Towards an update of the KDIGO Guideline for Glomerulonephritis

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Cliniques universitaires Saint-Luc
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Brussels, Belgium

KDIGO Controversies Conference on Glomerular Diseases 2017 Singapore

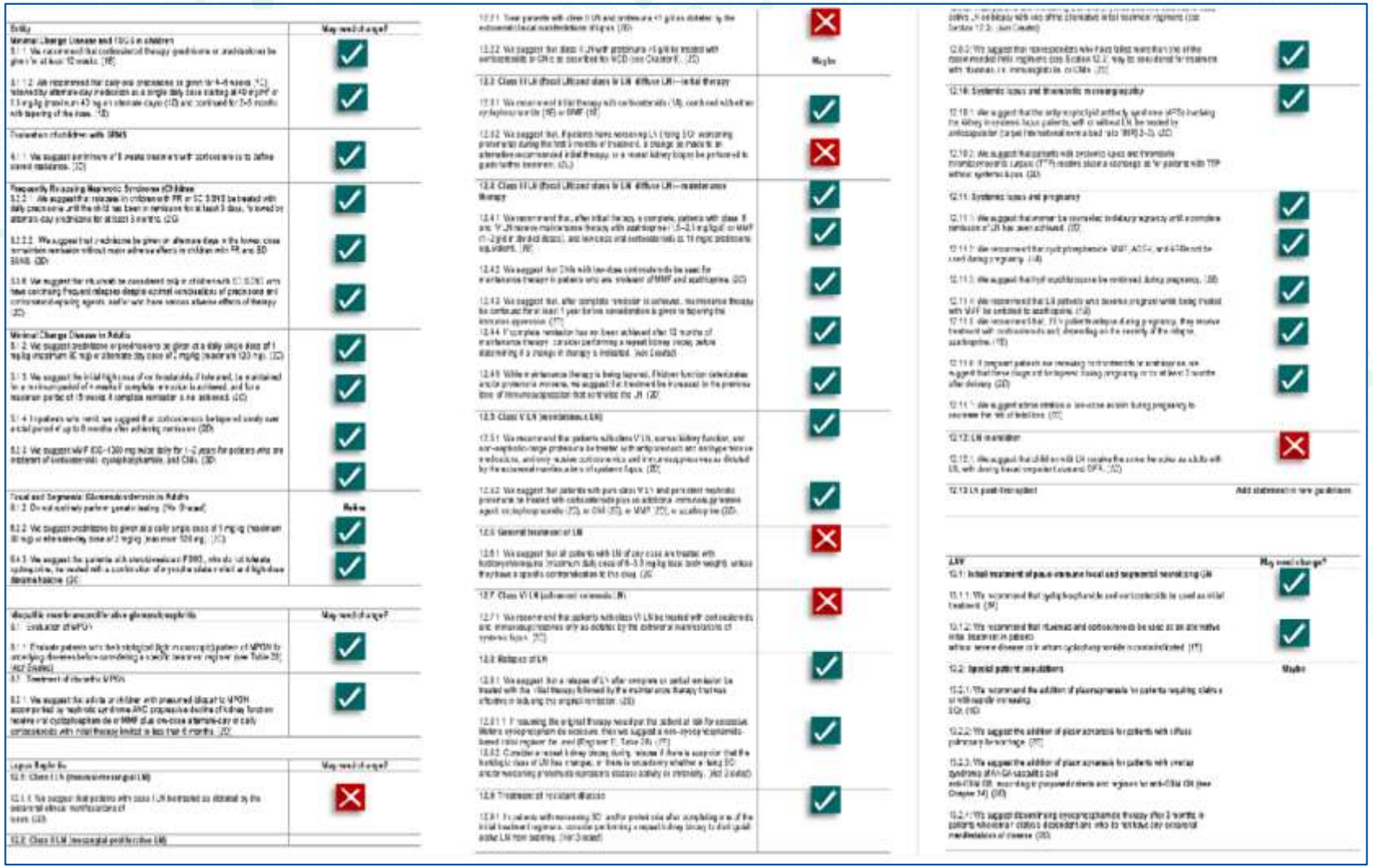
Slides: courtesy of Prof. Jürgen Floege (Aachen)

KDIGO Controversies Conference on Glomerular Diseases

Jürgen Floege - Conference Co-Chair
Brad Rovin - Conference Co-Chair

General Principles, MPGN, C3GN		IgAN		Membranous GN		MCD & FSGS		Lupus & ANCA	
(Swallow Room)		*(Galleria Ballroom)*		*(Falcon Room)*		*(Paradiso Room)*		*(Cardinal Room)*	
Breakout Group Co-Chairs									
Cattran (CA)	Dan	Barbour (CA)	Sean	Nachman (US)	Patrick	Gibson (US)	Keisha	Caster (US)	Dawn
Hogan (US)	Jonathan	Tang (HK)	Sydney	Wetzels (NL)	Jack	Moeller (DE)	Marcus	Roccatello (IT)	Dario

KEY QUESTION: WHICH OF THE 2012 GLOMERULAR DISEASE GUIDELINE RECOMMENDATIONS NEED REVISION?



GN Guideline Update Underway

- Held August 27 – 29, 2018
- Sheraton Amsterdam Airport Hotel
- Cochrane Renal & Transplant ERT
- next slides (statements/algorithms) are draft ones (no final recommendations as yet), except for HCV-associated GN

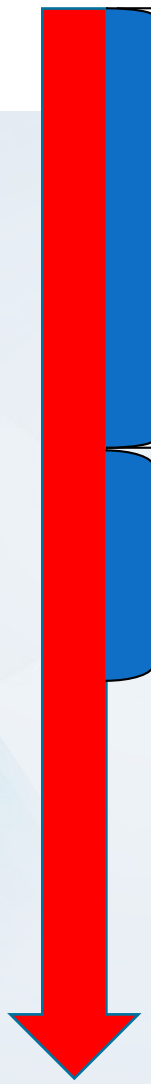
GN Guideline Update Work Group Members

KDIGO GN Guideline Update

Jürgen Floege - Guideline Co-Chair
Brad Rovin - Guideline Co-Chair

ANCA (Chapters 13 & 14)		**General** (Chapters 2 & 9)		**IgAN** (Chapters 10 & 11)		**MCD & FSGS** (Chapters 3, 4, 5, & 6)		**Membranous** (Chapter 7)		**MPGN / C3GN** (Chapter 8)		**SLE** (Chapter 12)	
Work Group Members													
Sanders (NL)	Jan-Stephan	Adler (US)	Sharon	Barratt (UK)	Jonathan	Gibson (US)	Keisha	Jha (IN)	Vivek	Bridoux (FR)	Frank	Chan (HK)	Daniel T.M.
Tesař (CZ)	Vladimír	Burdge (US)	Kelly	Cook (UK)	Terry	Liew (SG)	Adrian	Ronco (FR)	Pierre	Fervenza (US)	Fernando	Mejía Vilet (MX)	Juan Manuel
		Glassock (US)	Richard	Reich (CA)	Heather	Radhakrishnan (US)	Jai	Wetzels (NL)	Jack	Nester (US)	Carla		
		Rave (US)	Elizabeth	Tang (HK)	Sydney	Vivarelli (IT)	Marina			Sethi (US)	Sanjeev		

GN Guideline Update: Timeline



Feb 2018

Mar 2018

Apr 2018

May 2018

Jun 2018

Jul 2018

Aug 2018

Sep 2018

Oct 2018

Nov 2018

Dec 2018

Jan 2019

Feb 2019

Mar 2019

Apr 2019

May 2019

Jun 2019

Meeting '0' (February 5, 2018):
Formalize Scope of Work and PICO with ERT

ERT literature review

WG Meeting (Aug 27-29: Amsterdam)
Review evidence, strive for consensus on recommendation wording and grading

ERT to fine tune evidence review as needed

Next steps:

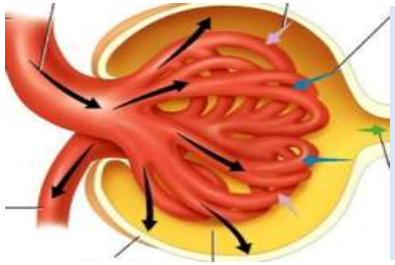
- **Possible WG Meeting 2? Final consensus on recs/rationale**
- **WG to prepare draft guideline for open review**
- **Public Review (1 month)**
- **WG to review public comments**
- **WG to refine guideline manuscript**
- **Manuscript submission**

GENERAL MANAGEMENT OF GLOMERULAR DISEASES

GENERAL MANAGEMENT

- **Kidney biopsy** remains the cornerstone + likely to expand significantly in the near-term
- need for electron microscopy for every biopsy remains controversial

- **ACR and PCR** helpful in general clinical management
- not sufficiently accurate for therapeut. decisions when using high-risk medications



- **eGFR equations** not validated in specific glomerular diseases and patient populations

Floege J, ….. Rovin BH. Submitted

GENERAL MANAGEMENT

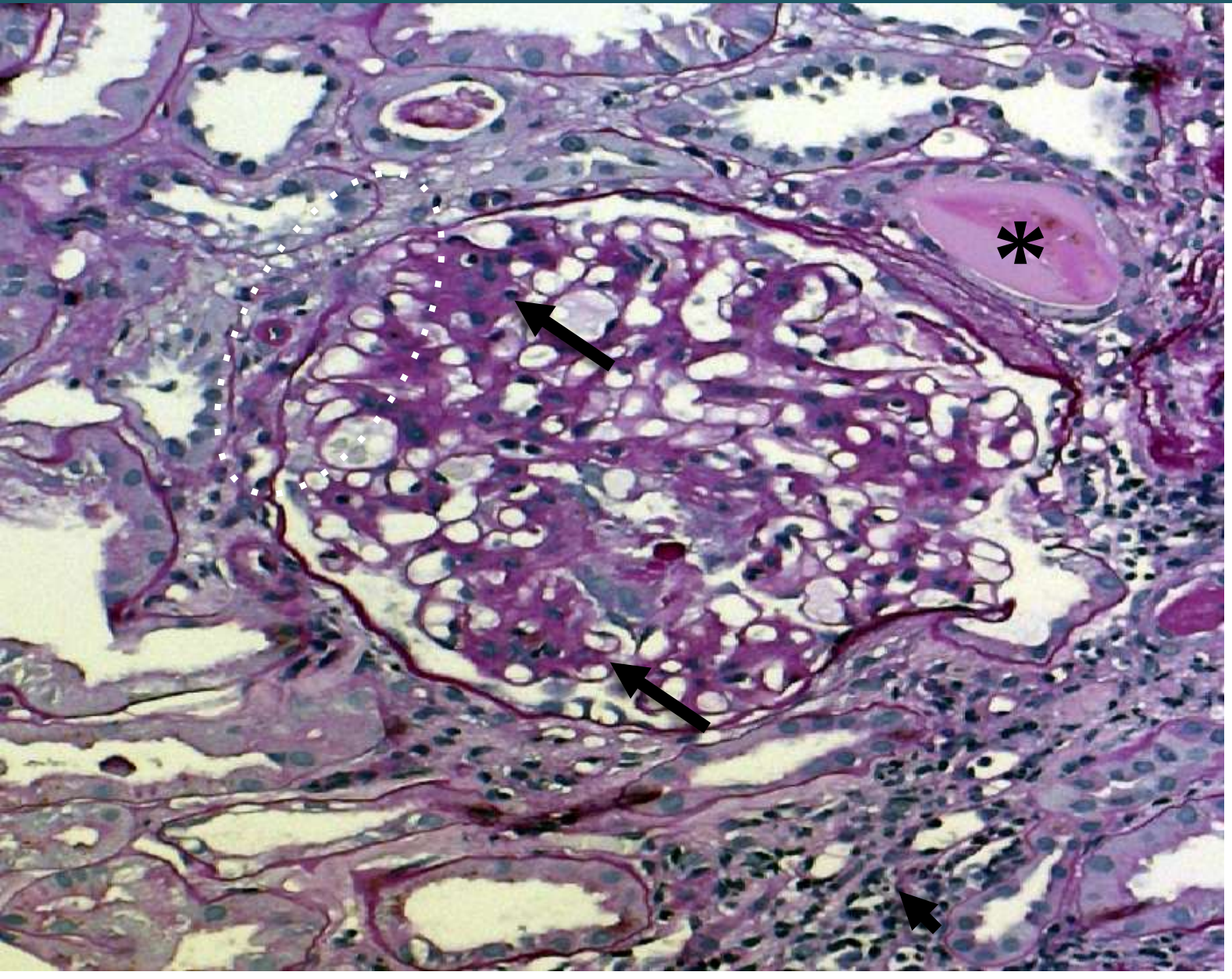
- **patient engagement** in determining clinical trial eligibility
- patient-related outcomes and measurements rapidly evolving

