POST INFECTIONOUS GLOMERULONEPHRITIS (PIGN)
One of the oldest recognized renal diseases.

Now less commonly seen in industrialized nations, but in the underprivileged world, the burden remains high.

Subclinical disease is 4-20 times more common.

Gp A streptococci were assumed the only strain capable of causing GN, recently epidemics sec to Gp C streptococci, S. zooepidemicus have been seen.

Bernando et al : JASN 2008
Incidence of PIGn in different Geographic Locations

Nature Rev Neph:2009
## Changing Trends

### Before
- Acute poststreptococcal glomerulonephritis (APSGN)
- Pathogeneic agents mainly group A streptococcus
- Age group - pediatric
- Prognosis- complete recovery >95% of patients

### Current
- Post Infectious glomerulonephritis (PIGN)
- Pathogeneic agent: includes staph and gram negative bacteria
- Age group – older
- Prognosis- complete recovery in 50-60% of patients
Change over years..
Pathogenesis and Histology
Histology

Nat Rev Neph:2009
Histology

Nat Rev Neph:2009
In 1903, von Pirquet, postulated the existence of antibody-driven pathogenic mechanism.

Numerous pathways by which streptococci initiate and perpetuate glomerular injury have been delineated.

At this time the glomerular-immune complex formation is thought to be the initial step.

Host factors are critical to determine who gets the disease.
# Theories

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Streptococcal nephritogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Molecular mimicry</strong></td>
<td>Cross-reactivity of streptococcal products with laminin, collagen, GBM etc.</td>
</tr>
</tbody>
</table>
| **Anti-Ig reactivity** | Streptococcal neuraminidase  
Streptococcal Ig-binding receptors |
| **Streptococcal-related glomerular plasmin-binding activity** | Streptokinase  
zSpeB/SpeB  
Enolase  
NAPIr–GAPDH |
| **Streptococcal nephritogenic antigens** | M protein  
Histone-like proteins  
NAPIr–GAPDH  
zSpeB/SpeB |
Immune complex deposition
Nephritis-Associated Plasmin Receptor and Acute Poststreptococcal Glomerulonephritis: Characterization of the Antigen and Associated Immune Response

Yoshisawa et al.: JASN 2004
Anti–NAPIr antibodies

Table 3. Anti-NAPIr antibody in patients with APSGN, patients with group A streptococcal infection without renal involvement, children, and normal adults

<table>
<thead>
<tr>
<th></th>
<th>Age in yr. range</th>
<th>Anti-NAPIr Antibody (positive rate)</th>
<th>Anti-NAPIr antibody titers$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>APSGN</td>
<td>5–75, mean 29.3</td>
<td>46/50 (92%)</td>
<td>566.0 ± 106.1$^c$</td>
</tr>
<tr>
<td>Streptococcal infection</td>
<td>8–64, mean 29.0</td>
<td>30/50 (60%)</td>
<td>227.1 ± 51.2</td>
</tr>
<tr>
<td>Pediatric I</td>
<td>0.2–10, mean 7.2</td>
<td>13/50 (26%)</td>
<td>138.9 ± 23.4</td>
</tr>
<tr>
<td>Pediatric II</td>
<td>11–20, mean 14.1</td>
<td>18/50 (36%)</td>
<td>166.0 ± 25.7</td>
</tr>
<tr>
<td>Normal adults I</td>
<td>25–35, mean 30.0</td>
<td>24/50 (48%)</td>
<td>100.1 ± 18</td>
</tr>
<tr>
<td>Normal adults II</td>
<td>52–59, mean 53.2</td>
<td>36/50 (72%)</td>
<td>186.0 ± 17.3</td>
</tr>
</tbody>
</table>

*Note: Tables and figures are not included in the provided text.*
Table 4. Immunofluorescence studies in patients with APSGN

