The 2020 KDIGO Guidelines for Glomerular Diseases

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DISCLOSURES

Dr. Rovin has the following relevant financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

Affiliation / Financial Interest	Organization
Research Grants	NIH
Medical/Scientific Advisor	Biogen, Lilly, GSK, Genentech, Pfizer, BMS, BioMarin, Aurinia, Retrophin, EMD-Serono, MorphoSys, Biocryst, Alexion, Novartis, Astra-Zenaca, Kezar

Unapproved or Off Label Disclosures

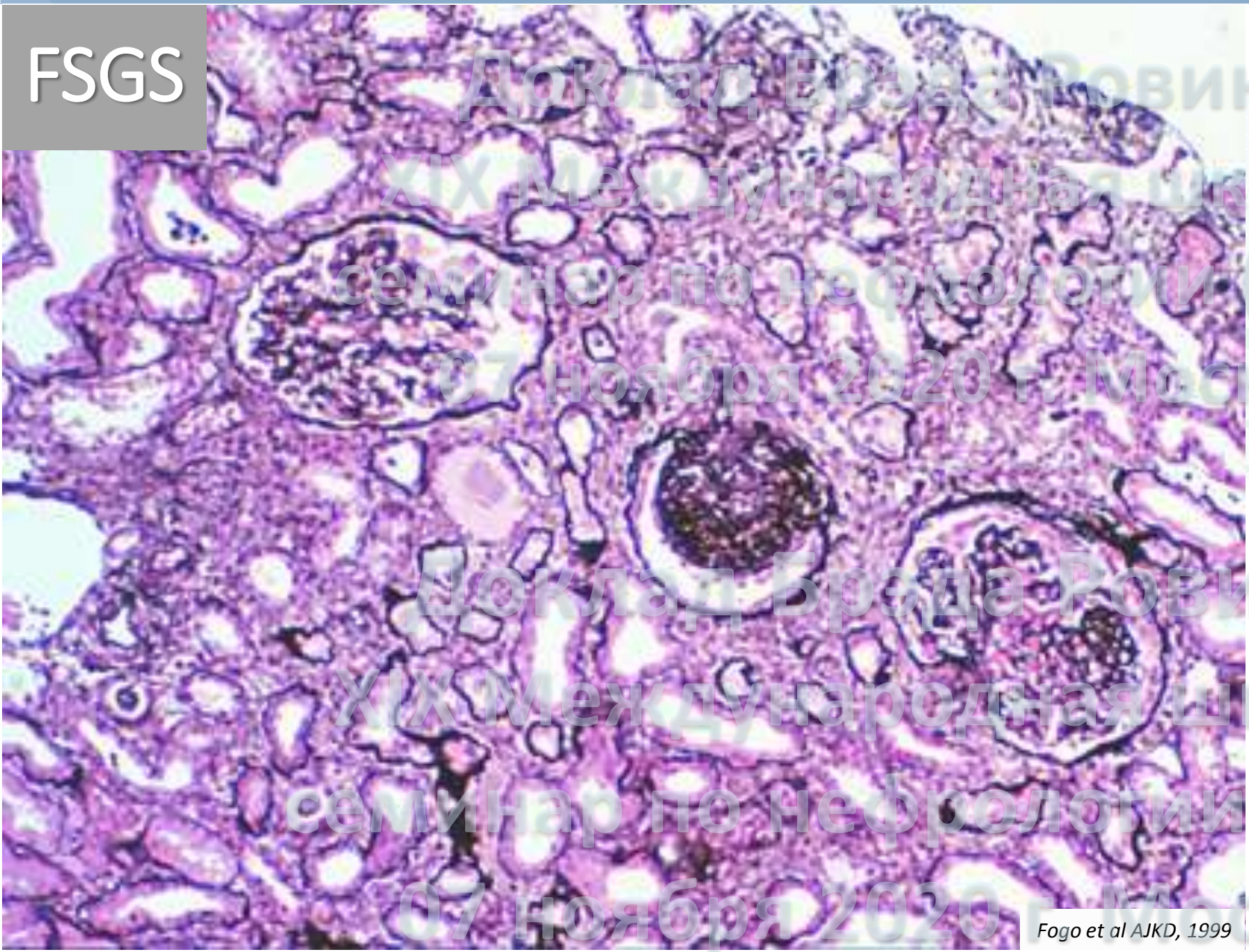
This presentation involves comments or discussion of unapproved or off-label, experimental or investigational use of Cyclophosphamide, MMF, AZA, Rituximab, CSA, Voclosporin, Belimumab, Obinutuzumab

Updates in Guideline Format in 2020

- Recommendations-based on RCTs
- Practice Points-based on a number of sources of evidence that are less rigorous than an RCT including expert opinion when there is nothing else
- The online version of the guidelines (MagicApp) is meant to be a living document that can be updated in real time as opposed to the print versions

Today, due to time constraints, I will highlight points that may be considered practice changing; a sort of potpourri of the guidelines, but will not be able to address every GN

FSGS



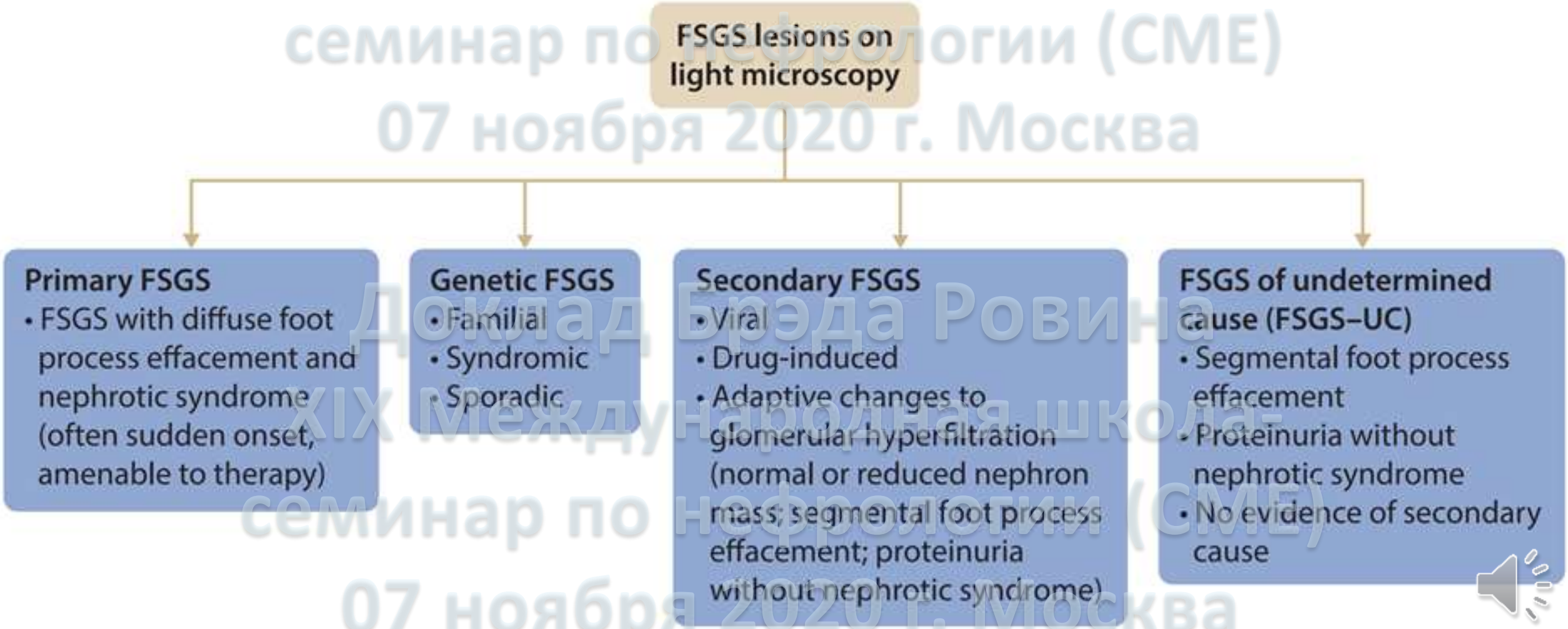
Fogo et al AJKD, 1999

Work Group:

