CPC: Glomerulonephritis
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Classification of Renal Glomerular Diseases
- Morphological
- Immunological
- Etiological
- Clinical

Vulnerability of Glomerulus to IC Injury
1. 20-25% 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 structural 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. OnPx 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

- **Ages:** 4 - 80 (mean 25) years (65% of patients in 2nd/3rd decade)
- **M/F:** 2/1
- Rare in blacks

Incidence (% primary glomerulopathies)

- **5-10%**
  - N. America
  - U.K.
  - Scandinavia
- **20-30%**
  - Europe
  - Australia
- **25-45%**
  - Asia

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 in 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 yrs

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

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

DDT                       10%                        40%
Fish oil (n=55)                (15)                          (15)  P=0.002
(55)                     (94)                          (83)
Placebo (n=51)               (10)                          (18)  (03)
(03)                       (80)                          (80)
• 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  Minimal mesangial
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)

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

Steinberg AD, Steinberg SC. Arthritis Rheum. 1991;34:945-950.
Multicenter Trial of MMF vs IV Cyc 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. IV C

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>32.0 ± 3.0</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 ± 6.4</td>
<td>58.70 ± 9.4</td>
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<tr>
<td>Sera Cholesterol, mg/dL</td>
<td>168% ± 96%</td>
<td>166% ± 94%</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>
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<tr>
<td>Urine Sediment</td>
<td></td>
<td></td>
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<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>
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<tr>
<td>Albumin, g/L</td>
<td>2.81 ± 0.95</td>
<td>2.69 ± 0.56</td>
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ACR Glisler et al 2003, ASN Appel et al 2003
WHO Renal Biopsy Classification of Study Population

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<th>IVC</th>
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<tr>
<td>(n=71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=69)</td>
<td></td>
<td></td>
</tr>
<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>
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<td>11</td>
</tr>
<tr>
<td>Membranous (V)</td>
<td>14</td>
<td>13</td>
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<tr>
<td>Mixed</td>
<td>7</td>
<td>8</td>
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Remission Rates: MMF vs. IVC

Intent-to-Treat Analysis

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<tr>
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<th>MMF</th>
<th>IVC</th>
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<tbody>
<tr>
<td>Remission Rates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent Responding</td>
<td>16/74</td>
<td>14/65</td>
</tr>
<tr>
<td>P</td>
<td>0.005</td>
<td>NS</td>
</tr>
<tr>
<td>P</td>
<td>0.005</td>
<td>0.009</td>
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Percent Responding

Change in Prednisone Dose

Change in Serum Creatinine and Urine Protein Excretion

Change in Urine Sediment

Change in Complement Components
• 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

### Change in Anti-dsDNA and Serum Albumin

<table>
<thead>
<tr>
<th>Anti-dsDNA Score</th>
<th>Serum Albumin (mg/dL)</th>
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<td>Anti-dsDNA Score</td>
<td>Serum Albumin (mg/dL)</td>
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### MMF vs IVCY Induction - 24 Wk Remission Rates: AA vs Others

<table>
<thead>
<tr>
<th>Remission Type</th>
<th>MMF Black</th>
<th>MMF Other</th>
<th>IVCY Black</th>
<th>IVCY Other</th>
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</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>[Graph]</td>
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<tr>
<td>Complete + Partial</td>
<td>[Graph]</td>
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Appel et al, ASN 2003
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

ANTIBODY-MEDIATED GLOMERULONEPHRITIS

- Circulating anti-GBM
- Circulating ANCA with antibodies with linear complex localization with paucity of glomerular IF staining
- Glomerular immune complex localization with linear IF staining
- Immunoglobulin staining

> 80% ANCA+
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 complex GN Immune
- Uremic Lung failure CHF + Renal failure