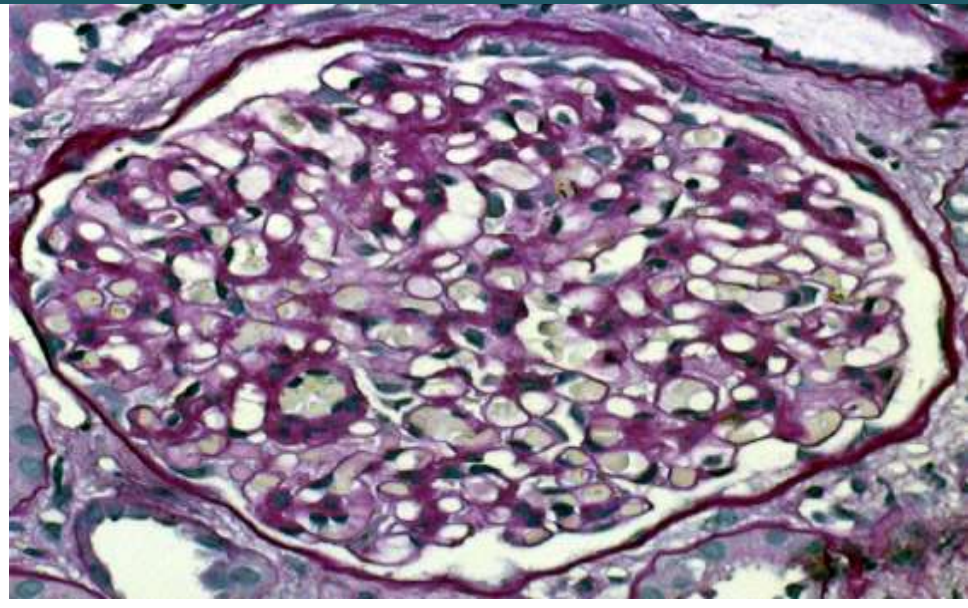
- **Newer determinants of progression**: pre-maturity, sleep disturbances, obesity, genetics

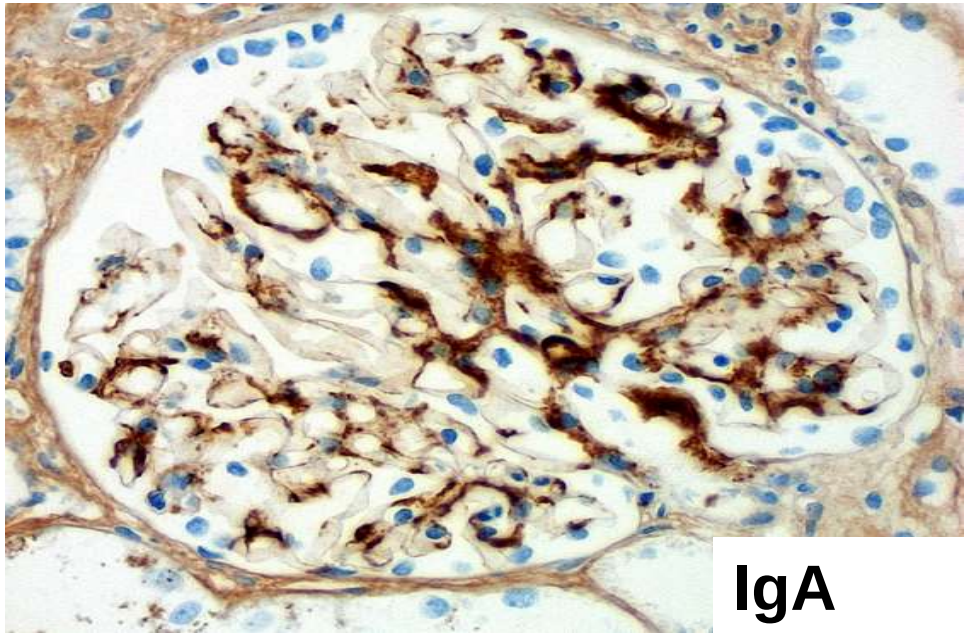
- **Hypertension + proteinuria**: no news
- **Uncertain**: aldosterone or SGLT2 blockers; PCSK9 inhibitors and NOAC in nephrotic pts.
- **multidisciplinary support, infection control**
- **Role of prophylactic anticoagulation discussed**

Floege J, ….. Rovin BH. Submitted

IgA-Nephropathy







THE STOP-IGAN TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

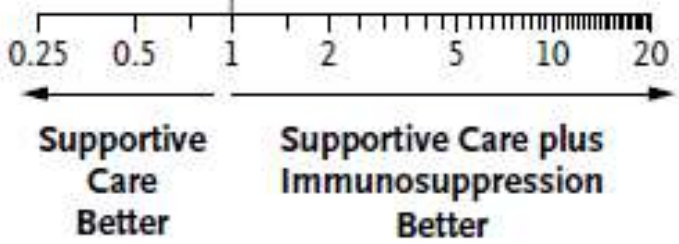
Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*

ABSTRACT

Rauen T et al, N Engl J Med 2015; 373: 2225-36

A In Full Clinical Remission

Subgroup	Supportive Care	Supportive Care plus Immunosuppression	Odds Ratio (95% CI)	P Value
	no. of events/total no.			
Full-analysis set	4/80	14/82	4.82 (1.43–16.30)	0.01
Available-case analysis	4/72	14/71	5.38 (1.55–18.66)	0.008



B eGFR Decrease ≥15 ml/min/1.73 m^2

Subgroup	Supportive Care	Supportive Care plus Immunosuppression	Odds Ratio (95% CI)	P Value
	no. of events/total no.			
Full-analysis set	22/80	21/82	0.89 (0.44–1.81)	0.75
Available-case analysis	18/76	17/78	0.89 (0.41–1.90)	0.76

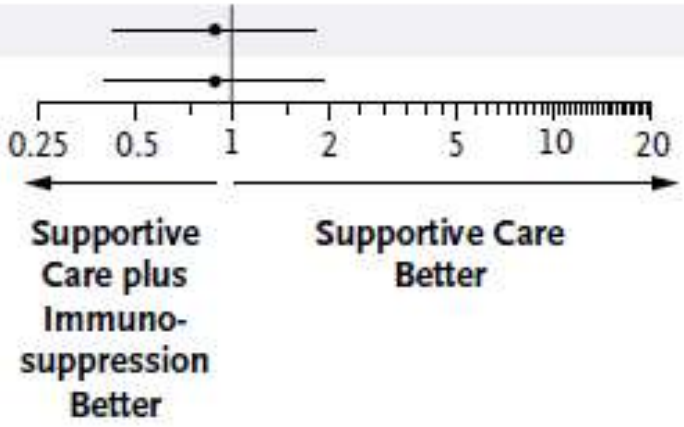


Table 3. Adverse Events during the Trial.

Variable	Supportive Care (N=80)	Supportive Care plus Immunosuppression (N=82)	P Value
Patients with ≥1 serious adverse event — no.	21	29	0.24
Total no. of serious adverse events	29	33	0.18
Total no. of events of infection	111	174	0.07
Total no. of serious adverse events of infection	3	8	0.21
Diverticulitis or appendicitis	1	3	0.62
Pneumonia or respiratory tract infection	1	3	0.62
Viral exanthema	1	1	1.00
Knee empyema	0	1	1.00
Death — no.*	1	1	1.00
Additional adverse events of interest — no. of patients			
≥1 incidence of increase in liver-enzyme level (i.e., alanine amino-transferase >50 IU/ml)	12	13	1.00
≥1 incidence of observed leukopenia (i.e., leukocyte count <4000/μl)	3	2	1.00
Malignant neoplasm	0	2	0.50
Impaired glucose tolerance or diabetes mellitus	1	9	0.02
Gastrointestinal bleeding	0	0	Not determined
Fracture	0	1	1.00
Osteonecrosis — no. of patients	0	0	Not determined
Weight gain (≥5 kg within the first year)	5	14	0.049

Research

JAMA | Original Investigation

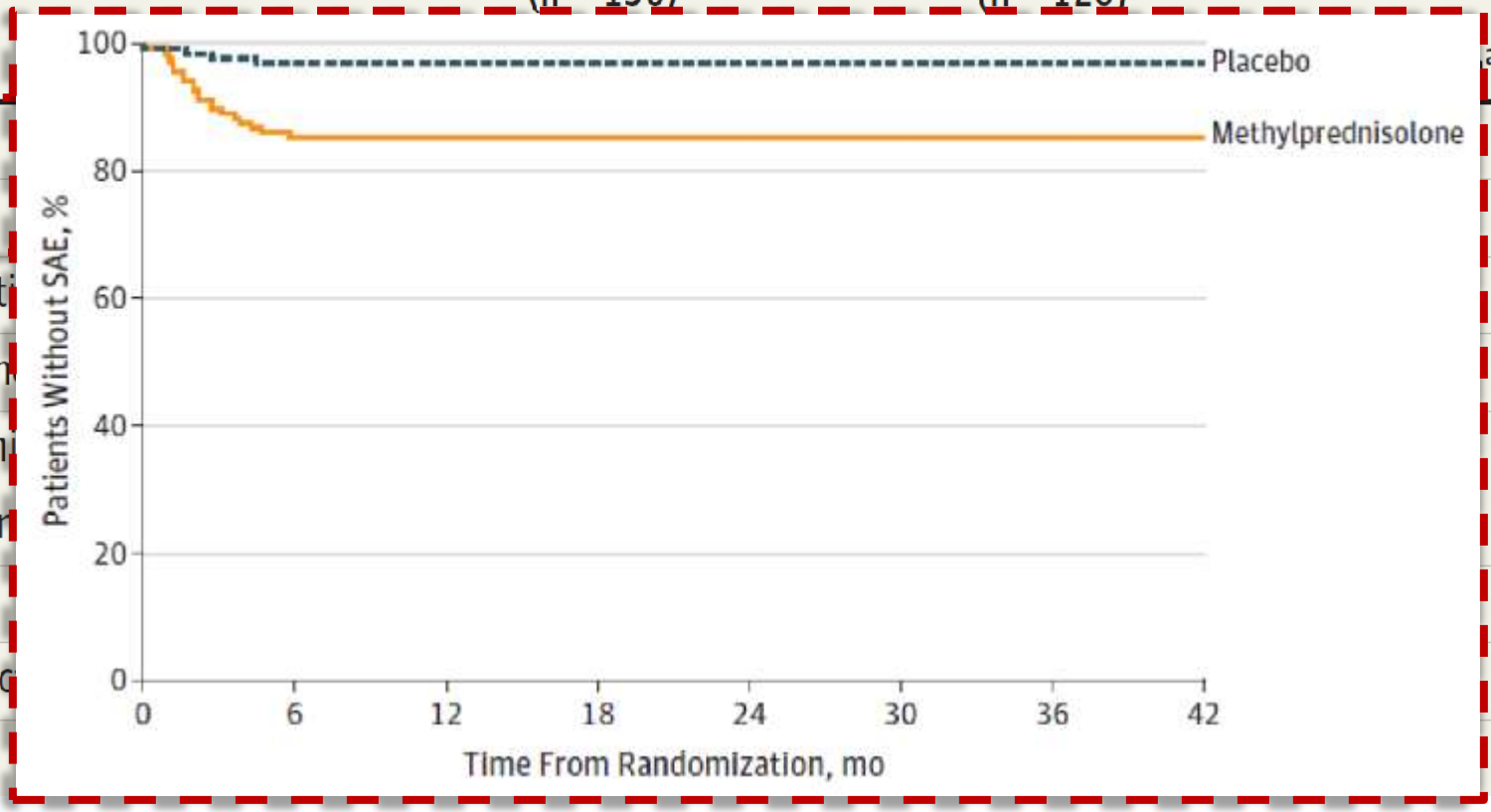
Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial