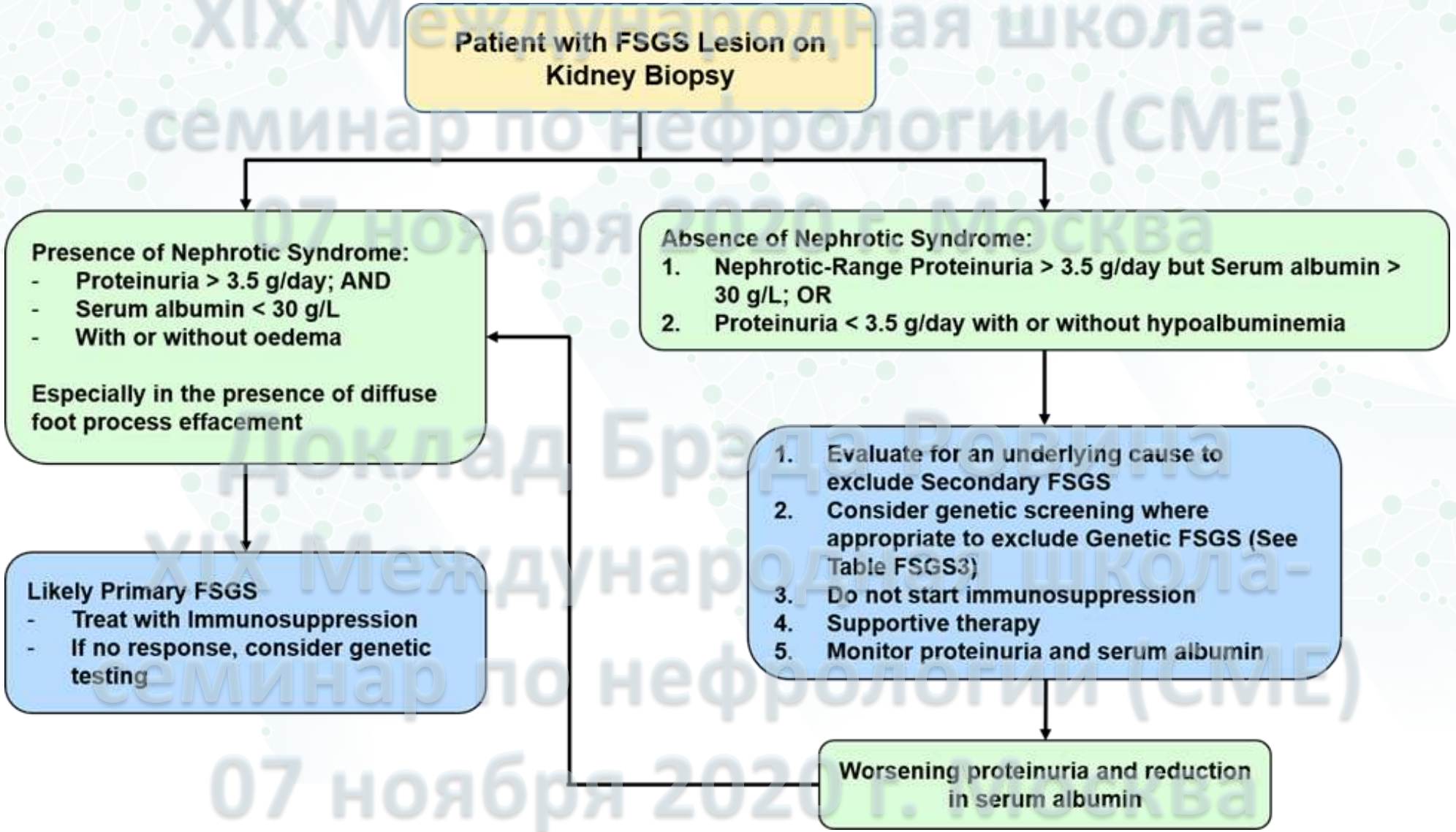
- **A Liew**
- **J Radhakrishnan**

Classification of FSGS

FSGS is not a single disease but a pattern of glomerular injury



Evaluation of FSGS



Treatment of Primary FSGS

Recommendation 6.2.2.1. We recommend that high-dose oral corticosteroids be used as the first-line immunosuppressive treatment for primary FSGS *(1D)*.

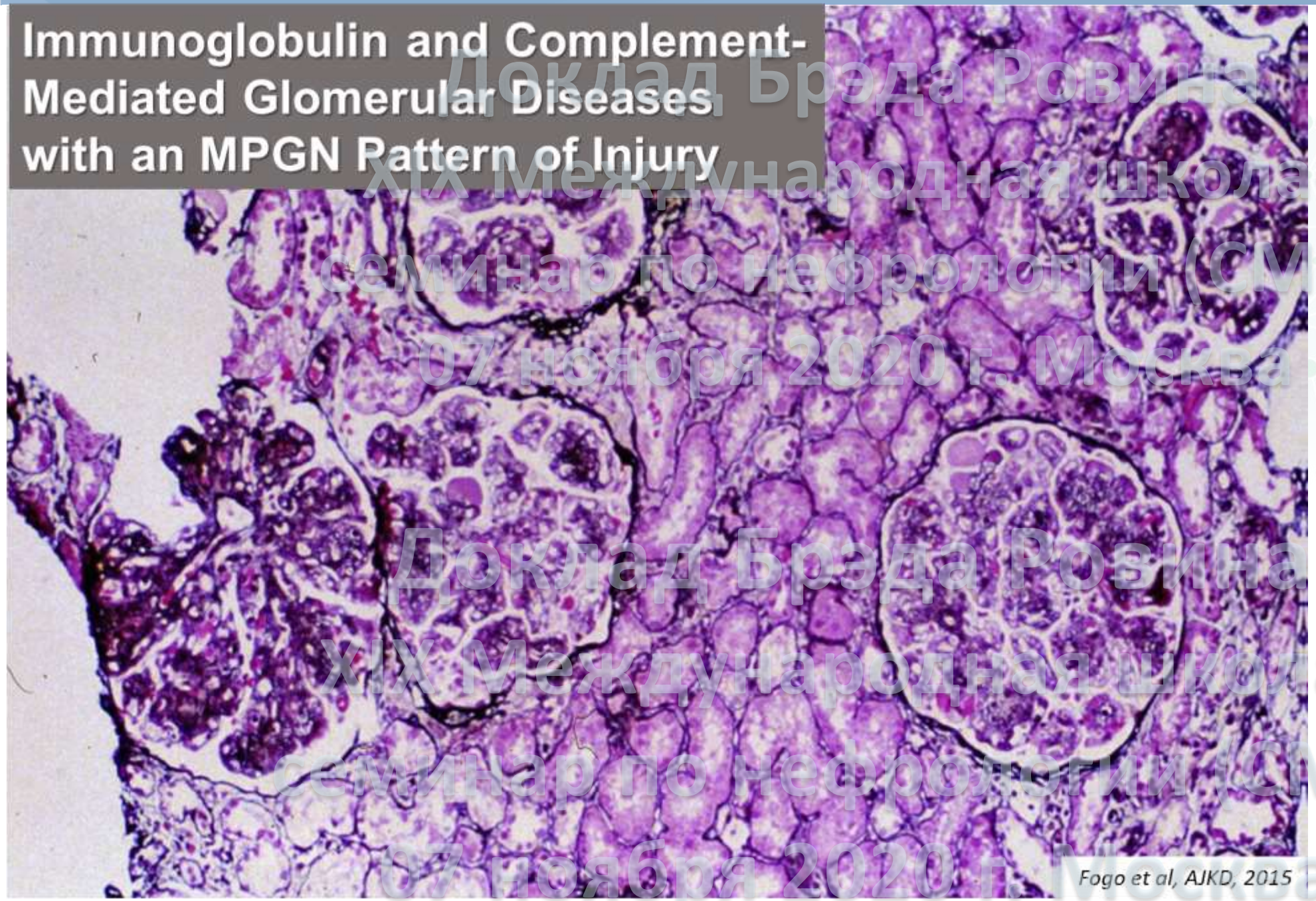
Recommendation 6.3.1.1. For adults with corticosteroid-resistant primary FSGS, we recommend that cyclosporine or tacrolimus be given for at least six months rather than continuing with corticosteroid monotherapy or not treating *(1C)*.

