Mrs. XY, born 1969

- CKD stage IIIa (eGFR 50-60 mL/min) 11/2020, biopsy shows IgAN (M0, E0, S1, T0, C0)
- Recurrent lower abdominal pain (negative for CED, celiac disease, etc.)
  - BP mostly <130/80 with 12 mg candesartan
  - 176 cm, 75 kg, no nicotine, little alcohol, "…no time for sports…"

Date	5-crea [mg/dL]	eGFR [mL/min]	Proteinuria [g/g crea]	
3/2020	1.1	57	1.3	
12/2020	1.32	47	1.69	**Biopsy, candesartan 16 ≥ 32 mg, diuretic**
3/2021	1.39	44	1.36	
6/2021	1.67	35	1.77	

Reich HN, Floege J. *Clin J Am Soc Nephrol.* 2022;17(8):1243-1246.

Supportive Therapy

- **Level 1 Recommendations**
  - Control blood pressure (sitting systolic BP in the 120s)
  - ACEI or ARB therapy with uptitration of dosage or combination
  - Avoid dihydropyridine calcium channel blockers
  - Control protein intake

ALL

- **Level 2 Recommendations**
  - Restrict NaCl and fluid intake, institute diuretic therapy
  - Non-dihydropyridine calcium channel blocker therapy
  - Control each component of the metabolic syndrome
  - Aldosterone antagonist therapy, ß-blocker therapy
  - Smoking cessation

As many measures as possible

Floege J, Eitner F. *J Am Soc Nephrol*. 2011;22(10):1785-1794.

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group

2021 Clinical Practice Guideline for the Management of Glomerular Diseases

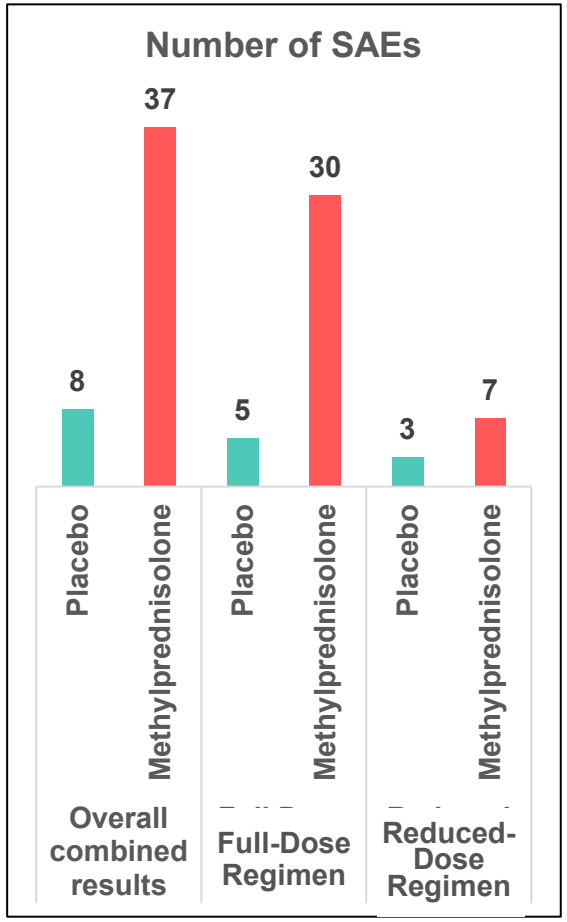
- **Recommendation 2.3.2**
  - **We recommend that all patients with proteinuria >0.5 g/24 h, irrespective of whether they have hypertension, are treated with either an ACEi or ARB *(1B)*.**

- **Recommendation 2.3.3**
  - **We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care are considered for a 6-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).**

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int*. 2021;100(4S):S1-S276.

TESTING Trial

Retarded Onset Primary Endpoint: Death, Dialysis, eGFR Loss >40%



- **Full-dose methylprednisolone**
  - 6x increase in SAEs

- **Half-dose methylprednisolone**
  - 2x as many SAEs
  - Still retarded onset of primary endpoint

- 95% Southeast Asian population
- Event rate parallel after ~2.5 years

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

Lv J, et al. *JAMA*. 2022;327(19):1888-1898.