Jicheng Lv, MD; Hong Zhang, PhD; Muh Geot Wong, PhD; Meg J. Jardine, PhD; Michelle Hladunewich, MD; Vivek Jha, MD; Helen Monaghan, PhD; Minghui Zhao, MD; Sean Barbour, MD; Heather Reich, MD; Daniel Cattran, MD; Richard Glassock, MD; Adeera Levin, FRCPC; David Wheeler, FRCP; Mark Woodward, PhD; Laurent Billot, MSc; Tak Mao Chan, MD; Zhi-Hong Liu, MD; David W. Johnson, MD; Alan Cass, FRACP; John Feehally, MD; Jürgen Floege, MD; Giuseppe Remuzzi, MD; Yangfeng Wu, MD; Rajiv Agarwal, MD; Hai-Yan Wang, MD; Vlado Perkovic, PhD; for the TESTING Study Group

TESTING: EARLY TRIAL TERMINATION

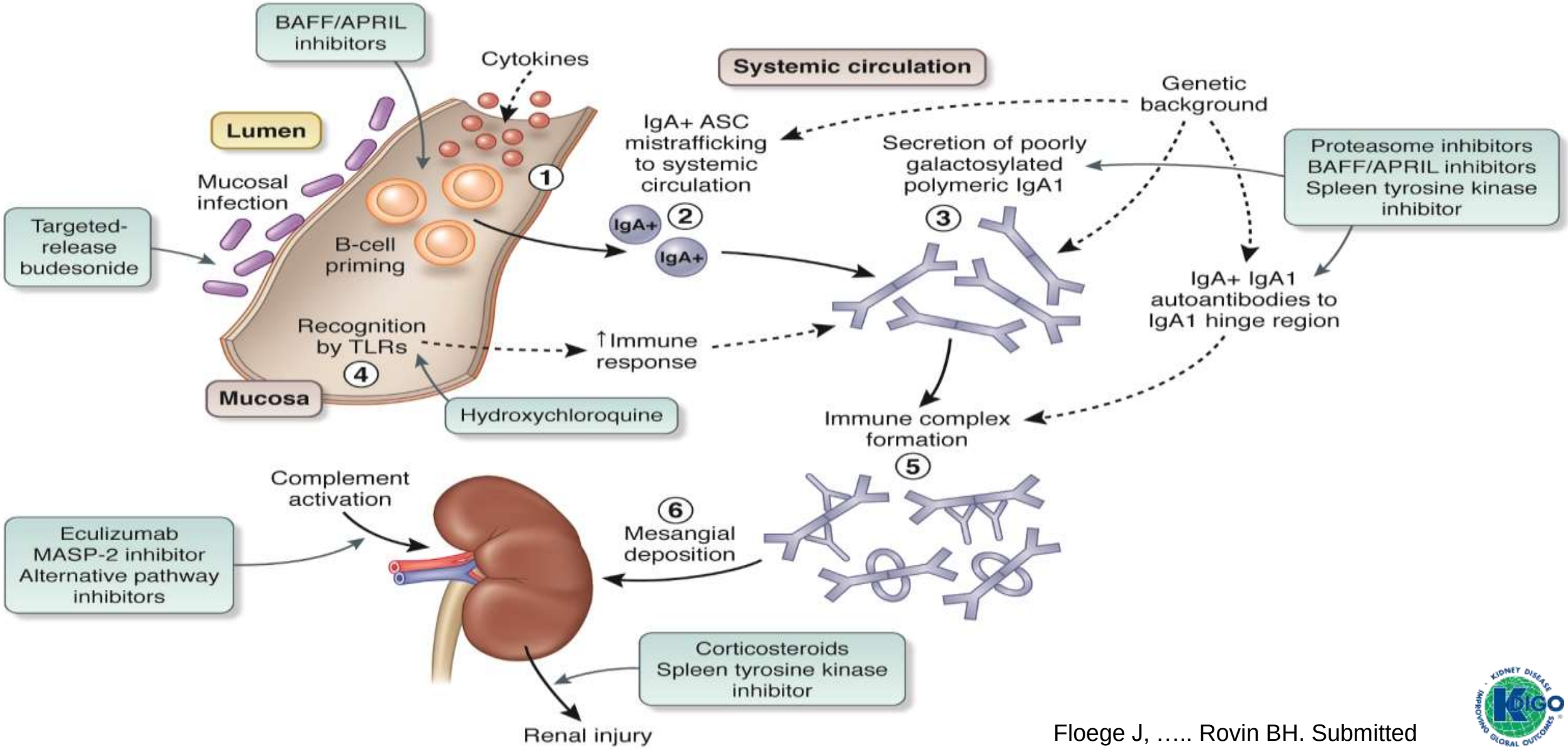
Table 2. Serious Adverse Events and Adverse Events of Special Interest by Treatment Group

Outcome	Methylprednisolone (n = 136)	Placebo (n = 126)
Total SAEs[b]		
SAEs of infection[c]		
Respiratory infecti		
Pneumoncystis pn		
Cryptococcal meni		
Nocardia infectior		
Perianal abscess		
Urinary tract infec		
Fever		