Treatment of Resistant FSGS

- Lack of quality evidence for any specific alternative agents
- Mycophenolate mofetil and high-dose dexamethasone, rituximab, and ACTH have been considered
- Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression
- Patients should be referred to specialized centers with the appropriate expertise, and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

Clinical Trials

Immunoglobulin and Complement-Mediated Glomerular Diseases with an MPGN Pattern of Injury



Fogo et al, AJKD, 2015

Work Group:

- C Nester
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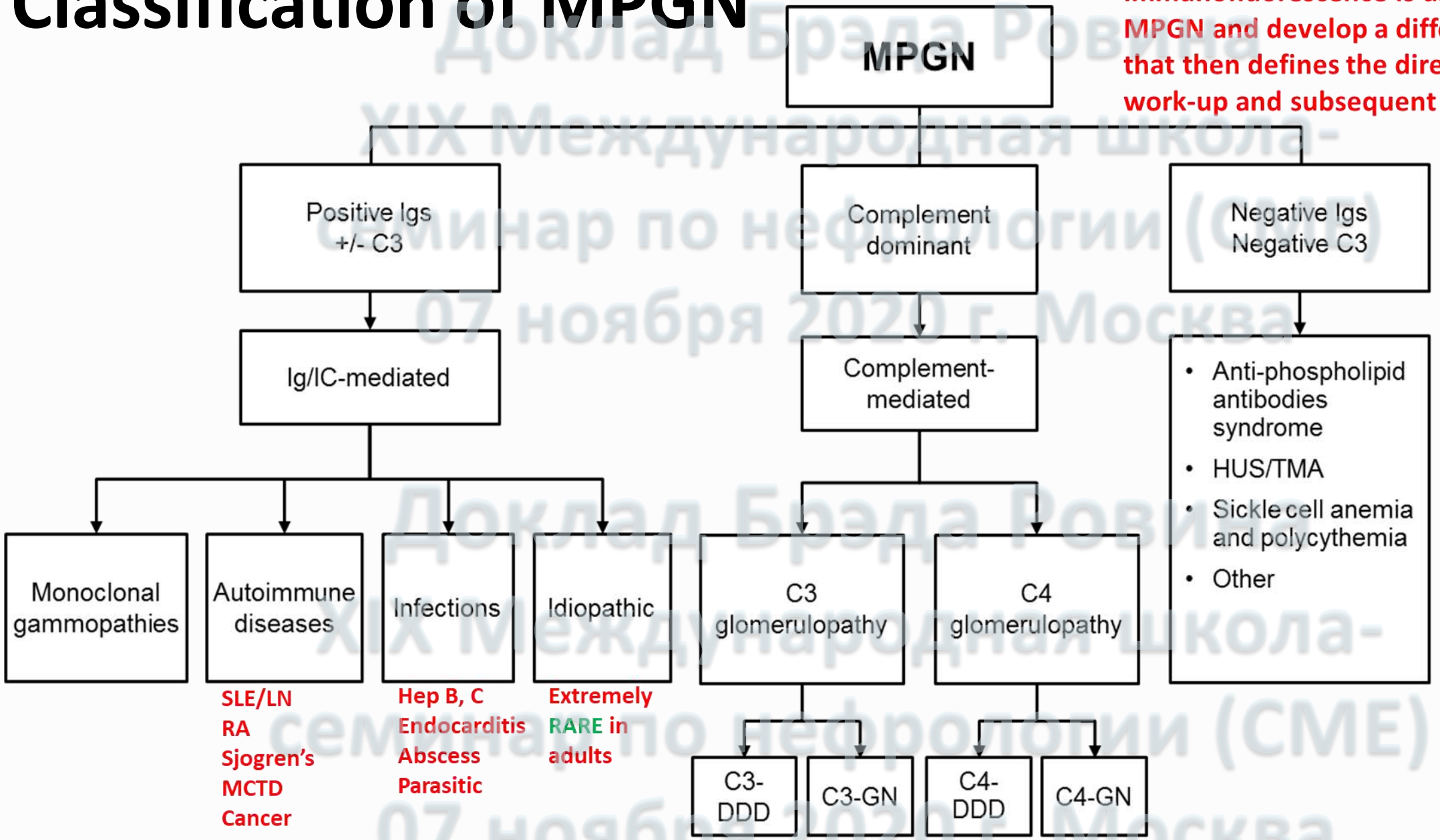
- S Sethi
- F Bridoux

The MPGN Spectrum

- **MPGN is not a single disease but a pattern of glomerular injury**
- The etiology of many of the glomerular diseases that often present with a membranoproliferative pattern of injury is better understood
- The MPGN pattern often derives from the glomerular deposition of immunoglobulins and complement, either as immune complexes, monoclonal immunoglobulins, or in the setting of a dysregulated alternative complement pathway
- The old nomenclature of MPGN Types I, II (DDD) and III should be abandoned
- Because trials in the past included a heterogeneous mix of patients, there is very little high-quality evidence on which to base recommendations, and therefore only practice points are offered

Classification of MPGN

Immunofluorescence is used to classify MPGN and develop a differential diagnosis that then defines the direction of diagnostic work-up and subsequent treatment



Potential Diagnostic Pitfalls

- **Practice Point. If no underlying etiology is found for ICGN after extensive work-up, evaluate for complement dysregulation.**
- **Practice Point. Rule out infection-associated glomerulonephritis or post-infectious glomerulonephritis prior to assigning the diagnosis of C3G**
- **Practice Point. Evaluate for the presence of a monoclonal protein in patients who present for the first time with a C3G diagnosis at >50 years of age.**

- **If an ICGN is found and an infection or autoimmune disease is not obvious, before declaring the process as idiopathic it is prudent to exclude dysregulated alternative pathway activation as this may inform treatment; complement may be dysregulated in ICGN and classic C3G may masquerade as an ICGN if infection was the trigger for C3G**

- **If a diagnosis of C3G is being considered it is prudent to exclude infection and monoclonal gammopathy as this may inform treatment; immunoglobulin may be masked in cases that look like C3G (pronase the tissue); monoclonal proteins may be able to active the alternative complement pathway**