Mrs. XY

Date	5-crea [mg/dL]	eGFR [mL/min]	Proteinuria [g/g crea]	
3/2020	1.1	57	1.3	
12/2020	1.32	47	1.69	Biopsy, candesartan 16 ≥ 32 mg, diuretic
3/2021	1.39	44	1.36	
6/2021	1.67	35	1.77	Convent. budesonide 9 mg/d
8/2021	1.77	33	1.19	Dapagliflozin 10 mg/day
9/2021	1.88	31	0.84	
1/2022	2.09	27	0.25	
7/2022	2.0	28	0.33	DVT + pulm. embolism
12/2022	1.98	28	0.82	Budesonide taper

Reich HN, Floege *J. Clin J Am Soc Nephrol.* 2022;17(8):1243-1246

Mr. JG, born 1975

- 47-year-old Caucasian man who presented with a 6-week history of increasing leg swelling associated with worsening fatigue, reduced exercise tolerance, and breathlessness on exertion
- Past medical history: obese (BMI 34), type 2 diabetes mellitus, hypertension, dyslipidemia
- Drug history: amlodipine 5 mg od, atorvastatin 20 mg nocte, gliclazide 80 mg bd, dapagliflozin 10 mg od
- Autoantibody screen (including anti-PLA2R) negative

Date	Serum creatinine [μmol/L]	eGFR [mL/min]	Serum albumin [g/L]	Blood glucose [mmol/L]	HBA1c [mmol/mol]	Total cholesterol [mmol/L]	Spot UPCR [mg/mmol]
First Visit	131	58	127	7.3	58	8.9	507

Mr. JG

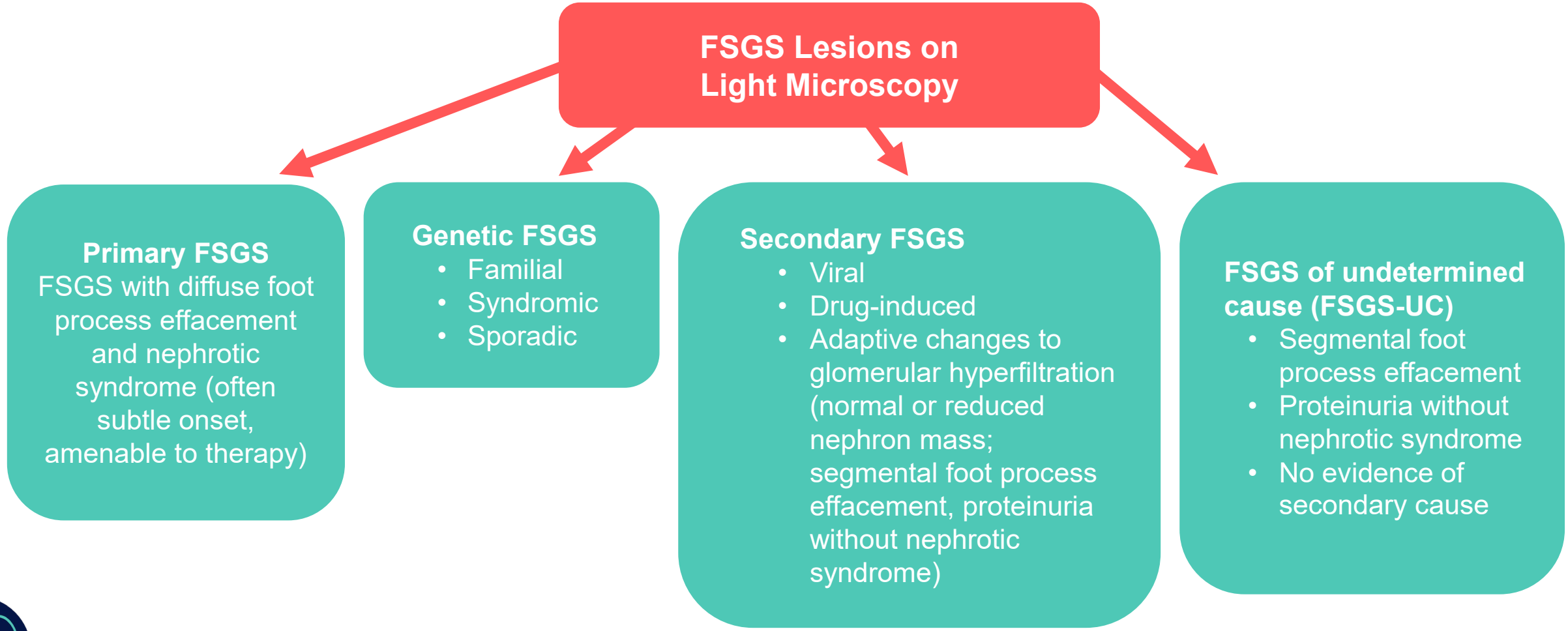
- Renal USS: 2 normal-sized kidneys, no anatomical abnormality
- Renal biopsy:

