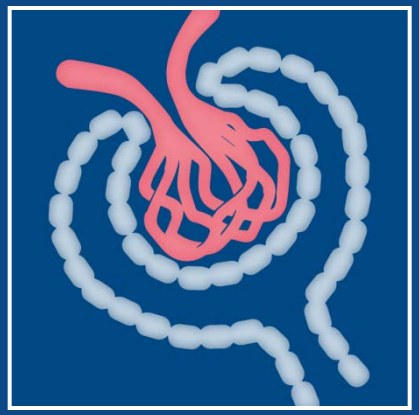
Nephro Update Europe 2018

5-6 October, Budapest

Glomerulonephritis



Jack Wetzels, Netherlands

Conflicts of Interest

Research Support: Achillion, Chemocentryx, Ipsen, Vifor Pharma

Lecturing: Vifor-Pharma, Shire

Consulting activities: Vifor-Pharma

Primary Glomerulonephritis:

- **membranous nephropathy**
- **IgA nephropathy**
- **MCD/FSGS**

C3-glomerulopathy

- **„ idiopathic“**
- **Paraprotein- associated**

(Paraprotein induced kidney injury:
-cast nephropathy)

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%)

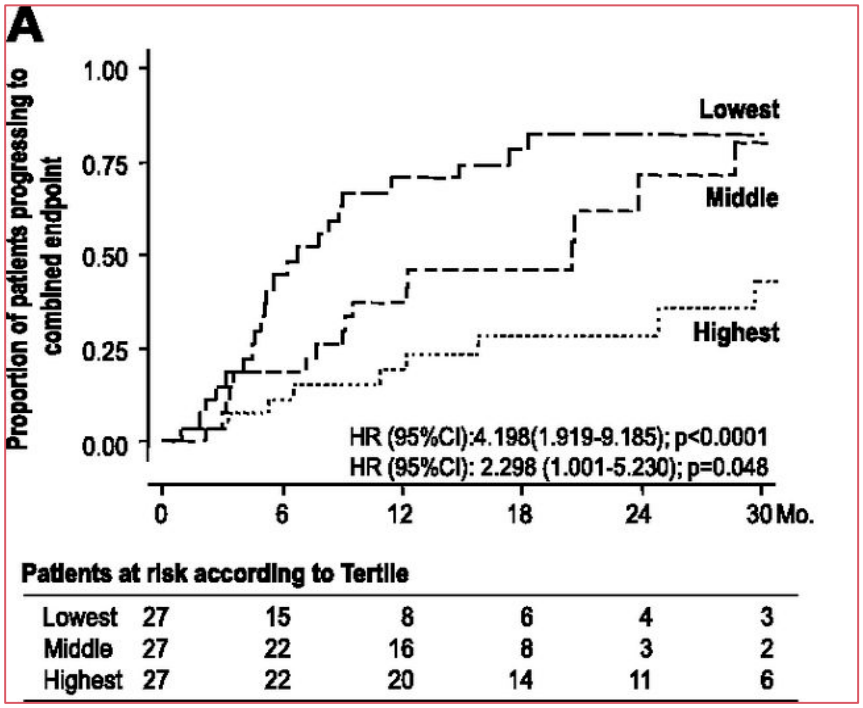
- Cyclophosphamide: RCT → remissions+ renal endpoint+
- Rituximab: RCT → remissions+ renal endpoint-
- Calcineurininhibitors: RCT → remissions+ renal endpoint-

Problem: new studies with 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: State of the Art

anti-PLA2R antibodies predict response to therapy



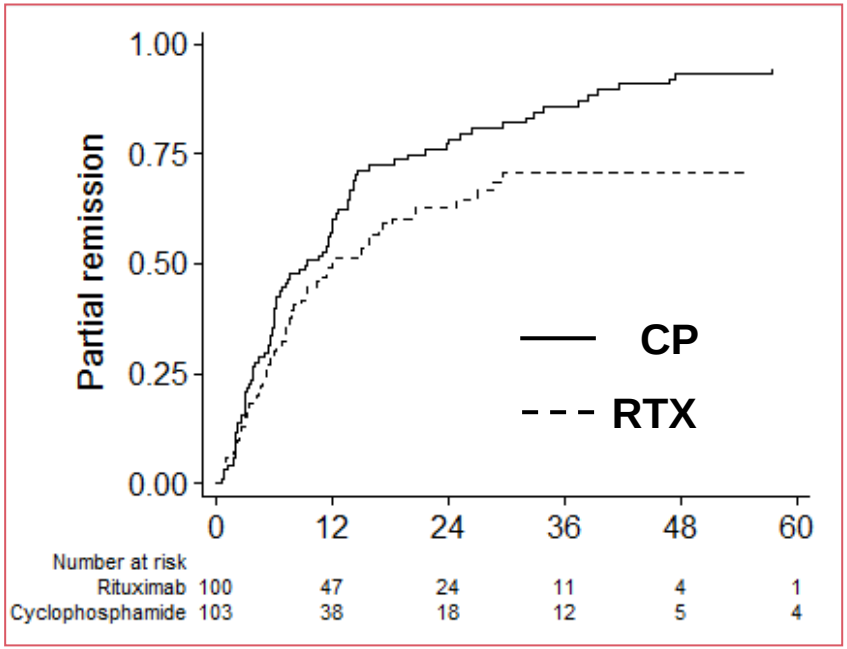
Rituximab treated patients, tertiles of PLA2Rab

Ruggenenti P et al. Anti-Phospholipase A2 Receptor Antibody Titer Predicts Post-Rituximab Outcome of Membranous Nephropathy. J Am Soc Nephrol. 2015;26(10):2545-58.

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

Membranous Nephropathy: State of the Art

Are all immunosuppressives equal?



Comparison of Dutch and Italian cohort; Rituximab (RTX) fewer (serious) adverse events, less partial remissions vs cyclophosphamide (CP).

Ruggenenti P et al. Anti-Phospholipase A2 Receptor Antibody Titer Predicts Post-Rituximab Outcome of Membranous Nephropathy. J Am Soc Nephrol. 2015;26(10):2545-58.

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

Membranous Nephropathy: new RCTs?

- **MENTOR trial (VS, Canada):**
- RCT comparison of 12 months Rituximab versus Ciclosporin: presented at ASN 2017.
- End-point: persistent remission at 24 months: Rituximab >> CsA
- No renal end-points! Not published! B-cells?

- **STARMEN trial (Spain, Netherlands):**
- RCT comparison of Cyclophosphamide + steroids versus tacrolimus + Rituximab
- End-point: remission at 24 months (no renal end-point)
- Expected: november 2019

Membranous Nephropathy: what is new?

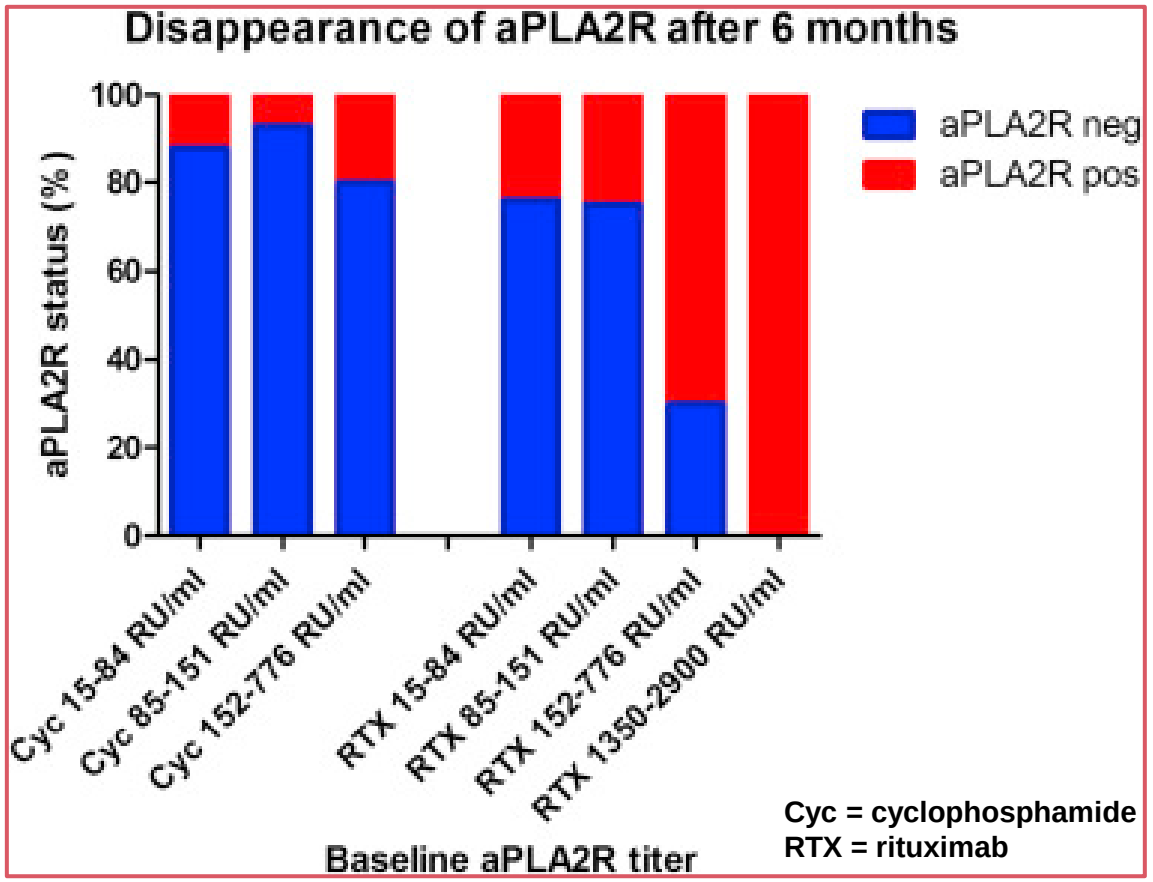
- Cyclophosphamide versus Rituximab:
- Comparison of immunological remission rate
- Cyclophosphamide treated (Nijmegen) versus Rituximab treated (Paris)

Van de Logt AE et al. Immunological remission in PLA2R-antibody-associated membranous nephropathy: cyclophosphamide versus rituximab. Kidney International 2018; 93: 1016-1017

Membranous Nephropathy: what is new?

- Cyclophosphamide versus Rituximab:

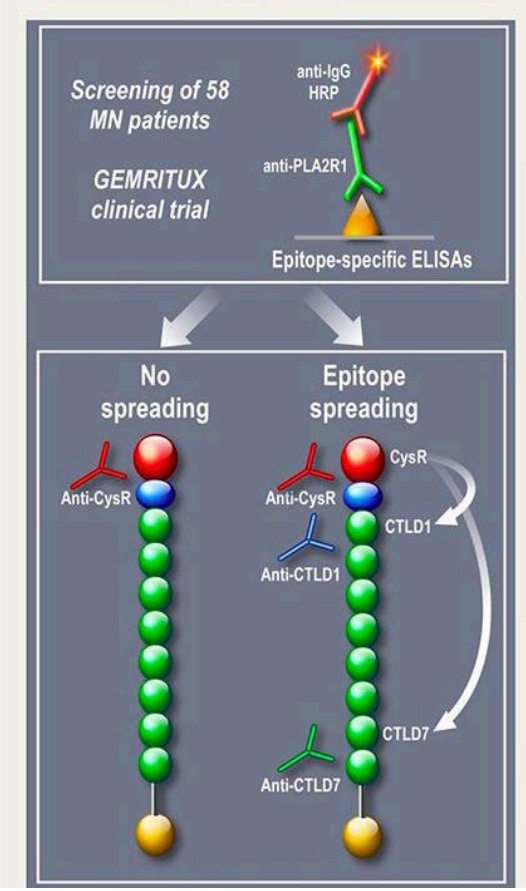
Cyclophosphamide > Rituximab in patients with high PLA2Rab



Van de Logt AE et al. Immunological remission in PLA2R-antibody-associated membranous nephropathy: cyclophosphamide versus rituximab. Kidney International 2018; 93: 1016-1017

Membranous Nephropathy: what is new?

