IGA NEPHROPATHY

Anjali Gupta, MD
Epidemiology

- Most common cause of primary glomerulonephritis
- Peak incidence in 2\textsuperscript{nd} to 3\textsuperscript{rd} decade of life
- 2:1 male to female ratio
- Most common in Caucasians and Asians
- Described in 1968 by Dr Berge
Clinical Presentations

- 40-50% present with gross hematuria, usually following an upper respiratory infection - classic presentation
- 30-40% present with microscopic hematuria and non-nephrotic proteinuria
- <5% present with nephrotic syndrome
- <5% acute RPGN
Diagnosis

Renal Biopsy
Pathology—Light Microscopy
### Pathological Classification

#### Table 1. Lee's Classification and the 3-Grade Classification

<table>
<thead>
<tr>
<th>Grade</th>
<th>Glomerular Changes</th>
<th>Tubular and Interstitial Changes</th>
<th>Grade</th>
<th>Glomerular Changes</th>
<th>Tubular and Interstitial Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mostly normal; occasional slight mesangial thickening (segmental) with or without hypercellularity</td>
<td>Absent</td>
<td>G1</td>
<td>Normal glomeruli or slight increase in mesangial matrix and/or cellularity</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>Less than half the glomeruli show localized mesangial proliferation and sclerosis; rarely, small crescent</td>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Diffuse mesangial proliferation and thickening with focal and segmental variation; occasional small crescents and adherions</td>
<td>Focal interstitial edema and infiltrate occasionally present; tubular atrophy rare</td>
<td>G2</td>
<td>Moderate focal or diffuse mesangial proliferation and/or focal segmental sclerosis and/or endocapillary proliferation and/or cellular crescents up to 50% of glomeruli</td>
<td>Tubular atrophy and interstitial fibrosis up to 1/3 of cortical area</td>
</tr>
<tr>
<td>IV</td>
<td>Marked diffuse mesangial proliferation and sclerosis; crescents present in up to 45% of glomeruli; partial or total glomerulosclerosis frequent</td>
<td>Tubular atrophy, interstitial inflammation, and occasional interstitial foam cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Similar to grade IV, but more severe; crescents present in &gt; 45% of glomeruli</td>
<td>Similar to grade IV, but more severe</td>
<td>G3</td>
<td>Cellular crescents in &gt; 50% of glomeruli and/or global glomerulosclerosis or fibrous crescents involving &gt; 1/3 of glomeruli and/or diffuse segmental sclerosis</td>
<td>Tubular atrophy and interstitial fibrosis involving &gt; 1/3 of cortical area</td>
</tr>
</tbody>
</table>

Survival curves for ESRD
Oxford MEST score

Pathological scoring of 265 renal biopsies of IgA nephropathy with proteinuria >0.5 g/d and eGFR ≥30 ml/min/1.73 m² followed for at least 1 year

1st step
Reproducibility assessed with intraclass correlation coefficients

7 histopathological features with reproducibility
- Mesangial-cell hypercellularity
- Segmental sclerosis or adhesion
- Global glomerulosclerosis*
- Endocapillary hypercellularity
- Cellular or fibrocellular crescents
- Interstitial fibrosis/tubular atrophy
- Arteriosclerosis

2nd step
Survival analyses using the rate of eGFR decline and a 50% decrease in eGFR/ESRD as outcomes

4 independent histopathological features with reproducibility and predictive power
- Mesangial-cell hypercellularity
- Segmental sclerosis or adhesion
- Endocapillary hypercellularity**
- Interstitial fibrosis/tubular atrophy

KI:2009
Pathogenesis: Characteristics of IgA in IgAN

IgA1-structure

Light chains

Cα1

Hinge

Cα2

Cα3

Amino acid sequence

Cα1
Pro
Ser
Thr
Pro
Pro
Thr
Pro
Ser
Thr
Pro
Pro
Ser
Thr
Pro
Pro
Ser
Cα1
Pro
Ser
Thr
Pro
Pro
Ser
Cα2