- Light:
  - 28 glomeruli, 3 with segmental scars
  - Remaining glomeruli all normal
  - Modest acute tubular injury
  - Tubulointerstitium < 10% interstitial fibrosis

- Immunofluorescence studies:
  - Negative for IgG, IgA, IgM, C3, C1q

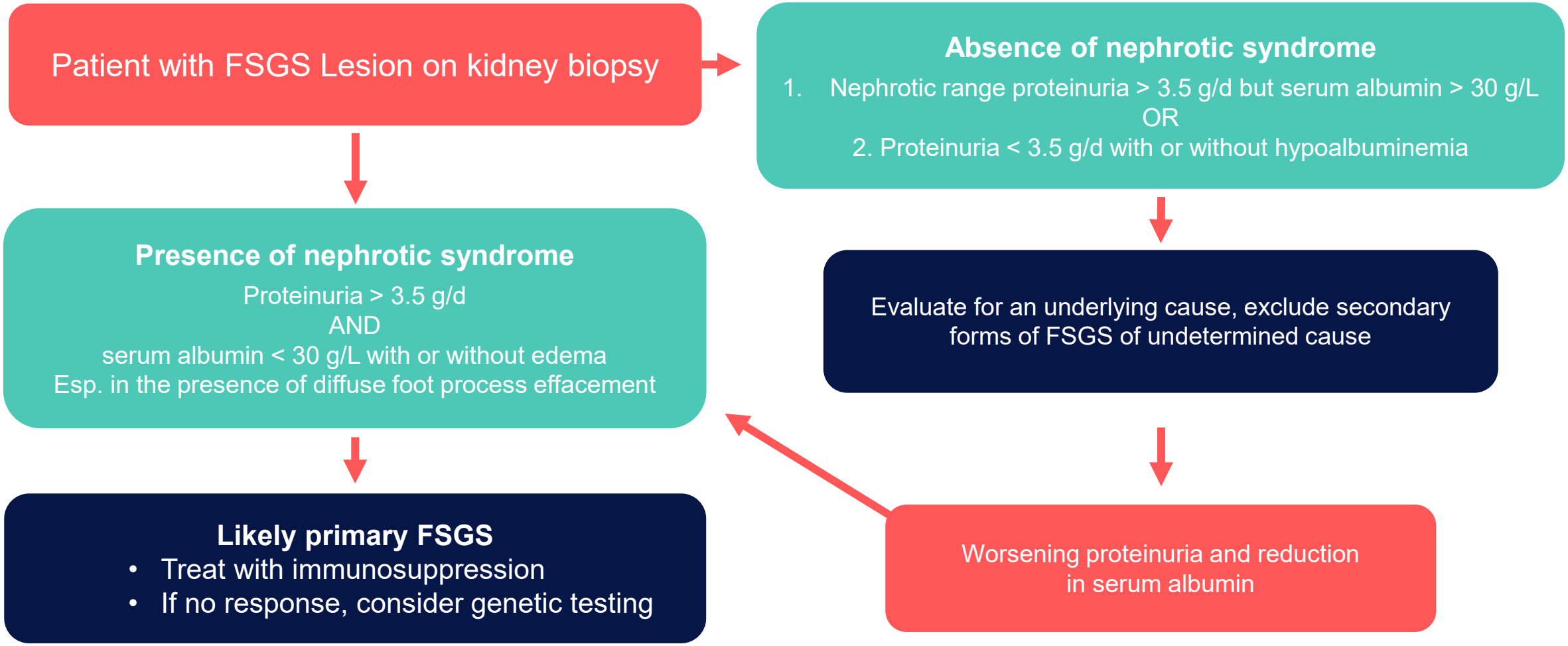
- Electron microscopy:
  - Widespread foot process effacement with microvillus formation
  - No electron-dense deposits seen
  - Normal GBM morphology & thickness

KDIGO: Classification of FSGS



Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int.* 2021;100(4S):S1-S276.