<table>
<thead>
<tr>
<th>Time from Onset to Biopsy</th>
<th>n</th>
<th>NAPl r</th>
<th>Plasminogen</th>
<th>Fibrinopen</th>
<th>C3</th>
<th>IgG</th>
<th>IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–14 d</td>
<td>25</td>
<td>25/25 (100)</td>
<td>10/25 (40)</td>
<td>15/25 (60)</td>
<td>25/25 (100)</td>
<td>16/25 (64)</td>
<td>11/25 (44)</td>
</tr>
<tr>
<td>15–30 d</td>
<td>18</td>
<td>11/18 (61)</td>
<td>5/18 (28)</td>
<td>11/18 (61)</td>
<td>18/18 (100)</td>
<td>11/18 (61)</td>
<td>8/18 (44)</td>
</tr>
<tr>
<td>31–90 d</td>
<td>7</td>
<td>0/7 (0)</td>
<td>0/7 (0)</td>
<td>4/7 (57)</td>
<td>6/7 (86)</td>
<td>3/7 (43)</td>
<td>3/7 (43)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>36/50 (72)</td>
<td>15/50 (30)</td>
<td>30/50 (60)</td>
<td>49/50 (98)</td>
<td>30/50 (60)</td>
<td>22/50 (44)</td>
</tr>
</tbody>
</table>

C3  NAPl r  Merege

IgG  NAPl r  Merege
Is the nephritogenic antigen in post-streptococcal glomerulonephritis pyrogenic exotoxin B (SPE B) or GAPDH?

![Graph showing SPEB antibody titers and GAPDH (ELISA extinction values)]

**Table 3.** Immunofluorescent staining for zymogen/SPE B and GAPDH in renal sections

<table>
<thead>
<tr>
<th>Renal sample</th>
<th>Zymogen/SPE B</th>
<th>GAPDH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive [intensity]</td>
<td>Borderline</td>
</tr>
<tr>
<td>APSGN N = 17</td>
<td>12/17 (1+)</td>
<td>2/17</td>
</tr>
<tr>
<td>Other GN N = 31</td>
<td>2/31 (1+)</td>
<td>0/31</td>
</tr>
<tr>
<td>Normal kidney N = 4</td>
<td>0/4</td>
<td>0/4</td>
</tr>
</tbody>
</table>

*Batsford et al: KI 2005*
Classically… in PIGN

- **Clinical presentation:**
  3 phase sequence: infection - interval - nephritic syndrome

- **Course of disease:**
  1 week: onset of diuresis
  4 weeks: normalization of creatinine
  3-6 months: resolution of hematuria; resolution of mesangial hypercellularity
  Years: resolution of proteinuria
Long term follow up studies: excellent prognosis for most children with the epidemic form

Japanese study followed 138 children with non-epidemic form: None developed renal insufficiency, all had normal serum complement within 12 weeks, resolution of proteinuria within 3 yrs and hematuria within 4 yrs (Kasahara T et al, Pediatr Int 2001; 43: 364)

A 12-17 yrs f/u study of 534 children and adults in Trinidad showed complete recovery in 96.5% (Potter EV et al, NEJM 1982; 307: 725)

When all studies reporting children followed for 10 to 20 yr after acute PSGN are taken into account, approximately 20% of the patients have abnormal urine analyses, but the incidence of azotemia in 1%
Long term Prognosis in Adults

- Retrospective analysis of 50 adults with PIGN (1977-1999) followed for 90±78 Months
- After average follow up of 7.5 years
  - Complete remission: 43%
  - Partial remission: 20%
  - Renal insufficiency: 27%
  - Dialysis dependent: 10%

- On multivariate analysis, underlying co-morbidities and interstitial inflammation in biopsy were independent predictors of incomplete recovery.

