Membranous Nephropathy

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- Treatment
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Introduction

Membranous nephropathy (MN) is a common cause of adult nephrotic syndrome and is seen less commonly in children.

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Classification

Case: A 46-year-old Asian woman is referred for a gradual 10-pound weight gain and newonset leg edema, as well as protein (3+) and trace blood on urine analysis. Blood pressure 145/85 mm Hg, pitting edema (2+). Laboratory testing shows a serum creatinine level of 1.03 mg/dL, serum albumin level of 3.1 g/dL, total cholesterol level of 278 mg/. You initiate supportive care for hernephrotic syndrome with renin angiotensin system inhibition, diuretics and sodium restriction, and a statin.

Question

A) Kidney biopsy

b) Duplex ultrasonography of her renal vessels

c) Titer of phospholipase A2 receptor (PLA2R) antibodies

d) Antiphospholipid antibody test

Continue…

- MN has been classified as idiopathic or secondary MN on the basis of clinical and pathologic clues.
- “Primary” to describe disease in which there is a humoral autoimmune response to a normal podocyte antigen in the absence of secondary features or etiologies of disease.
- “Secondary” MN refers to setting of systemic processes such as infection, malignancy, or drug exposure in which treatment of the underlying disorder is expected to lead to the resolution of the MN.

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Common Causes of Primary, Secondary, or Alloimmune MN

Primary MNa

- PLA2R-associated
- THSD7A-associated
- NELL-1–associated
- Sema3B-associated
- Uncharacterized

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Secondary MN

- Autoimmune/collagen-vascular disease: SLE and mixed connective tissue disease (includes EXT1/EXT2-associated), Sjogren's, thyroiditis, sarcoidosis, dermatitis herpetiformis
- Infection
- Drugs, toxins, other adulterants: NSAIDs, gold salts, penicillamine, mercury, cationic bovine serum albumin (infant formula)
- Malignancy

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Alloimmune MN

- Antenatal alloimmune MN caused by anti-NEP antibodies
- De novo MN in kidney allograft
- Graft-vs-host disease

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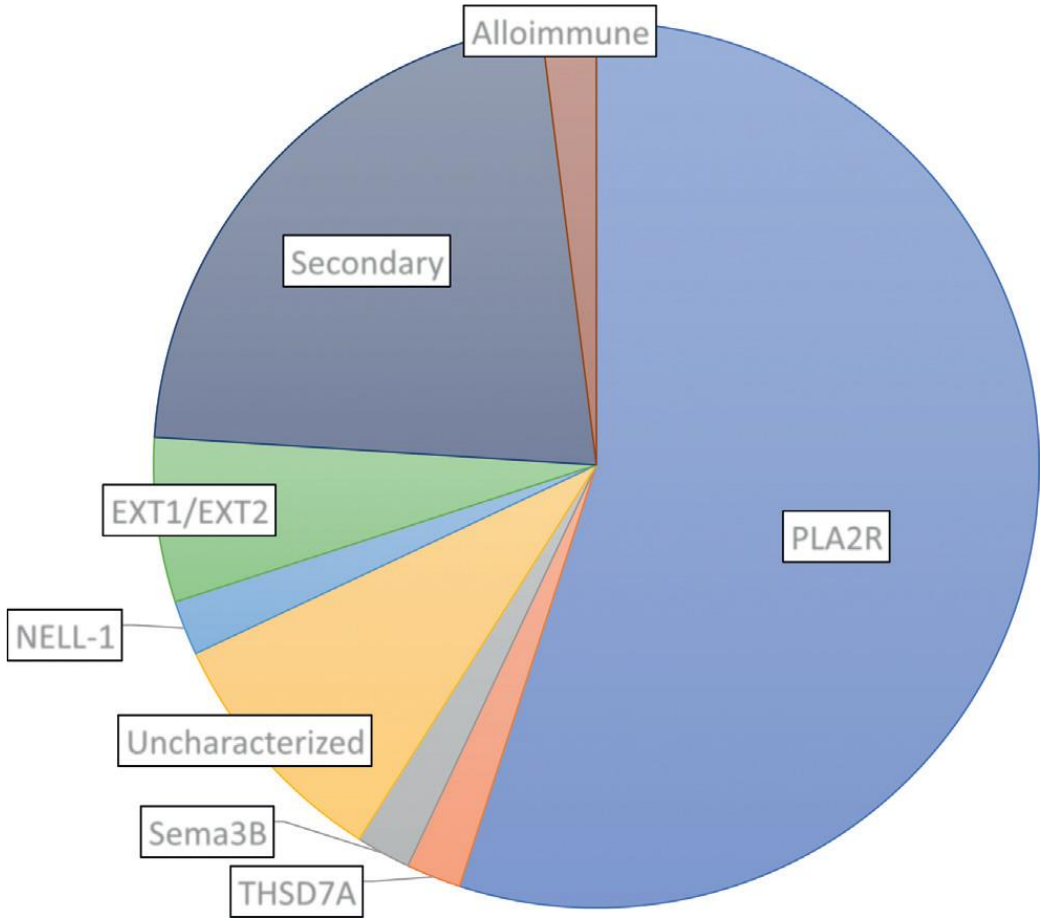
Alloimmune
Secondary
EXT1/EXT2
NELL-1
Uncharacterized
Sema3B
THSD7A
PLA2R

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Antigens Implicated in Primary MN PLA2R

PLA2R is a 180-kDa transmembrane glycoprotein expressed by the human podocyte, Autoantibodies to PLA2R may be responsible for primary MN in as many as 80% of patients (55% of all MN cases found on biopsy).

