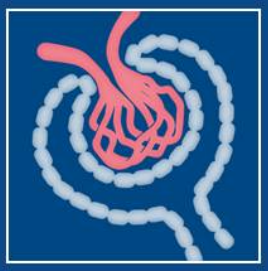
# Nephro Update Europe 2019
## 20 – 21 September, Prague

# Glomerulonephritis



Jack Wetzels, Netherlands



# Primary Glomerulonephritis: membranous nephropathy

## Membranous Nephropathy: State of the Art

- Most common cause of nephrotic syndrome in adults
- 2009: anti-PLA2R antibodies (present in 70% of patients)
- Immunosuppressive therapy in *high risk* patients
  *(proteinuria > 4g/day and >50% over baseline after 6 months conservative therapy [OR] ΔScreat > + 30%)*
- Cyclophosphamide: RCT → remissions+ renal endpoint+

- Rituximab: RCT → remissions+ renal endpoint-
- Calcineurininhibitors: RCT → remissions+ renal endpoint-

**Problem: few studies, short follow-up, renal survival not evaluated**

*Kidney disease: Improving Global Outcome (KDIGO) Glomerulonephritis Work Group: KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int, Suppl 2012; 2: 186-197*
*Dahan K et al. Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. J Am Soc Nephrol. 2017;28(1):348-358.*



## Membranous Nephropathy: new RCTs?

- **MENTOR trial (VS, Canada):**
- RCT comparison Rituximab vs CsA

- **STARMEN trial (Spain, Netherlands):**
- RCT comparison of Cyclophosphamide + steroids versus tacrolimus + Rituximab
- End-point: remission at 24 months
- Expected: november 2019

*Fervenza F et al. Rituximab or Cyclosporin in the treatment of membranous nephropathy. New Engl J Med: 2019; 381: 36 -46*

## Membranous Nephropathy: MENTOR

- RCT in patients with membranous nephropathy
- Rituximab 1000 mg, week 0 and 2
- CsA 3.5 mg/kg/day, target levels 125-175 ng/ml

- Evaluation at week 26:
- Treatment failure (ΔUPCR < 25%): exit from trial
- Complete remission: withdraw CsA, no added Ritux.
- Reduction of proteinuria (ΔUPCR > 25%):
  - continue CsA, start taper at month 12
  - new course Rituximab

*Fervenza F et al. Rituximab or Cyclosporin in the treatment of membranous nephropathy. New Engl J Med: 2019; 381: 36 -46*

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## Membranous Nephropathy: MENTOR

**Patiënt characteristics**

| | Rituximab ( n=65) | CsA (n=65) |
|---|---|---|
| Age (yrs) | 52 (13) | 52 (12) |
| Gender (Male) | 72% | 82% |
| Previous IRx | 29% | 31% |
| Screat (umol/l) | 115 (35) | 115 (35) |
| Salb (g/l) | 2.5 (2.1-2.9) | 2.5 (2.1-2.9) |
| UPCR (g/g) | 6.2 (2.6) | 6.2 (3.3) |
| PLA2Rab + (%) | 77% | 71% |

*Fervenza F et al. Rituximab or Cyclosporin in the treatment of membranous nephropathy. New Engl J Med: 2019; 381: 36 -46*

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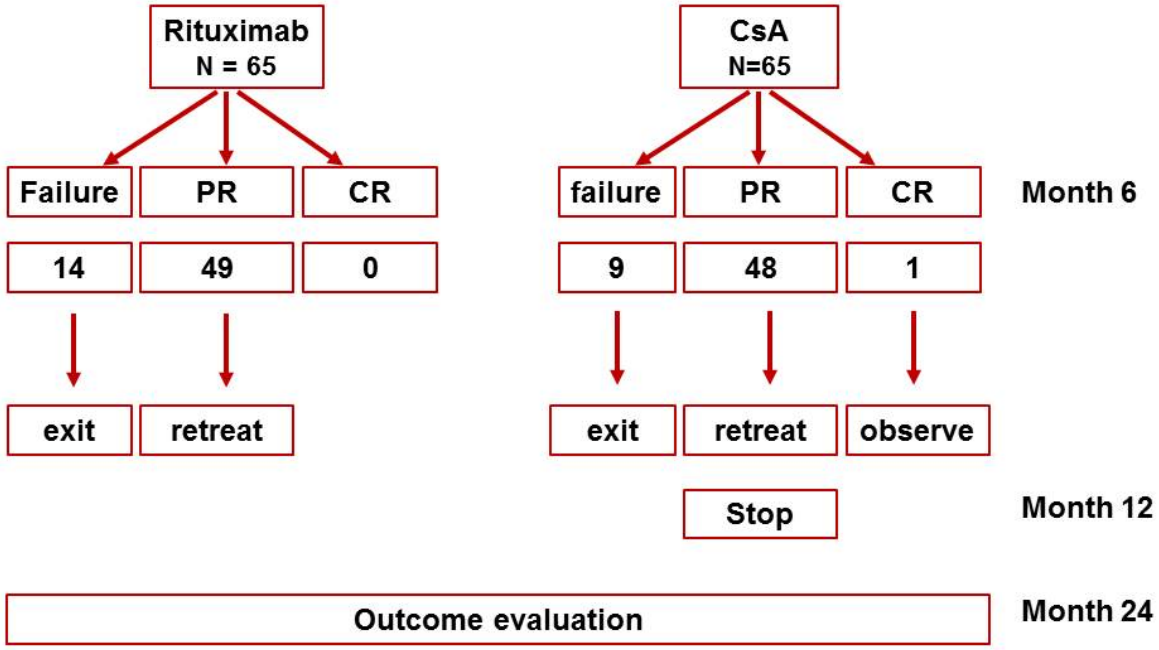
## Membranous Nephropathy: MENTOR




*Fervenza F et al. Rituximab or Cyclosporin in the treatment of membranous nephropathy. New Engl J Med: 2019; 381: 36 -46*

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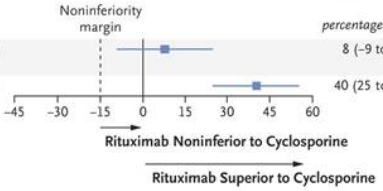
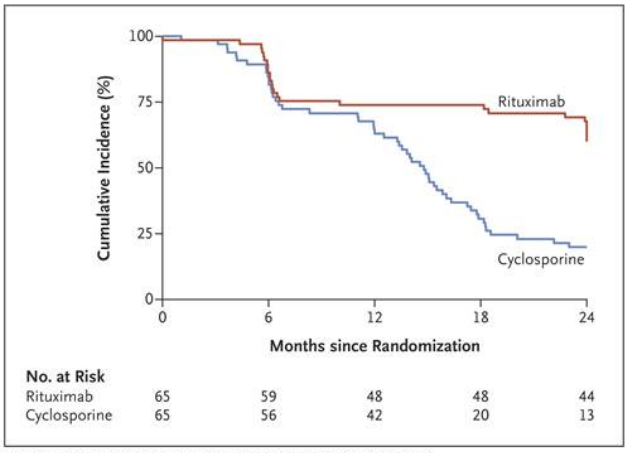
## Membranous Nephropathy: MENTOR

| Evaluation Time Point | Rituximab (N=65) | Cyclosporine (N=65) | Risk Difference (95% CI) | P Value for Noninferiority | P Value for Superiority |
|---|---|---|---|---|---|
| | *no. with complete or partial remission (%)* | | *percentage points* | | |
| End of treatment period at 12 mo | 39 (60) | 34 (52) | 8 (−9 to 25) | 0.004 | — |
| End of follow-up at 24 mo | 39 (60) | 13 (20) | 40 (25 to 55) | <0.001 | <0.001 |