  Moroni et al: NDT 2002
Long term Prognosis in Adults

- Divided into Gp1(29) n Gp 2(21) based on co moridities
  - Complete remission 64% (Gp1) as c/w 14% (Gp2)
  - Renal insufficency 11% (Gp1) as c/w 43% (Gp2)

- 24 pts (Gp1/2 13/11) were treated with steroids

- 54% pts treated with steroids received complete remission as c/w 76% which did not

Moroni et al : NDT 2002
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Germany</td>
<td>France</td>
<td>Italy</td>
<td>United States</td>
</tr>
<tr>
<td>No. of patients</td>
<td>30</td>
<td>76</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td>Biopsy incidence, %</td>
<td>4.5</td>
<td>4.6</td>
<td>1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Median age (yr)</td>
<td>49</td>
<td>NA</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>M:F</td>
<td>3:1</td>
<td>2.4:1</td>
<td>1.5:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Patients with alcoholism, %</td>
<td>57</td>
<td>30</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Patients with diabetes, %</td>
<td>NA</td>
<td>8</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>Most common site of infection (%)</td>
<td>Teeth (23) Skin (13)</td>
<td>URT (28) Skin (25)</td>
<td>URT (44) Lung (16)</td>
<td>URT (23) Skin (17.5)</td>
</tr>
<tr>
<td></td>
<td>Lung (18)</td>
<td>Teeth (13)</td>
<td>Urinary tract (12)</td>
<td>Lung (17.5)</td>
</tr>
<tr>
<td></td>
<td>Endocarditis (13)</td>
<td></td>
<td></td>
<td>Endocarditis (12)</td>
</tr>
<tr>
<td>Most common bacteria (%)</td>
<td>Streptococcus* (40)</td>
<td>Staphylococcus (17)</td>
<td>Streptococcus* (47)</td>
<td>Streptococcus* (28)</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus (13)</td>
<td>Gram-negative bacteria (14)</td>
<td>Gram-negative bacteria (22)</td>
<td>Staphylococcus (24)</td>
</tr>
<tr>
<td></td>
<td>Streptococcus* (14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with no clinical evidence of infection, %</td>
<td>10</td>
<td>7</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Patients with no identifiable offending microorganism, %</td>
<td>43</td>
<td>59</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>Follow-up, mo (mean)</td>
<td>1–76 (12.5)</td>
<td>1–108</td>
<td>20–138 (90)</td>
<td>3–120 (25)</td>
</tr>
<tr>
<td>CR, %</td>
<td>64</td>
<td>28</td>
<td>43</td>
<td>56</td>
</tr>
<tr>
<td>PRD, %</td>
<td>28</td>
<td>53</td>
<td>47</td>
<td>27</td>
</tr>
<tr>
<td>ESRD, %</td>
<td>4</td>
<td>8</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Death, %</td>
<td>4</td>
<td>11</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Correlates of renal outcome</td>
<td>CR, Age &gt; 60 yr, URT, infection, endocapillary hypercellularity, Starry sky pattern</td>
<td>Absence of underlying disease, absence of interstitial inflammation, absence of crescents, absence of subendothelial deposits</td>
<td>Younger age, sex, absence of immunocompromised state, lower serum creatinine at biopsy, absence of interstitial inflammation</td>
<td></td>
</tr>
<tr>
<td>PRD</td>
<td>Alcoholism*, crescentic glomerulonephritis*</td>
<td>Nephrotic syndrome, crescentic glomerulonephritis, interstitial fibrosis</td>
<td>Higher serum creatinine at biopsy, underlying DGS</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Postinfectious Glomerulonephritis in the Elderly

## Table 1. Demographics and predisposing factors to infection (109 patients)

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>80/29 (73/27)</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
</tr>
<tr>
<td>65 to 69</td>
<td>37 (34)</td>
</tr>
<tr>
<td>70 to 79</td>
<td>52 (48)</td>
</tr>
<tr>
<td>≥80</td>
<td>20 (18)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>82 (75)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (6)</td>
</tr>
<tr>
<td>African American</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Native American</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Undisclosed</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Predisposing factors for infection</td>
<td>67 (61)</td>
</tr>
<tr>
<td>DM</td>
<td>53 (49)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>15 (14)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Severe malnutrition</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Synthetic heart valve</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus.