KDIGO: Evaluation of a Patient with FSGS



Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int.* 2021;100(4S):S1-S276.

Factors to Consider in Treatment

- Nephrotic
- High proteinuria
- Impaired kidney function

IMMUNOSUPRESSION → **STEROIDS**

- Diabetes
- Obesity
- Hypertension
- Dyslipidemia

CONTRAINDICATIONS → **STEROIDS**

Mr. JG

- Treatment
  - Calcineurin inhibitor, tacrolimus
- Outcome
  - No edema
- He is now enrolled in a clinical trial

Date	Serum creatinine [μmol/L]	eGFR [mL/min]	Serum albumin [g/L]	Blood glucose [mmol/L]	HBA1c [mmol/mol]	Total cholesterol [mmol/L]	Spot UPCR [mg/mmol]
First Visit	131	58	127	7.3	58	8.9	507
6 Months Later	139	57	**39**	--	--	**4.9**	**223**

FSGS Clinical Trials

- APOL1 mutation
- Podocyte biology/glomerular signaling
- Chemokine receptor 2 antagonist
- TRPC5 inhibitor
- Sparsentan: dual angiotensin receptor blocker & endothelium antagonist

DUET: A Phase 2 Study Evaluating the Efficacy and Safety of Sparsentan in Patients with FSGS

Sparsentan has shown a very clear antiproteinuric effect and preservation of GFR.

Trachtman H, et al. *J Am Soc Nephrol*. 2018;29(11):2745-2754.

Study Design of the Phase 3 Sparsentan Versus Irbesartan (DUPLEX) Study in Patients with Focal Segmental Glomerulosclerosis

Baseline Characteristics of Adults Enrolled in the Ongoing Phase 3 Randomized, Double-Blind, Active-Control Trial of Sparsentan for the Treatment of Immunoglobulin A Nephropathy (PROTECT)

Sparsentan has a significant antiproteinuric effect in FSGS, but also in IgA nephropathy.

Komers R, et al. *Kidney Int Rep*. 2020;5(4):494-502; Wong M, Barratt J, et al. *Nephrol Dial Transplant*. 2022;37(Supplement_3):gfac067.008. Abstract MO209.

Mechanisms of Progressive Kidney Disease

- Glomerular sclerosis
- Tubular interstitial fibrosis & inflammation
- Mode of action of RAAS inhibitors
- Altering glomerular hemodynamics
- Endothelium receptor antagonism