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THSD7A

(THSD7A) was the next podocyte protein identified as a target antigen in adult primary MN.

THSD7A is also overexpressed by certain malignancies and may incite a humoral reaction against tumor and glomerular THSD7A, leading to MN.

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Neural Epidermal Growth Factor-Like-1

(NELL-1) are a recent addition to the MN disease spectrum and may be more prevalent than anti-THSD7A antibodies.

Unlike PLA2R- and THSD7Aassociated MN, autoantibodies in NELL-1 associated MN are immunoglobulin (Ig) G1-predominant.

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Exostosin 1/ Exostosin 2

Detection of this protein complex within immune deposits is associated with systemic autoimmune diseases such as lupus (class V lupus nephritis).

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Secondary MN

As many as 30% of all biopsy diagnoses of MN represent disease that is most likely secondary to autoimmune/ collagen vascular disease; infections; drugs, toxins, or other adulterants; or malignancy.

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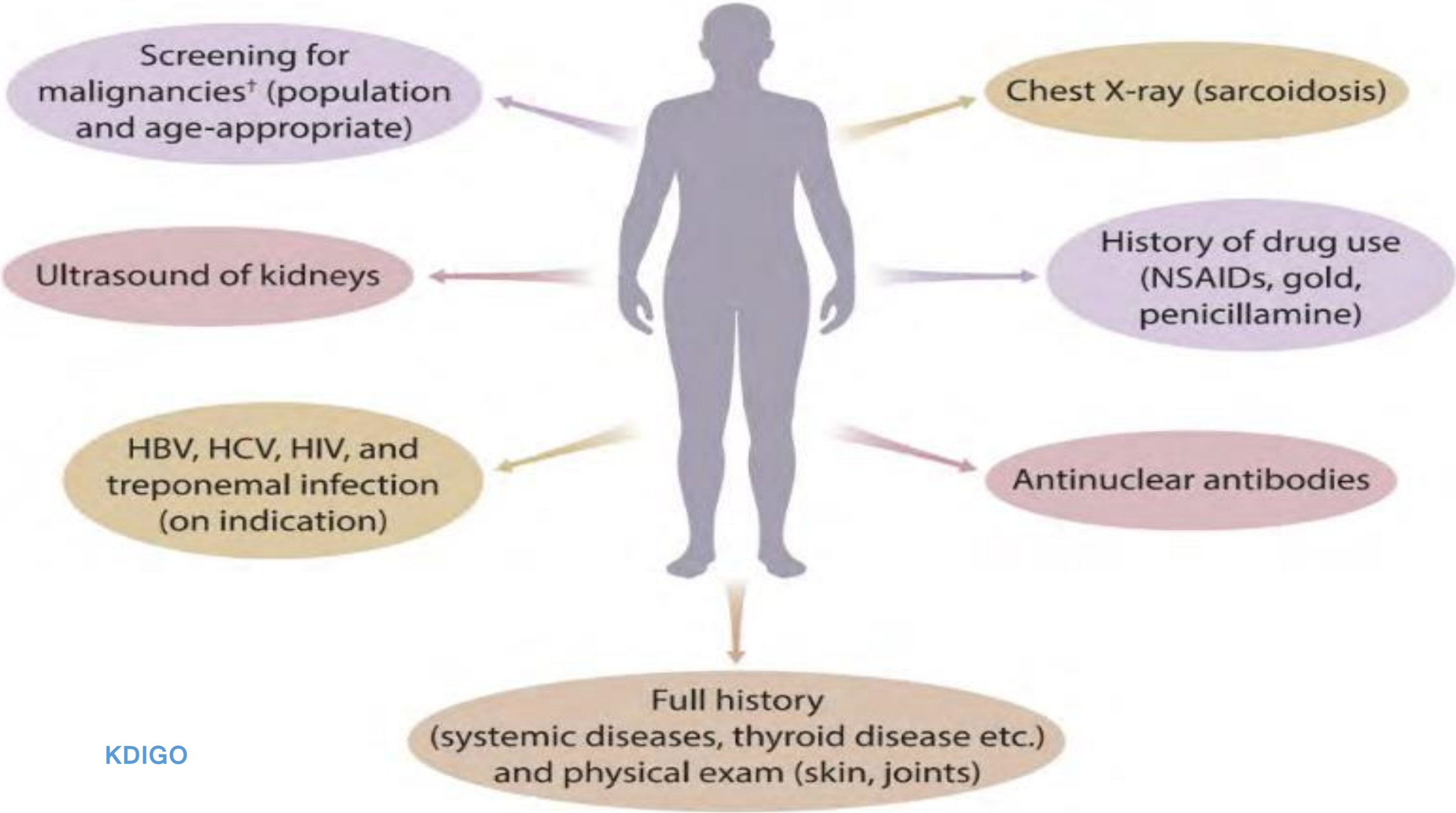
Screening for malignancies† (population and age-appropriate)
Chest X-ray (sarcoidosis)
Ultrasound of kidneys
History of drug use (NSAIDs, gold, penicillamine)
HBV, HCV, HIV, and treponemal infection (on indication)
Antinuclear antibodies
Full history (systemic diseases, thyroid disease etc.) and physical exam (skin, joints)

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Alloimmune MN

There are alloimmune etiologies of MN (antenatal and de novo post transplantation MN) in which inconsistencies between host and donor antigens and humoral immune systems lead to the phenotype of MN.