**Comparable rate of remissions at month 12.**

**More sustained remissions with rituximab at month 24**




*Fervenza F et al. Rituximab or Cyclosporin in the treatment of membranous nephropathy. New Engl J Med: 2019; 381: 36 -46*

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## Membranous Nephropathy: MENTOR

**Conclusion: Rituximab is superior to CsA**

**Two views: RITUXIMAB is good or CsA is bad?**

**Very high relapse rate with CsA (unexpected)**

- 12 months therapy is too short
- Tapering in 2 months is too fast
- Low dose prednisone may have added value

*Fervenza F et al. Rituximab or Cyclosporin in the treatment of membranous nephropathy. New Engl J Med: 2019; 381: 36 -46*

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## Membranous Nephropathy: MENTOR

**Rituximab: not all benefit!**

**High non-responder rate with Rituximab: 40%**

| Time from randomization | Rituximab | | Cyclosporine | | Risk difference (95% CI) |
|---|---|---|---|---|---|
| | n | CR/PR (%) | n | CR/PR (%) | |
| Immunological response | | | | | |
| 6 months | 50 | 26 (52.0) | 46 | 13 (28.3) | 23.7 (4.7 to 42.7) |
| 12 months | 50 | 33 (66.0) | 46 | 14 (30.4) | 35.6 (16.9 to 54.3) |
| 18 months | 50 | 32 (64.0) | 46 | 5 (10.9) | 53.1 (37.1 to 69.2) |
| 24 months | 50 | 33 (66.0) | 46 | 6 (13.0) | 53.0 (36.6 to 69.3) |
| Complete or partial remission | | | | | |
| 6 months | 50 | 16 (32.0) | 46 | 20 (43.5) | -11.5 (-30.8 to 7.8) |
| 12 months | 50 | 29 (58.0) | 46 | 21 (45.7) | 12.3 (-7.5 to 32.2) |
| 18 months | 50 | 28 (56.0) | 46 | 7 (15.2) | 40.8 (23.5 to 58.0) |
| 24 months | 50 | 28 (56.0) | 46 | 6 (13.0) | 43.0 (26.1 to 59.8) |

Immunological response defined as a drop of anti-PLA2R levels to ≤40 u/mL; Analyses of immunological response are post hoc.

*Fervenza F et al. Rituximab or Cyclosporin in the treatment of membranous nephropathy. New Engl J Med: 2019; 381: 36 -46*

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# Membranous Nephropathy: MENTOR

## Rituximab is superior to CsA: is RITUXIMAB good or CsA bad?

## High non-responder rate with Rituximab: predicted by PLA2Rab

| Time from randomization | Anti-PLA2R Tertile | Rituximab n | Rituximab CR/PR (%) | Cyclosporine n | Cyclosporine CR/PR (%) | Risk difference (95% CI) | P for trend |
|---|---|---|---|---|---|---|---|
| Immunological response | | | | | | | |
| 6 months | 1 | 17 | 12 (70.6) | 15 | 7 (46.7) | 23.9 (-9.3 to 57.2) | 0.49 |
| | 2 | 17 | 9 (52.9) | 15 | 4 (26.7) | 26.3 (-6.3 to 58.9) | |
| | 3 | 16 | 5 (31.3) | 16 | 2 (12.5) | 18.8 (-9.2 to 46.7) | |
| 12 months | 1 | 17 | 14 (82.4) | 15 | 7 (46.7) | 35.7 (4.6 to 66.8) | 0.38 |
| | 2 | 17 | 13 (76.5) | 15 | 6 (40.0) | 36.5 (4.5 to 68.4) | |
| | 3 | 16 | 6 (37.5) | 16 | 1 (6.3) | 31.3 (4.7 to 57.8) | |
| 18 months | 1 | 17 | 14 (82.4) | 15 | 2 (13.3) | 69.0 (44.0 to 94.0) | 0.041 |
| | 2 | 17 | 11 (64.7) | 15 | 2 (13.3) | 51.4 (22.9 to 79.9) | |
| | 3 | 16 | 7 (43.8) | 16 | 1 (6.3) | 37.5 (10.5 to 64.5) | |
| 24 months | 1 | 17 | 14 (82.4) | 15 | 3 (20.0) | 62.4 (35.2 to 89.5) | 0.21 |
| | 2 | 17 | 12 (70.6) | 15 | 2 (13.3) | 57.3 (29.6 to 84.9) | |
| | 3 | 16 | 7 (43.8) | 16 | 1 (6.3) | 37.5 (10.5 to 64.5) | |

*Fervenza F et al. Rituximab or Cyclosporin in the treatment of membranous nephropathy. New Engl J Med: 2019; 381: 36 -46*

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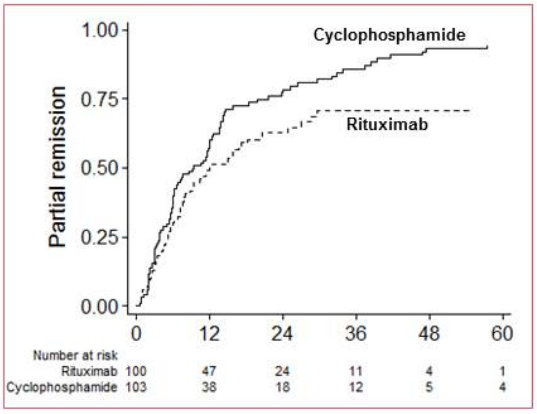
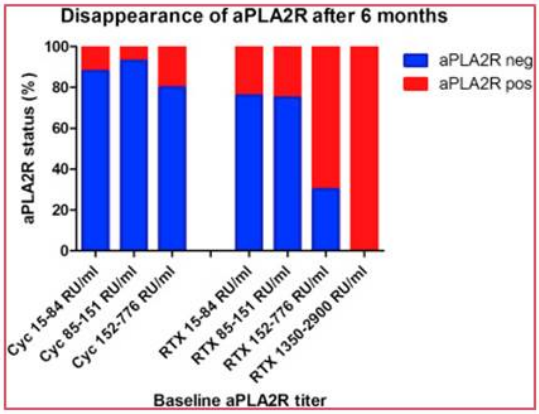
# Membranous Nephropathy: rituximab better?




