>Drug 2</th>
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<tbody>
<tr>
<td><strong>Complete Remission</strong></td>
<td>MMF Black</td>
<td>MMF Other</td>
</tr>
<tr>
<td><strong>Complete + Partial</strong></td>
<td>MMF Black</td>
<td>MMF Other</td>
</tr>
</tbody>
</table>

Appel et al, ASN 2003
• 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