Management of ICGN-Practice Points

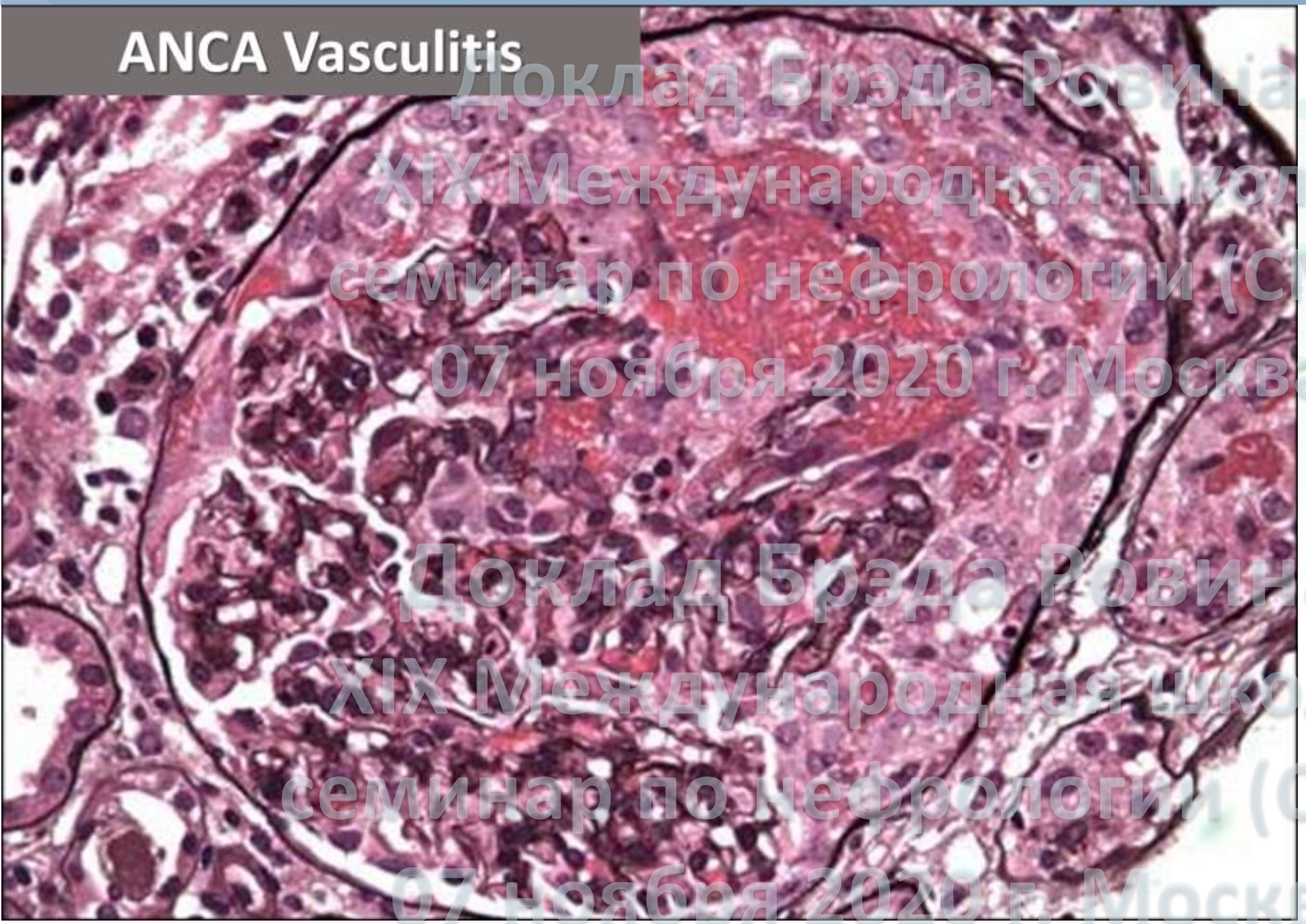
- For patients with idiopathic ICGN and proteinuria <3.5 g/day, the absence of the nephrotic syndrome, and a normal eGFR, we suggest supportive therapy with RAS inhibition alone
- For patients with idiopathic ICGN, nephrotic syndrome and normal or near-normal serum creatinine, try a limited treatment course of corticosteroids
- For patients with idiopathic ICGN, abnormal kidney function (but without crescents), active urine sediment, with or without nephrotic-range proteinuria, add corticosteroids and immunosuppressive therapy to supportive care
- For patients with rapidly progressive crescentic idiopathic ICGN treat with high-dose corticosteroids and cyclophosphamide
- For most patients with idiopathic ICGN presenting with a serum creatinine > 3 mg/dl or an eGFR <30 ml/min/1.73m^2 treat with supportive care alone *(evaluate bx activity)*

Management of C3G-Practice Points

- In the absence of a monoclonal gammopathy, C3G in patients with moderate to severe disease should be treated initially with MMF, and if this fails eculizumab

- Patients who fail to respond to treatment approaches should be considered for a clinical trial where available

ANCA Vasculitis



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- **D Jayne**

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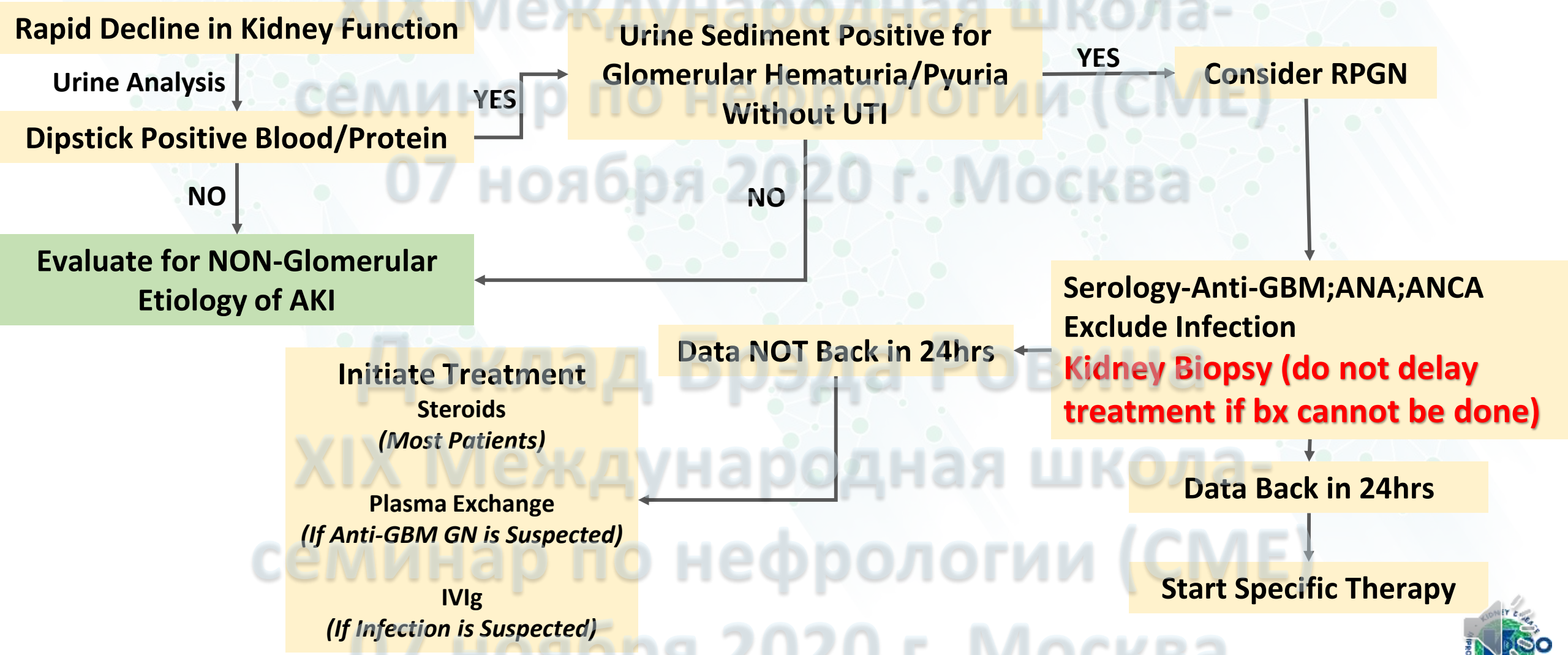
Work-Up of RPGN



Treatment of ANCA-Associated Nephritis

Recommendation. Corticosteroids in combination with cyclophosphamide or rituximab should be used as initial treatment of new-onset AAV *(1B)*

Rituximab preferred	Cyclophosphamide preferred
Children and adolescents	Low baseline IgG < 3 g/l
Pre-menopausal women and men concerned about their fertility	Hepatitis B exposure (HBsAg positive)
Frail elderly	Rituximab difficult to access
Glucocorticoid-sparing especially important	Severe GN (SCr at diagnosis > 350 µmol/L) Combination of two iv pulses of cyclophosphamide with rituximab can be considered
Relapsing disease	
PR3-ANCA disease	
In the intensive care unit (minimizes leukopenia risk)	

Recommendation. Rituximab or azathioprine and low dose glucocorticoids should be used for maintenance after induction of remission *(1C)*