Lv J et al, JAMA. 2017;318(5):432-442

IgA Nephropathy – new options for therapy

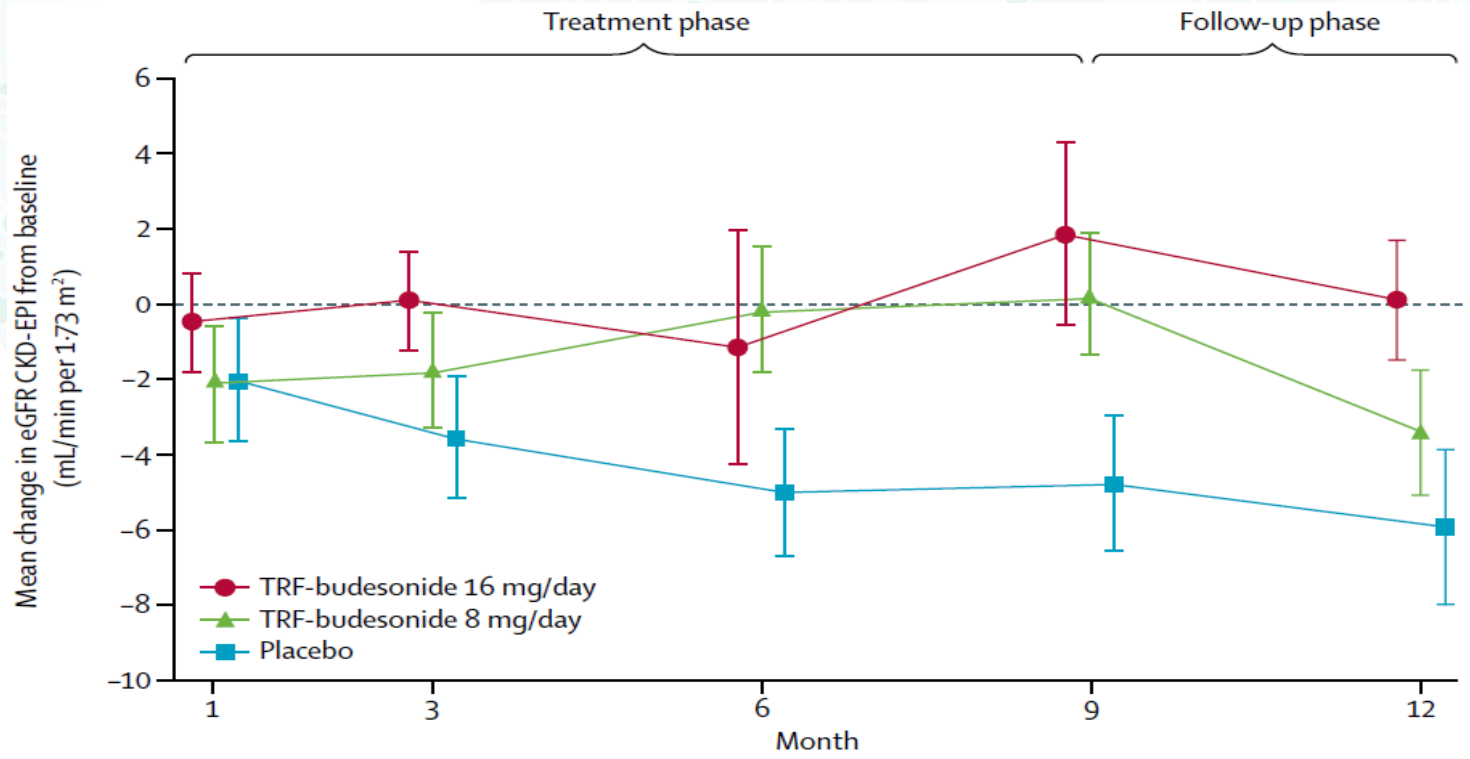


Floege J, ….. Rovin BH. Submitted

Lancet 2017; 389: 2117–27

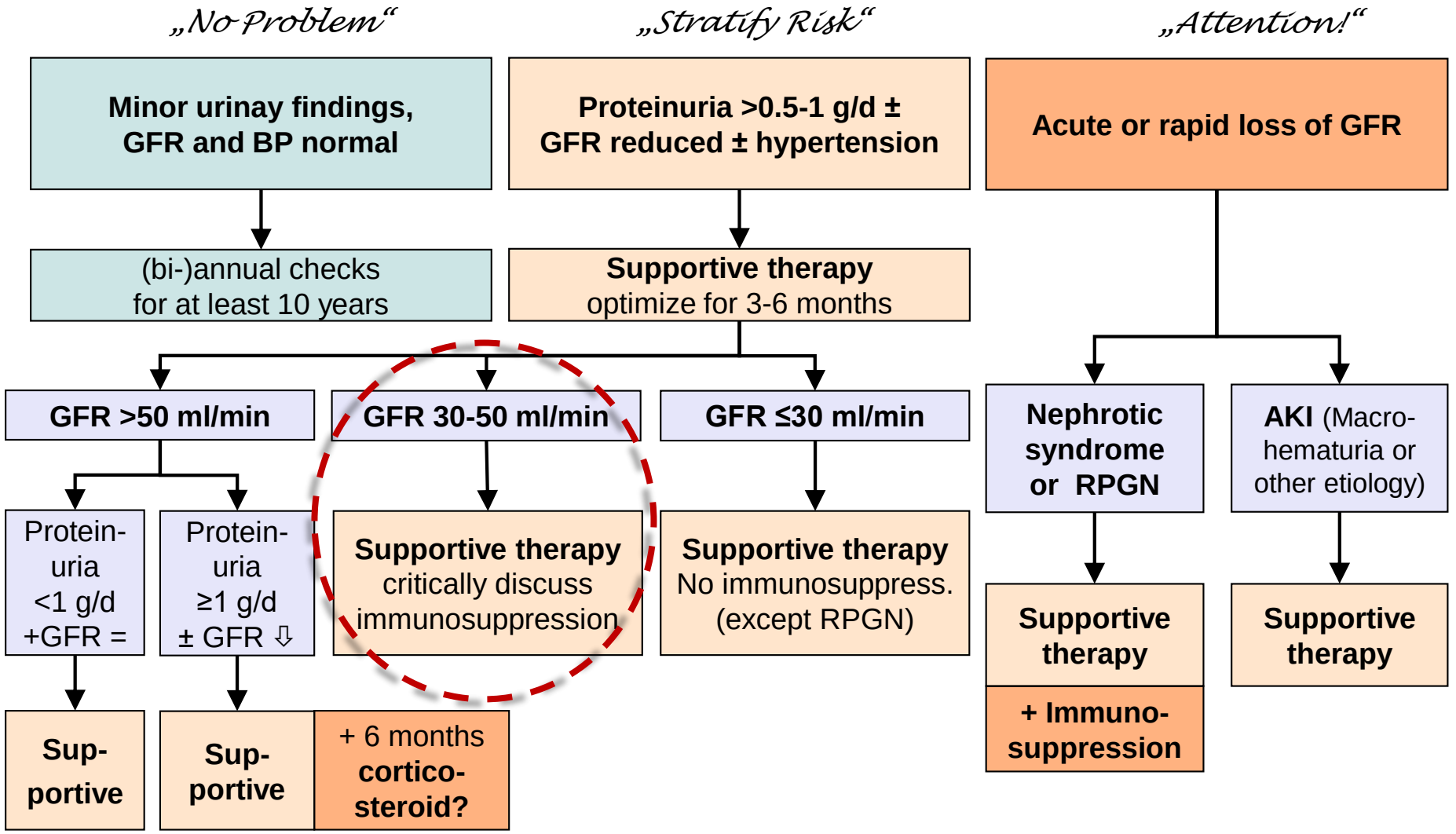
Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren S Sørensen, Vladimir Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators

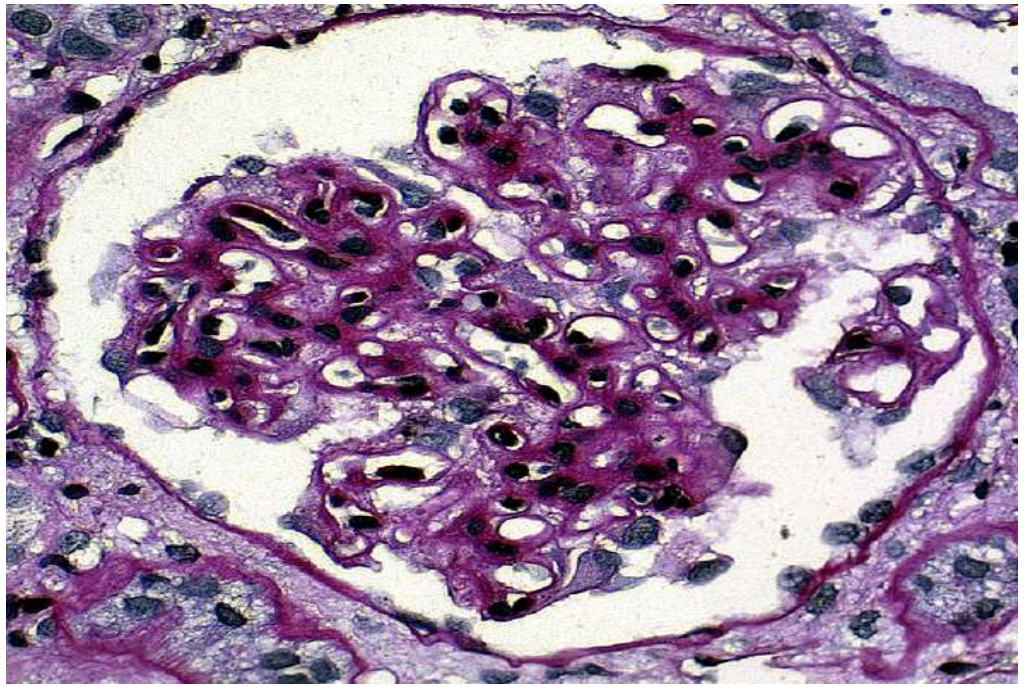


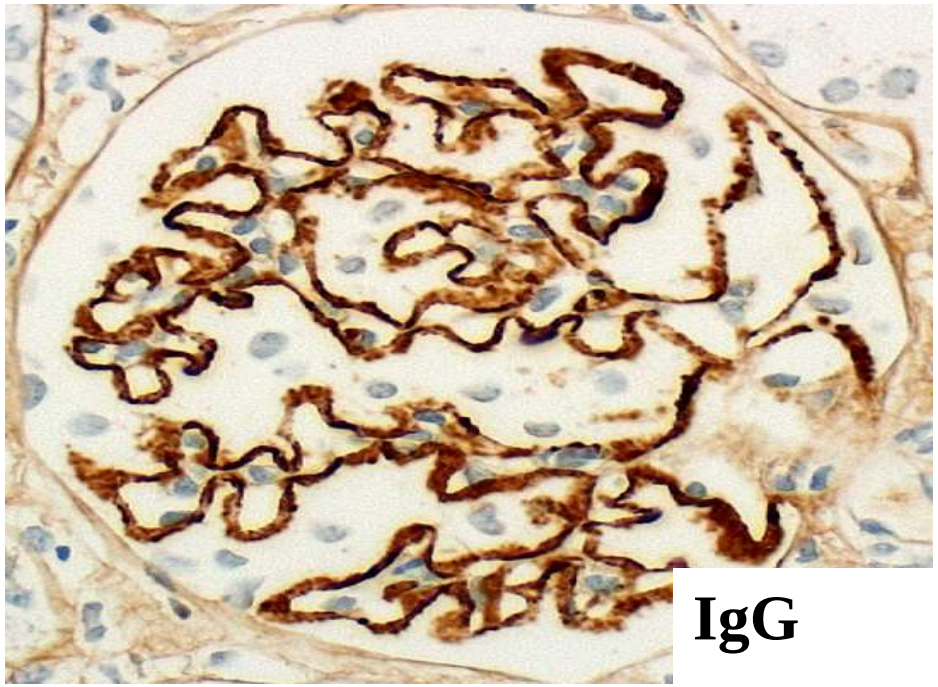
DRAFT !