- Anti-PLA2R antibodies: epitope-specificity as predictors?



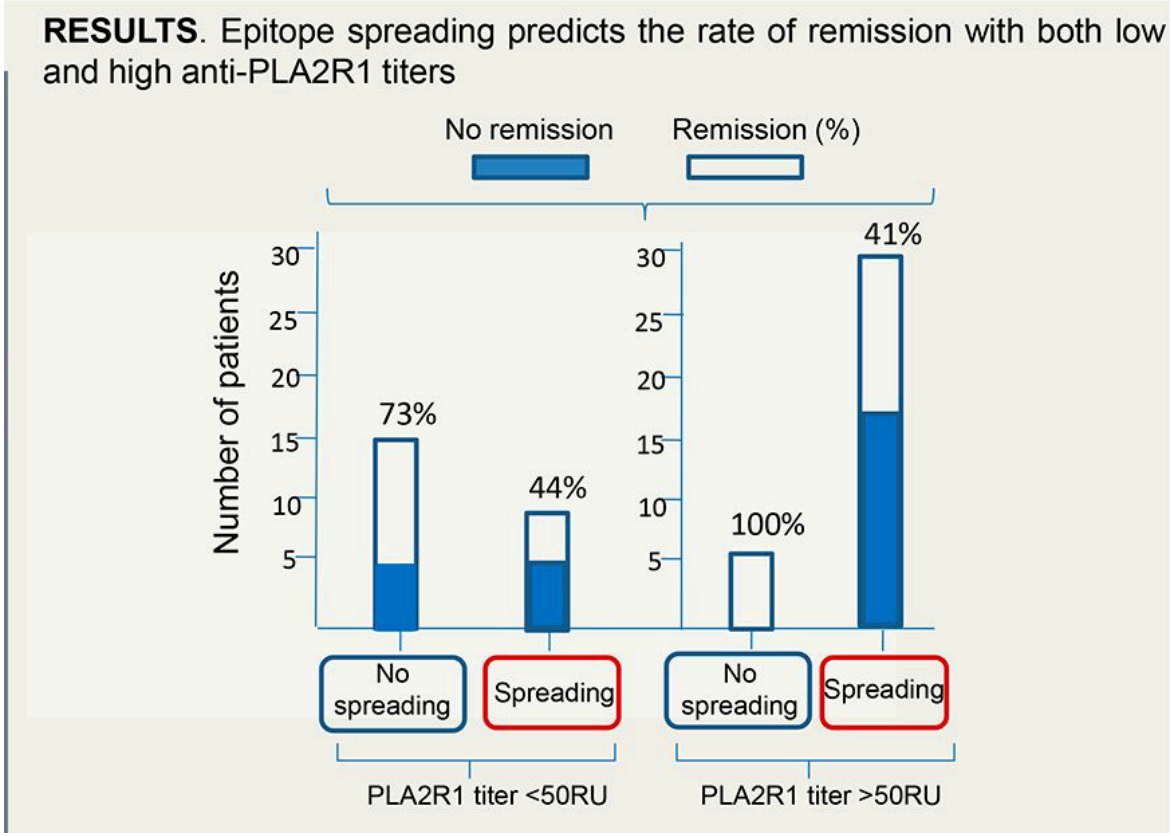
Anti-CysR = non spreading
Anti-CysR + anti CTLD1/7 = spreading

	No spreading (n=20)	spreading (n=38)
Age (yrs)	59 (44-62)	52(41-64)
Male/Female	15/5	27/11
PLA2Rab titer (RU/ml)	**32 (18-54)**	**377 (76-747)**
sCreatinine (µmol/l)		
sAlbumin (g/l)	22 (20-26)	21 (18-25)
uPCR (g/g)	7.9 (3.5-8.5)	8.3 (6.2-10.4)

Seitz-Polski B et al. Phospholipase A2 receptor 1 epitope spreading at baseline predicts reduced likelihood of remission of membranous nephropathy. JASN 2018; 29: 401-408

Membranous Nephropathy: what is new?

„Epitope spreading at baseline was associated with a decreased remission rate, independent from age, proteinuria, sex, treatment, and anti-PLA2Rab titer“



Seitz-Polski B et al. Phospholipase A2 receptor 1 epitope spreading at baseline predicts reduced likelihood of remission of membranous nephropathy. JASN 2018; 29: 401-408

Membranous Nephropathy: what is new?

Comments:

- ***Small cohort***
- ***Added value over anti-PLA2Rab titer unclear***
- ***Epitope assay: not available***
- ***Accuracy?***

Control group

	No spreading	Spreading
Remission	8	5
No remission	3	13

Rituximab

	No spreading	Spreading
Remission	8	11
No remission	1	9

Spreading predicts progression:
Specificity 72%

Rituximab is not very effective in spreaders: 55% remission rate

Seitz-Polski B et al. Phospholipase A2 receptor 1 epitope spreading at baseline predicts reduced likelihood of remission of membranous nephropathy. JASN 2018; 29: 401-408

Take-Home Message

- Results of MENTOR and STARMEN needed
- Rituximab is not effective in patients with high PLA2R antibody levels
- Usefulness of epitope specific antibody assays unproven → validation/accuracy
- Cyclophosphamide: still usefull (although not in all patients)

Primary Glomerulonephritis: IgA nephropathy

IgA Nephropathy: State of the Art

- Maximal supportive therapy is needed in IgAN. Target low BP (< 125/75 mmHg), don‘t be afraid for ACEi+ARB, consider dietary sodium, lower cholesterol

- Prednisone reduces proteinuria and hematuria in IgAN (both important predictors of outcome)

- Prednisone attenuates decrease of eGFR in progressive IgAN

→ ***Consider prednisone in progressive IgAN (ΔeGFR > 3ml/min/yr; marked proteinuria > 1.5 – 2.5 g/day)***

- Budosenide reduces proteinuria; long-term benefits ??

Nephro-Update 2017

IgA Nephropathy: take home message

- No trials in 2018 → 2017 conclusions still hold.

- Budosenide: phase 3 trial is ongoing

- Ongoing studies:
  - role of complement, use of complement-inhibitors
  - Role of B cell activation factors

Primary Glomerulonephritis: Minimal Change Disease/FSGS

Minimal change disease/FSGS: state of the Art

- Most common cause of idiopathic nephrotic syndrome
- **Steroid sensitive** → frequent relapses/steroid dependence → steroid side effects
- Alternative drugs in SSNS: tacrolimus, mycophenolate mofetil, rituximab
- **Steroid resistant** → tacrolimus
- **Steroid resistant:** 25% genetic cause (age < 25 years)

Minimal change disease/FSGS: what is new?

RITURNS: Rituximab for relapse prevention in nephrotic syndrome

- Children 3-16 years
- Steroid dependent nephrotic sydrome, in remission
- eGFR > 80 ml/min/1.73m^2

treatment

- Tacrolimus: 0.2 mg/kg/day, target trough level 5-7 ng/ml

+ prednison alternate day with taper to 0 after 6 months

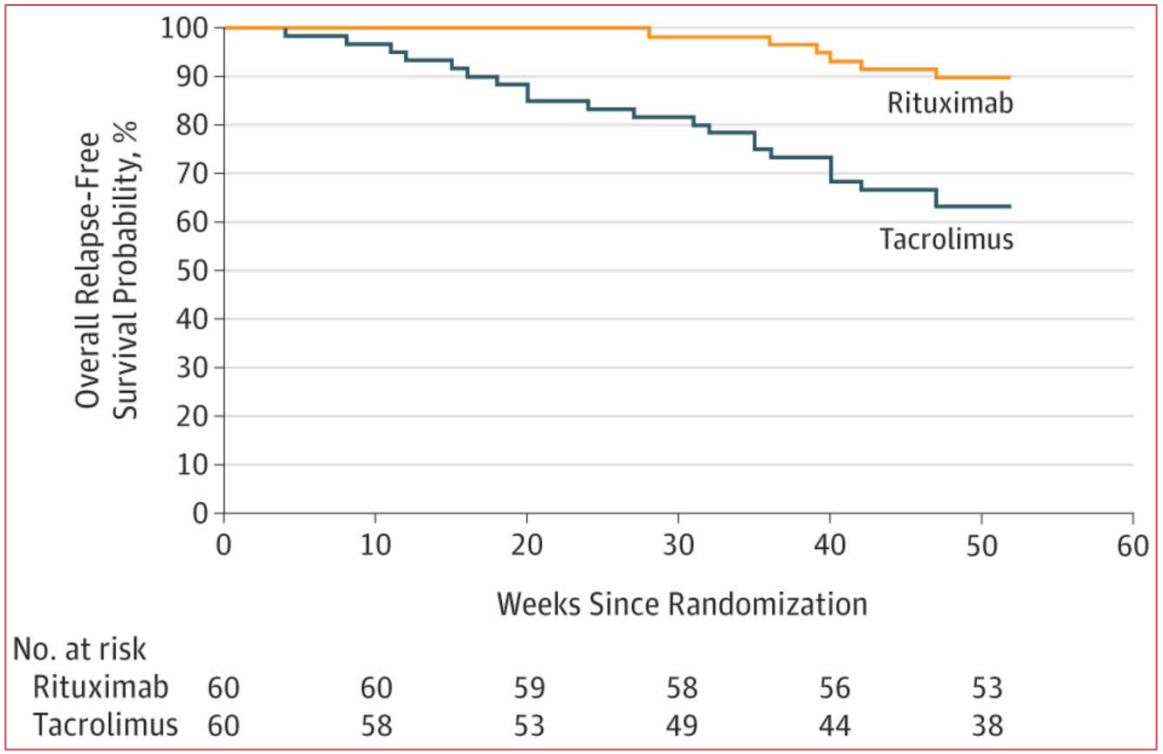
- Rituximab: 2 infusions of 375/m^2 + prednisone 4 weeks

- 5/2015 – 9/2015: 176 patients screened, 120 randomized

Basu B et al Efficacy of Rituximab vs tacrolimus in pediatric corticosteroid-dependent nephrotic syndrome: a randomized clinical trial. JAMA Pediatr 2018 ;172: 757

Minimal change disease/FSGS: what is new?

- End-point: relapse-free survival at 12 months



- Rituximab: lower prednisone dose

Basu B et al Efficacy of Rituximab vs tacrolimus in pediatric corticosteroid-dependent nephrotic syndrome: a randomized clinical trial . JAMA Pediatr 2018 : 172: 757

Minimal change disease/FSGS: what is new?