Possible O-glycan structures

α1
Ser/Thr —O— GalNAc

α1
β1,3
Ser/Thr —O— GalNAc— Gal

α1
β1,3
α2,3
Ser/Thr —O— GalNAc— Gal — NANA

α1
Ser/Thr —O— GalNAc

| α2,6
NANA

α1
β1,3
Ser/Thr —O— GalNAc— Gal

| α2,6
NANA

α1
β1,3
α2,3
Ser/Thr —O— GalNAc— Gal — NANA

| α2,6
NANA
Pathogenesis

Reduction in glycosylation

Polymeric Ig A1

Ig G autoantibodies

CIC

Binding to FcR Receptors on MC

Decrease clearance by liver

In situ IC

Mesangial Inflammation
Clinical Prognostic Markers

**Poor Prognosis:**
- Severity of proteinuria
- HTN
- Renal impairment
- Increasing age
- Duration of preceding symptoms
- Increased BMI

**Good Prognosis:**
- Recurrent macroscopic hematuria

**No Impact on Prognosis:**
- Gender
- Ethnicity
- Serum IgA level
Prognosis

- 15% to 40% of adults and children will progress to ESRD
- 15 to 20% develop ESRD within 10 years of onset
- 30 to 35% develop ESRD within 20 years of onset
Treatment

- Conservative treatment
- ACE inhibitors
- Steroids
- Cytotoxic agent
- Combination therapies
- Others- Fish Oil
Conservative Treatment

- Normal renal function, normotension and only minor urinary abnormalities, such as isolated microscopic haematuria, and/or mild proteinuria

- Up to 23% of patients will have a spontaneous complete remission
Maschio et al randomized 44 patients to enalapril or other non-ACE/ARB antihypertensive.

Patients had >0.5g/day proteinuria and Cr<1.6.

At six years, renal survival more likely in ACE-I group (92%) than in control (55%).

Other Trial- HKVIN and IgACE- underpowered Trials.
**Beneficial effects of high-dose losartan in IgA nephritis**


- 6-year randomized trial, 207 patients, high-dose ARB (losartan 200 mg/day) with normal dose ARB (losartan 100 mg/day), normal dose ACEI (20 mg/day) and low-dose ACEI (10 mg/day)

- High dose ARB had significantly higher eGFR ($p < 0.0005$) and lower proteinuria ($p < 0.005$) at the end of the study

- Loss of eGFR was 0.7 ml/min/year for high-dose ARB compared to 3.2 - 3.5 ml/min/year for the other 3 groups ($p = 0.0005$)
To Summarize.....

- Lowering blood pressure and decrease proteinuria, are modifiable risk factors for progressive disease

- Patient with persistent proteinuria (>500 or >1000 mg/day) should be started on an ACE/ARB
A Controlled Trial of Fish Oil in IgA Nephropathy

multicenter, placebo-controlled, randomized trial

James V. Donadio Jr., Erik J. Bergstralh, Kenneth P. Offord, Dorothy C. Spencer and Keith E. Holley for the Mayo Nephrology Collaborative Group

Denadio et al in 1994 published in NEJM a study that randomized 104 patients (Bl Cr 1.5 & proteinuria of 2.5-3gm) to fish oil 12g daily vs placebo with olive oil.

- Primary end point: 50% increase in serum creatinine.
- At four years of follow-up, fish oil group had lower incidence of primary end point (6% vs 33%) and lower incidence of death or ESRD (10% vs 40%).
- Benefits continued at six years of follow up.
Forest plot - Fish Oil

- **Hamazaki** (p=.01)
- **Bennett** (p=.79)
- **Cheng** (p=.96)
- **Pettersson** (p=.24)
- **Donadio** (p=.009)
- **All Studies** (p=.27)
Fish Oil

To summarize...

- Fish oil use shows a trend toward renal function preservation
- Patients who meet criteria for angiotensin inhibition Should also receive fish oil
Pozzi et al conducted a prospective trial of 86 patients with proteinuria and normal to mild renal function. Follow up 5 yrs.

Patients randomized to supportive therapy alone or 6 month of steroids.

Primary end point: doubling of serum Cr.

Those on steroids had lower incidence of primary end point at 5 years (2% vs 21%) and at 10 years (2% vs 30%).

However, did not assess for effect of ACE-I.