Rituximab preferred	Azathioprine preferred
Relapsing disease	Hepatitis B exposure (HBsAg positive)
PR3-ANCA disease	Limited availability of Rituximab
Frail elderly	
Glucocorticoid-sparing especially important	
Azathioprine allergy	

Futility During Induction

Practice Point. Discontinue immunosuppressive therapy after three months in patients who remain dialysis-dependent and who do not have any extrarenal manifestations of disease

Plasma Exchange for AAV

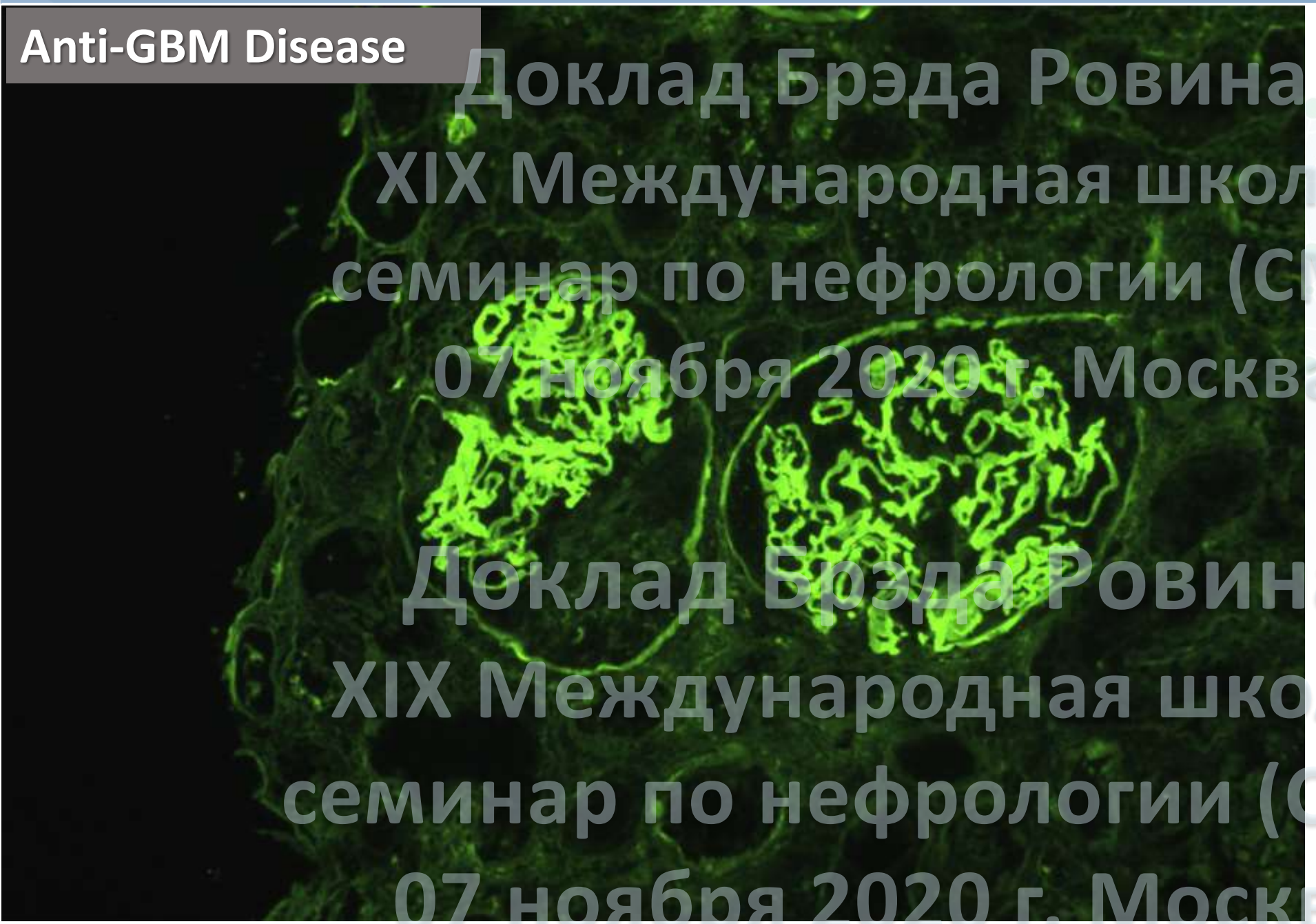
Practice Point. Consider plasma exchange for patients requiring dialysis or with rapidly increasing SCR, and in patient with diffuse alveolar hemorrhage who have hypoxemia

- PLEX remains controversial-earlier studies (MEPEX) suggested a benefit in kidney outcomes for patients presenting with severe kidney failure (SCr > 500 µmol/L)
- A meta-analysis suggested reduced incidence of ESKD at 12 months
- PEXIVAS was recently reported-PLEX in patients presenting with eGFR < 50 ml/min or alveolar hemorrhage did not delay the time to ESKD or death over a median follow-up of 2.9 years
- Caveats:
  - No kidney biopsy required for trial so patients with poor kidney function and chronicity could not be distinguished from patients with poor kidney function, inflammation, and no chronicity
  - Subgroup analysis suggested patients with severe pulmonary hemorrhage may benefit from PLEX (HR 0.67; 95% CI 0.28-1.64)

PLEX should not be routinely added to patients with AAV and kidney failure but certain subgroups may benefit, and PLEX can be considered

Jayne et al, JASN, 2007; Walsh et al, AJKD, 2011 Walsh et al. NEJM, 2020

Anti-GBM Disease



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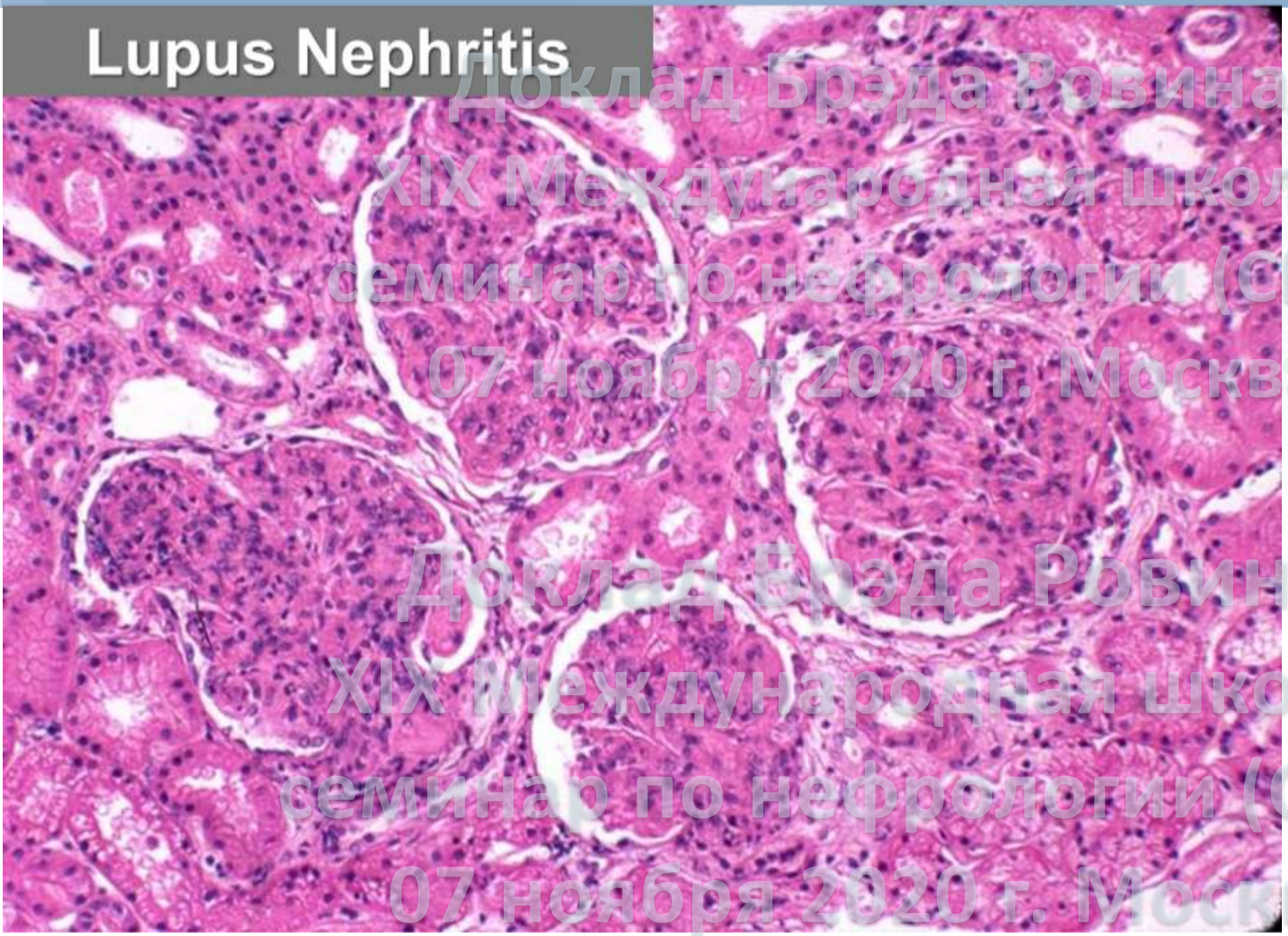
Treatment of Anti-GBM GN