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Laboratory Testing for Circulating Autoantibodies

The enzyme-linked immunosorbent assay reports the titer of anti-PLA2R IgG and is useful for initial detection of anti-PLA2R as well as monitoring the change in titer over time.

- Values <14 RU/mL are considered negative by the manufacturer.
- (IF) test uses cells transfected with recombinant human PLA2R to assay for the antibodies.

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Although more sensitive than the enzymelinked immunosorbent assay for low-titer anti-PLA2R, the indirect IF test yields only semiquantitative titers.

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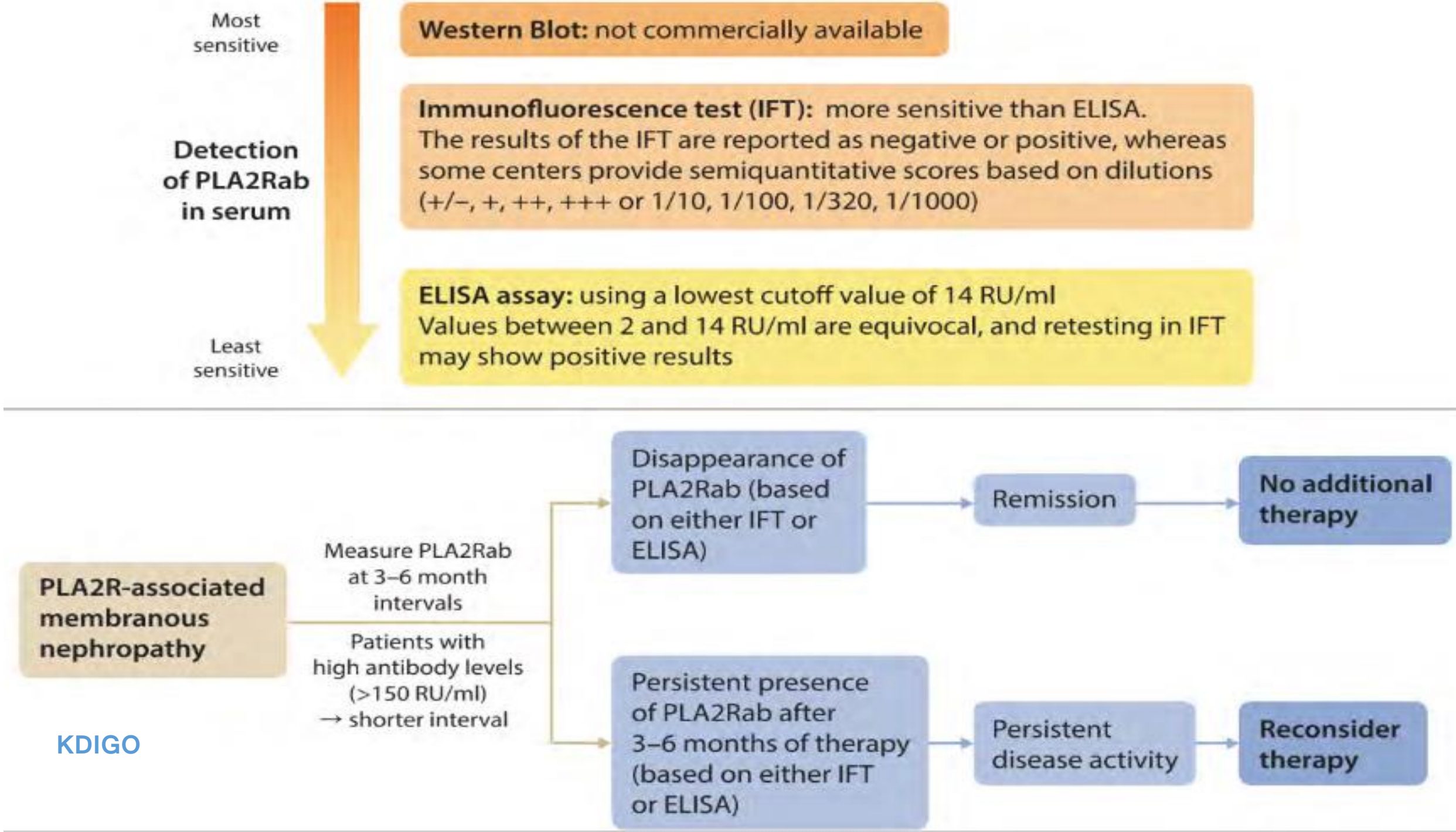
Most sensitive
Detection of PLA2Rab in serum
Least sensitive
Western Blot: not commercially available
Immunofluorescence test (IFT): more sensitive than ELISA.
The results of the IFT are reported as negative or positive, whereas some centers provide semiquantitative scores based on dilutions (+/–, +, ++, +++ or 1/10, 1/100, 1/320, 1/1000)
ELISA assay: using a lowest cutoff value of 14 RU/ml
Values between 2 and 14 RU/ml are equivocal, and retesting in IFT may show positive results
PLA2R-associated membranous nephropathy
Measure PLA2Rab at 3–6 month intervals
Patients with high antibody levels (>150 RU/ml) → shorter interval
Disappearance of PLA2Rab (based on either IFT or ELISA)
Remission
No additional therapy
Persistent presence of PLA2Rab after 3–6 months of therapy (based on either IFT or ELISA)
Persistent disease activity
Reconsider therapy
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Epidemiology

- MN is one of the most common causes of nephrotic syndrome in white, nondiabetic adults.
- MN has an incidence of approximately 1 case per 100,000 persons per year.
- The median age of onset is in the early 50s.
- In the pediatric population, primary MN is quite rare

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Clinical Features

The clinical presentations of MN from a renal standpoint are similar in primary and secondary forms of disease and often involve features of the nephrotic syndrome.