Lancet 1999
### Efficacy and Safety of Glucocorticoids: Meta-Analysis

#### Study ID

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral prednisone group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lv 2009</td>
<td>0.14 (0.04, 0.57)</td>
<td>25.21</td>
</tr>
<tr>
<td>Ronald 2006</td>
<td>0.57 (0.12, 2.84)</td>
<td>17.77</td>
</tr>
<tr>
<td>Katafuchi 2003</td>
<td>0.26 (0.05, 1.29)</td>
<td>16.84</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.411)</td>
<td>0.25 (0.11, 0.60)</td>
<td>59.82</td>
</tr>
<tr>
<td>Intravenous MP plus oral prednisone group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pozzi 2004</td>
<td>0.14 (0.05, 0.41)</td>
<td>40.18</td>
</tr>
<tr>
<td>Subtotal (I² = 0.0%, p = 0.513)</td>
<td>0.14 (0.05, 0.40)</td>
<td>40.18</td>
</tr>
<tr>
<td>Overall (I² = 0.0%, p = 0.475)</td>
<td>0.20 (0.10, 0.39)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

#### Fig. 2.
Comparison of glucocorticoids versus controls on renal survival.

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Efficacy and Safety of Glucocorticoids: Meta-Analysis

<table>
<thead>
<tr>
<th>Study or subcategory</th>
<th>N</th>
<th>Treatment mean (SD)</th>
<th>N</th>
<th>Control mean (SD)</th>
<th>SMD (fixed) 95% CI</th>
<th>Weight %</th>
<th>SMD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pozzi</td>
<td>43</td>
<td>0.67 (0.50)</td>
<td>43</td>
<td>1.48 (1.87)</td>
<td>-</td>
<td>26.36</td>
<td>-0.59 (-1.02, -0.15)</td>
</tr>
<tr>
<td>Lv</td>
<td>33</td>
<td>1.04 (0.54)</td>
<td>30</td>
<td>1.57 (0.86)</td>
<td>-</td>
<td>18.78</td>
<td>-0.74 (-1.25, -0.22)</td>
</tr>
<tr>
<td>Julian</td>
<td>17</td>
<td>1.30 (1.24)</td>
<td>18</td>
<td>1.80 (2.97)</td>
<td>-</td>
<td>11.13</td>
<td>-0.21 (-0.88, 0.45)</td>
</tr>
<tr>
<td>Katafuchi</td>
<td>43</td>
<td>-0.84 (1.78)</td>
<td>47</td>
<td>-0.26 (1.65)</td>
<td>-</td>
<td>28.35</td>
<td>-0.34 (-0.75, 0.08)</td>
</tr>
<tr>
<td>Lai</td>
<td>17</td>
<td>2.30 (2.20)</td>
<td>17</td>
<td>3.30 (3.10)</td>
<td>-</td>
<td>10.69</td>
<td>-0.36 (-1.04, 0.32)</td>
</tr>
<tr>
<td>Shoji</td>
<td>11</td>
<td>0.29 (0.23)</td>
<td>8</td>
<td>0.71 (0.39)</td>
<td>-</td>
<td>4.69</td>
<td>-1.31 (-2.33, -0.29)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>164</td>
<td></td>
<td>163</td>
<td></td>
<td>100.00</td>
<td>-0.51</td>
<td>(-0.73, -0.29)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 4.84$, d.f. = 5 ($p = 0.44$), $I^2 = 0$
Test for overall effect: $Z = 4.52$ ($p < 0.00001$)

Fig. 3. Comparison of glucocorticoids versus controls on daily proteinuria.

Low gaded score studies, short follow up of 2-5 years, small limits

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ACE + STEROIDS

Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy

Carlo Manno, Diletta Domenica Torres, Michele Rossini, Francesco Pesce

Nephrol Dial Transplant (2009)
ACE + STEROIDS

- Prospective, open-label, multicentre, RCT

- Inclusion criteria: Moderate histologic lesions, 24-h proteinuria $\geq 1.0$ g ( $<3$ gm ) and (eGFR) $\geq 50$ ml/min followed upto 96 months
ACE + STEROIDS

Primary outcome

ESRD
ACE + STEROIDS

- Primary end Point: 4.2% in combination group as c/w 26.5% in ACE alone \( p=0.003 \)

- ESRD free survival 96.7% versus 75.5% \( p = 0.024 \)

- Proteinuria no long term difference between the two groups

- Progression of renal disease HR 0.13 (0.03-0.61)
Steroids

- Patients with sustained proteinuria despite achieving BP of 125/75mm Hg with full RAS blockade
- Nephrotic range proteinuria
Immunosuppressive Therapy
Steroids + Cytotoxic agents

Controlled Prospective Trial of Prednisolone and Cytotoxics in Progressive IgA Nephropathy