Recommendation. Initiate immunosuppression with cyclophosphamide and corticosteroids plus plasmapheresis in all patients with anti-GBM GN except those who are dialysis-dependent at presentation have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage (1C).

- **Practice Point. Treatment for anti-GBM disease should start without delay**
- **Practice Point. Plasma exchange should be performed until anti-GBM titers are no longer detectable**
- **Practice Point. No maintenance therapy of anti-GBM disease is necessary**
- **Practice Point. Anti-GBM and ANCA double positives should be treated with maintenance therapy**
- **Practice Point. In refractory anti-GBM disease, rituximab may be tried**
- **Practice Point. Kidney transplantation in patients with kidney failure due to anti-GBM disease should be postponed until anti-GBM antibodies remain undetectable for at least six months**

Lupus Nephritis



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An Important Update for LN Induction

INDUCTION THERAPY for PROLIFERATIVE LN-2012-KDIGO

IV Methylprednisolone 0.5-1g/d for 1-3 days, followed by
Oral Prednisone, up to 1mg/kg/d ideal body weight
PLUS:

- IV CYC 0.5-1g/m² q Mo X6
- PO CYC 1-1.5mg/kg/d, maximum 150 mg/d for 2-4 months
- IV CYC 500 mg q2 Wks X6
- Oral MMF 2-3g/d for 6 months

Rovin et al, Kidney Int Supplements, 2012

INDUCTION THERAPY for PROLIFERATIVE LN-2020 KDIGO

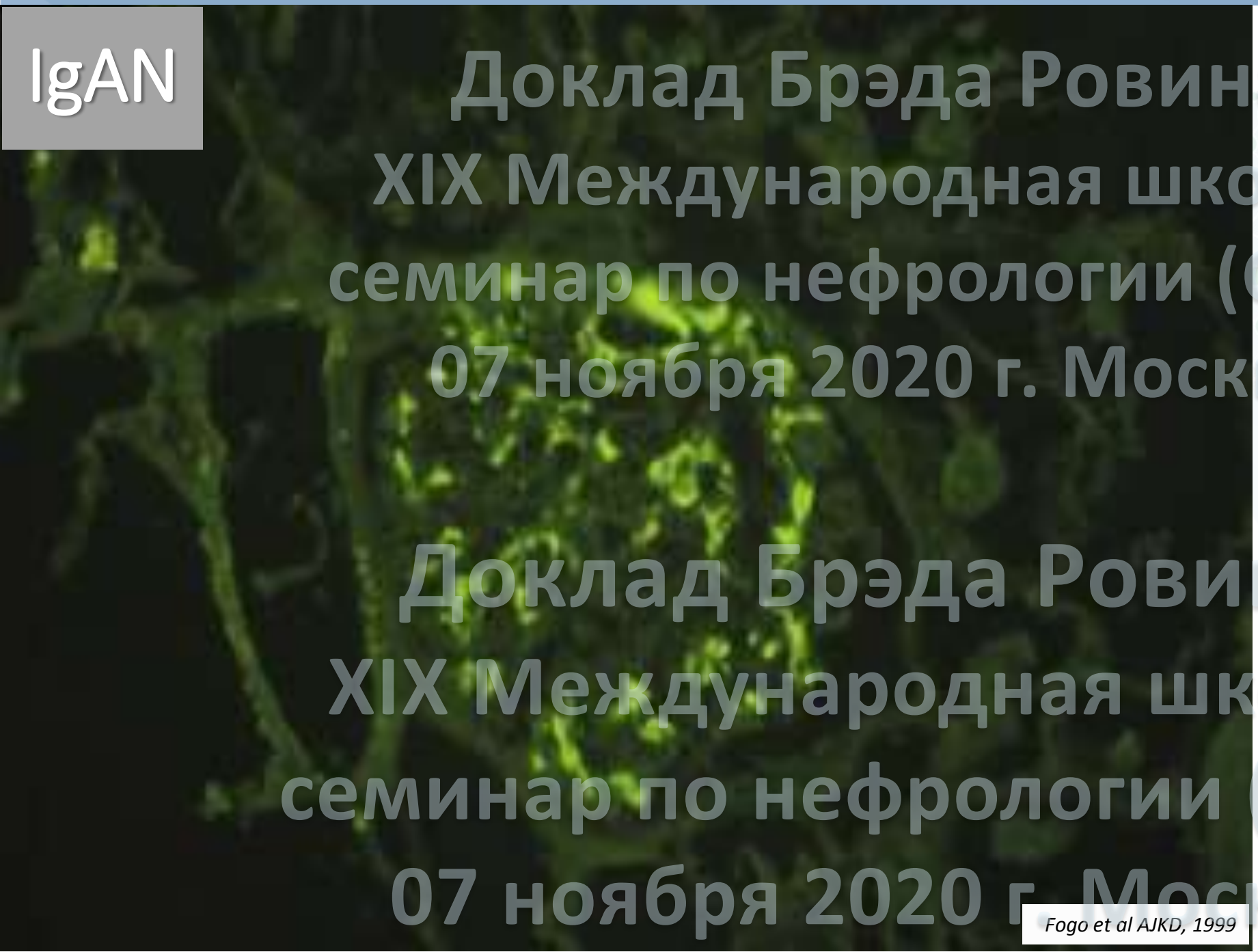
IV Methylprednisolone 0.75-1.5g total, followed by
Oral Prednisone 0.6-1mg/kg/d ideal body weight, Taper to ≤7.5 mg/d by end of 3 months
PLUS:

- IV CYC 500 mg q2 Wks X6
- *Or*
- Oral MMF 2-3g/d for 6 months

Chan et al, KDIGO, 2020

	Standard-dose scheme	Reduced-dose scheme
Methylprednisolone pulses	0.25–0.5 g/day × 3	0.25–0.5 g/day × 2–3
Oral prednisone equivalent		
Week 0–2	0.6–1.0 mg/kg (max 80 mg/day)	20–25 mg
Week 3–4	0.3–0.5 mg/kg	20 mg
Week 5–6	20 mg	15 mg
Week 7–8	15 mg	10 mg
Week 9–10	12.5 mg	7.5 mg
Week 11–12	10 mg	5 mg
Week > 12	5.0–7.5 mg	2.5 mg