- Heavy proteinuria
- Hypoalbuminemia
- Edema or anasarca
- Hyperlipidemia
- lipiduria.

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- Proteinuria has typically been ongoing for months to even years at a subclinical level before diagnosis. The degree of proteinuria at presentation is variable, ranging from subnephrotic to more than 20 g/d.

- Microscopic hematuria is not uncommon but is usually trace or 1+.

- Red blood cell casts are not seen

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- Blood pressure is normal at presentation in 70% of patients, and (GFR) is preserved in most patients.
- If GFR is or becomes reduced, one should consider:

➢ Renal vein thrombosis,

➢Concomitant interstitial nephritis

➢Crescentic glomerulonephritis,

➢An iatrogenic effect of therapy by overdiuresis or introduction of inhibitors of the renin angiotensin system or the calcineurin pathway.

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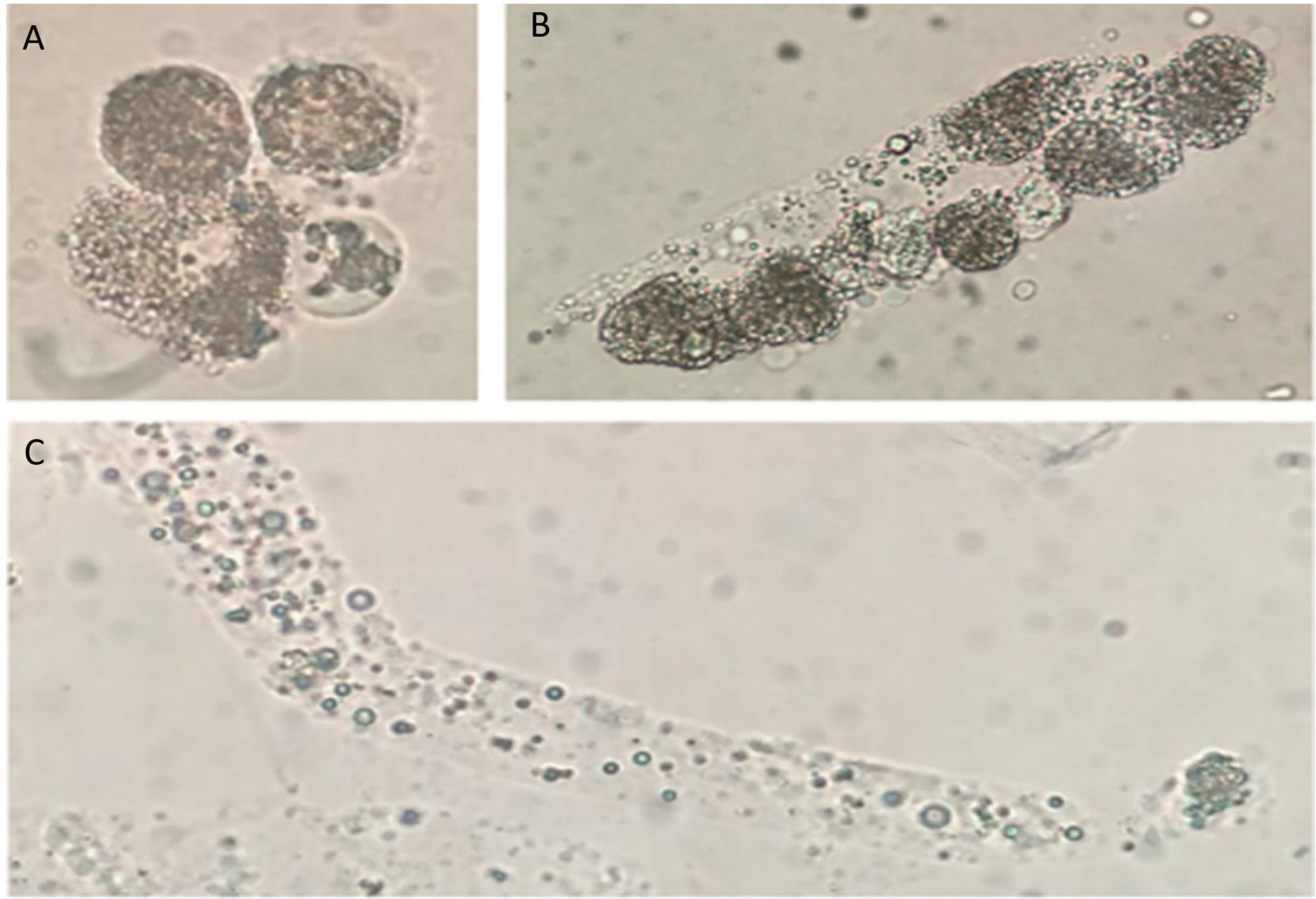

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Natural History

- Even patients in a highly nephrotic state to undergo spontaneous remission, but often treated with immunosuppression to avoid the adverse consequences of the prolonged nephrotic state.
- One third of patients will exhibit spontaneous remission

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Because of the slow time frame in which MN resolves, patients often experience a partial remission (>50% decrease in proteinuria from baseline to <3.5 g/d) well before a complete remission (<0.3 g/d).