Treatment of IgAN

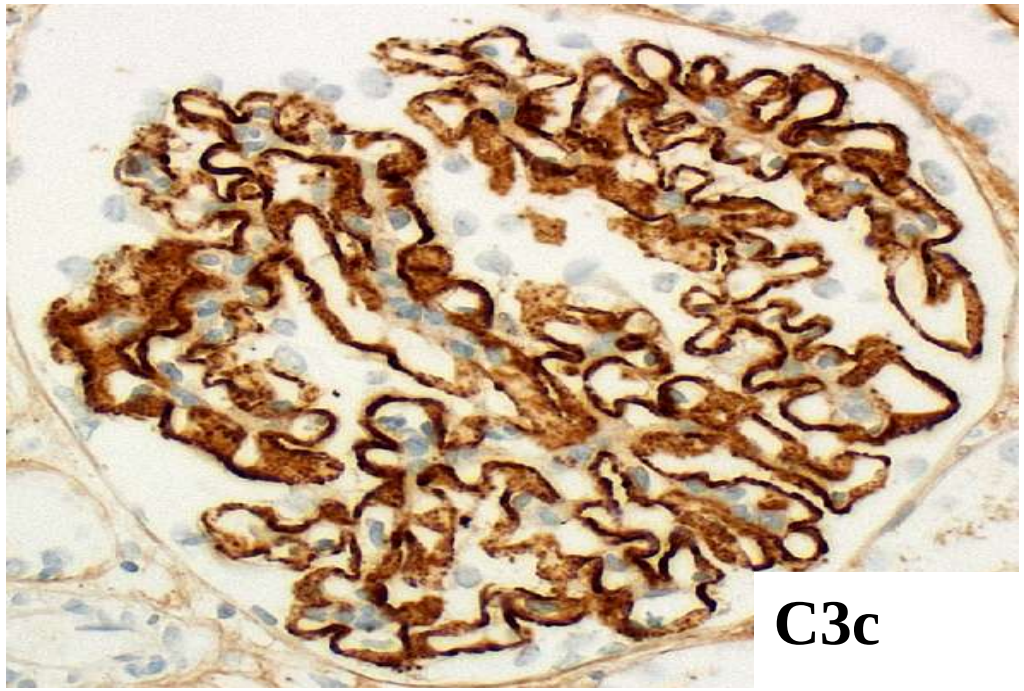


MEMBRANOUS GN

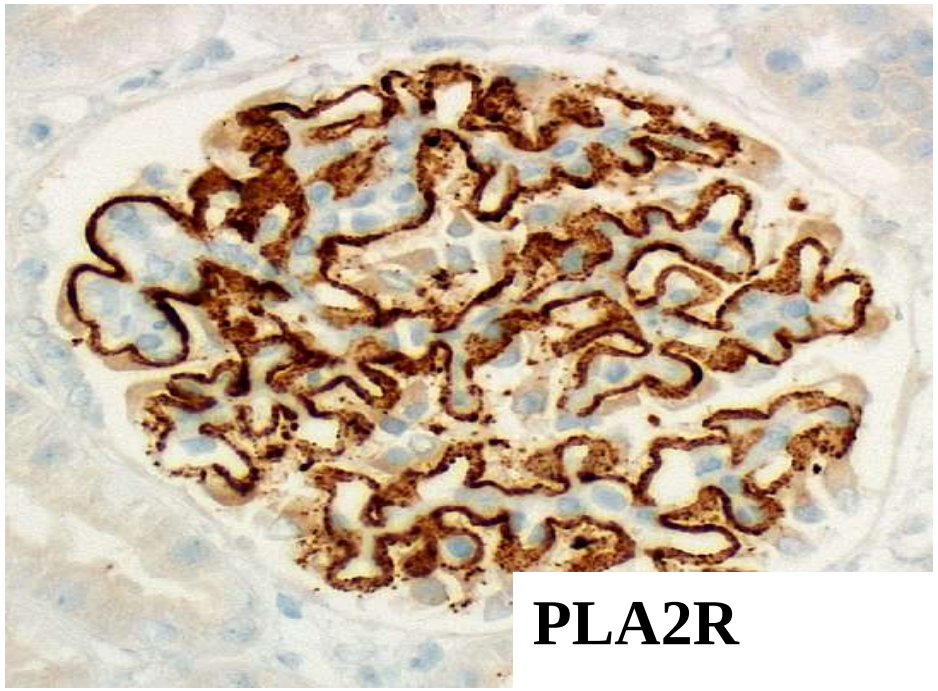




IgG

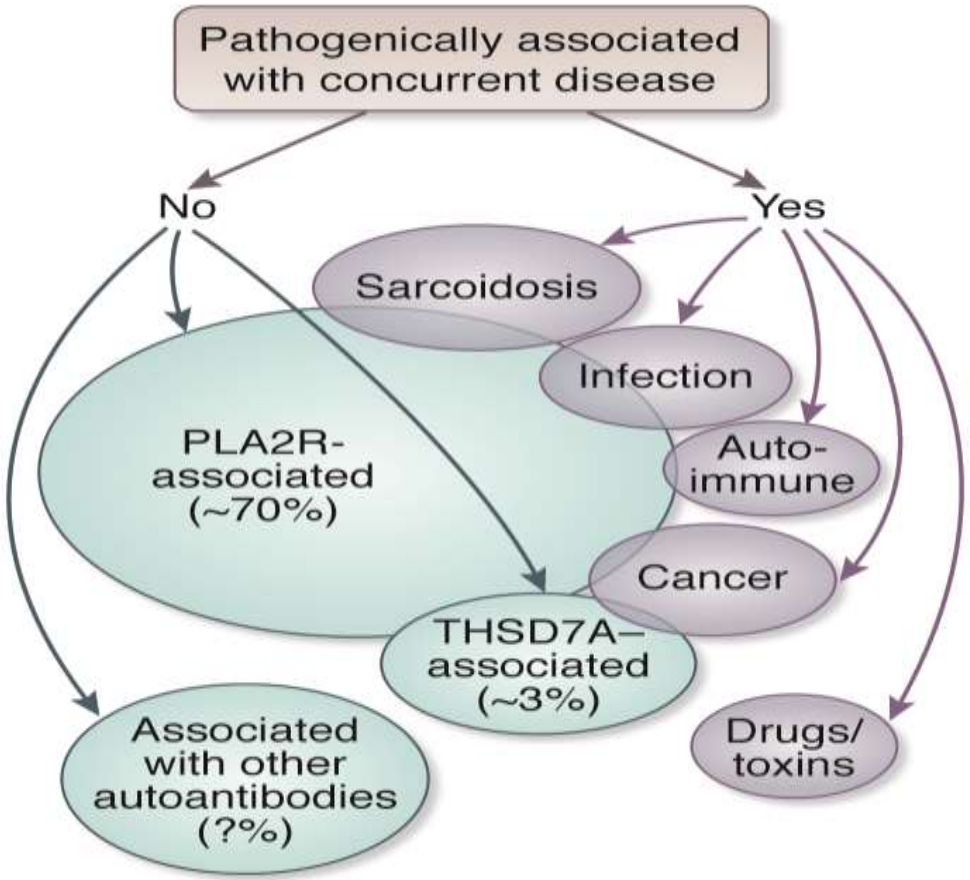


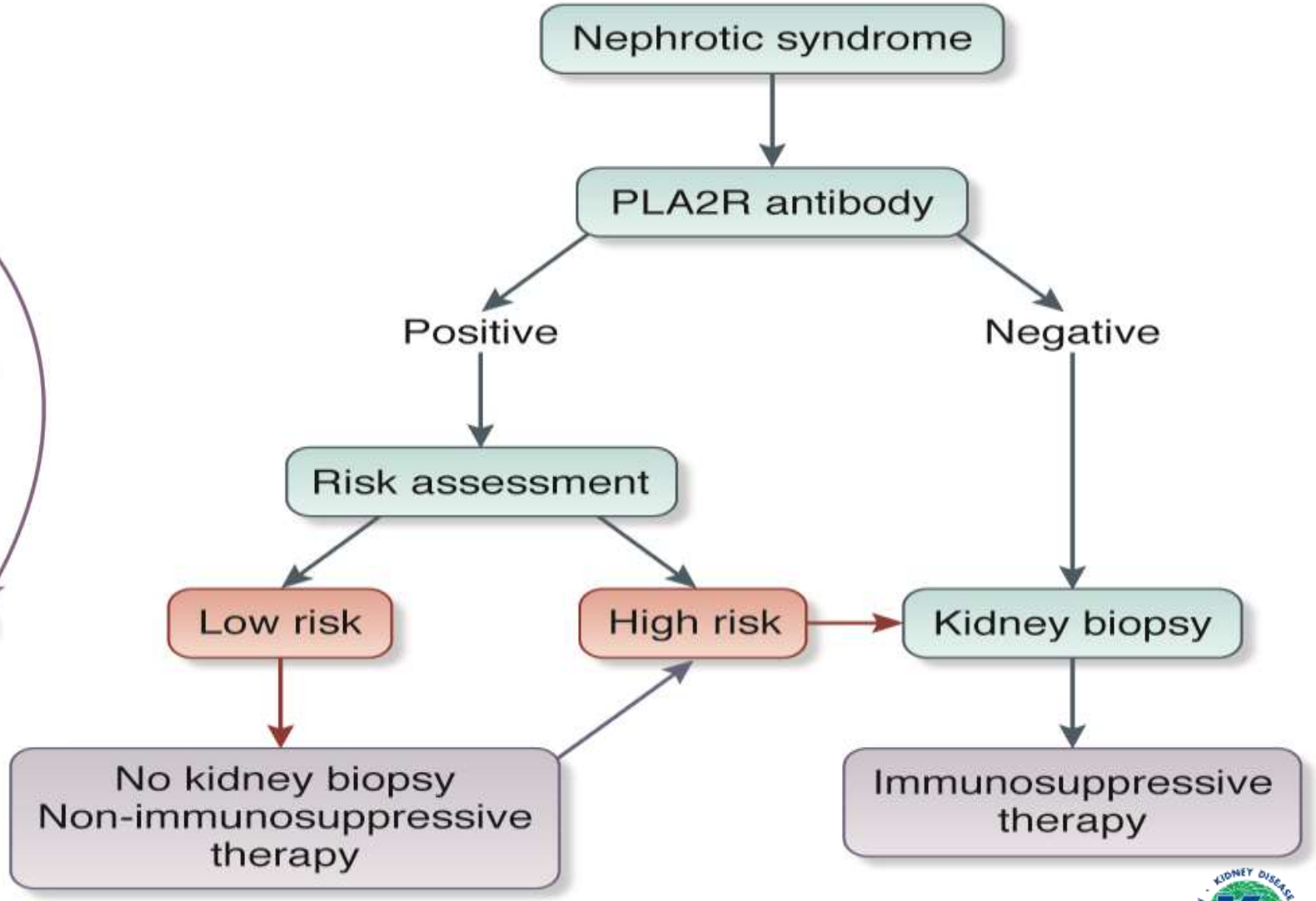
C3c



PLA2R

MEMBRANOUS GN – WORK-UP + THERAPY





Floege J, ….. Rovin BH. Submitted

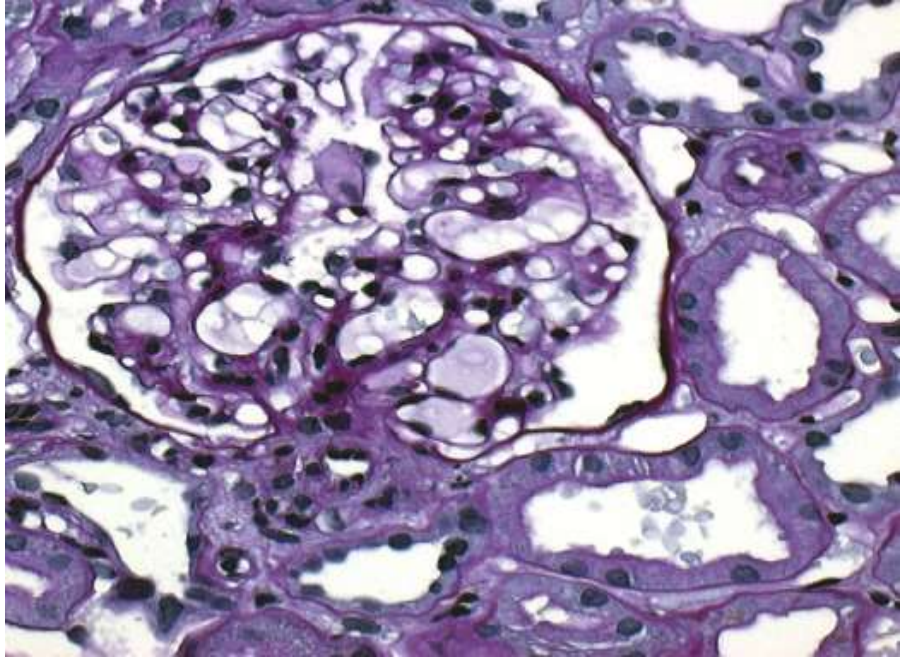
MEMBRANOUS GN – IMMUNOSUPPRESSION

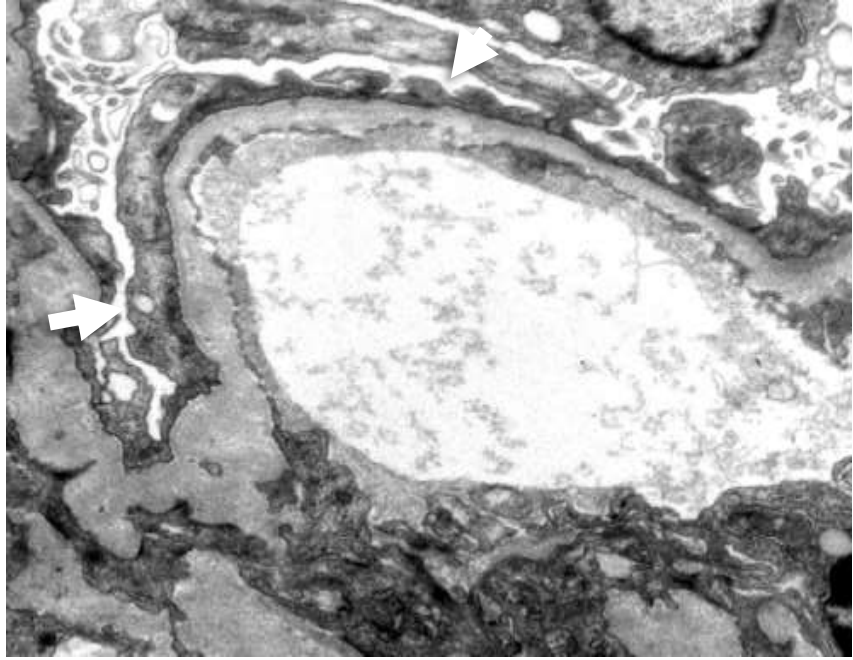
Alkylating agents	• experienced physicians • restricted to pts at high-risk of progression
Calcineurin inhibitors	• remission rates similar to cyclophosphamide, but greater likelihood of relapse
Rituximab	• *GEMRITUX*: rituximab more effective than placebo in inducing remissions • *MENTOR*: rituximab more effective than CyA in maintaining remission 24 months after enrollment; non-response rate to rituximab approximately 35%. (late breaking ASN 2017 presentation, full paper still to be published)

…It is likely that the choice of therapy may be determined by improved risk-stratification models incl. autoantibody levels …