Levamisole versus placebo in SSNS

- Children 2 – 18 years
- Steroid sensitive nephrotic sydrome, in remission

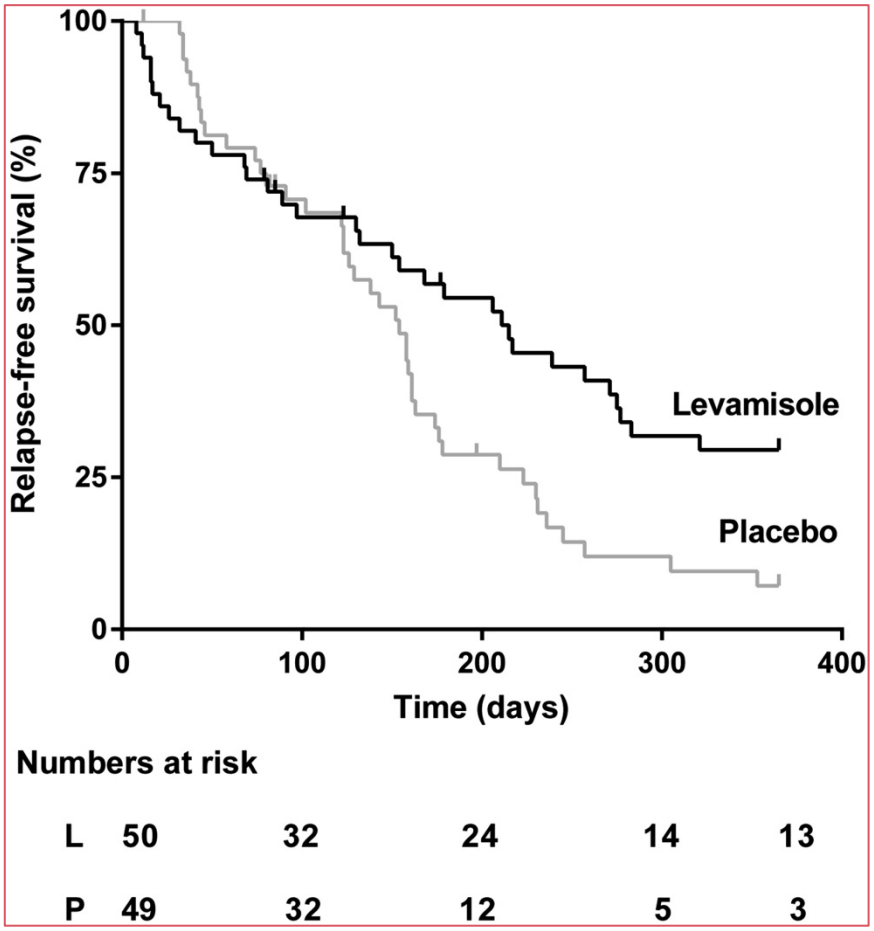
treatment

- Levamisole 2.5 mg/kg alternate days , max 150 mg + prednisone (60mg/m^2 every other day, with taper to 0 after 16 weeks)
- Placebo + prednisone

- 13 sites, 6 countries, 10/2007 – 03/2012: 103 patients

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

Minimal change disease/FSGS: what is new



Fewer relapses with levamisole
Few side effects (neutropenia, vasculitis)

However:

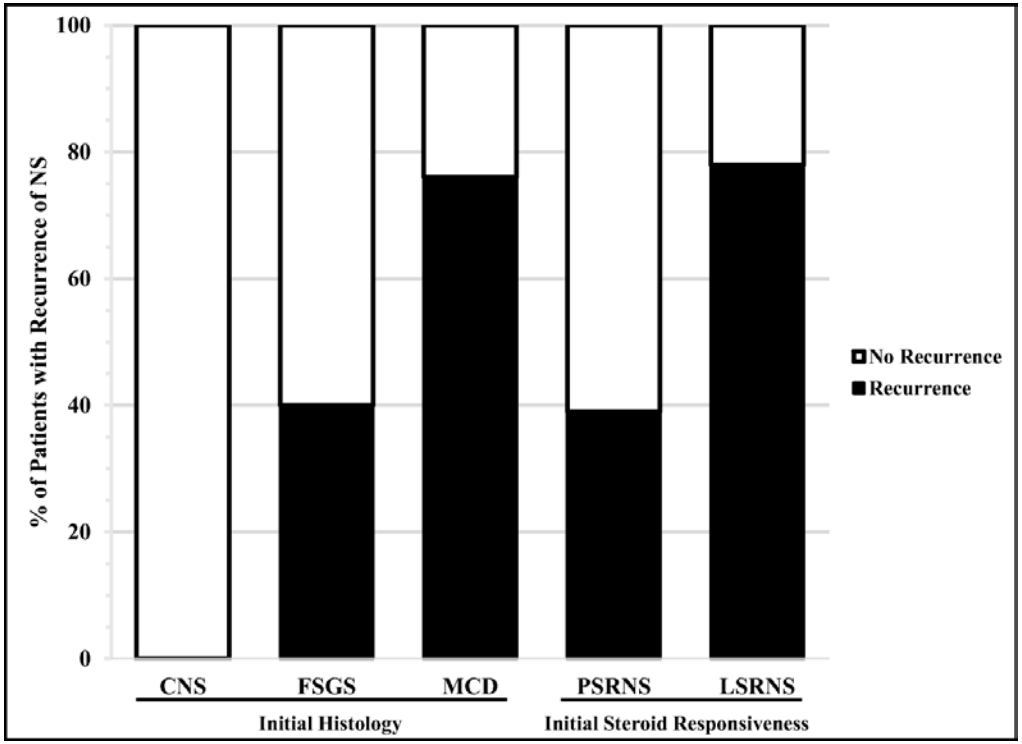
SAE: Levamisole 9, Plac 1

Basu 2015:
Relapse free survival with levamisole lower than with MMF (16% vs 38%)

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
Basu B et al Efficacy and safety of mycophenolate mofetil versus levamisole in children and adolescents with idiopathic nephrotic syndrome: results of a randomized clinical trial. AJKD doi10.1053/j.ajkd 2015; 04.048

Minimal change disease/FSGS: what is new

- **Steroid sensitive** → secondary steroid resistance
- Is Late steroid resistance a risk factor for recurrence after transplantation?
- Multicenter cohort study of SRNS, who received a transplant



Pelletier JH et al. Recurrence of nephrotic syndrome following kidney transplantation is associated with initial native kidney biopsy findings. Pediatric Nephrology 2018 Jul 7 online

MCD/FSGS Take-Home Message

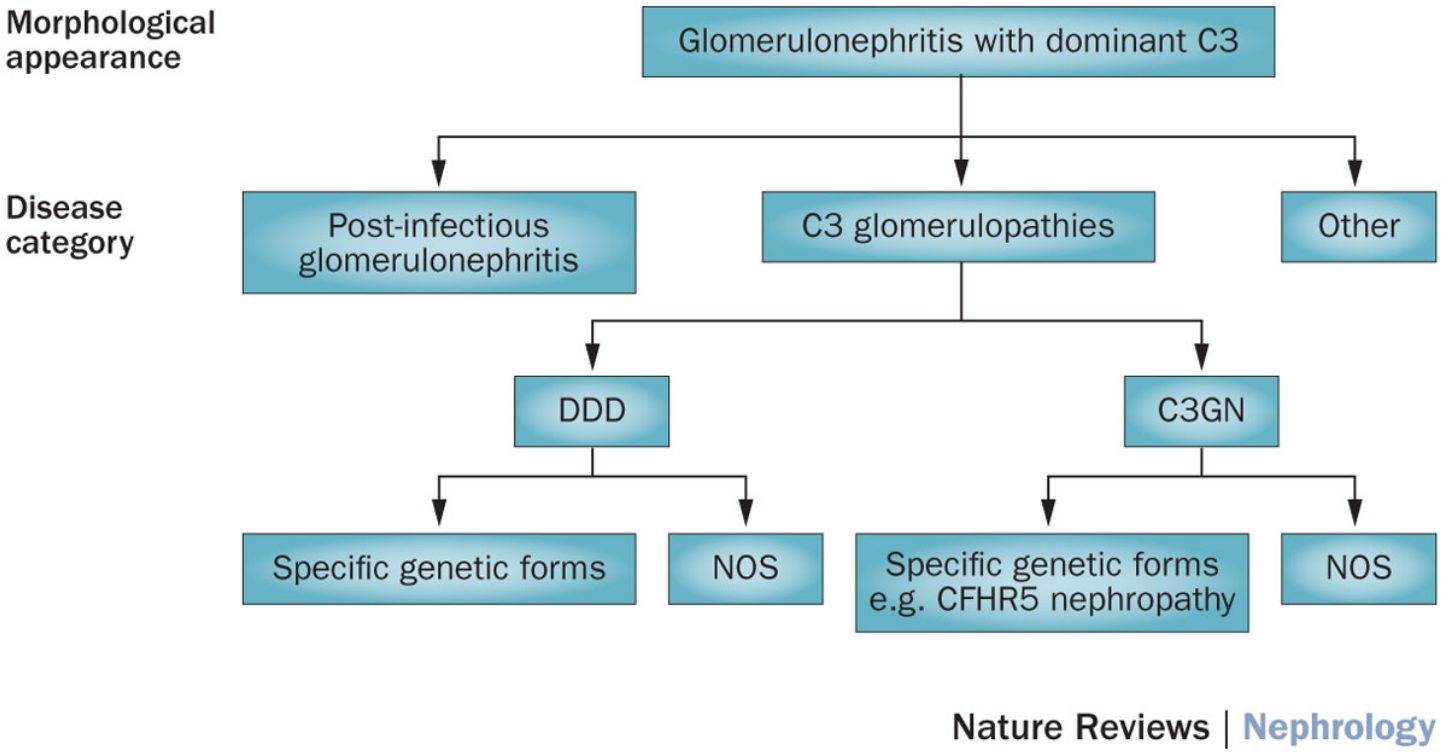
- Steroid sensitive idiopathic nephrotic syndrome: most patients suffer form steroid side effects
- There are many alternative (steroid) sparing drugs.
- None is curative, relapses occur during or after treatment.
- Rituximab > tacrolimus > MMF > levamisole
- Therapeutic drug monitoring??