Therefore, long-term follow-up (≥5 years) is needed Relapses of MN occur in approximately 25%- 30% of cases, often years after a complete remission

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In secondary MN, treatment of the underlying disease or cessation of the offending agent should result in eventual remission

In class V (“membranous”) lupus nephritis, prognosis depends on whether it is found alone or in combination with another class of lupus nephritis.

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Kidney Pathology

- Changes are due to the immune complexes of antigen
- Immunoglobulin
- Complement components that form beneath the podocyte (ie, are subepithelial) or to the reaction of the podocyte to injury
- loss of slit diaphragms and foot processes, and production of new matrix material between and around the deposits.

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Light Microscopy

Early in the course of the disease, the only change noted may be rigid-appearing capillary walls without evidence of deposits.

In longstanding disease, signs of chronic damage including glomerular sclerosis, interstitial fibrosis, and tubular atrophy can be found.

These features are associated with an inferior kidney prognosis.

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IF and Immunohistochemistry

- IF is generally more sensitive than light or electron microscopy in detecting early deposits.
- The renal pathologist will stain frozen kidney biopsy tissue sections for IgG, IgA, IgM, C3, and C1q.
- In primary MN, IgG and C3 are nearly always positive.
- Secondary etiology of MN include a moderate to strong presence of IF reactants beyond C3 and IgG, such as the “full-house” pattern

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- Staining for IgG subclasses can assist in the determination of etiology.
- Usually a mixture of IgG subclasses in any type of MN, IgG4 tends to be predominant or codominant in primary forms of MN.
- In secondary causes such as lupus or malignancy, IgG1, IgG2, or IgG3 may predominate.

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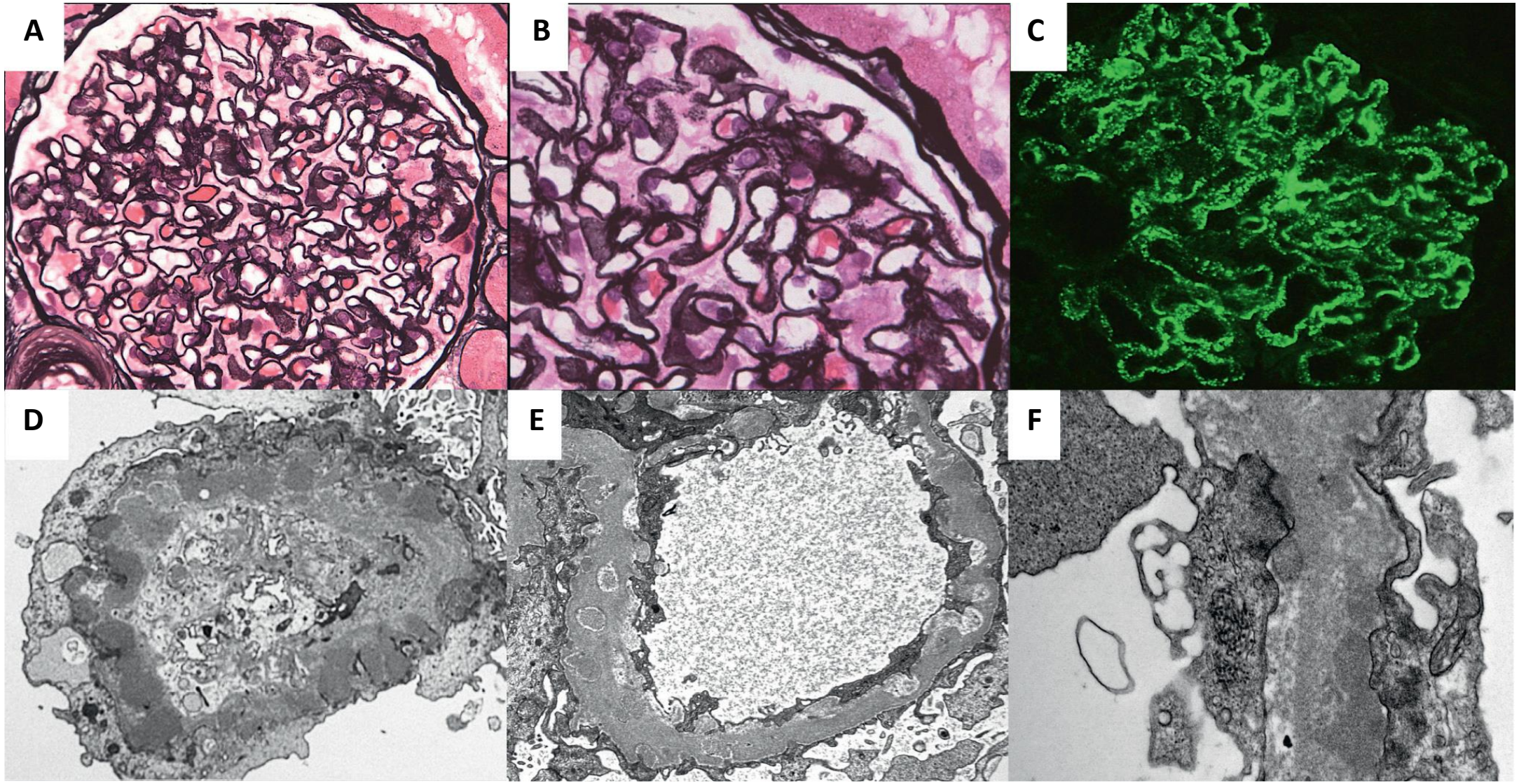

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Genetics

- There is a heritable component of MN and a very strong link to the human leukocyte antigen (HLA) locus on chromosome 6

- HLA class II phenotypes common in the White population such as DR3.