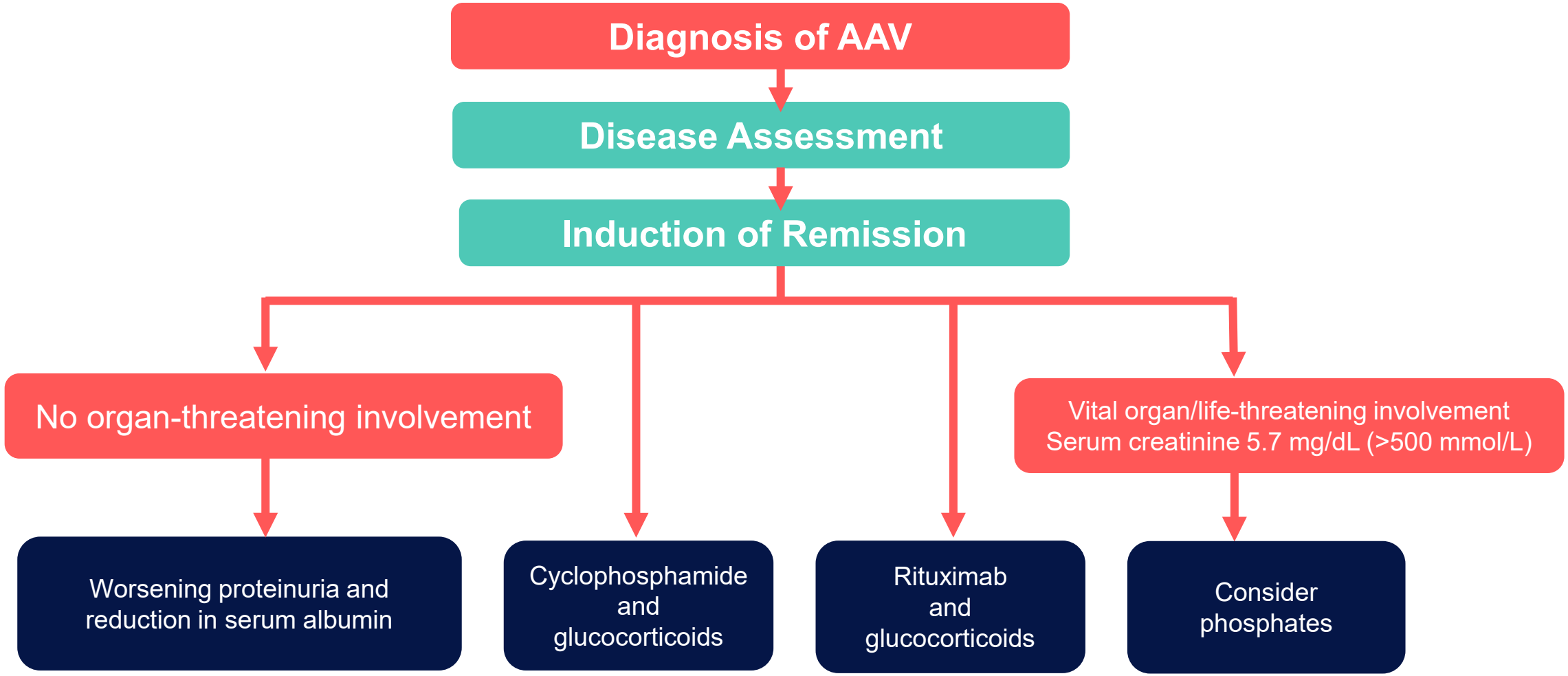
- Glomerular hyperfiltration & scarring
- Proteinuria
- Tubular interstitial response

Ms. MF, born 1955

- History
  - 6 months: flitting polyarthritis, 3 kg weight loss, drenching night sweats
  - 2 weeks: cough with hemoptysis, nasal congestion, epistaxis, profound malaise/fatigue
- Investigations
  - 3+ proteinuria, 3+ hematuria, normal kidney size on ultrasound
  - Hemoglobin 87 g/L, white count 15.3 $x10^9$/L, PR3-ANCA negative, MPO-ANCA 130 (normal < 3), anti-GBM negative, ANA negative, complements normal
  - Scattered infiltrates on chest CT with normal pO_2 on room air
- Kidney biopsy
  - > 50% glomeruli mixed cellular and fibrous crescents, foci of acute glomerular necrosis with neutrophil debris, 50% tubular-interstitial atrophy and inflammation; Berden class “mixed”
- Diagnosis
  - Microscopic polyangiitis

- Acute kidney injury
- Progressive multisystem features
- Recent prominent lung involvement

KDIGO: Recommendations in AAV



Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int.* 2021;100(4S):S1-S276.

AAV Treatment Comparison and Selection

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Premenopausal women and men concerned about fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3-ANCA disease	• Rituximab difficult to access • Severe GN (SCr > 4 mg/dL [35 mmol/L]), combination of 2 IV pulses of cyclophosphamide with rituximab can be considered