- Secondary steroid resistance: a predictor of recurrent disease after transplantation

C3 glomerulopathy “idiopathic“

C3 glomerulopathy: State of the Art

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

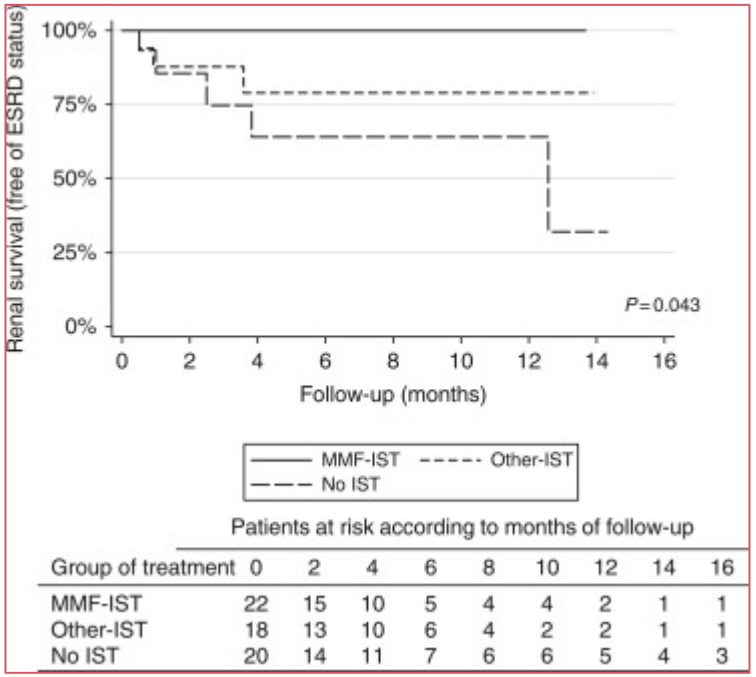


Cook, H. T. & Pickering, M. C. (2014) Histopathology of MPGN and C3 glomerulopathies. *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2014.217

C3 glomerulopathy: what is new-treatment

- C3 glomerulopathy: treatment not evidence based
- In 2015 Spanish study suggested efficacy of MMF

	MMF (n=22)
Age (yrs)	35 (13-66)
Male/Female	14/8
C3Nef	48%
Low C3	15 (68%)
Nephrotic	17 (77%)
eGFR (ml/min/1.73m^2)	67 (23-119)
Proteinuria (g/day)	6.5 (3.9-8.6)



Rabasco C et al. Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. Kidney International 2015; 88: 1153-1160

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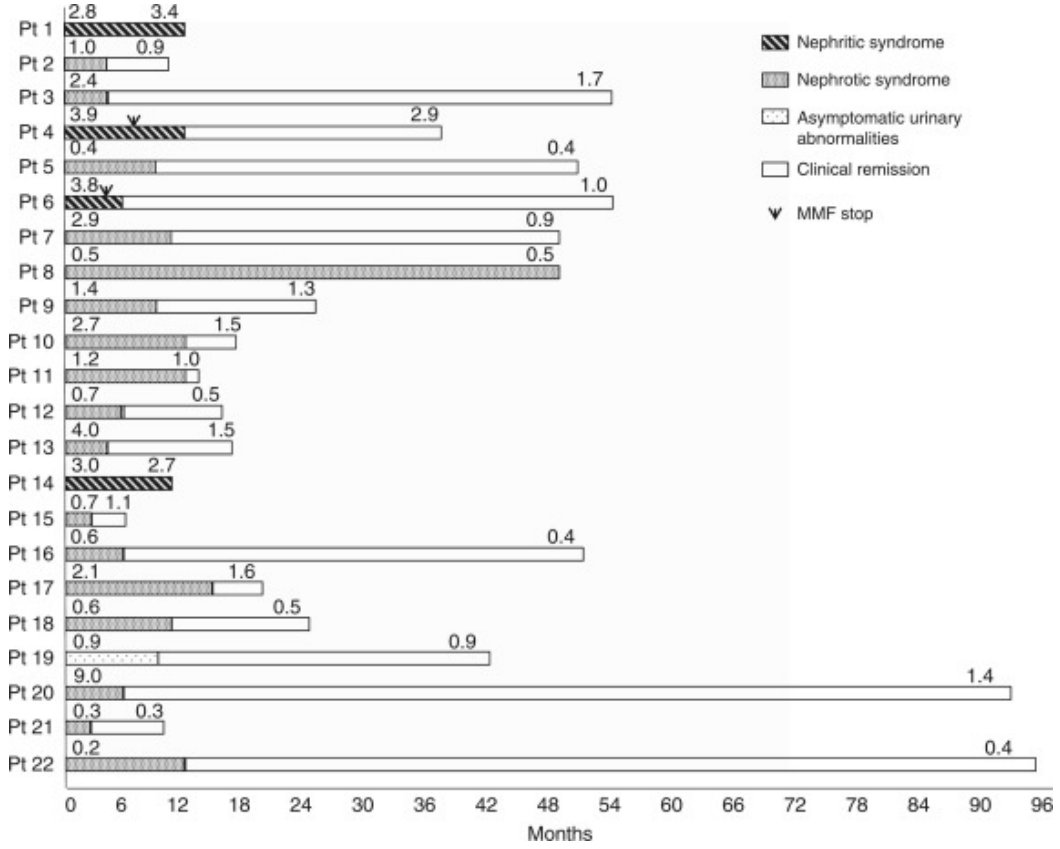


mycophenolate mofetil:
Initial dose 0.75-2g/day
Continued treatment in all but 2 patients
All patients started prednisone 1g/day

6 relapses during dose reduction

C3NeF predicts?
Rem 8/10 + vs 3/8 – (overall)

Rabasco C et al. Effectiveness of mycophenolate mofetil in C3 glomerulonephritis. Kidney International 2015; 88: 1153-1160

C3 glomerulopathy: what is new-treatment

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

	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/1.73m^2)	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

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

C3 glomerulopathy: what is new-treatment

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

	Responder (n=20)	Non-responder (n=10)
Age (yrs)	24 (18-28)	27(19-44)
Male/Female	11/9	6/4
Low C3	70%	70%
Nephrotic	5 (25%)	4 (40%)
eGFR (ml/min/1.73m^2)	67 (54-103)	62 (30-89)
Proteinuria (g/g)	3.2(1.7-6.7)	5.0 (2.8 – 8.9)

Response rate 67%; relapse after withdrawal 50% (4/8). Better response in patients with elevated MAC? Increased 8/9 vs normal 2/4

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

C3 glomerulopathy: what is new-treatment

- Eculizumab in C3GN? Retrospective case series of eculizumab treated patients 2010-2016 France+Québec

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

C3 glomerulopathy: what is new-treatment

- Eculizumab in C3GN: predictors of response?

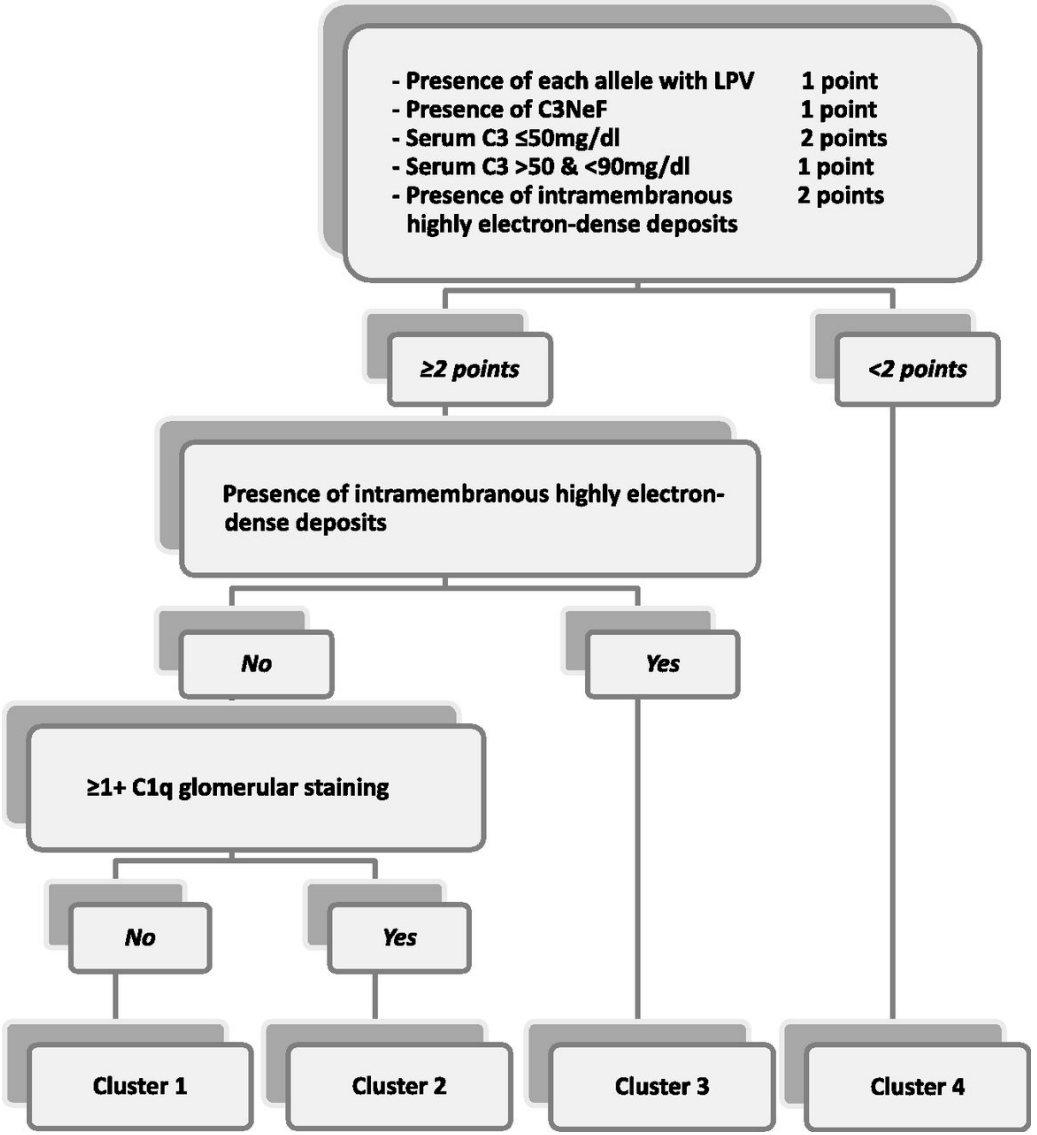
	Global response (n=6)	Partial response (n=6)	No response (n=14)
Screat (mg/dl)	4.8 (0.5-6)	0.7 (0.6-1.1)	1.2 (0.2-9.9)
UPCR (g/g)	9.4 (0.24 – 12)	3.9 (0.4-6.2)	3.0 (1.3 -10)
RPGN	5 (83%)	0 (0%)	2 (14%)
Crescents > 25%	4 (66%)	0 (0%)	0 (0%)
Interstitial fibrosis > 25%	3 (50%)	1 (20%)	1 (11%)