Francis W. Ballardie* and Ian S. D. Roberts

Steroids + Cytotoxic agents

COMBINATION THERAPY

- single center study of 38 patients with IgAN with impaired renal function (Cr<2.8) and declining @15%/year
- Randomized to no therapy or prednisone, cyclophosphamide, and azathioprine
- Those with combination therapy had significant reduction in proteinuria during the first 6 months (1.8g/day vs 4.4g/day) and higher renal survival at 2 years (82% vs 68%) and at 5 years (72% vs 6%)
Insufficient evidence to support the use of cyclophosphamide in IgAN, except in crescentic IgAN with rapidly progressive renal failure
# Mycophenolate Mofetil Treatment for IgA Nephropathy: A Meta Analysis

**Review:** Meta-analysis of MMF treatment for IgAN (increase in Scr)

**Comparison:** 03 MMF versus control

**Outcome:** 03 Increase in Scr

<table>
<thead>
<tr>
<th>Study</th>
<th>MMF n/N</th>
<th>Control n/N</th>
<th>RR fixed</th>
<th>Weight %</th>
<th>RR fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maes et al. [7]</td>
<td>3/21</td>
<td>0/13</td>
<td>5.53</td>
<td></td>
<td>4.45 (0.25, 79.87)</td>
</tr>
<tr>
<td>Frisch et al. [8]</td>
<td>10/17</td>
<td>7/15</td>
<td></td>
<td>67.32</td>
<td>1.26 (0.64, 2.47)</td>
</tr>
<tr>
<td>Tang et al. [6]</td>
<td>1/20</td>
<td>3/20</td>
<td>27.15</td>
<td></td>
<td>0.33 (0.04, 2.94)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>58</td>
<td>48</td>
<td></td>
<td>100.00</td>
<td>1.19 (0.62, 2.25)</td>
</tr>
</tbody>
</table>

- Total events: 14 (MMF), 10 (control)
- Test for heterogeneity: $\chi^2 = 2.15$, d.f. = 2 (p = 0.34), $I^2 = 6.8\%$
- Test for overall effect: $Z = 0.52$ (p = 0.60)

*Am J Nephrol 2009*;
## Mycophenolate Mofetil Treatment for IgA Nephropathy: A Meta Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>MMF n/N</th>
<th>Control n/N</th>
<th>RR random (95% CI)</th>
<th>Weight %</th>
<th>RR random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. [5]</td>
<td>28/31</td>
<td>19/31</td>
<td>1.47 (1.09, 1.99)</td>
<td>34.75</td>
<td></td>
</tr>
<tr>
<td>Maes et al. [7]</td>
<td>14/21</td>
<td>11/13</td>
<td>0.79 (0.54, 1.15)</td>
<td>32.75</td>
<td></td>
</tr>
<tr>
<td>Frisch et al. [8]</td>
<td>3/17</td>
<td>2/15</td>
<td>1.32 (0.25, 6.88)</td>
<td>8.71</td>
<td></td>
</tr>
<tr>
<td>Tang et al. [6]</td>
<td>16/20</td>
<td>6/20</td>
<td>2.67 (1.32, 5.39)</td>
<td>23.79</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>79</td>
<td>1.37 (0.79, 2.38)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 61 (MMF), 38 (control)

Test for heterogeneity: $\chi^2 = 12.23$, d.f. = 3 (p = 0.007), $I^2 = 75.5\%$

Test for overall effect: Z = 1.12 (p = 0.26)

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Ongoing Trials – STOP IGAN Trial

IgAN, 18-70 years old, GFR > 30 ml/min, proteinuria > 0.75 g/d plus hypertension or GFR < 90 ml/min

Optimal supportive therapy
(ACEI, ARB, target-BP < 125/75 mm Hg, Statin, etc.)
Baseline after 6 months: BP, proteinuria, GFR

Responder
Proteinuria <0.75 g/d
optimal supp. therapy;
periodic proteinuria checks

Proteinuria >0.75 g/d

Non-Responder
Proteinuria >0.75 g/d

Randomization

Optimal supportive
(n=74)

Optimal supportive +
immunosuppression
(n=74)

GFR ≥ 60 ml/min

Steroids for a total of 6
months (methylprednisolone
in bolus plus oral prednisolone)

GFR 30-59 ml/min

Cyclophosphamide (1.5
mg/kg/d p.o.) for 3 months
Azathioprine (1.5 mg/kg/d)
Steroids (40 mg/d reduce to
7.5 mg/d)

Dropout
Proteinuria > 3.5 g/d
GFR-Loss > 20%

Run-in Phase
(6 months)

Study Phase
(3 years)
Thank You