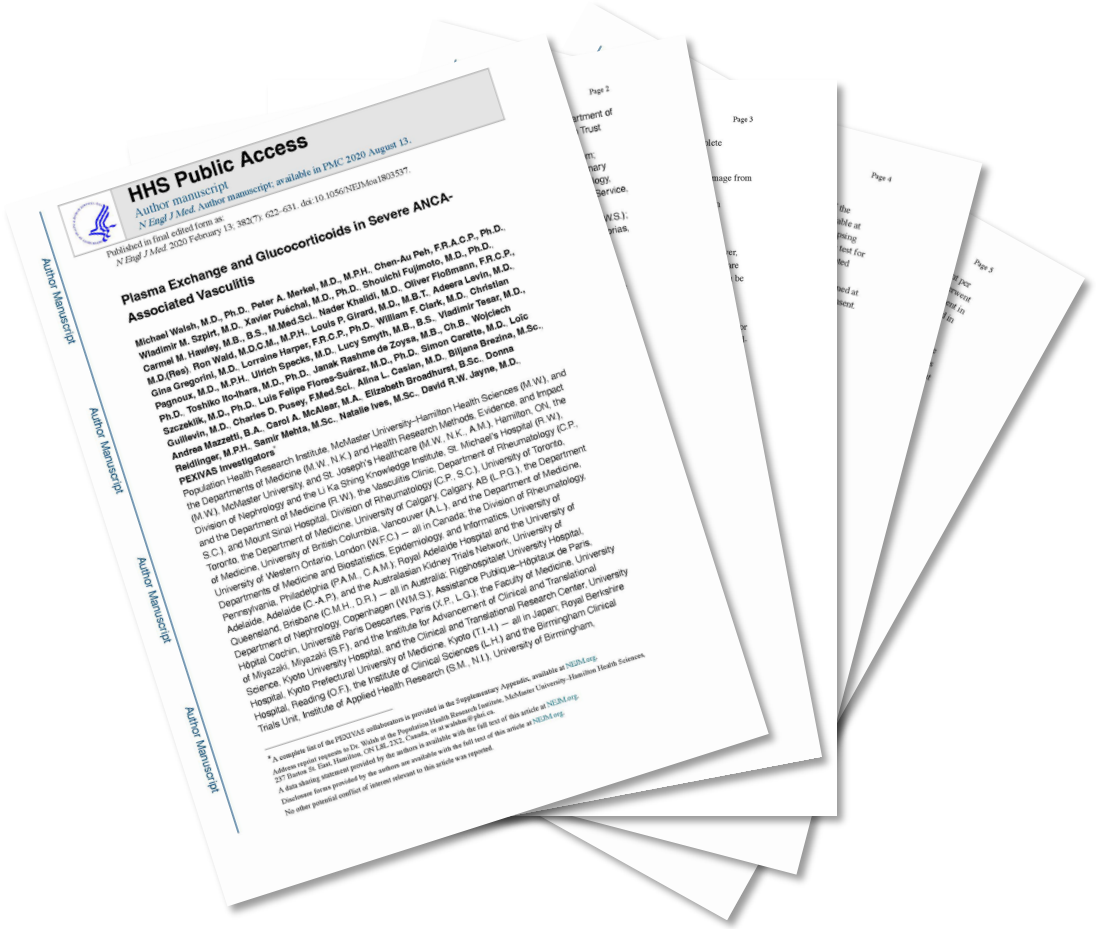
Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int*. 2021;100(4S):S1-S276.

Discussion Points

- Lack of data for rituximab + steroids in acute kidney injury with serum creatinine > 350
- Less data for rituximab + steroids in MPO-ANCA patients than for PR3-ANCA[1]
- Rituximab/cyclophosphamide combination was assessed in the RITUXVAS trial and subsequent observational series[2,3]
- Role of plasma exchange[4]

1. Stone J, et al. *N Engl J Med*. 2010;363(3):221-232; 2. Jones R, et al. *N Engl J Med*. 2010;363(3):211-20; 3. Pepper R, et al. *Rheumatology (Oxford)*. 2019;58(2):260-268; 4. Zeng L, et al. *BMJ*. 2022;376:e064597.

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis



Walsh M, et al. *N Engl J Med*. 2020;382(7):622-631.

PEXIVAS found the reduced regimen had around a 50% reduction in steroid exposure compared to a standard regimen.

Ms. MF

December 2022

- Current status
  - Received rituximab/cyclophosphamide combination and PEXIVAS reduced-dose steroid
  - No inflammatory or respiratory symptoms, remains fatigued, prednisolone 5 mg/day
- Investigations
  - 1+ proteinuria, no hematuria, serum creatinine 185 μmol/L, MPO-ANCA 15 (<3)
- Future plan
  - Withdraw steroid
  - Rituximab 500 mg every 6 months for 2 years

Avacopan

- Oral inhibitor of the complement C5a receptor 1
- Shown in randomized clinical trial (ADVOCATE) to have several benefits for patients with ANCA vasculitis
  - Improved recovery of kidney function compared to glucocorticoids
  - Reduced long-term risk of end-stage renal disease
  - Improved patient quality of life
  - Reduced risk of serious infection vs steroid taper

Jayne DRW, et al. *N Engl J Med*. 2021;384(7):599-609.