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

C3 glomerulopathy: what is new-diagnosis

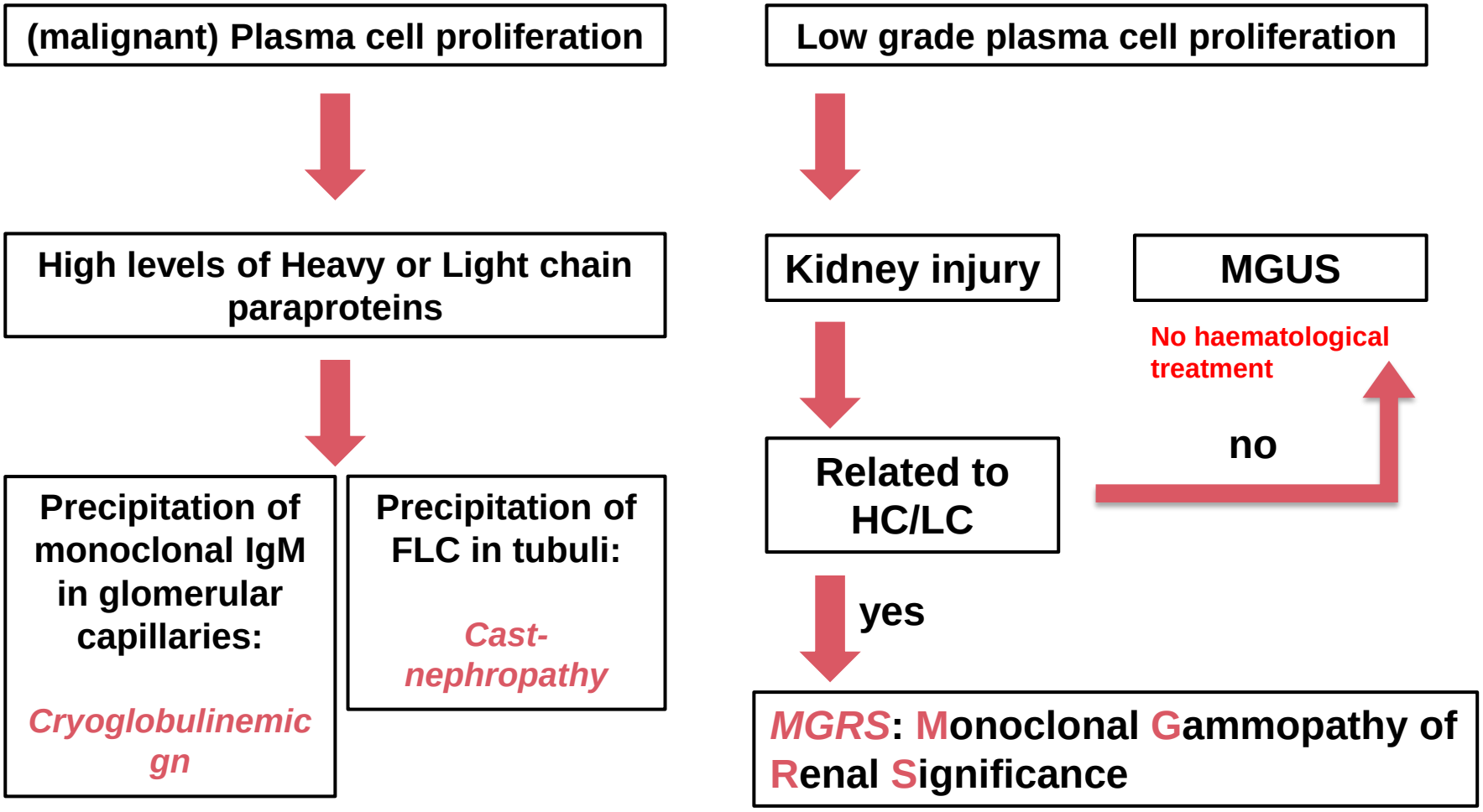
- C3 glomerulopathy: not always **dominant** C3 (vs IgG)
- Clusteranalysis of patients with C3GN or Immunecomplex MPGN from Italian registry
- Parameters: complement gene/antibodies, complement levels, electronmicroscopy. Immunofluorescence.
- Identified 4 clusters



Iatropoulos P et al. Cluster analysis identifies distinct pathogenetic patterns in C3 glomerulopathies/immune-complex mediated MPGN. JASN 2018; 29: 283-294

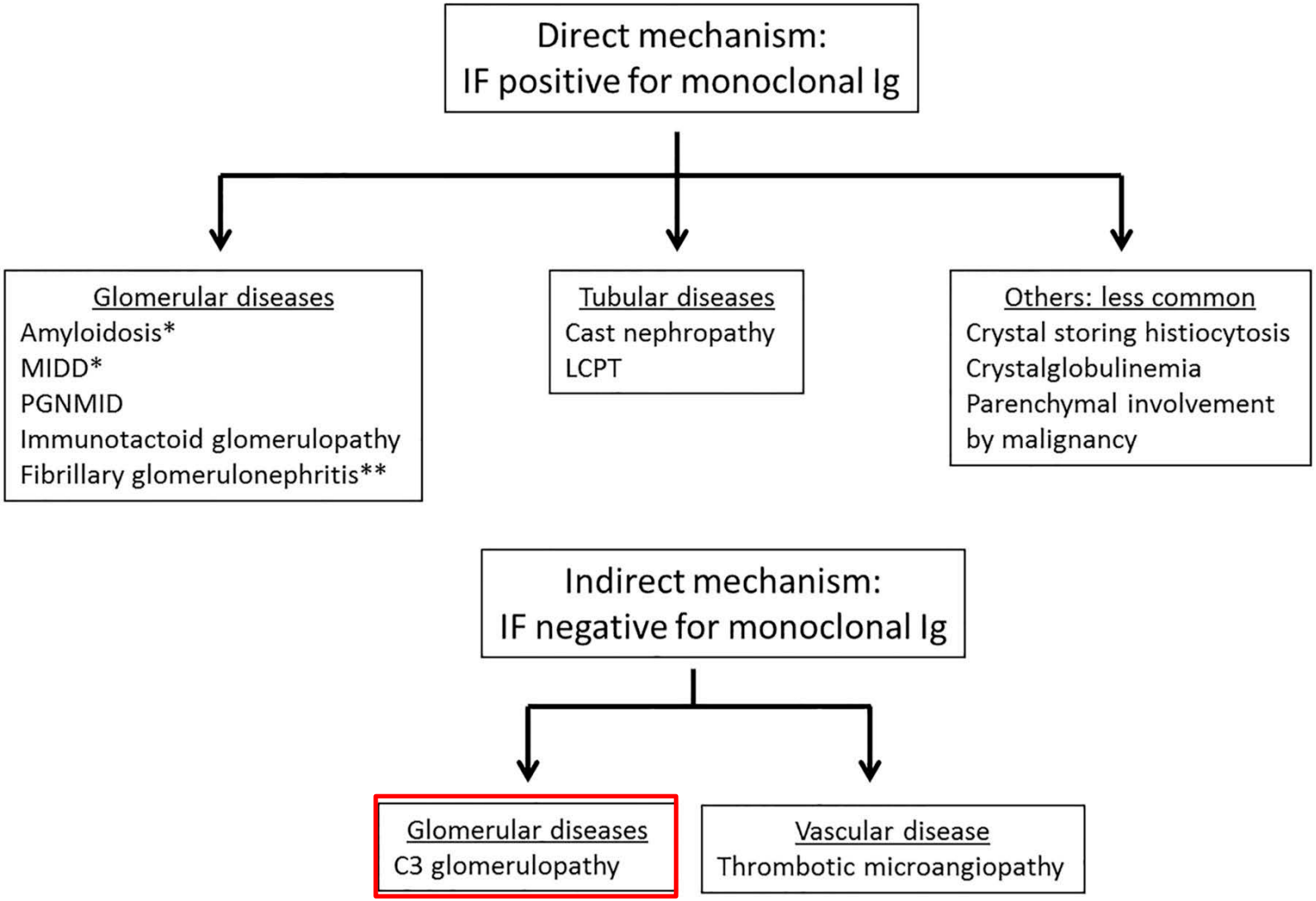
C3 glomerulopathy “paraprotein associated“

Paraproteins and kidney damage: new view



----------Haematological Treatment----------

Pathology of monoclonal Ig–associated renal disease.



Sanjeev Sethi et al. The complexity and heterogeneity of monoclonal immunoglobulin-associated renal diseases. JASN 2018;29:1810-1823

Paraproteins and C3 Nephropathy

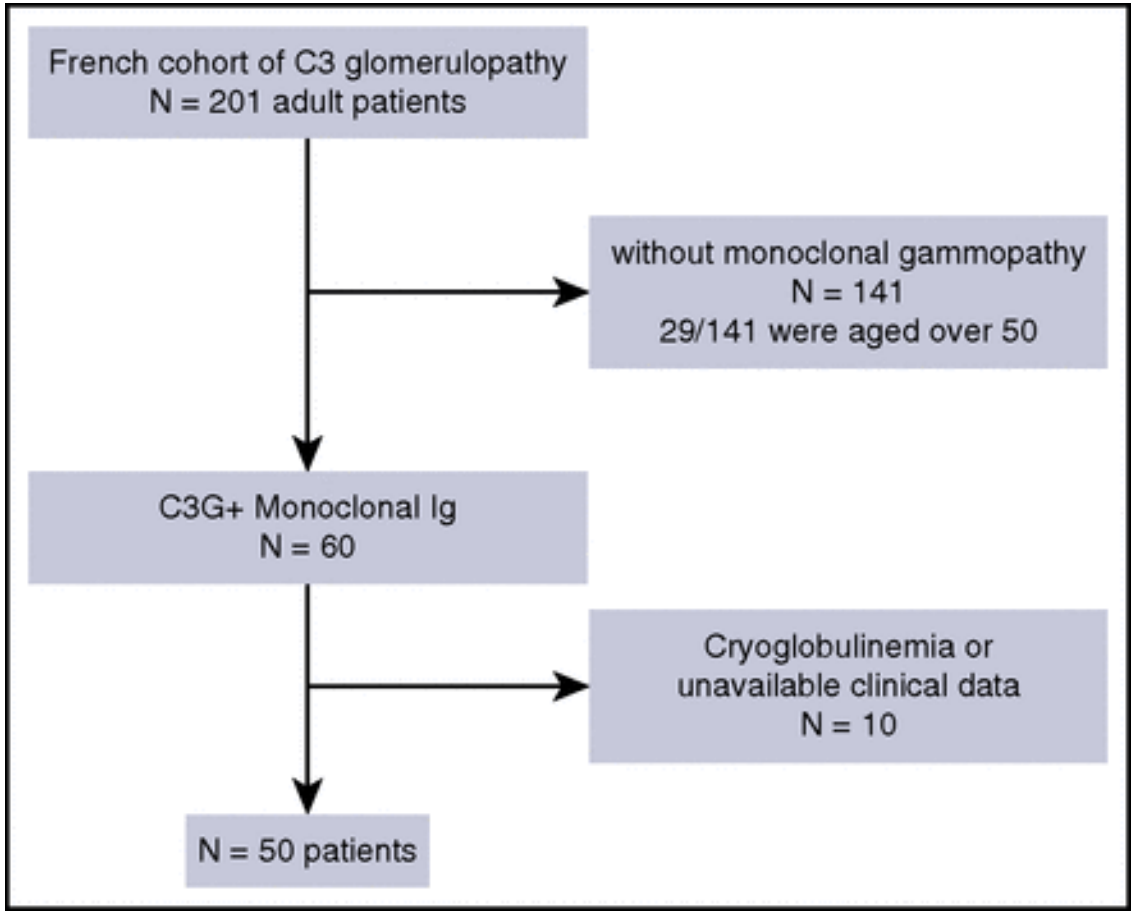
- C3 glomerulonephritis: dominant C3 (≥ 2+ vs IgG)

Disorder	Symptoms	LM	IF	EM	Serum Urine
C3 glomerulopathy with monoclonal gammopathy	Proteinuria Nephrotic Hematuria CKD	MPGN Mesangial proliferative Endocapill. proliferative	Granular C3 **No Ig**	Intramembranous dense deposits (DDD) Subendothelial and mesangial deposits (C3N)	sIEF 100% FLC 75-100%

Bridoux F et al. Diagnosis of monoclonal gammopathy of renal significance. Kidney International 2015, 87: 698–711

MGRS and C3 Nephropathy: what is new

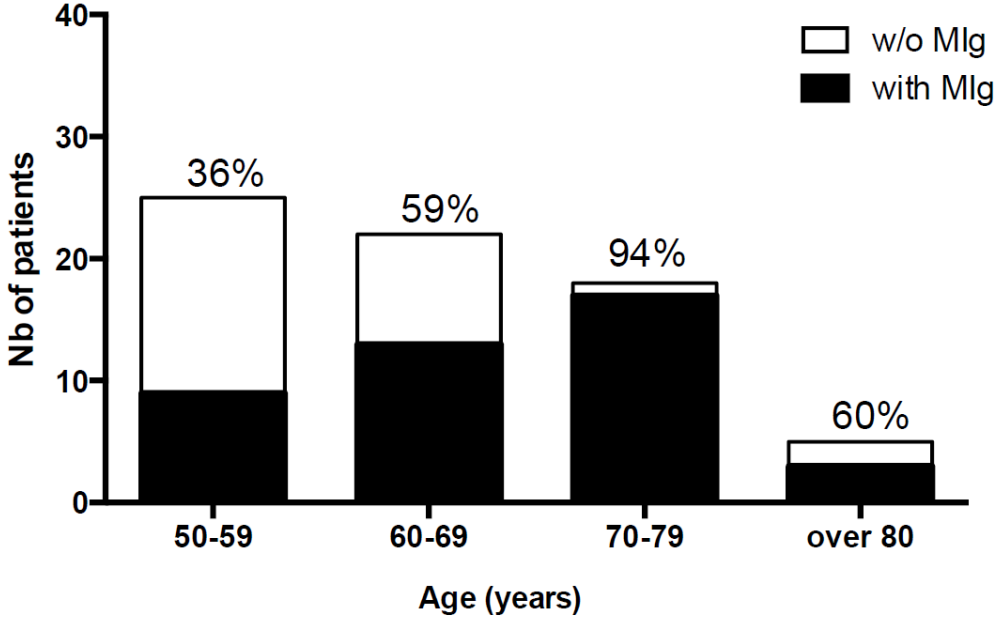
- Retrospective study, French study group.