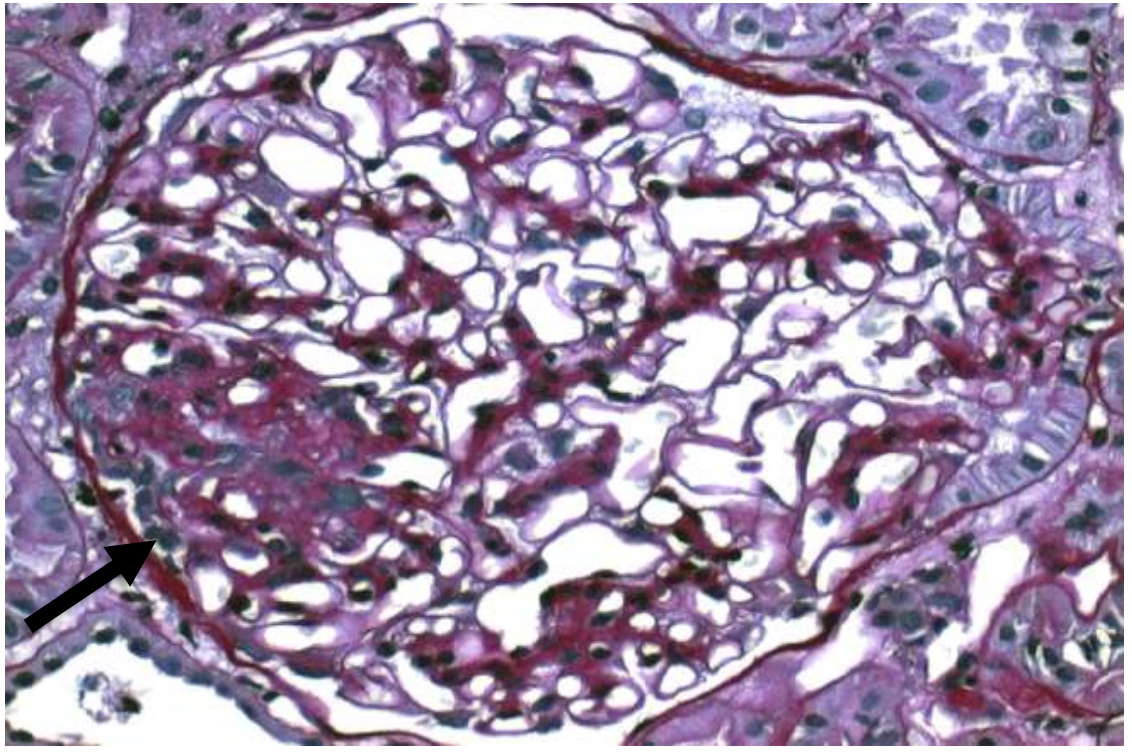
Floege J, ….. Rovin BH. Submitted

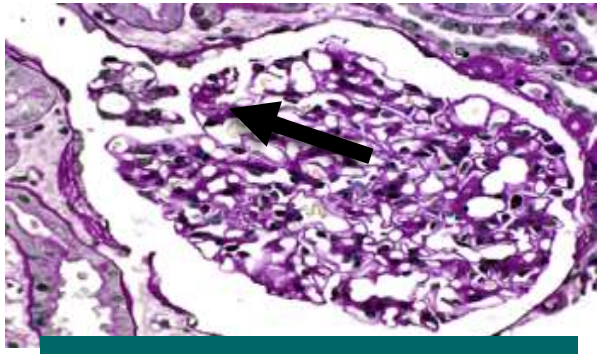
Minimal Change Nephropathy



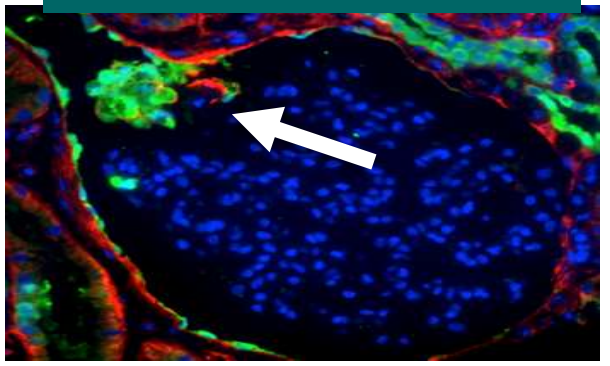


Focal Segmental Glomerulo-sclerosis





Parietal cell activation

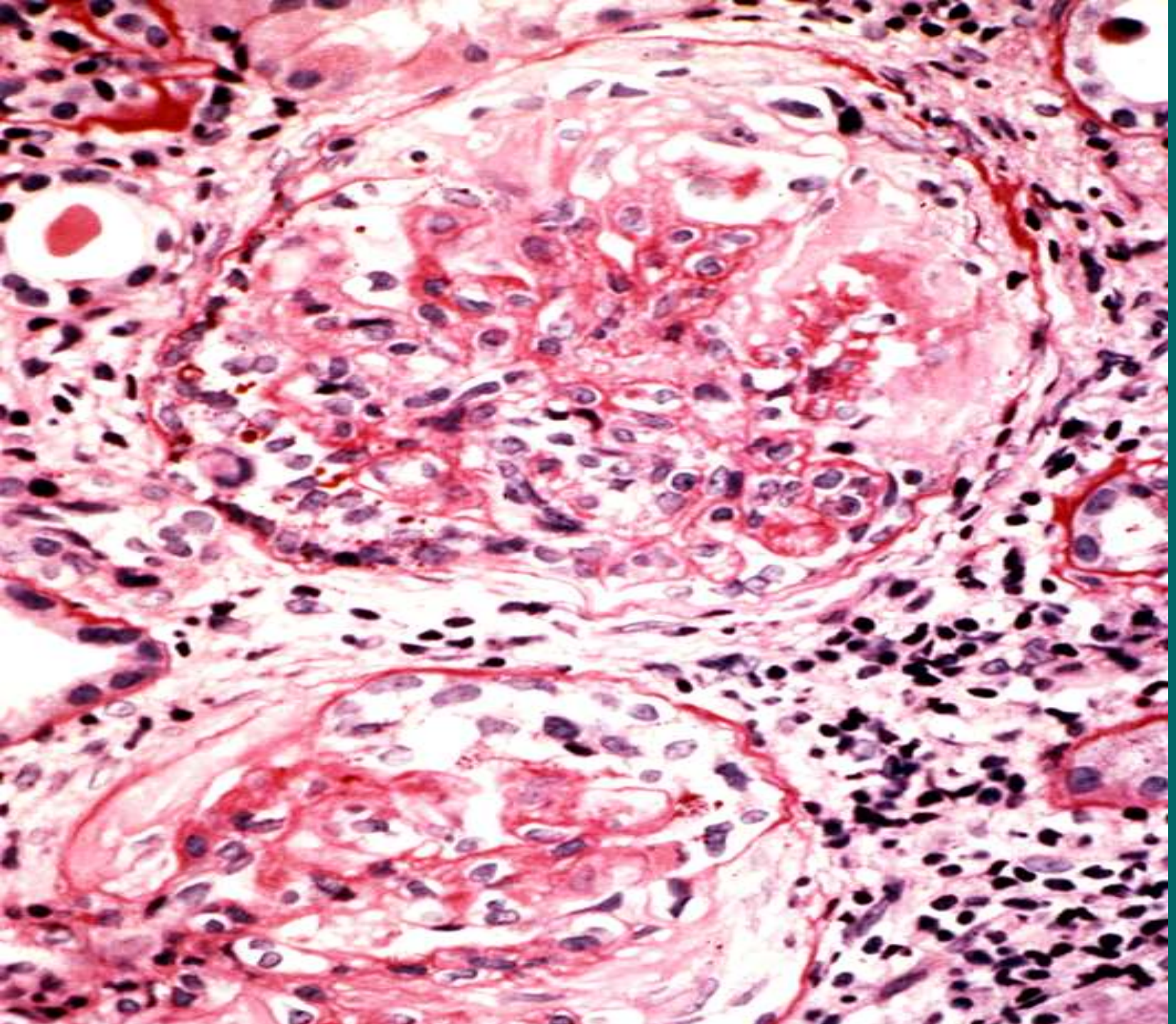


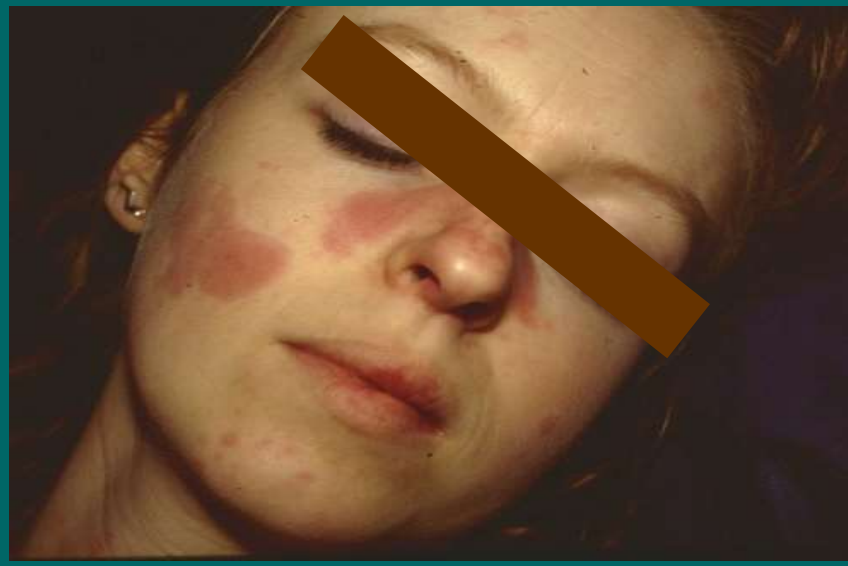
MINIMAL CHANGE GN & FSGS

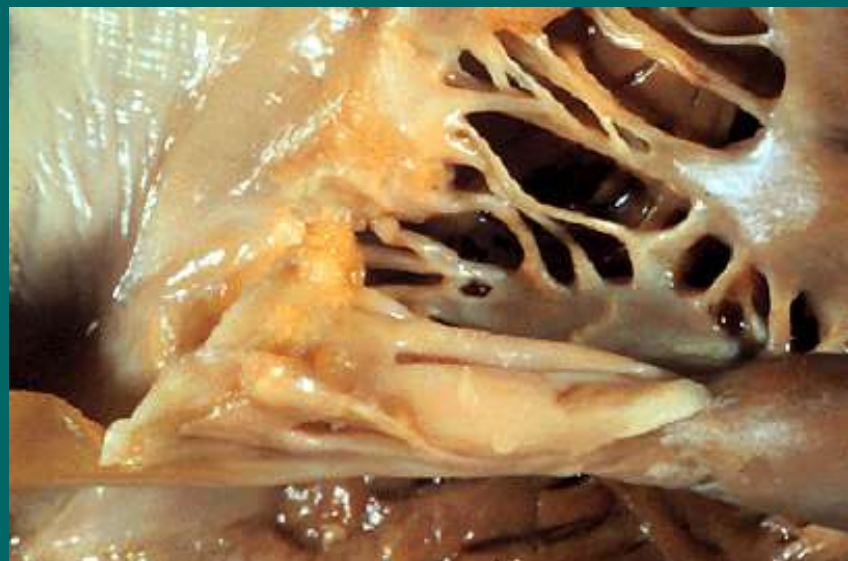
- **"Steroid sensitive" and "steroid-resistant NS"** should remain
- Term **"primary/idiopathic FSGS"** may require revision.
- **Genetic testing:** patients with congenital/infantile forms of nephrotic syndrome, syndromic features, familial forms
- ***Children***: Steroids first in all nephrotic pts; need for a global definition of "steroid resistance," precise order of CYC, MMF, CNI and rituximab not well determined.
- ***Adults:*** minimum 16 weeks of high-dose steroids as first-line therapy for FSGS or MCD controversial. Several studies indicate that > 8-12 weeks steroids does not reduce relapse. CNIs or CYC second-line agents in adults with MCD. RTX emerging second-line therapy in MCD. CNIs and MMF second- and third-line treatments, resp., for FSGS.