**Cyc = cyclophosphamide**
**RTX = rituximab**

*Van den Brand J et al: Safety of Rituximab compared with steroids and cyclophosphamide for idiopathic membranous nephropathy. J Am Soc Nephrol. 2017; 28: 2729 – 2737.*
*Van de Logt AE et al. Immunological remission in PLA2R-antibody-associated membranous nephropathy: cyclophosphamide versus rituximab. Kidney International 2018; 93: 1016-1017*

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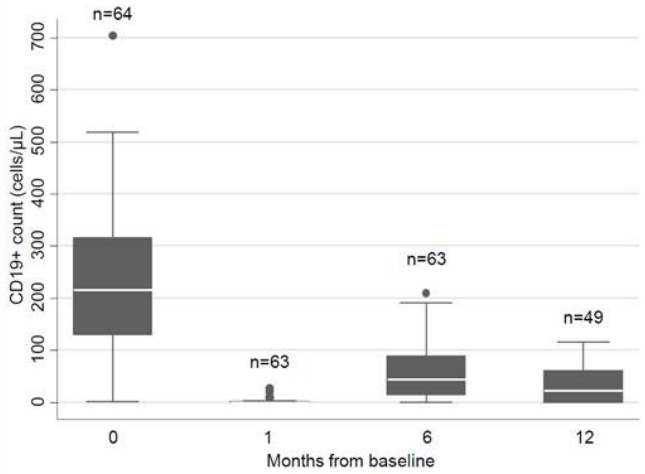
# Membranous Nephropathy: MENTOR

**Rituximab is superior to CsA: is RITUXIMAB good or CsA bad?**

**Maintained remissions wit rituximab: too short follow-up?**

**Figure S3: CD19+ Counts in patients randomized to rituximab**




**Recovery of B cells > 12 - 18 months**
**All patients received rituximab**
**2 g at baseline**
**2 g at month 6**
**→ End of therapy = month 24**

**→ Need remission rate at month 36!!**

*Fervenza F et al. Rituximab or Cyclosporin in the treatment of membranous nephropathy. New Engl J Med: 2019; 381: 36 -46*

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# Take-Home Message membranous nephropathy

- MENTOR study illustrates inefficacy of one year CNI
- MENTOR shows benefits of Rituximab
- Longer follow-up needed!
- Rituximab resistance is a problem, predictable by measuring PLA2Rab
- Debate on rituximab treatment dose (MENTOR = 4 g versus Bergamo 750 mg)
- Cyclophosphamide: not outdated yet (patients with deteriorating eGFR and/or high PLA2Rab levels

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# Primary Glomerulonephritis: IgA nephropathy

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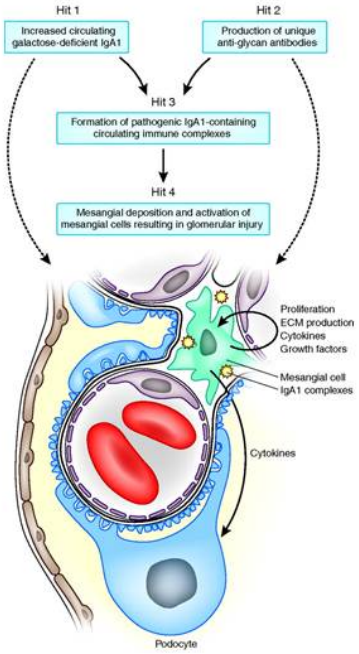
## IgA Nephropathy: State of the Art

- Most common glomerulonephritis in adults
- Slowly progressive course
  - ESRD 5-60%
- Pathogenesis and progressions: multiple steps
  - Gd-IgA
  - role of gut




*Kidney disease: Improving Global Outcome (KDIGO) Glomerulonephritis Work Group: KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int, Suppl 2012; 2: 197-210*

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# IgA Nephropathy: State of the Art

- Treatment
  - ✓ ACE-inhibitors and/or ARB:
  - ✓ Other conservative measures:

| |
|---|
| Control blood pressure: target sitting systolic RR 120-130 mm Hg |
| Maximum tolerated dose ACE/ARB, target proteinuria < 1g/day |
| Avoid Dihydropyridine CCB as first line therapy |
| Control protein intake |
| Other: control obesity, salt intake, smoking, stimulate exercise, add anti-RR therapy |

  - Immunosuppression
    - Steroids +/- alkylating agents/cMMF: heavily debated:
      - STOP-IgA: no benefit
      - TESTING: stopped because of serious adverse events

***Floege J: Editorial. Am J Kidney Dis: 2019: 74: 6-7***

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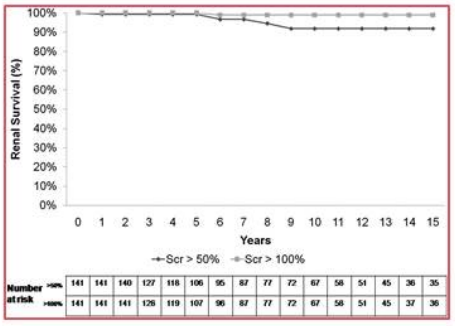
# IgA Nephropathy: State of the Art

**Outcome is good in IgA nephropathy**

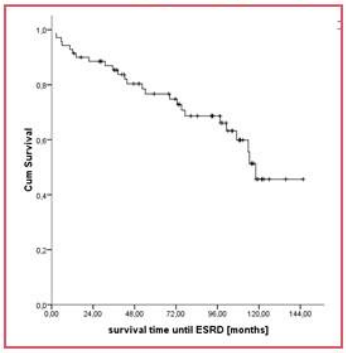
**China/Spain: isolated hematuria with long follow-up**
**Renal failure in < 10%**
**Resolution of disease in 14%**




***Gutiérrez E et al. Long-term outcomes of IgA nephropathy presenting with no or minimal proteinuria. J Am Soc Nephrol. 2012 Oct;23(10):1753-60***

**Outcome is bad in IgA nephropathy**

**Nijmegen:**

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## IgA Nephropathy: what is new?

**Production of Gd-IgA in the Gut:**

→ Budosenide Phase 3 study

**Production of anti-IgA antibodies**

→ **Immunosuppression: high risk**
**→ Risk calculator**

**Prevent progression**

→ **Non-immunosuppressive therapy**
**→ hydroxychloroquine**
→ sparsentan
→ anticomplement

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## IgA Nephropathy: Risk Calculation

| Derivation cohort | Validation cohort |
|---|---|
| VALIGA 1192 | Oxford 302 |
| Nanjing 1021 | Bejing 249 |
| Tokyo 568 | Fukuoka 595 |

**Only data at time of Biopsy**

**Limited time of follow-up (5 yr risk)**

| Model 1 | Model 2 | Model 3 |
|---|---|---|
| eGFR/Uprot/RR | eGFR/Uprot/RR | eGFR/Uprot/RR |
| | MEST score | MEST score |
| | | Age, sex, crescents, BMI, RAAS, steroids |

*Barbour S et al: Evaluating a new international risk prediction tool in IgA nephropathy JAMA Intern Med: 2019;179: 942-952*