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

MGRS and C3 Nephropathy: what is new

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

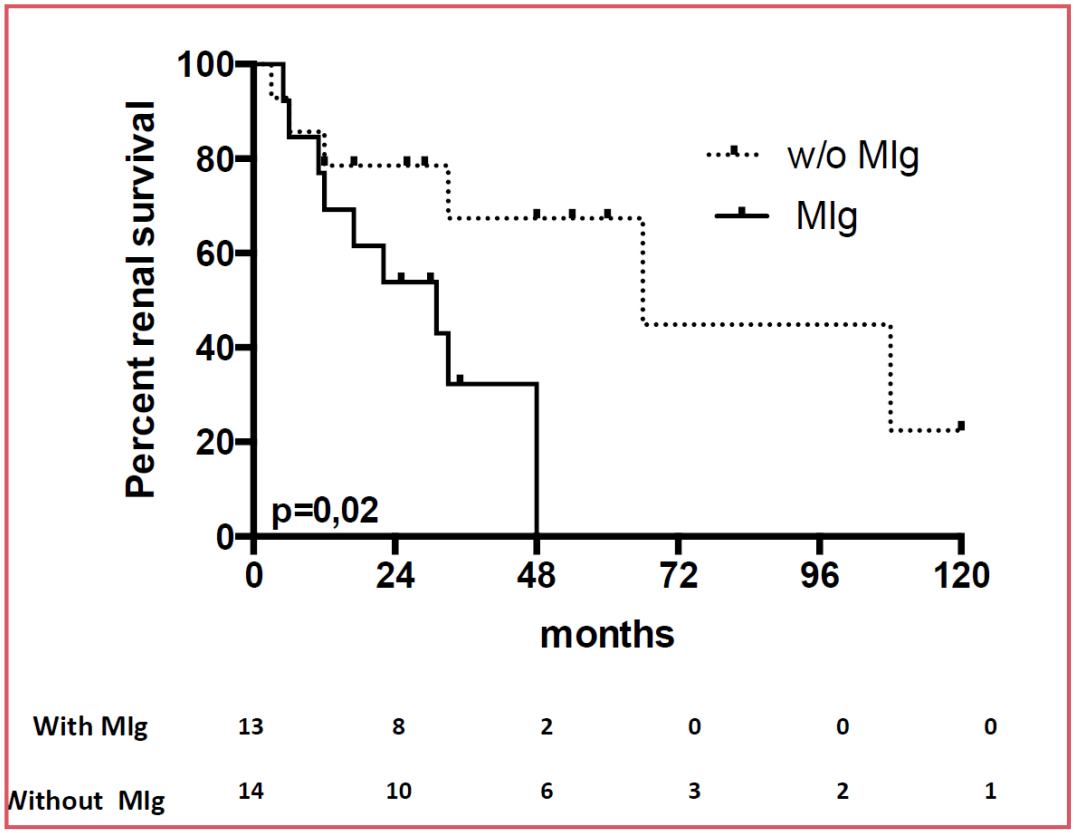
MGRS and C3 glomerulopathy: what is new?

- Retrospective study, French study group, chemotherapy

	Chemotherapy (n=29)	Prednisone+ (n=8)	Conservative (n=13)
Age (yrs)	69 (36-83)	64 (57-70)	60 (40-77)
Screat (umol/l)	158 (66-990)	168 (135-280)	150 (70-317)
Proteinuria (g/day)	4 (0.7-14)	1.7 (0.4-10)	1.8 (0.1-10)
MGRS/sMM/MM/CLL	12/13/2/2	7/1/0/0	11/1/0/1
Abnormal FLC	55%	67%	43%
mIG (g/l)	11 (2-38)	6 (2-15)	9 (3-30)
Low C3	48%	38%	46%
Elevated C5b-9	83%	86%	67%
C3NeF/antiCFH	1//4	1//3	1//2

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

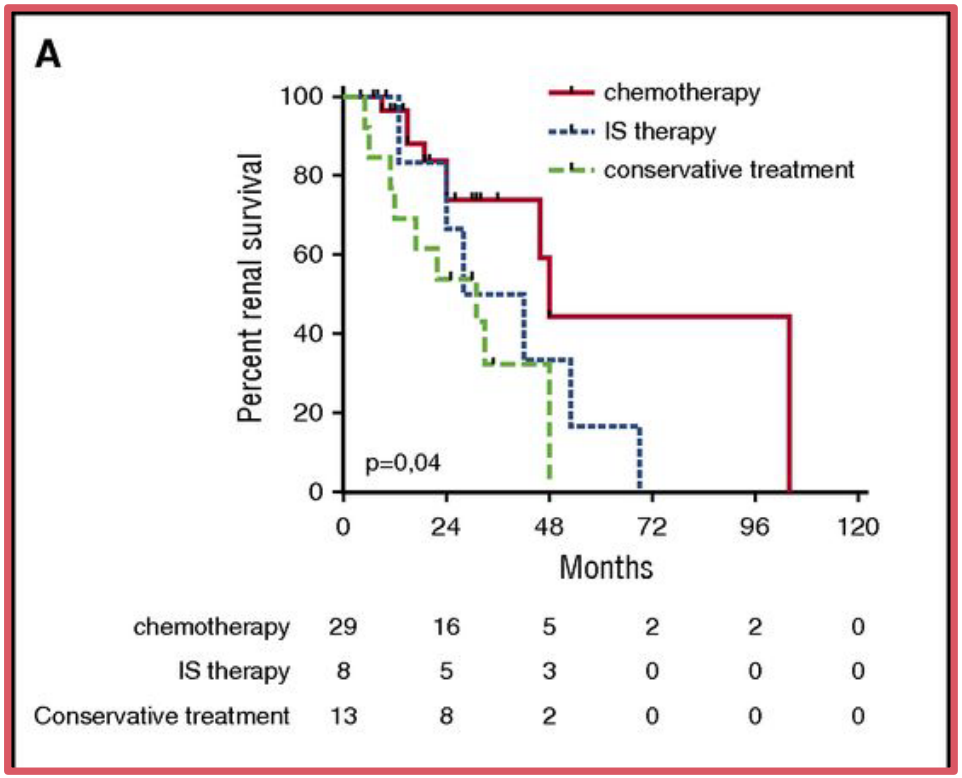
MGRS and C3 Nephropathy: what is new

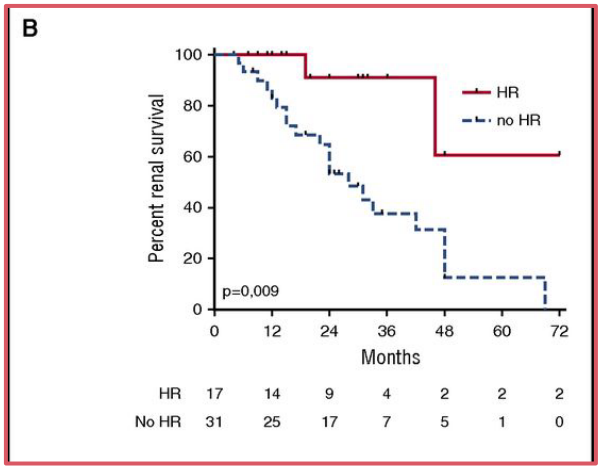


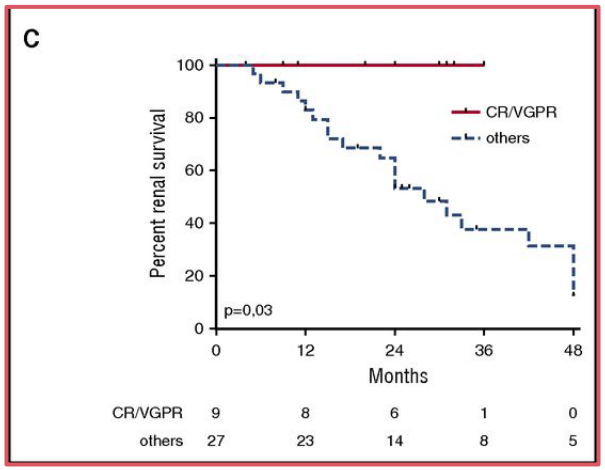
No treatment: outcome is worse in C3GN associated with paraprotein

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

MGRS and C3 Nephropathy: what is new







Bcell directed therapy improves outcome; hematological remission → renal remission

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

C3-nephropathy Take-Home Message

- Definition of C3GN: *presence of IgG or C1q does not exclude C3GN → expert pathologist!*
- C3GN: *paraprotein-associated in patients > 50 years*
- Idiopathic C3GN:
  - *Treatment: MMF + prednisone (outcome in studies biased)*
  - *Eculizumab: maybe effective in RPGN + crescents*
  - *New complement inhibitors are coming (factor D/C5aR)*
  - *→ refer patients for study*
- Paraprotein-associated C3GN:
  - *Haematological remission should be the goal*
  - *Not all patients need therapy (age/progression rate/risks)*