## Table 4. Clinical characteristics at presentation

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset hypertension</td>
<td>13 (12)</td>
</tr>
<tr>
<td>Long-standing hypertension</td>
<td>78 (72)</td>
</tr>
<tr>
<td>Periperal edema</td>
<td>72/106 (68)</td>
</tr>
<tr>
<td>New onset congestive heart failure</td>
<td>28/106 (26)</td>
</tr>
<tr>
<td>Proteinuria &lt;1 g/24 h</td>
<td>19/72 (26)</td>
</tr>
<tr>
<td>Proteinuria 1 to 3 g/24 h</td>
<td>22/72 (31)</td>
</tr>
<tr>
<td>Proteinuria &gt;3 g/24 h</td>
<td>31/72 (43)</td>
</tr>
<tr>
<td>Full nephrotic syndrome</td>
<td>23/87 (26)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>83/91 (91)</td>
</tr>
<tr>
<td>Hematuria</td>
<td></td>
</tr>
<tr>
<td>Microscopic or macroscopic</td>
<td>98/103 (95)</td>
</tr>
<tr>
<td>Macroscopic hematuria</td>
<td>19 (17)</td>
</tr>
<tr>
<td>Leukocyturia</td>
<td>63/97 (65)</td>
</tr>
<tr>
<td>Creatinine =1.2 mg/dl</td>
<td>4/108 (4)</td>
</tr>
<tr>
<td>Creatinine 1.21 to 2.0 mg/dl</td>
<td>14/108 (13)</td>
</tr>
<tr>
<td>Creatinine &gt;2.0 mg/dl</td>
<td>90/108 (83)</td>
</tr>
<tr>
<td>Dialysis at biopsy</td>
<td>48/105 (46)</td>
</tr>
<tr>
<td>Low C3</td>
<td>57/83 (69)</td>
</tr>
<tr>
<td>Low C4</td>
<td>29/83 (35)</td>
</tr>
<tr>
<td>Low C3 or C4</td>
<td>60/83 (72)</td>
</tr>
<tr>
<td>Low C3 and C4</td>
<td>26/83 (31)</td>
</tr>
</tbody>
</table>

*Nasr et al: JASN 2011*
## Results

<table>
<thead>
<tr>
<th>Infectious Agent(^a)</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus</td>
<td>50 (46)</td>
</tr>
<tr>
<td>Streptococcus(^b)</td>
<td>17 (16)</td>
</tr>
<tr>
<td>E. coli</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Actinobacter</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Proteus</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Candida</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>37 (34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of Infection(^a)</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>31 (28)</td>
</tr>
<tr>
<td>Lung</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Deep-seated abscess</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Empyema</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Infected pancreatic cyst</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sepsis (source not identified)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>No clinical evidence of infection</td>
<td>19 (17)</td>
</tr>
</tbody>
</table>
1. 26 pts with follow up of < 3 months- 15 were dialysis dependant, 11 had PRD. 14 of these 26 pts died.
2. 32 who were dialysis dependant at biopsy- 17 remained on dialysis, 5 had CR and rest had PRD
3. Correlates to reach ESRD by Multivariate analysis were, high serum creatinine on presentation and greater degree of tubular atrophy and interstitial fibrosis
Treatment

- Conservative management- BP control, Diuresis, Treatment of infection

- Does steroids or immunusupression help?
  Small retrospective studies involving 15-50 patients- pt treated with steroids± Cysclophosphamide with equivocal benefits
Thank You
Nephritogenic Antigens

Nephritogenic streptococcus GAPDH (NAPIr)
- Mesangial and GBM binding
- Plasmin entrapment and sustained activity
- Inflammatory reactivity (PMN, Mo) degradation of GBM

Nephritogenic streptococcus zSpbB/SpeB
- Anti-zSeB/SpeB antibodies
- (SpeB-antiSpeB)
- zSpeB, SpeB anti-SpeB
- Circulating (SpeB-antiSpeB) deposition and in situ SpeB-antiSpeB formation

Immune complex-mediated glomerulonephritis