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# IgA Nephropathy: Risk Calculation

| | Derivation | Validation |
|---|---|---|
| Patients | 2781 | 1146 |
| Year of biopsy | 2006 | 1998 |
| Age (yrs) | 36 (28-45) | 35 (27-45) |
| Gender (% male) | 58% | 49% |
| Race (% white) | 42% | 16% |
| Screat (umol/l) | 92 (71-124) | 84 (66-111) |
| Proteinuria (g/day) | 1.2 (0.7 – 2.2) | 1.3 (0.6-2.4) |
| MAP (mm Hg) | 97 (89-106) | 93 (85-103) |
| RAAS (at biopsy/follow-up) | 32%-87% | 30%-66% |
| Immunosuppression (B/F) | 9%-44% | 7%-31% |
| MEST score (M1E1S1T1T2C1-2) | 38/17/77/25-5/34 | 42/42/80/18-11/56 |
| Follow-up (yrs) | 4.8 (3.0-7.6) | 5.8 (3.4 -8.5) |
| Outcome (ESRD or ΔeGFR 50%) | 17.7% | 18.6% |

*Barbour S et al: Evaluating a new international risk prediction tool in IgA nephropathy JAMA Intern Med: 2019;179: 942-952*

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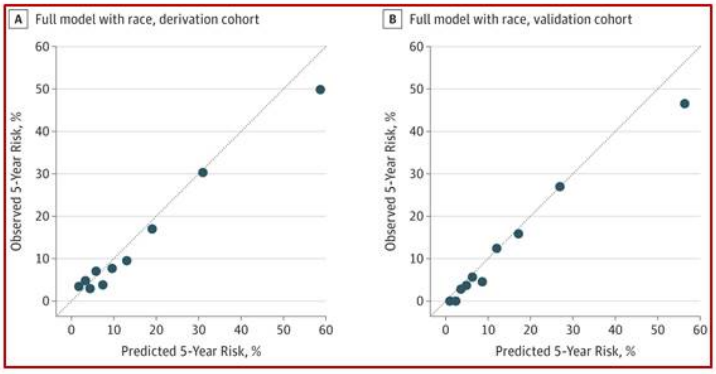
# IgA Nephropathy: Risk Calculation

**C-statistic**

| Model 1 | Model 2 | Model 3 |
|---|---|---|
| 0.78 | 0.80 | 0.82 |
| | Δ | Δ |
| | 0.02 (0.02-0.03) | 0.04 (0.03-0.04) |

**Full model > clinical model; good calibration**

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# IgA Nephropathy: Risk Calculation

**You can calulate risk at Qxmd.com/calculate-by-qxmd**

| age | Gender | eGFR | Uprot | MAP | ACE | MES | T | 5yr risk |
|---|---|---|---|---|---|---|---|---|
| 35 | M | 70 | 2 | 135/80 | - | M0E0S0 | T0 | 7.32% |
| 35 | M | 70 | 2 | 135/80 | - | M1E1S1 | T0 | 8.22% |
| 35 | M | 70 | 2 | 135/80 | - | M0E0S0 | T2 | 17.92% |
| 35 | M | 70 | 2 | 135/80 | + | M1E1S1 | T0 | 10.40% |
| 35 | M | 70 | 1 | 135/80 | - | M1E1S1 | T0 | 5.90% |
| 35 | M | 50 | 2 | 135/80 | - | M1E1S1 | T0 | 12.65% |
| 35 | M | 50 | 2 | 145/90 | - | M1E1S1 | T0 | 13.13% |

**MEST-C score: disagreement between pathologists!**

**Is it really relevant clinically? Are elements of risk score treatable? Proteinuria versus T score?**

**8-9% = eGFR decrease > 2 ml/min/yr**

*Barbour S et al: Evaluating a new international risk prediction tool in IgA nephropathy JAMA Intern Med: 2019;179: 942-952*

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# IgA Nephropathy: new treatments

## Hydrochloroquine:

Immunomodulator:

- Toll-like receptors
- Cytokine production
- Cell activation and proliferation

Used in SLE

Uncontrolled studies suggested effects on proteinuria in IgAN

*Liu LJ et al Effects of hydroxychloroquine on proteinuria in igA Nephropathy: a randomized controlled trial. Am J Kidney Dis 2019; 74:15-22*

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# IgA Nephropathy: hydroxychloroquine RCT

## Randomized controlled trial

## Country: China

## Inclusion criteria:

- Biopsy proven IgAN
- Age: 18 – 80 years
- eGFR > 30 ml/min/1.73m$^2$
- Uprot: 0.75 – 3.5 g/day despite maximal RAASi

**Treatment duration: 6 months**

**Treatment protocol**:

| | |
|---|---|
| eGFR > 60 ml/min/1.73m$^2$ | HCQ: 2 dd 200 mg |
| eGFR 45-60 ml/min/1.73m$^2$ | HCQ: 3 dd 100 mg |
| eGFR 30-45 ml/min/1.73m$^2$ | HCQ: 2 dd 100 mg |
| eGFR < 30 ml/min/1.73m$^2$ | HCQ: 1 dd 100 mg |

*Liu LJ et al Effects of hydroxychloroquine on proteinuria in igA Nephropathy: a randomized controlled trial. Am J Kidney Dis 2019; 74:15-22*

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# IgA Nephropathy: hydroxychloroquine RCT

## Results

| | HCQ N=30 | Placebo N=30 |
|---|---|---|
| Age (yr) | 38 ± 12 | 36 ± 10 |
| Gender (% Male) | 63% | 67% |
| RR (mmHg) | 124 ± 10<br>80 ± 7 | 122 ± 11<br>77 ± 8 |
| eGFR (ml/min/1.73m2) | 52 ± 20 | 56 ± 19 |
| Uprot (g/day) | 1.6 (1.1-2.2) | 1.9 (1.3 – 2.6) |
| RAASi (%) | 97% | 100% |
| M1 (%) | 65% | 57% |

*Liu LJ et al Effects of hydroxychloroquine on proteinuria in igA Nephropathy: a randomized controlled trial. Am J Kidney Dis 2019; 74:15-22*

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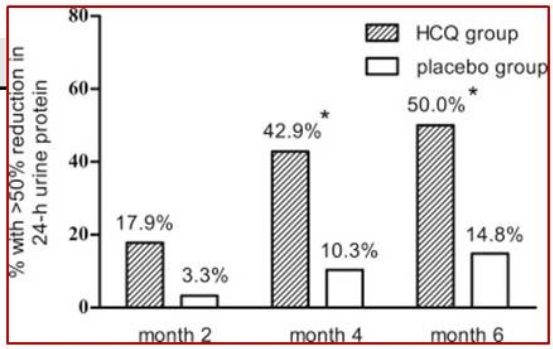
# IgA Nephropathy: hydroxychloroquine RCT

## Results

| | HCQ N=30 | Placebo N=30 |
|---|---|---|
| U protein g/day | | |
| Baseline | 1.6 (1.1-2.2) | 1.9 (1.3-2.6) |
| 2 months | 1.2 (0.8-1.7) | 1.9 (1.5-2.5) |
| 4 months | 1.0 (0.7-1.4) | 2.0 (1.1-2.5) |
| 6 months | 0.9 (0.6-1.0) | 1.9 (0.9-2.6) |