Cast-nephropathy

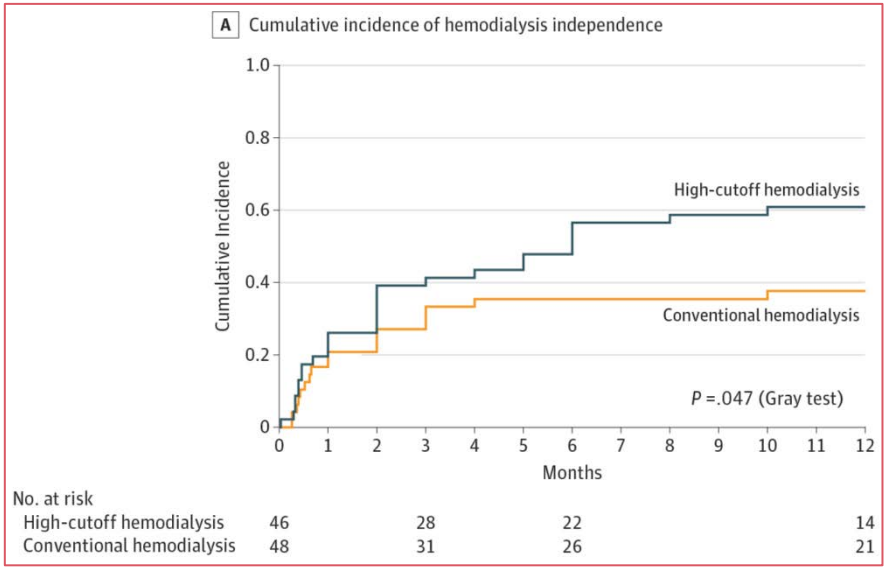
Not a glomerular disease
Paraprotein associated – not MGRS

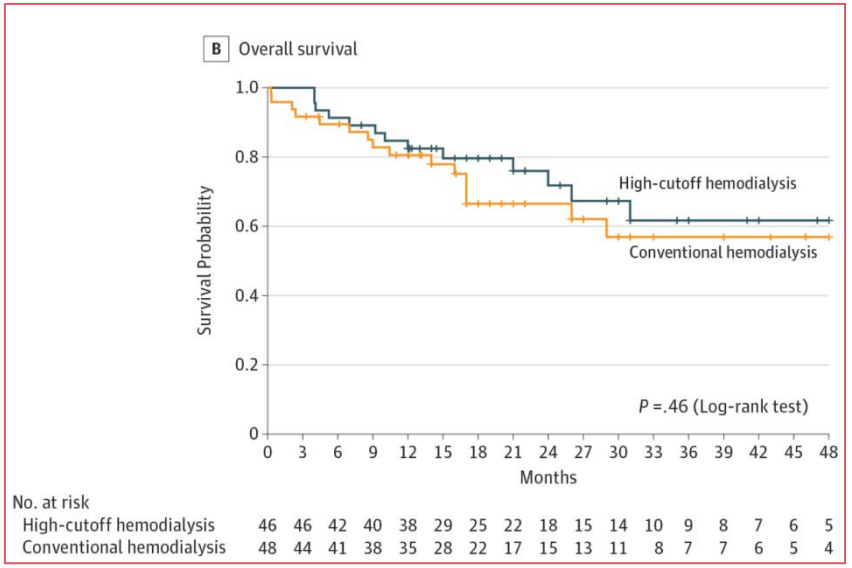
Cast nephropathy: state of the Art

- Most common cause of kidney involvement in MM
- Serum Free Light Chains mostly above 1000 mg/L
- Mild proteinuria (predominantly LC)
- Urinary protein +, Albustix – suggestive for LC
- Often AKI due to tubular obstruction by light chain casts
- Cast formation enhanced by dehydration, triggered by hypercalcemia, infection, NSAID or iv contrast
- Casts consists of LC and Tamm-Horsfall protein secreted in ascending limb of loop of Henle
- Obstructed tubules cause extensive TIN

Cast nephropathy: what is new?

Results:





The primary end-point: no difference! 41.3% HCO vs 33.3% CHD

Conclusions and Relevance Among patients with myeloma cast nephropathy treated with a bortezomib-based chemotherapy regimen, the use of high-cutoff hemodialysis compared with conventional hemodialysis did not result in a statistically significant difference in hemodialysis independence at 3 months. However, the study may have been underpowered to identify an early clinically important difference.

Bridoux F et al. Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy. A Randomized clinical trial. JAMA 2017;318: 2099-2110

Cast nephropathy: what is new?

- RCT: dialysis with HCO membrane vs standard membrane; eight sessions of 5 hours within 10 days; Bortezomib+Dexamethasone
- 98 patients included in 48 centers 2011-2016
- Primary end-point: dialysis independence at 3 months

	HCO dialysis (n=46)	Conventional HD (n=48)
Age (yrs)	68.4	68.8
Male/Female	23/23	29/19
Hypertension	50%	63%
Known MGUS/sMM	9%	29%
Screat (mg/dl)	6.4 (5.3-8.1)	7.3 (5.2-9.2)
Known CKD	6%	17%
Serum FLC (mg/l)	6590	5230

Bridoux F et al. Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy. A Randomized clinical trial. JAMA 2017;318: 2099-2110

Cast nephropathy: what is new?

- Results in detail

	HCO dialysis (n=46)	Conventional HD (n=48)	P value
HD independence M3	19 (41.3%)	16 (33.3%)	ns
HD independence M6	26 (56.5%)	17 (35.4%)	0.04
HD independence M12	28 (60.9%)	18 (37.5%)	0.02
Death	9 (20%)	10 (21%)	ns
Hematol. Response M3 Very good partial or complete	41 (89 %) 28 (60 %)	30 (63%) 21 (44%)	0.003 0.22
Hematol. Response M6 Very good partial or complete	36 (78%) 32 (70%)	29 (60%) 23 (48%)	0.06 0.03
ΔsFLC after 3HD (%)	72 (65-80)	34 (16-57)	<0.001
ΔsFLC after 1st cycle(%)	89 (61-99)	71 (22-91)	0.02

ASCT: performed in 13 patients HCO and in 6 patients CHD

Bridoux F et al. Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy. A Randomized clinical trial. JAMA 2017;318: 2099-2110

MGRS and C3 glomerulopathy: what is new?

- Retrospective study, Mayo Clinic, 95 patients with C3GN

	With monoclonal Ig (n=36)	w/o monoclonal Ig (n=59)
Age (yrs)	60 (20-85)	28 (4-84)
Male/female	25/11	28/31
Screat (mg/dl)	1.9 (0.8 – 14.7)	1.3 (0.3-7.9)
Proteinuria (g/day)	3 (0.2-15)	1.7 (0.3-24.2)
MGRS/sMM/MM/CLL/CryoT1	26/2/5/2/1	
Low C3	34%	48%
Elevated C5b-9	83%	86%
C3NeF/antiCFH	46%/12%	38%/17%

Study confirmed better outcome in C3GN without paraprotein; response to B cell targeted therapy: hematological remission predicts outcome.
Response in 7/10 with and 0/5 w/o hematological remission.

Ravindran A et al. C3 glomerulopathy associated with monoclonal IgG is a distinct subtype. Kidney Int 2018;94:178-186

C3 glomerulopathy: what is new-treatment

- Eculizumab in C3GN? Retrospective case series of eculizumab treated patients 2010-2016 France+Québec

	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/1.73m^2)	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

Monoclonal Gammopathy of Renal Significance

Description:

Glomerular/tubular

Organized/non-organized

A search for paraproteins

Serum IEF/immunofixation
urine IEF/ immunofixation
Serum Free light Chains

Kidney Biopsy
LM
IF: paraproteins?
EM

No technique is 100% accurate!
Pronase digestion needed?!

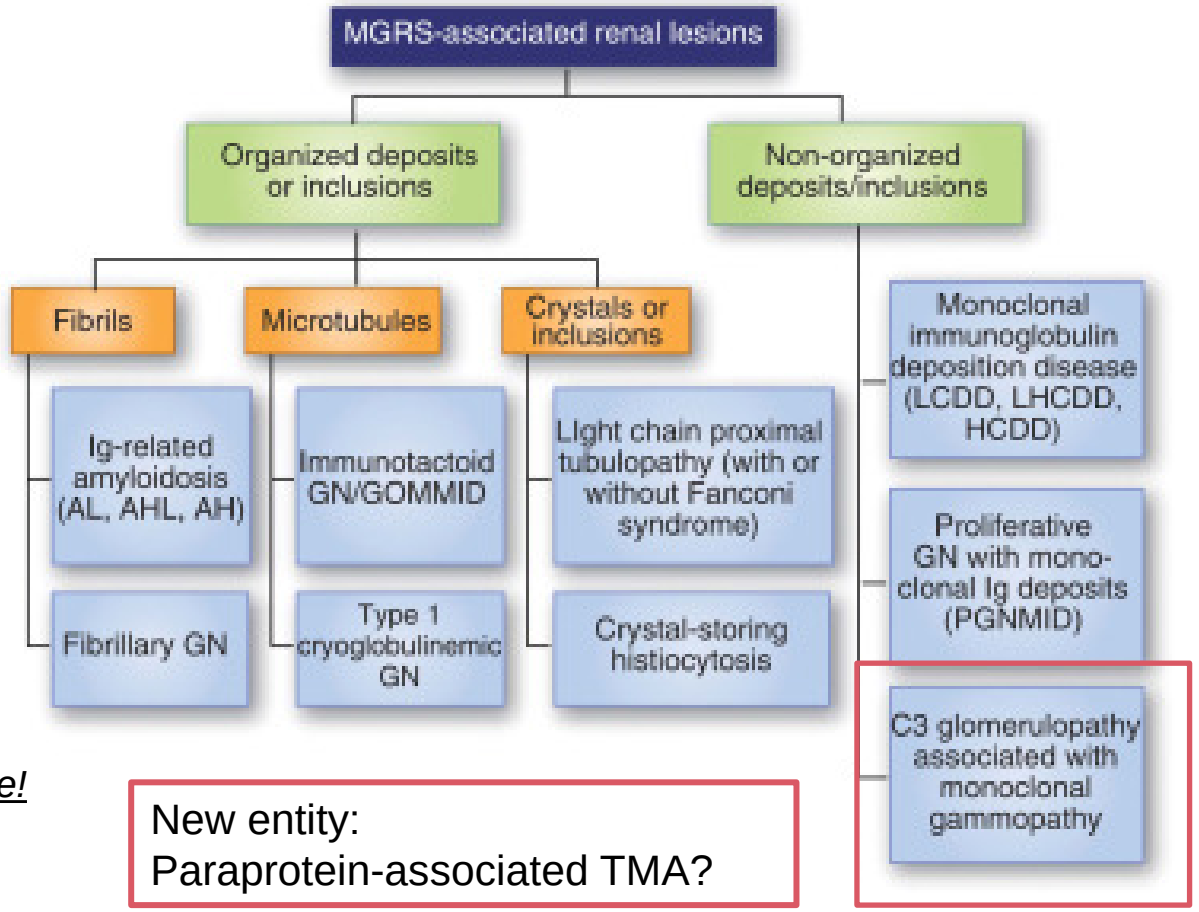


Figure 2. Diagram of MGRS-associated renal lesions. AH, immunoglobulin heavy chain amyloidosis; AHL, immunoglobulin heavy and light chain amyloidosis; AL, immunoglobulin light chain amyloidosis; GN, glomerulonephritis; GOMMID glomerulonephritis with organized microtubular monoclonal immune deposits

Bridoux F et al. Diagnosis of monoclonal gammopathy of renal significance. Kidney International 2015, 87: 698–711

Cast nephropathy: what is new?

- Variables associated with kidney outcome (free of dialysis)

	Odds ratio Univariable	Odds ratio multivariable
Age > 65 yr	0.85 (0.36-2.02)	
CKD pre-existing	0.80 (0.28-2.25)	
Myeloma type Ig vs LC only	2.62 (1.14-6.05)	2.75 (1.11-6.80)
sFLC level (>12000 vs <3000 mg/l)	0.40 (0.12-1.32)	
sFLC < 500 mg/l after 1st cycle	3.0 (1.25-7.18)	2.51 (1.00-6.33)
Treatment group: HCO	2.59 (1.13-5.97)	2.78 (1.13-6.80)

ASCT: performed in 13 patients HCO and in 6 patients CHD

Bridoux F et al. Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy. A Randomized clinical trial. JAMA 2017;318: 2099-2110

Cast nephropathy: what is new?