Rovin BH, ….. Floege J. Submitted

LUPUS ERYTHEMATOSUS







LUPUS NEPHRITIS

ISN/RPS classification	• does not consider tubulointerstitial injury, vascular lesions, or podocytopathies
Genetic testing	• no clear clinical benefit from testing • risks & benefits of *APOL1* testing to be clarified
Repeat renal biopsy	• patients with clinical remission can still have histologic activity and vice versa
Prediction & Monitoring	• proteinuria at one year best predictor of long term renal outcome • biomarker panels will be required to accurately stratify risk, predict flare, determine + monitor treatment, and predict prognosis

Rovin BH, ….. Floege J. Submitted

LUPUS NEPHRITIS

Antimalarials	• recommended for all patients with LN
Cortico-steroids	• use at lowest possible dose during maintenance • Low/zero-steroids protocols under investigation
CYC-/MMF-regimens	• remain the gold standard therapy for remission induction
Calcineurin-inhibitors	• Ongoing studies address role and toxicity in ethnically diverse populations
Maintenance Therapy	• minimum of 3 years, prolonged B-cell depletion with a RTX plus CYC may reduce the duration • A repeat kidney biopsy may be helpful

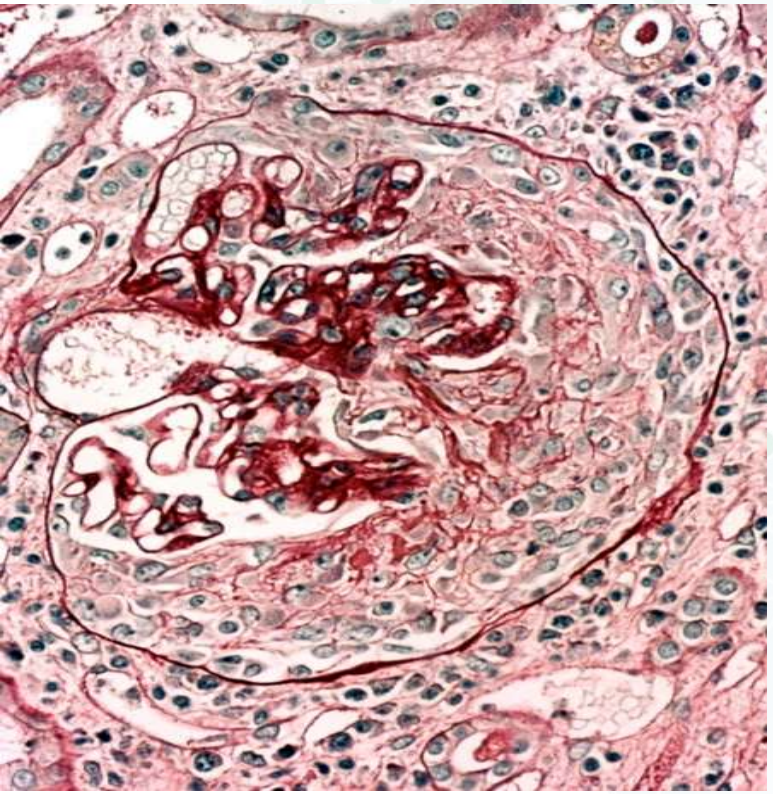
Rovin BH, ….. Floege J. Submitted

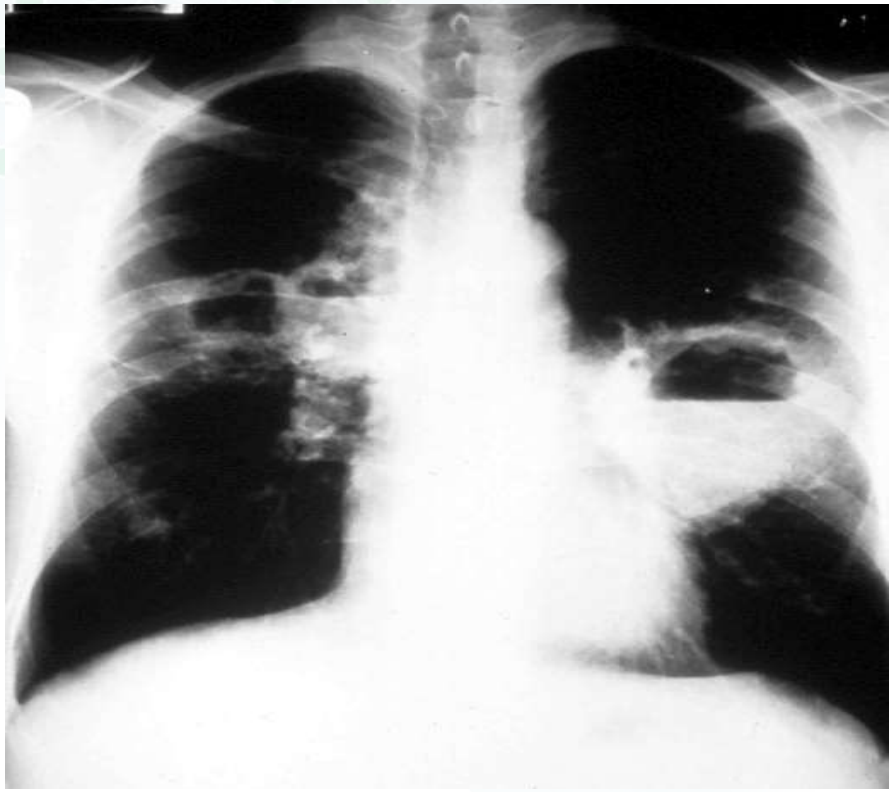
REFRACTORY LUPUS NEPHRITIS

1	• Verify adherence (check mycophenolic level if on MMF/check infusion records if on CYC)
2	• Repeat biopsy if concern for chronicity or other diagnosis (?TMA, etc.)
3	• Switch from MMF to CYC or vice versa
4	• Consider regimen with combined MMF/CNI 'multi-target' therapy *or* • Addition of Rituximab *or* • Consider prolonged course of IV pulse CYC
5	• Consider intravenous IgG *or* plasmapheresis (especially in setting of concomitant TMA or refractory APS). *Minimal evidence outside of case reports*

Rovin BH, ….. Floege J. Submitted

ANCA Vasculitis



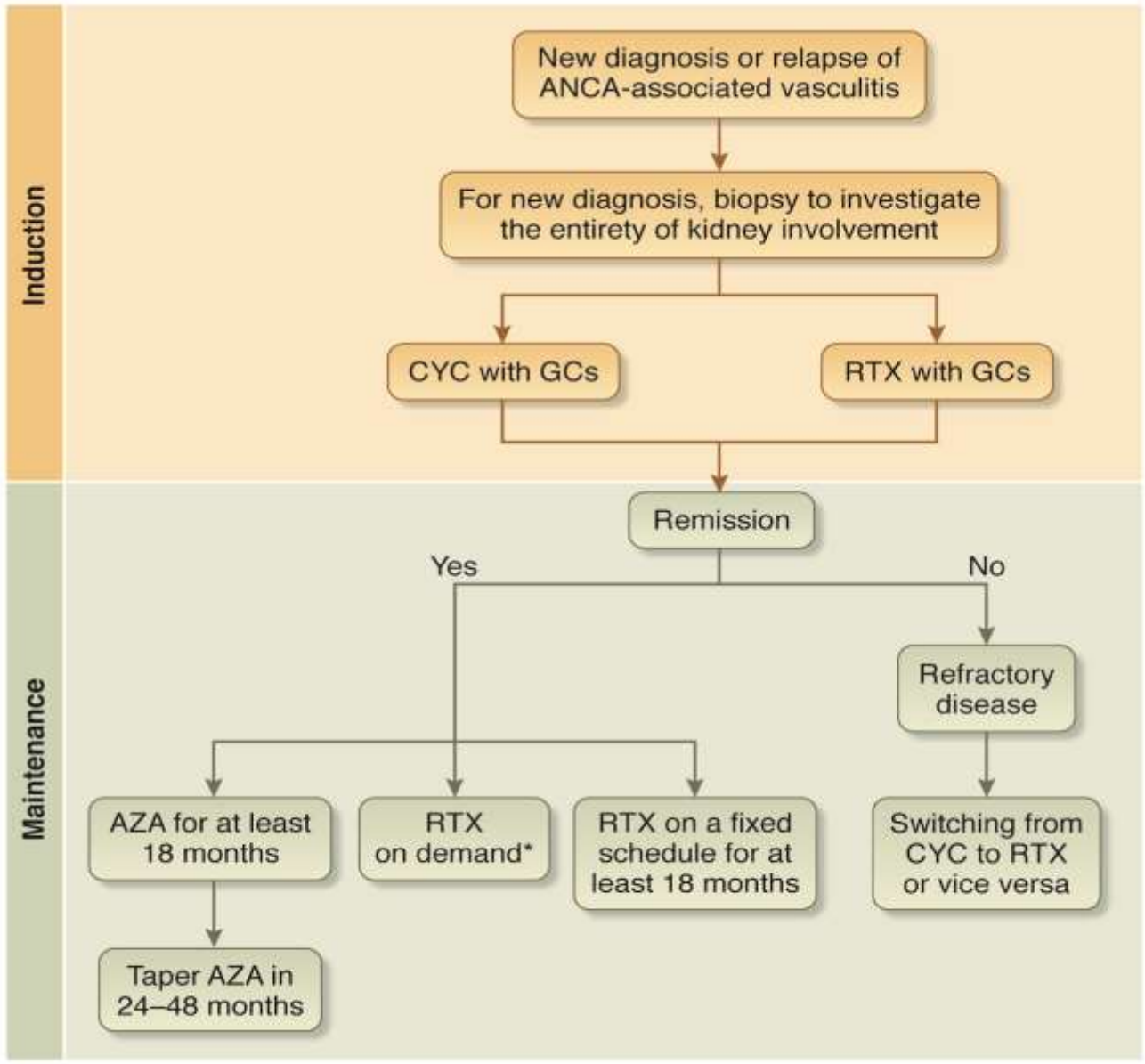


ANCA VASCULITIDES

ANCA serology and Biomarkers	• MPO vs. PR3 ANCA has predictive value with respect to outcomes and risk of relapse • New biomarkers: Serum - CXCL 13, MMP-3, TIMP-1 Urine - soluble CD163