IgAN



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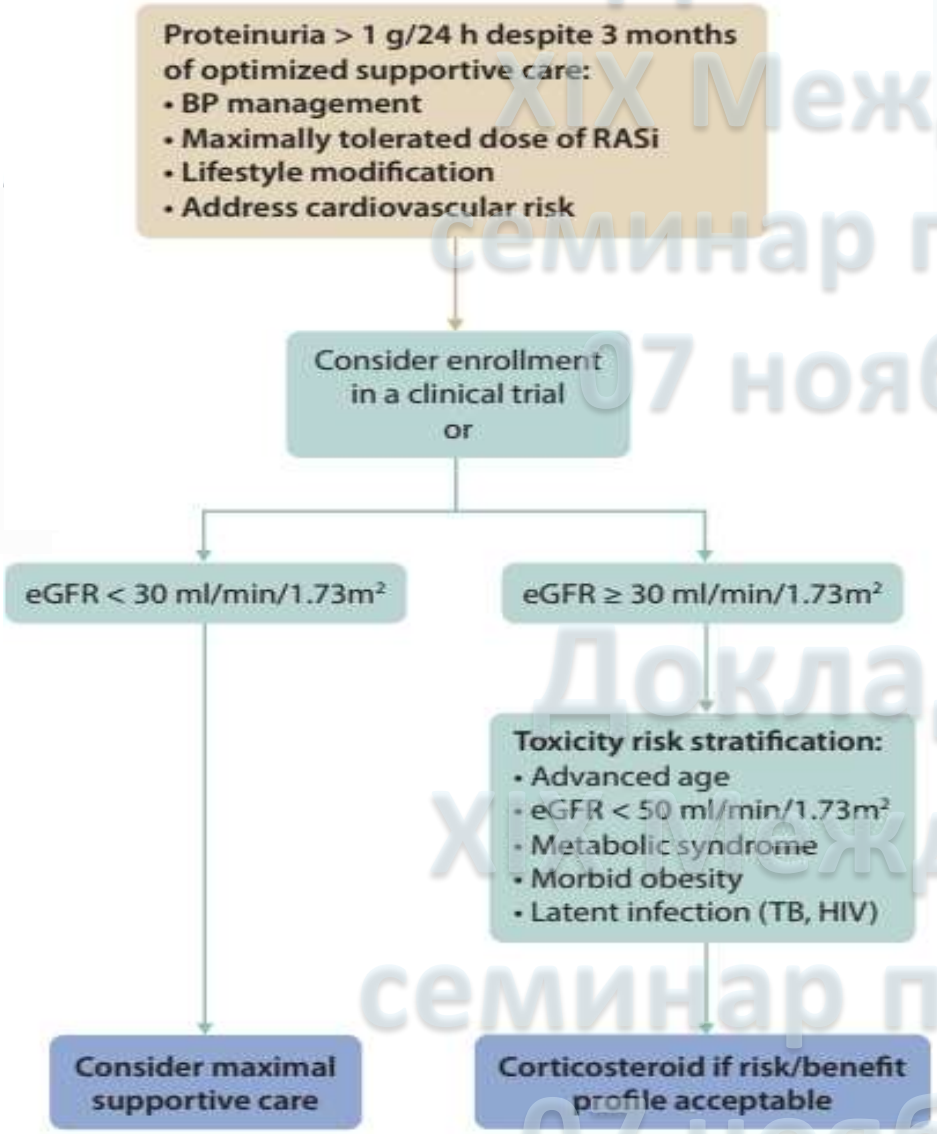
Fogo et al AJKD, 1999

Treatment of IgAN



Recommendation. We recommend that all patients with proteinuria >0.5 g/24h, irrespective of whether they have hypertension, are treated with either an ACEi or ARB *(1B)*.

Recommendation. We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care are considered for a six-month course of corticosteroid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR below 50 ml/min/1.73 m^2 *(2B)*.

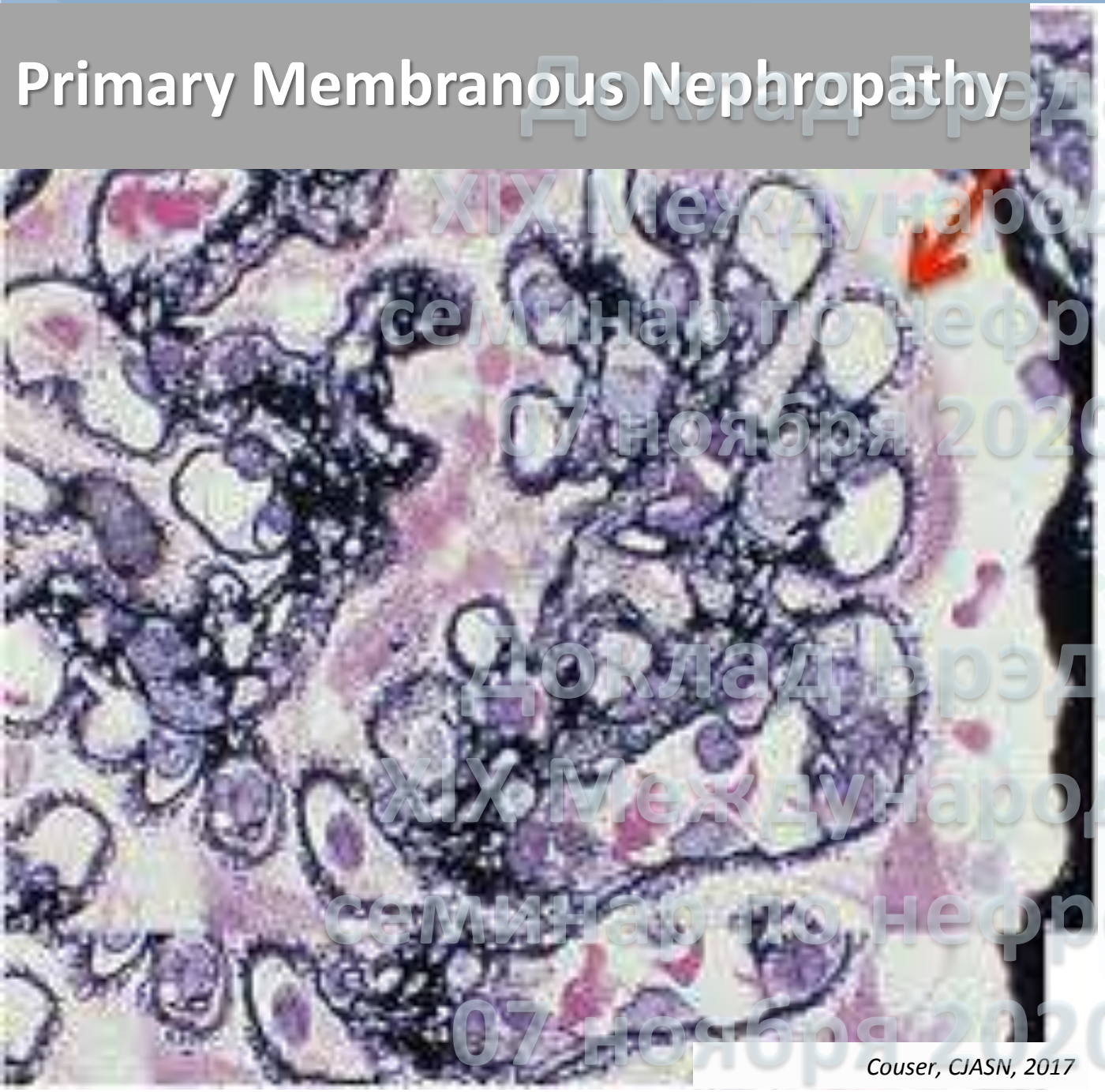
What Not to Use to Treat IgAN

Agent	Suggested usage	Remarks
Anti-platelet agents	Not recommended	No documented evidence of efficacy
Anticoagulants	Not recommended	No documented evidence of efficacy
Azathioprine	Not recommended	No evidence for efficacy as monotherapy or when combined with corticosteroids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom corticosteroids are being considered MMF may be used as a steroid-sparing agent	In a single RCT conducted in China, MMF with low dose corticosteroids was non-inferior to standard dose corticosteroids for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/day. There were significantly fewer corticosteroid related side effects in the combination therapy arm. (PICO 18.16)
	Non-Chinese patients There is insufficient evidence to support the use of mycophenolate mofetil	In the RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy. (PICO 18.15)