**Significant decrease in proteinuria**

**Few side effects**

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# Take-Home Message IgA Nephropathy

- Immunosuppressive therapy:
  - Only use in high-risk patients
  - High-risk patients can be selected based on proteinuria (> 1-2 gram/day with optimal conservative therapy)
  - IgA risk calculator: easy to use, needs validation in long-term outcome studies
  - Results of Budosenide trial pending
- Hydroxychloroquine: if confirmed powerful new drug

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# Primary Glomerulonephritis: MCD/FSGS

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## Minimal change disease/FSGS: State of the Art

- Most common cause of idiopathic nephrotic syndrome
- **Steroid sensitive (MCD in adults)**

→ frequent relapses/steroid dependence

→ steroid side effects

- Alternative drugs: cyclophosphamide; tacrolimus, CsA, mycophenolate mofetil
- **Steroid resistant** → tacrolimus
- **Steroid resistant:** 25% genetic cause (age < 25 years)

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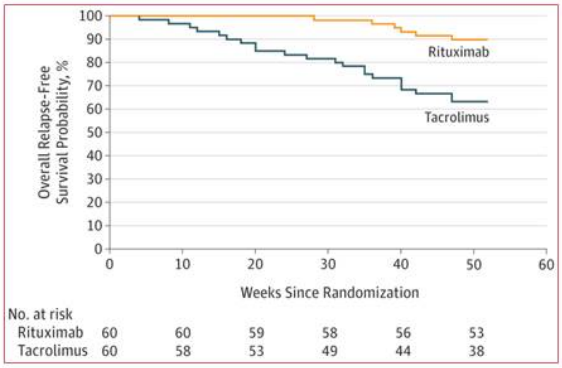
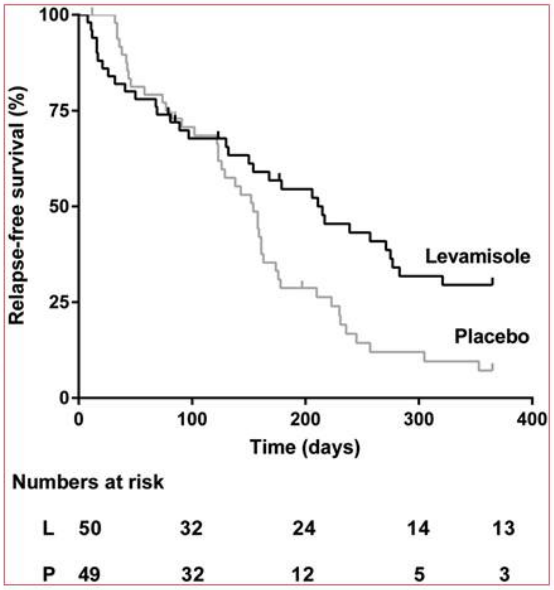
# Minimal change disease/FSGS: state of the Art




**2018: rituximab and levamisole effective in reducing relapse rate**

**Most data from studies in children**

*Basu B et al Efficacy of Rituximab vs tacrolimus in pediatric corticosteroid-dependent nephrotic syndrome: a randomized clinical trial . JAMA Pediatr 2018 : 172: 757; Gruppen M et al. A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome. Kidney Int 2018 ;93: 510-518*

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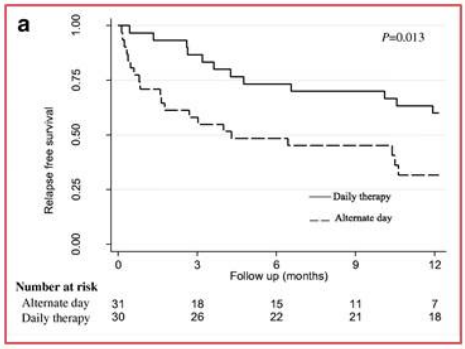
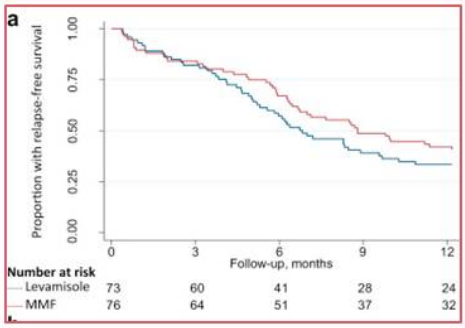
# MCD/FSGS: what is new?




**Studies in children:**

1. **Daily prednisone is more effective than alternate day prednisone (upper figure)**
2. **ACTH i.m. is not effective**
   **(relapse rate 93% vs 94%; data not shown)**
3. **MMF is not superior to levamisole (lower figure)**
   **(incidence rate ratio 0.79 (0.58-1.07)**

**(although significantly better in steroid dependent patients)**

*Yadav M et al. Efficacy of low-dose versus alternate-dose prednisolone in frequently relapsing neprhotic syndrome: an open-label randomized controlled trial. Pediatric Nephrology 2019; 34: 829-835;*
*Sinha A. et al. Efficacy and safety of mycophenolate mofetil versus levamisole in frequently relapsing nephrotic syndrome: an open-label randomized trial. Kidney int 2019;95:210-218*

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## MCD/FSGS: what is new in adults?

**Treatment with MMF → lower initial dose of prednisone?**

- **Randomized controlled trial**
- **France: 32 centers**
- **Patients: n =116**
- **Period: november 2009 – june 2014**
- **Patients with biopsy-proven MCD**
- **Initial treatment:**
  - **Control group: prednisone 1 mg/kg/day (max 80 mg)**
  - **Test group: Mycophenolate sodium 2 dd 720 mg + prednisone 0.5 mg/kg/day (max 40 mg)**

*Rémy P et al. An open-label randomized controlled trial of low-dose cortocosteroid plus enteric coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults. Kidney Int 2018;94:1217-1226*

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## MCD/FSGS: what is new?

**characteristics**

| | MMF+low dose prednisone N=58 | Prednisone N=58 |
|---|---|---|
| Age (yr) | 47 (31-61) | 42 (32-55) |
| Gender (% Male) | 62% | 50% |
| RR (mmHg) | 130 (120-132)<br>78 (70-82) | 127 (119-140)<br>75 (68-84) |
| eGFR (ml/min/1.73m2) | 89 (54-111) | 84 (50-109) |
| Salbumin (g/l) | 16 (13-21) | 17 (13-22) |
| UPCR (g/10 mmol) | 8.2 (6-12) | 9.5 (5.3-13.7) |
| Recurrent disease (%) | 1 | 2 |

**Median (IQR)**

*Rémy P et al. An open-label randomized controlled trial of low-dose cortocosteroid plus enteric coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults. Kidney Int 2018;94:1217-1226*

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# MCD/FSGS: what is new?