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Role of Complement

- Primary MN like PLA2R-associated MN is that the predominant IgG4 subclass does not activate the classical complement pathway.

- IgG4 may activate the lectin pathway of complement activation.

- Alternative pathway is most likely the main maintenance pathway that amplifies complement activation and results in formation of the podocytopathic membrane attack complex C5b-9.

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Case:

The anti-PLA2R titer for your patient is 185 RU/mL. The biopsy is uncomplicated and shows stage 2 MN with strong staining of the deposits for PLA2R. At her return visit in 3 months, repeat testing reveals a serum creatinine level of 1.1 mg/dL, serum albumin level of 2.9 g/dL, and urinary protein-creatinine ratio of 7.6 g/g despite 100 mg losartan. Her blood pressure is better controlled at 132/78 mm Hg, and her leg edema has resolved with diuretic treatment. A repeat anti-PLA2R measurement is 312 RU/mL.

Question

a) Watchful waiting with 6-month follow-up to see if her urinary protein-creatinine ratio has decreased to <4 g/g

b) Initiation of immunosuppression because spontaneous remission is unlikely with increasing anti-PLA2R titers

c) Repeat kidney biopsy to assess for progression to MN with stage 3 deposits

Relationship Between Immunologic and Clinical Course of Disease

The ability to measure specific autoantibodies in MN in clinical practice has opened a new window onto the immunologic course of disease.

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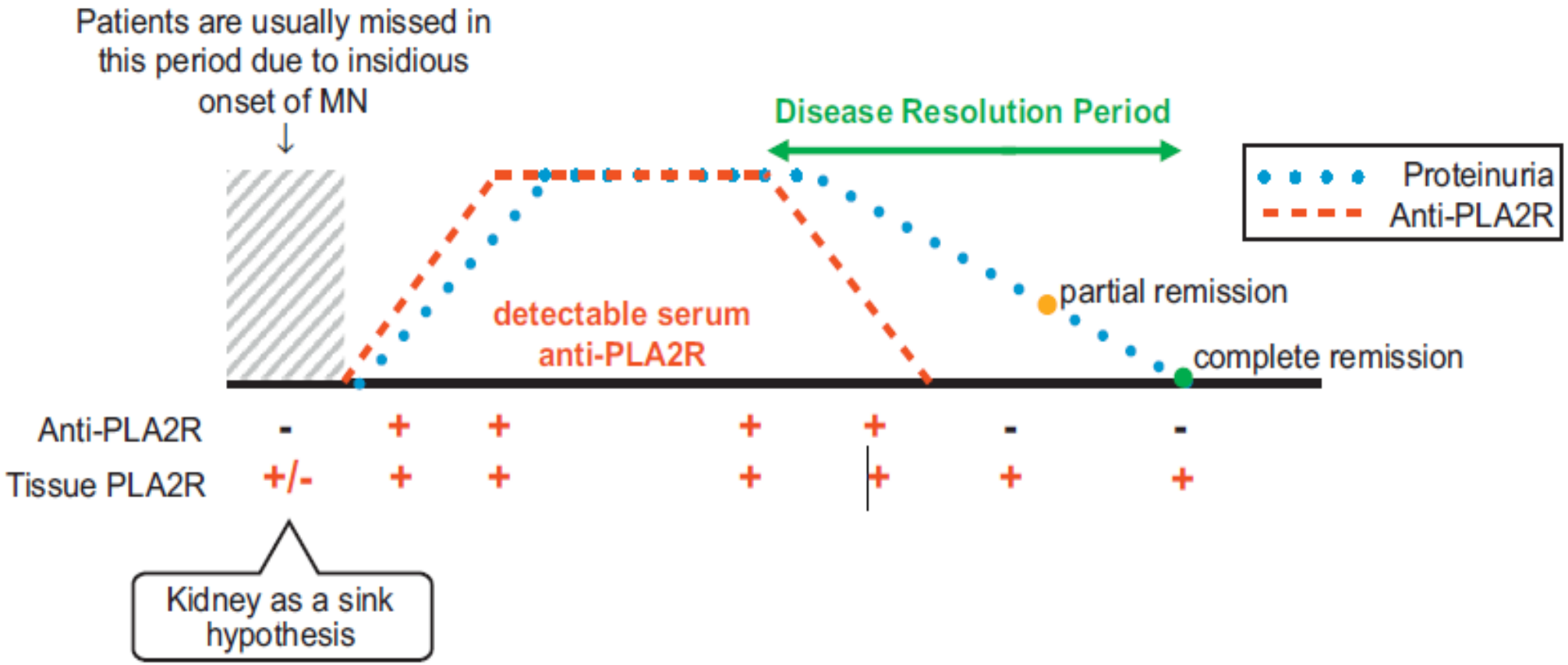
Patients are usually missed in this period due to insidious onset of MN
Disease Resolution Period
Proteinuria
Anti-PLA2R
detectable serum anti-PLA2R
partial remission
complete remission
Anti-PLA2R
Tissue PLA2R
- + + + + - -
+/- + + + + + +
Kidney as a sink hypothesis

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In the process of spontaneous or treatment-induced remission, anti-PLA2R levels will decrease and predicts the clinical response.