Practice Point. Tonsillectomy in IgAN:

- **Tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients.**
- **Tonsillectomy may be indicated in some national guidelines for the treatment of recurrent tonsillitis in patients with IgAN.**
- **Multiple studies from Japan have reported improved kidney survival and partial or complete remission of hematuria and proteinuria following tonsillectomy alone or with pulsed corticosteroids.**

Primary Membranous Nephropathy



Couser, CJASN, 2017

Work Group:

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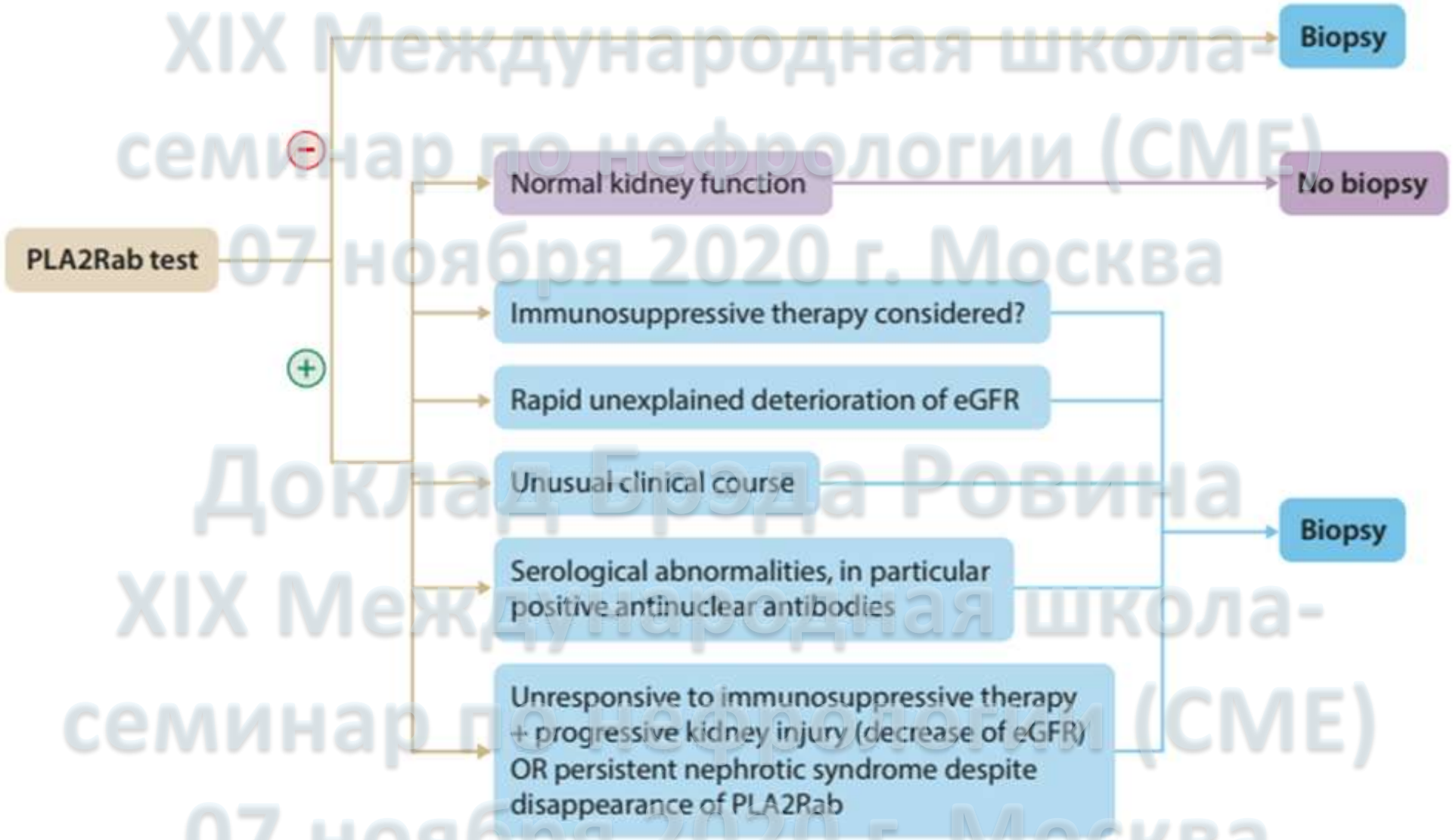
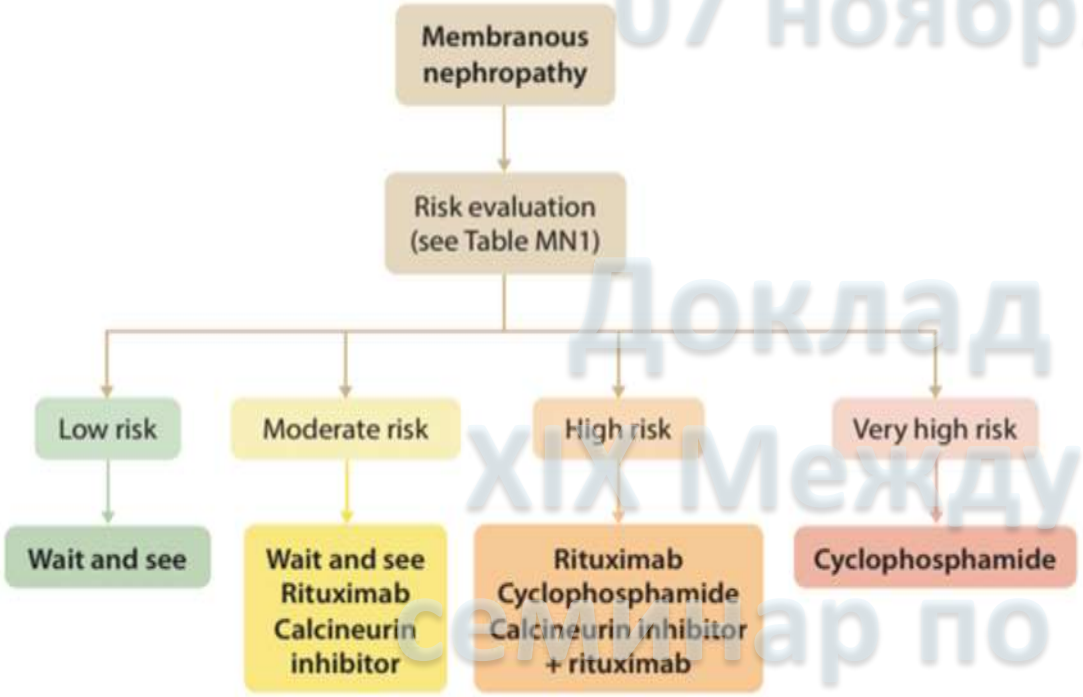
Biopsy for PLA2R+ Proteinuric Patient



Treatment of Primary MN

Recommendation. For patients with MN and at least one risk factor for disease progression, we recommend using rituximab or cyclophosphamide and steroids for six months, or tacrolimus-based therapy for at least six months, with the choice of treatment depending on the risk estimate *(1B)*.



Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria < 3.5 g/d and/or serum albumin > 30 g/L	• Normal eGFR, proteinuria > 4 g/d and no decrease > 50% after 6 months of conservative therapy with angiotensin-converting enzyme inhibitors/ angiotensin II-receptor blocker • PLA2Rab < 50 RU/ml • Mild low molecular weight proteinuria • Selectivity index < 0.15 • U IgG < 250 mg/d	• eGFR < 60 ml/min/1.73 m² • Proteinuria > 8 g/d for > 6 months • PLA2Rab > 150 RU/ml • High low molecular weight proteinuria • U IgG > 250 mg/d • Selectivity index > 0.20	• Life-threatening nephrotic syndrome • Rapid deterioration of kidney function not otherwise explained • High low molecular weight proteinuria in two urine samples collected with interval of 6–12 months

Public Review is Over
Revisions Being Completed
Anticipate a Release Date of Winter