**outcome**

| | MMF+low dose prednisone | Prednisone |
|---|---|---|
| Patients at 4 weeks | 52 | 57 |
| *Complete remission(%)* | *61.5%* | *57.9 %* |
| *Partial Remission (%)* | *7.7%* | *10.5 %* |
| Patients at 8 weeks | 46 | 50 |
| *Complete remission(%)* | *82.6 %* | *70 %* |
| *Partial Remission (%)* | *6.5%* | *18%* |
| Patients at 24 weeks | 46 | 44 |
| *Complete remission(%)* | *80.4 %* | *79.5 %* |
| *Partial Remission (%)* | | |
| Patients at 52 weeks | 40 | 38 |
| *Complete remission(%)* | *67.5%* | *78.9%* |
| *Partial Remission (%)* | | |

**no difference in remission rate; incomplete follow-up !**

*Rémy P et al. An open-label randomized controlled trial of low-dose cortocosteroid plus enteric coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults. Kidney Int 2018;94:1217-1226*

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# MCD/FSGS: what is new?

**Adverse events**

| | MMF+low dose prednisone N=58 | Prednisone N=58 |
|---|---|---|
| *Patients with adverse events (N;%)* | *53 (91%)* | *51 (88%)* |
| *Patients with serious adverse events (N;%)* | *9 (15.5%)* | *9 (15.5%)* |
| *Death* | *2* | *3* |
| *Infections* | *5* | *2* |
| *AKI* | *1* | *2* |
| *Diabetes* | *0* | *2* |
| *Bone fracture* | *0* | *2* |
| *Pulm embolism* | *1* | *0* |

*Rémy P et al. An open-label randomized controlled trial of low-dose cortocosteroid plus enteric coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults. Kidney Int 2018;94:1217-1226*

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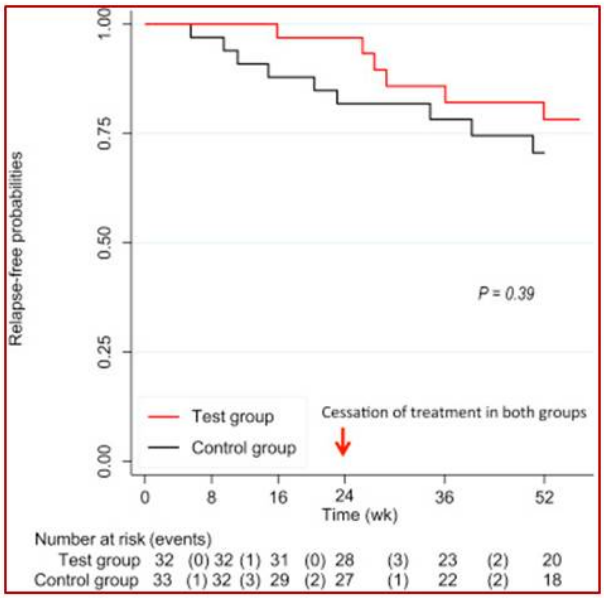
# MCD/FSGS: what is new?

**Relapse in patients with complete remission at week 4**




*Rémy P et al. An open-label randomized controlled trial of low-dose cortocosteroid plus enteric coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults. Kidney Int 2018;94:1217-1226*

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# MCD/FSGS: what is new?

**STUDY LIMITATIONS:**

- **Many patients lost to follow-up**
- **Therapeutic drug monitoring not done → MMF efficacy might even be higher**
- **Do we need high dose steroids in all patients?**
- **No differences in adverse events → this was reason for study**

*Rémy P et al. An open-label randomized controlled trial of low-dose cortocosteroid plus enteric coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults. Kidney Int 2018;94:1217-1226*

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## Take-Home Message

- Steroid sensitive idiopathic nephrotic syndrome: most patients suffer from steroid side effects
- Initial therapy with prednisone: lower prednisone dose is possible with tacrolimus or MMF
- Maintenance therapy: many alternative (steroid) sparing drugs: Rituximab > tacrolimus > MMF > levamisole

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## Secondary Glomerulonephritis: C3-glomerulopathy

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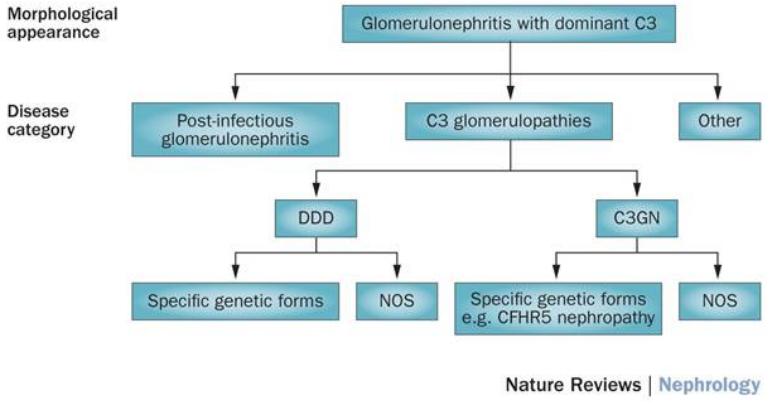
# C3 glomerulopathy: State of the Art

- C3 glomerulonephritis: **dominant** C3 ( ≥ 2+ vs IgG)




*Cook, H. T. & Pickering, M. C. Histopathology of MPGN and C3 glomerulopathies. Nat. Rev. Nephrol. 2015 Jan;11(1):14-22. doi: 10.1038/nrneph.2014.217. Epub 2014 Dec 2*

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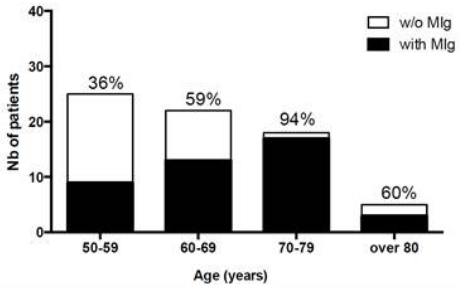
# C3 Nephropathy: State of the Art

**Causes: Complement dysregulation**
**- genetic, auto-immune (C3-nephritic factor): young patients**
**- Monoclonal immunoglobulin: older patients**

Figure 1: monoclonal gammopathy frequency in C3G patients according to age range. Abbreviations: MIg, monoclonal immunoglobulin; w/o, without.