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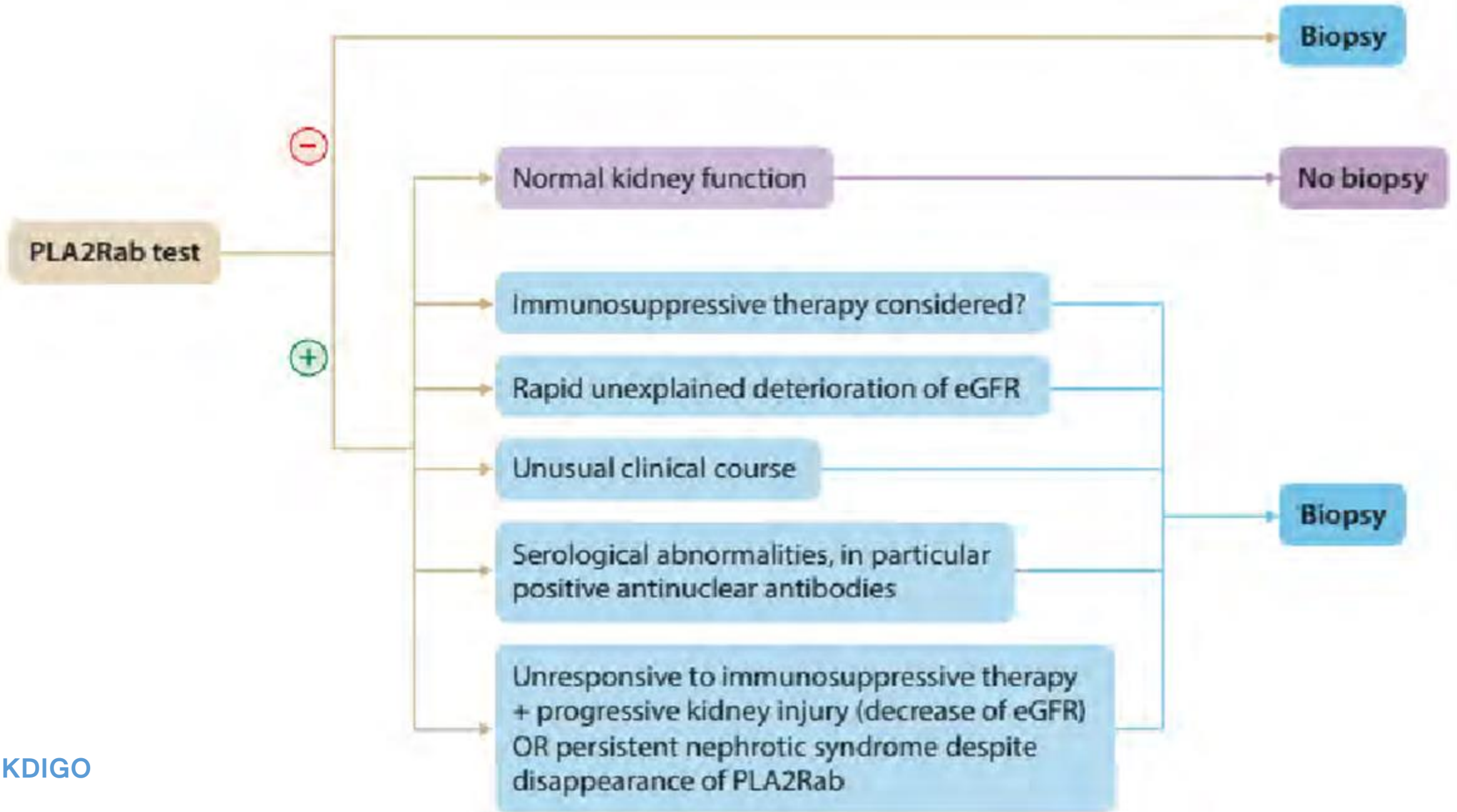
*When to consider a kidney biopsy in a PLA2Rab-positive patient**



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Case:

You and your patient agree to starting immunosuppressive treatment, but, as a result of fears about the adverse effects, she would like to avoid cyclophosphamide.

Question : Which therapy is most likely to achieve a

complete remission at 24 months in this patient?

a) Prednisone

b) Cyclosporine

c) Mycophenolate

d) Rituximab

Treatment and Response

All patients with MN should receive

angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

- Optimal blood pressure control,
- Dietary sodium restriction,
- Diuretic therapy as needed
- Cholesterol-lowering therapies are often necessary as a result of hyperlipidemia.

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- Decisions regarding the initiation of immunosuppressive therapy should be made in consideration of the risks of treatment
- Patients are first classified as being at low, moderate, high, very high risk for disease progression.

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- The trajectory of anti-PLA2R, followed every 1-3 months according to clinical context, is important

- Patients in a nephrotic state with increasing autoantibody titers would be expected to worsen whereas decreasing titers or disappearance of anti- PLA2R could watchful waiting for a spontaneous remission.