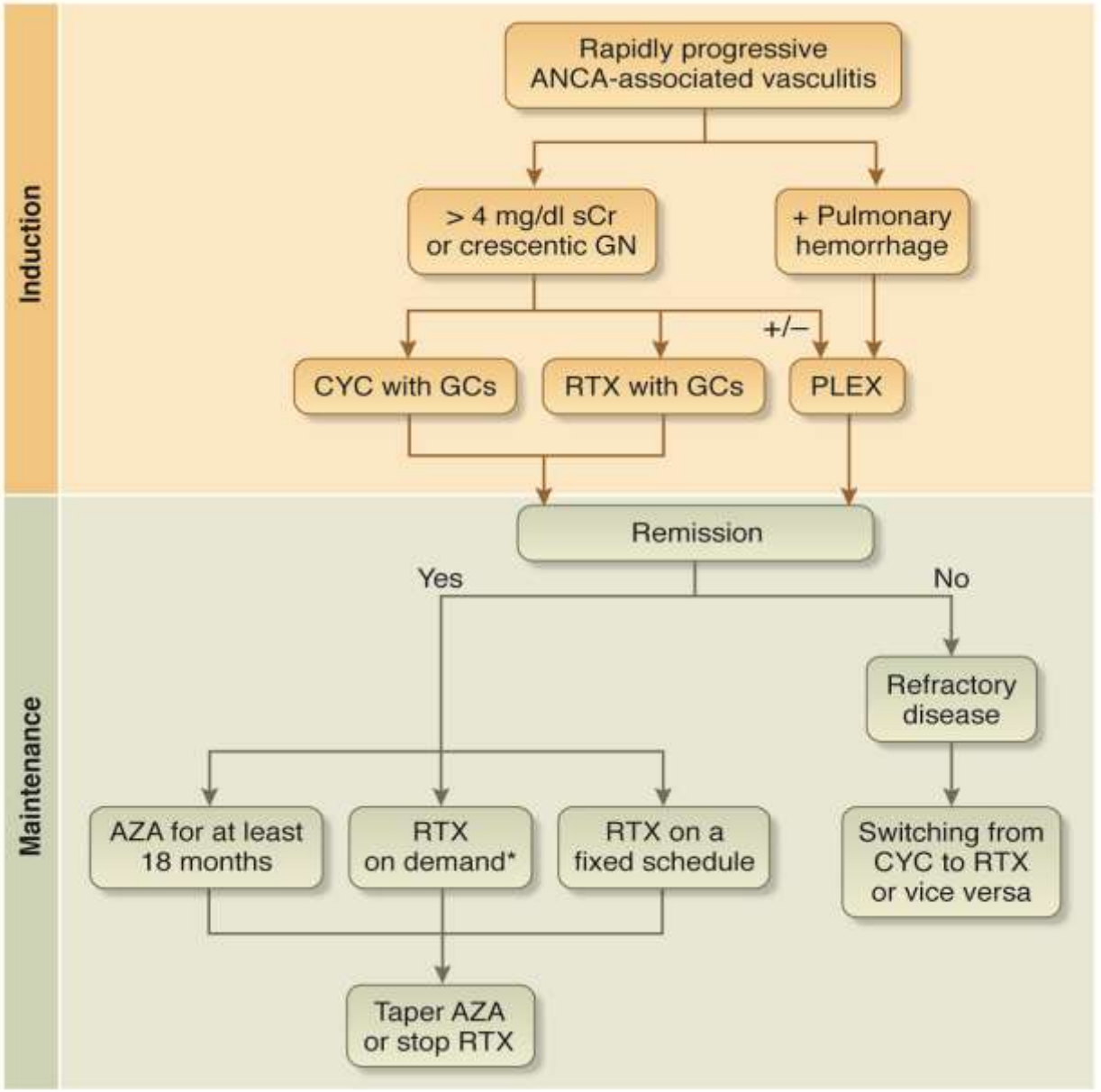
Rovin BH, ….. Floege J. Submitted

ANCA VASCULITIDES



Rovin BH, …..
Floege J. Submitted

SEVERE ANCA VASCULITIDES



Rovin BH, …..
Floege J. Submitted

REFRACTORY ANCA VASCULITIDES

Refractory disease:

- No improvement in 4 weeks
- Improvement of less than 50% in 6 weeks of treatment (as measured by BVAS/WG)
- Chronic persistent disease after more than 12 weeks

Change in therapy:

- Switch to RTX if previously treated with CYC (especially in PR3-ANCA patients) or vice versa
- Oral CYC if previous IV CYC failure (and RTX unavailable)
- IVIg 0.4 gr/kg for 5 days especially if persistent low disease activity

Potential pitfalls

- Vasculitis mimic?
- Adequate therapy?

Symptoms related to:

- Damage (ENT, proteinuria, neuropathy)
- Infection
- Cancer-related comorbidity

Rovin BH, …..
Floege J. Submitted

ANCA VASCULITIDES – RITUXIMAB REGIMENS

Induction
• Four weekly intravenous doses of 375 mg/m^2
• Four weekly intravenous doses of 375 mg/m^2 and 1 monthly infusion one and 2 months apart
Maintenance
• 1000 mg every 6 months
• 1000 mg every 4 months
• 1000 mg every 6 months for 24 months
• 4 weekly doses of 375 mg/m^2 or two biweekly doses of 1000 mg, given on the basis of laboratory parameters
• 375 mg/m^2 every 6 months
• 1000 mg every 6 months
• 1000 mg every 12 months
• 500 mg on days 1 and 15, again every 6 mon for a total of 5 doses

Rovin BH, ….. Floege J. Submitted

CLINICAL RESEARCH www.jasn.org

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

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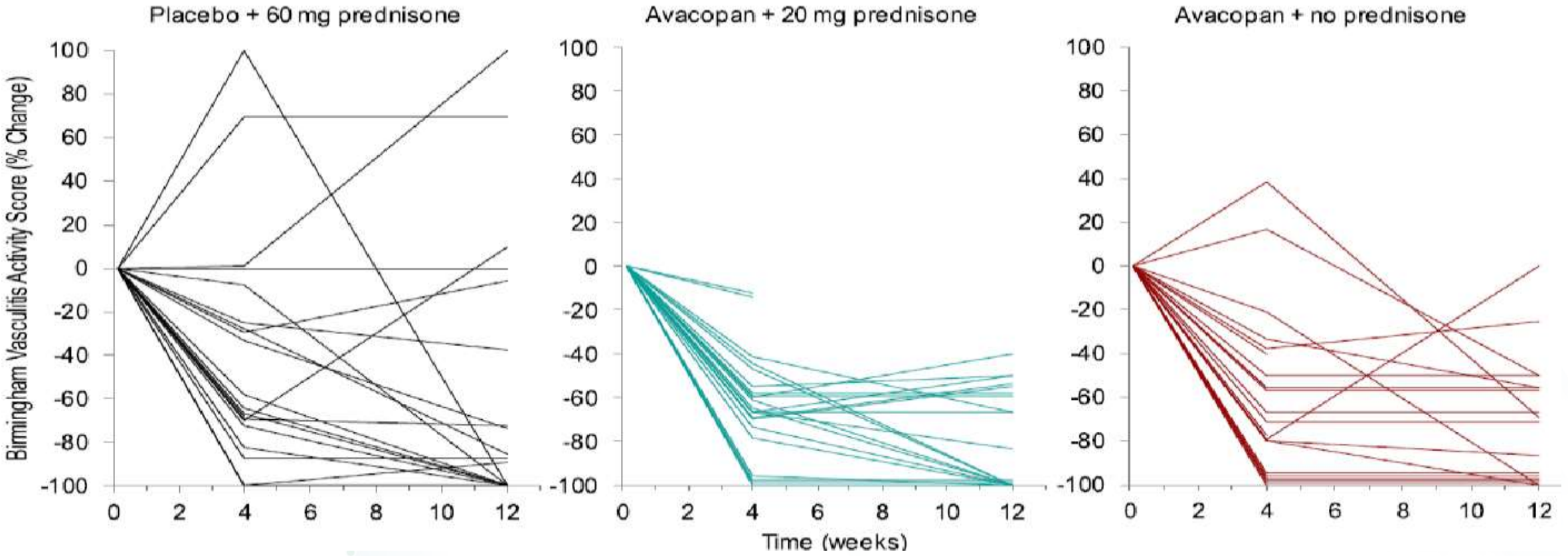
Double –blind double-placebo RCT
Avacopan : oral drug, C5a receptor inhibitor

Jayne D et al, J Am Soc Nephrol 2017

AVACOPAN FOR ANCA VASCULITIS

- **67 pts with newly diagnosed or relapsing ANCA vasculitis**
- **All treated with cyclophosphamide or rituximab.**



Jayne D et al, J Am Soc Nephrol 2017

MPGN

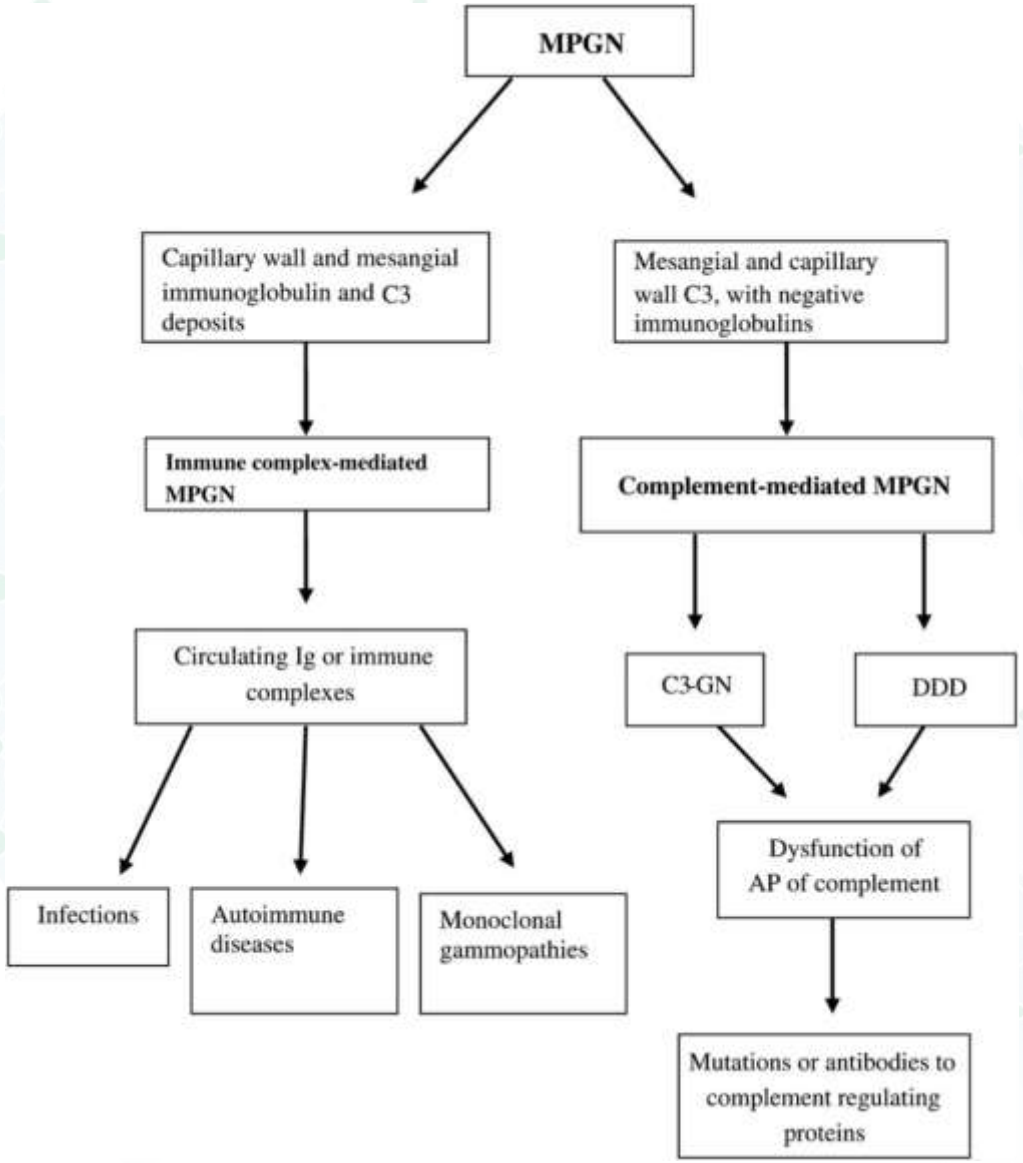
need for a new nomenclature based on pathogenesis and injury pattern

Nephrol Dial Transplant (2012) 27: 4288–4294
doi: 10.1093/ndt/gfs288
Advance Access publication 13 July 2012

Full Review

Idiopathic membranoproliferative glomerulonephritis: does it exist?

Fernando C. Fervenza[1], Sanjeev Sethi[1,2] and Richard J. Glassock[2,3]



Infectious GN

- No RCT in HBV or HIV- associated GN
- Still, arguments supporting the impact of HAART and RAAS Blockade in HIV-associated GN
- HCV- associated GN covered by update of GL on HCV in CKD (publication KI supplement + exec summary in KI on sept 19, 2018)

Conclusion

- Update of KDIGO GN Guideline underway
- Full update : many new important studies , moving field
- Publication may be expected in late 2019
- Public review : spring /summer 2019 ; register at www.kdigo.org