**In patients with C3GN: always look for paraproteins, especially if > 50 years**

*Chauvet S et al. Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy-associated C3 glomerulopathy. Blood 2017;129:1437-1447*

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# C3 glomerulopathy: State of the Art

## Initial therapy with MMF

| | MMF (n=30) |
|---|---|
| Age (yrs) | 25 (18-36) |
| Male/Female | 17/13 |
| C3Nef | 21% |
| Low C3 | 70% (9/13 elevated MAC) |
| Nephrotic | 9 (30%) |
| eGFR (ml/min/1.73m²) | 62 (39-102) |
| Proteinuria (g/g) | 2.5 (1.4-4.8) |

30 patients treated with MMF 2g/day > 3 months

All but 2 patients + steroids

Median duration: 24 months

Response rate: 67%

2018 US study , retrospective, selection of treated patients (33/120 patients with C3GN).

Avasare RS et al. Mycophenolate mofetil in combination with steroids for treatment of C3 glomerulopathy. CJASN 2018; 13:406-413

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# C3 glomerulopathy: State of the Art

Complement mediated disease → eculizumab?

| | Children (n=13) | Adults (n=13) |
|---|---|---|
| Age (yrs) | 12 (9-17) | 43 (18-65) |
| Male/Female | 8/5 | 4/9 |
| Interval Dx –eculizumab (mo) | 19 (1-58) | 36 (0.5-150) |
| Nephrotic | 9 (69%) | 10 (77%) |
| eGFR (ml/min/1.73m²) | 110 (10-150) | 36 (8-111) |
| Proteinuria (g/g) | 3.6(0.24-12) | 5.4(1.32 – 9.4) |
| RPGN | 1 (8%) | 6 (46%) |

Duration of eculizumab treatment 14 months; adults < children; discontinuation 9 adults and 5 children.
Low C3 88%, C3NeF 67%, elevated C5b-9 80%

Le Quintrec M et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. AJKD 2018;72: 84-92

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# C3 glomerulopathy: State of the Art

## Eculizumab beneficial in patients with RPGN

| | Global response (n=6) | Partial response (n=6) | No response (n=14) |
|---|---|---|---|
| Screat (mg/dl) | 4.8 (0.5-6) | 0.7 (0.6-1.1) | 1.2 (0.2-9.9) |
| UPCR (g/g) | 9.4 (0.24 – 12) | 3.9 (0.4-6.2) | 3.0 (1.3 -10) |
| RPGN | 5 (83%) | 0 (0%) | 2 (14%) |
| Crescents > 25% | 4 (66%) | 0 (0%) | 0 (0%) |
| Interstitial fibrosis > 25% | 3 (50%) | 1 (20%) | 1 (11%) |

C3, C3NeF, C5b-9: no predictive value

Le Quintrec M et al. Patterns of clinical response to eculizumab in patients with C3 glomerulopathy. AJKD 2018;72: 84-92

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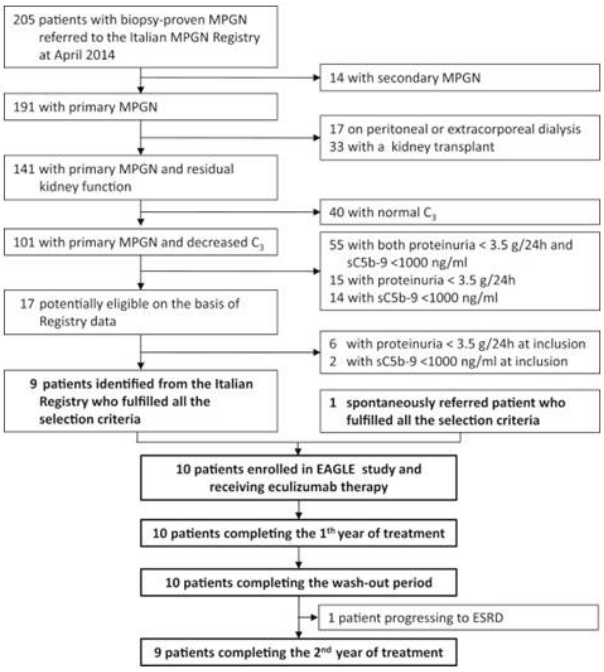
# C3 glomerulopathy: what is new




**Eculizumab in MPGN:**

**Protocol:**
**Off-on-off-on**
**10-48-12-48 weeks**

**Standard dose aHUS**

**Inclusion: increased C5b-9, Uprot > 3.5 g/day**

**MPGN-IC: n=6**
**MPGN: C3GN n=4**

Ruggenenti P et al. C5 convertase blockade in membranoproliferative glomerulonephritis: a singe arm clinical trial. Am J Kidney Dis 2019 Aug;74(2):224-238. doi: 10.1053/j.ajkd.2018.12.046. Epub 2019 Mar 28.

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## C3 glomerulopathy: what is new

| | C3GN N=4 | IC-MPGN N=6 |
|---|---|---|
| Age (yrs) | 22 (18) | 19 (6) |
| Male sex | 2 | 4 |
| Screat (mg/dl) | 1.58 (1.1) | 0.97 (0.9) |
| Salb (g/l) | 2.1 (0.7) | 2.6 (0.3) |
| Uprot (g/24hr) | 9.9 (6-14) | 5.5 (4.8-6.2) |
| RAASi | 4 | 6 |

Five children and five adults;
C3 nephritic factor in 3 C3GN and 2 IC-MPGN

Ruggenenti P et al. C5 convertase blockade in membranoproliferative glomerulonephritis: a singe arm clinical trial. Am J Kidney Dis 2019 Aug;74(2):224-238. doi: 10.1053/j.ajkd.2018.12.046. Epub 2019 Mar 28.

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## C3 glomerulopathy: what is new

**Eculizumab:**

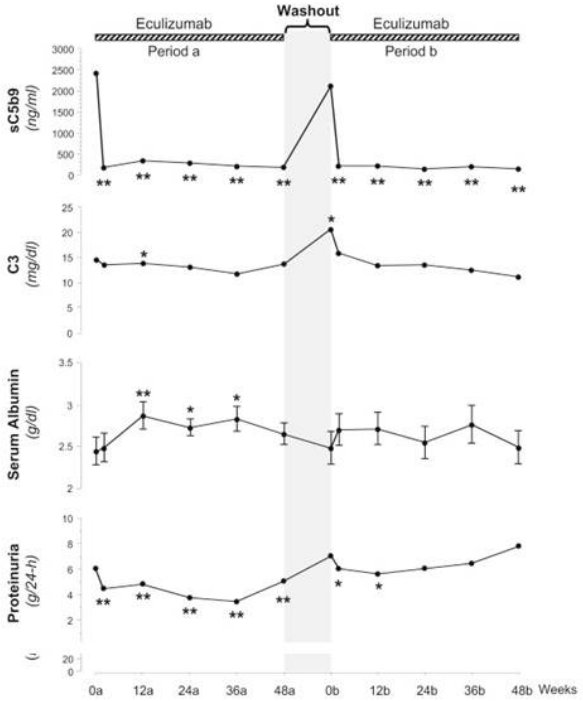
**Effective reduction of C5b-9**

**Overall: no response**

**Subanalysis:**

**3 responders**

**7 non-responders**




Ruggenenti P et al. C5 convertase blockade in membranoproliferative glomerulonephritis: a singe arm clinical trial. Am J Kidney Dis 2019 Aug;74(2):224-238. doi: 10.1053/j.ajkd.2018.12.046. Epub 2019 Mar 28.