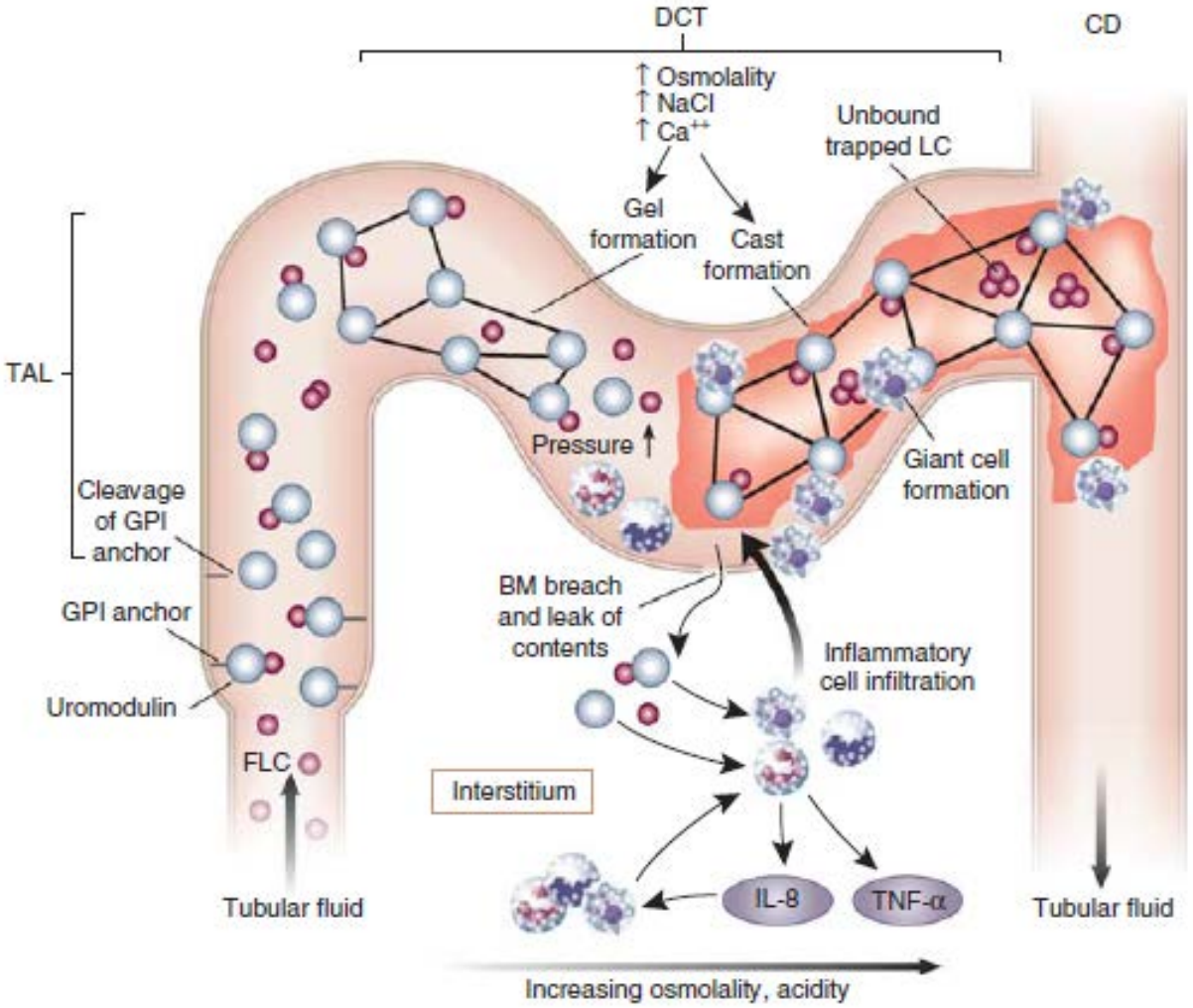
- Results in detail

	HCO dialysis (n=46)	Conventional HD (n=48)	P value
sFLC after 1st cycle < 500 mg/l	20 (43.5%)	15 (31.2%)	0.29
Hematol. Response M3 Very good partial or complete	41 (89 %) 28 (60 %)	30 (63%) 21 (44%)	0.003 0.22
Hematol. Response M6 Very good partial or complete	36 (78%) 32 (70%)	29 (60%) 23 (48%)	0.06 0.03
ΔsFLC after 3HD (%)	72 (65-80)	34 (16-57)	<0.001
ΔsFLC after 1st cycle(%)	89 (61-99)	71 (22-91)	0.02

Why was sFLC after 1st cycle used in the multivariable analysis? Hematological response is more discriminative

Bridoux F et al. Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy. A Randomized clinical trial. JAMA 2017;318: 2099-2110

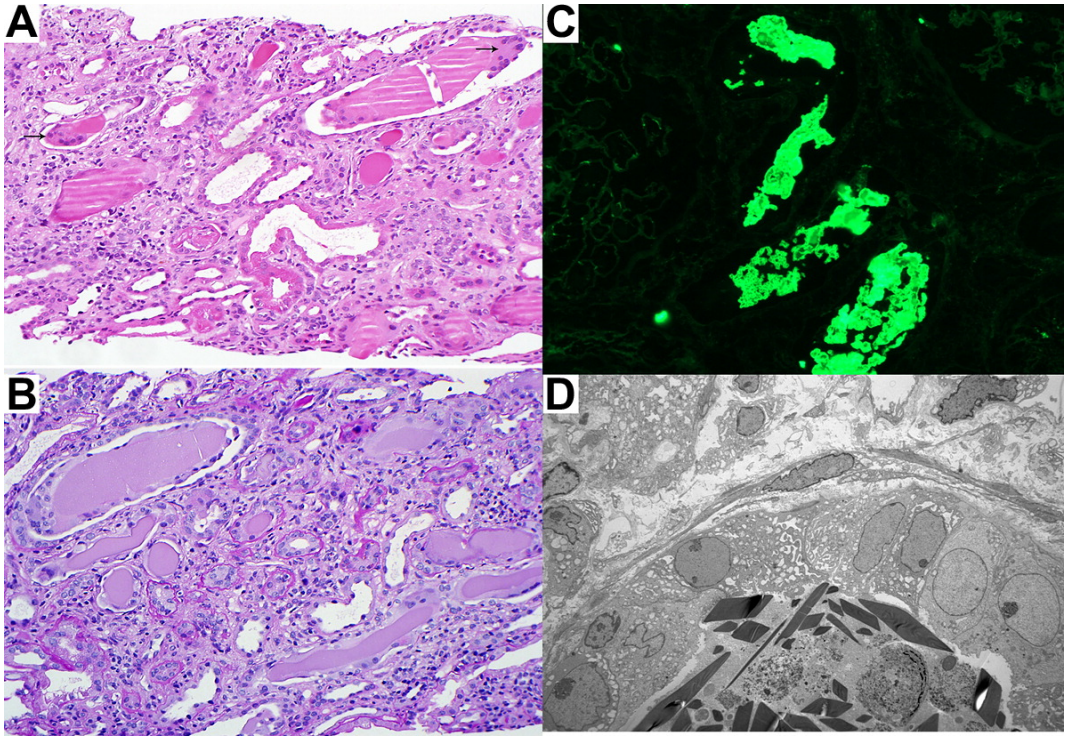
Interactions of FLC in distal nephron



Basnayaka et al. KI 2011; 79: 1289-1301

Cast nephropathy: histology

LM:
Large casts
Hypereosinophilic
Fractured
Giant cell reaction
Interstitial inflammation with predominantly monocytes



IF:
Brightly positive for single LC

EM:
Myeloma casts sometimes contain crystals

Leung & Nasr. Adv Chronic Kidney Disease **2014 21, 36-47**

Cast nephropathy: state of the Art

- “ standard” treatment according guidelines for MM in patients with cast-nephropathy
- Goal: rapid clearance of FLC; 50% reduction in 3 weeks
- In patients with Acute Kidney Injury:
  - Hydration
  - Treat acidosis, treat hypercalcemia, avoid contrast media
- Plasmapheresis: not effective
- Dialysis treatment with a high-cut off filter? Initial studies positive, however Bortezomib not used. Need RCT → The EULITE trial

The EULITE trial in cast-nephropathy

- RCT in patients with AKI (dialysis) and cast-nephropathy
- “ standard” treatment with bortezomib, doxorubicin, dexamethasone
- Experimental group: dialysis with HCO1100 Gambro
- Trial started in 2008, abstract in 2016, ASN 2017
- N = 90 patients

The EULITE trial in cast-nephropathy

- N = 90 patients

- FLC: kappa exp 12000 mg/l control 18000 mg/l
- FLC: lambda exp 6031 mg/l control 8400 mg/l

- First dialysis: FLC reduction: Exp: 76%-71% control 20%-9%

- After 3 weeks: no difference FLC levels

- Renal recovery: 58.1% exp vs 66.0% control
- Survival 2 years: 55.8% exp vs 76.6% control (p = 0.037)

Cast nephropathy: what is new?

- retrospective cohort study: intensive hemodialysis using PMMA membrane versus standard hemodialysis

	IHD (n=21)	SHD (n=20)
Age (yrs)	68 (19)	77 (10)
Male/female	9/12	11/9
Screatinine (umol/l)	477 (375)	723 (822)
Proteinuria (g/d)	2.7 (1.5)	3.7 (3)
sFLC (mg/l)	5475 (10396)	9680 (16276)
Hypercalcemia	3 (15%)	2 (10%)

At 3 months dialysis independent 38% vs 35%; at 12 months 57% vs 30%
Hematological remission +: dialysis independent 14/25
Hematological remission -: dialysis independent 1/16
More hematological responders in IHD group (71 vs 50%)
FLC > 50% of baseline at 3 months 0 renal responders

Hudier L et al. Intensive haemodialysis using PMMA dialyser does not increase renal response rate in multiple myeloma patients with acute kidney injury. CKJ 2018;11:230-235

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List of Abbreviations

- PLA_2R: phospholipase A_2 receptor
- RCT: randomized controlled trial
- GFR: glomerular filtration rate
- ST-CP: steroid-cyclophosphamide
- CYC: cyclophosphamide
- RTX: rituximab
- CSA: ciclosporin
- UPCR urine protein creatinine ratio
- IS: immunosuppressive
- BP: blood pressure
- FSGS: focal segmental glomerulosclerosis
- SSNS: steroid sensitive nephrotic syndrome
- MMF: mycophenolate mofetil
- MPGN: membranoproliferative glomerulonephritis
- C3NEF: C3 nephritic factor
- C3GN: C3 glomerulopathy
- FLC: free light chains
- HC: heavy chain
- LC: light chain
- MGUS: monoclonal gammopathy of undetermined significance
- MGRS: monoclonal gammopathy of renal significance
- SMM: smouldering multiple myeloma
- MM: multiple myeloma
- $CryoT_1$: cryoglobulinemia type I
- CFH: complement factor H
- TIN: tubulointerstitial nephritis
- HCO: high cutoff
- M3: month 3
- Δs FLC: change in serum free light chains
- HD: hemodialysis