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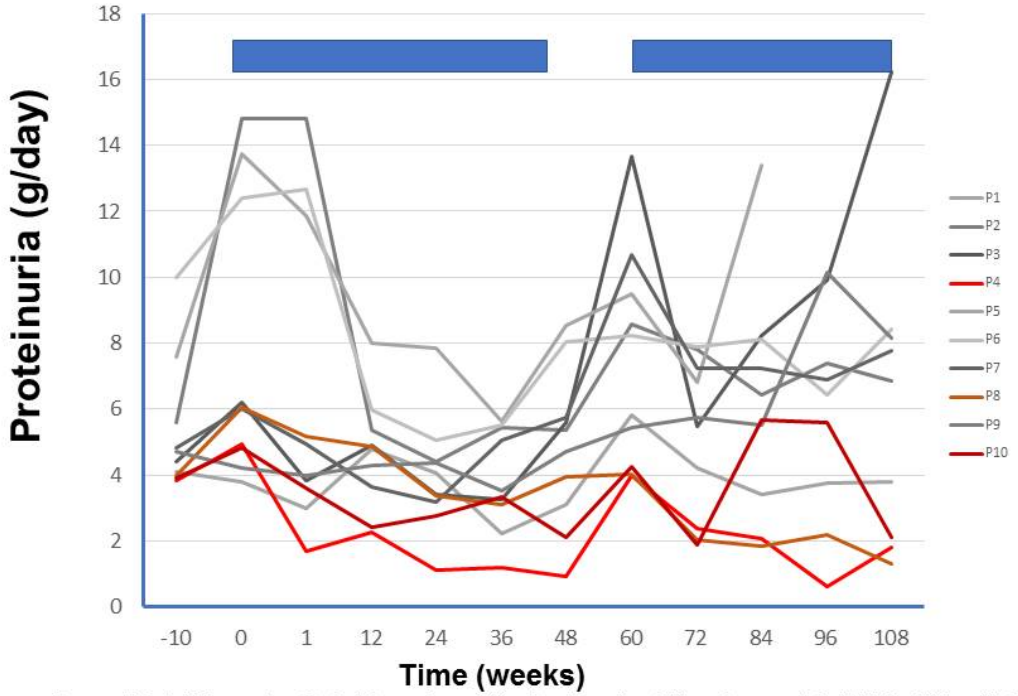
## C3 glomerulopathy: real response?




Ruggenenti P et al. C5 convertase blockade in membranoproliferative glomerulonephritis: a singe arm clinical trial. Am J Kidney Dis 2019 Aug;74(2):224-238. doi: 10.1053/j.ajkd.2018.12.046. Epub 2019 Mar 28.

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## Take-Home Message C3-glomerulopathy

- Complement mediated
- In patients > 50 years: look for monoclonal Ig
- Treatment of non monoclonal Ig associated C3GN:
  - mycophenolate mofetil
  - Eculizumab: questionable efficacy → RPGN only?
  - Activation of terminal complement is not the main problem
  - Alternative therapies needed

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## C3 glomerulopathy: what is new

New complement therapies

- Avacopan (C5a Receptor antagonist)
- Factor D inhibitor (achillion)
- Factor B inhibitor (Novartis)
- C3-inhibitor (Apellis)

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## Special feature
## Serum albumin assay

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## Serum albumin assay

Serum albumin values are used in clinical care:

1. To define nephrotic syndrome
2. To guide treatment e.g anticoagulant therapy

Variations in serum creatinine assays caused errors when using the MDRD-formula → calibration and standardisation

Variations in serum albumin assays: not appreciated

Laboratory methods: Brome cresol green
Brome cresol purple
immuneturbidimetric

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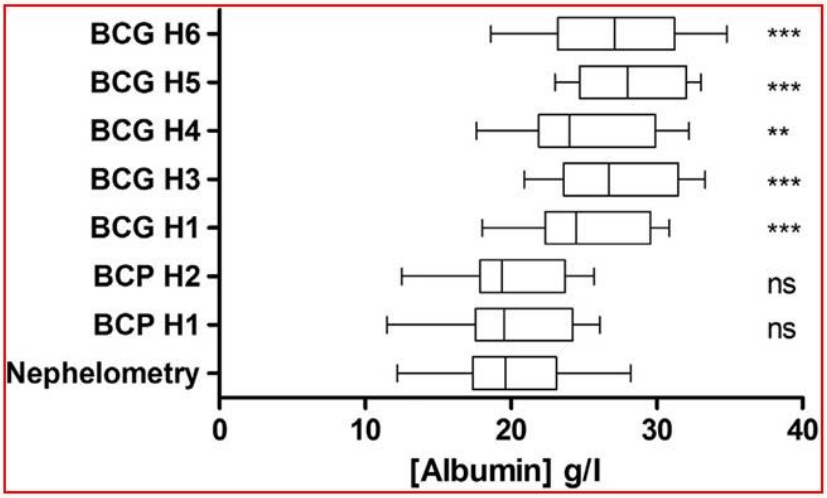
## Serum albumin assay

Bias between assays: BCG overestimates serum albumin by 5-7 g/L




Van de Logt AE et al. The bias between different albumin assays may affect clinical decision making. Kidney Int 2019; 95:1514-1517

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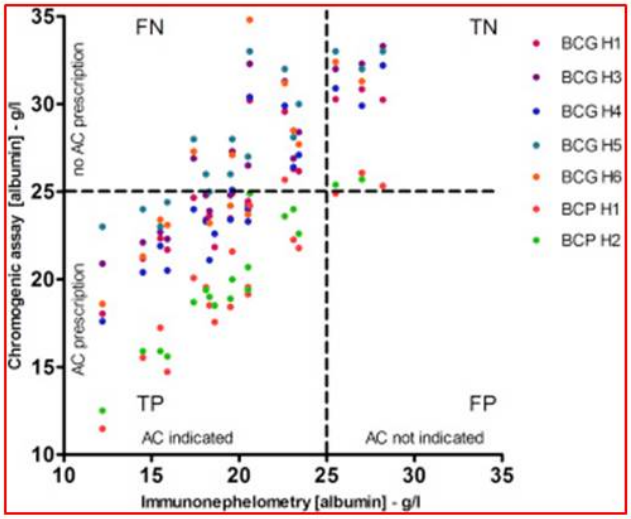
# Serum albumin assay

Bias between assays affects clinical decision making




**Anticoagulant therapy in membranous nephropathy**

Van de Logt AE et al. The bias between different albumin assays may affect clinical decision making. Kidney Int 2019; 95:1514-1517

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# List of Abbreviations

- $PLA_2R$: phospholipase $A_2$ receptor
- RCT: randomized controlled trial
- eGFR: estimated glomerular filtration rate
- mGFR: measured glomerulr filtration rate
- UPCR: Urine Protein/Creatinine Ratio
- CYC: cyclophosphamide
- RTX: rituximab
- CsA: ciclosporin
- ESRD End Stage Renal Disease
- Gd-IgA: galactose-deficient IgA
- RAASi: Renin Angiotensine Aldosterone inhibitors, include ACE-inhibitors and Angiotensin receptor blockers
- BP: blood pressure
- FSGS: focal segmental glomerulosclerosis
- MCD: minimal change disease
- SSNS: steroid sensitive nephrotic syndrome
- MMF: mycophenolate mofetil
- MPGN: membranoproliferative glomerulonephritis
- RPGN: rapidly progressive glomerulonephritis
- C3NEF: C3 nephritic factor
- C3GN: C3 glomerulopathy
- ECC: endogenous creatinine clearance
- Salb: serum albumin
- Sb2M: serum b2-microglobulin