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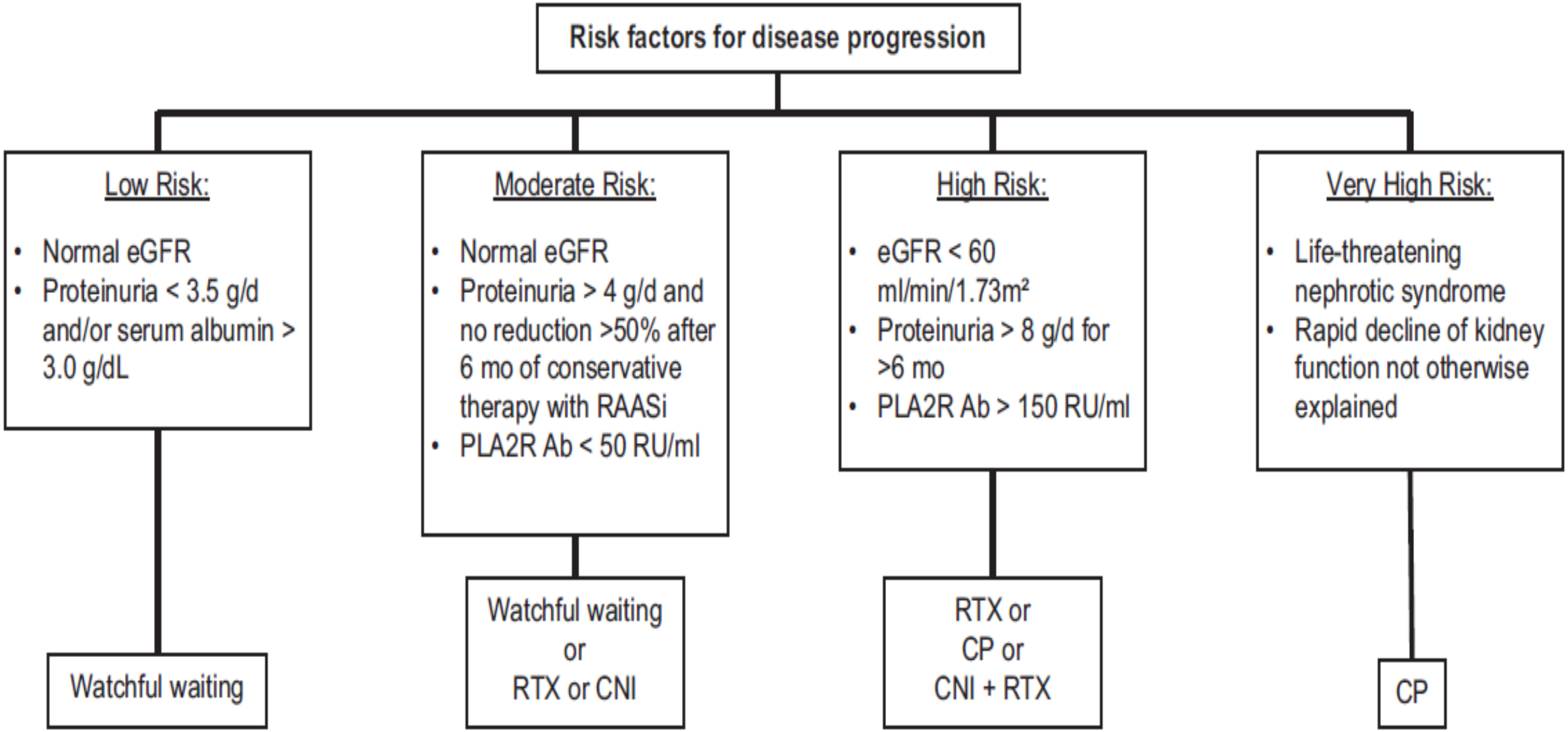
Risk factors for disease progression
Low Risk:
• Normal eGFR
• Proteinuria < 3.5 g/d and/or serum albumin > 3.0 g/dL
Watchful waiting
Moderate Risk:
• Normal eGFR
• Proteinuria > 4 g/d and no reduction >50% after 6 mo of conservative therapy with RAASi
• PLA2R Ab < 50 RU/ml
Watchful waiting or RTX or CNI
High Risk:
• eGFR < 60 ml/min/1.73m²
• Proteinuria > 8 g/d for >6 mo
• PLA2R Ab > 150 RU/ml
RTX or CP or CNI + RTX
Very High Risk:
• Life-threatening nephrotic syndrome
• Rapid decline of kidney function not otherwise explained
CP

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Cyclophosphamide and Corticosteroids

Dutch protocol used daily cyclophosphamide for as long as 1 year with 6 months of daily or alternate-day prednisone followed by a tapering steroid dose. This protocol also achieved a good clinical response, but with significant adverse events that were associated with a higher cumulative dose of cyclophosphamide.

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Rituximab

- limited adverse effects of rituximab, it may be considered in patients with advanced chronic kidney disease and immunologically active MN, as successful treatment of the MN may help to preserve remaining GFR.

- Second-generation anti-CD20 agents such as ofatumumab have been used successfully in cases in which MN becomes refractory to rituximab.

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Increased risk of reactivation of HBV and tuberculosis, and prophylactic treatment of both conditions during the B-cell depletion period should be considered in previously exposed patients.

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CNIs

Trials with cyclosporine and low-dose prednisone or with tacrolimus monotherapy have shown increased remission rates compared with supportive therapy alone.

If these agents are to be used for therapy for primary MN, serum autoantibodies should be followed every 3-6 months

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Other Therapies

- Limited data suggest a utility of adrenocorticotropic hormone for the treatment of MN
- Mycophenolate monotherapy is not effective for the treatment of MN, although mycophenolate may have a role as an alternative therapy when combined with corticosteroids or a CNI.
- No antigen-specific therapy is currently available, although the field is hopeful that such agents can be developed

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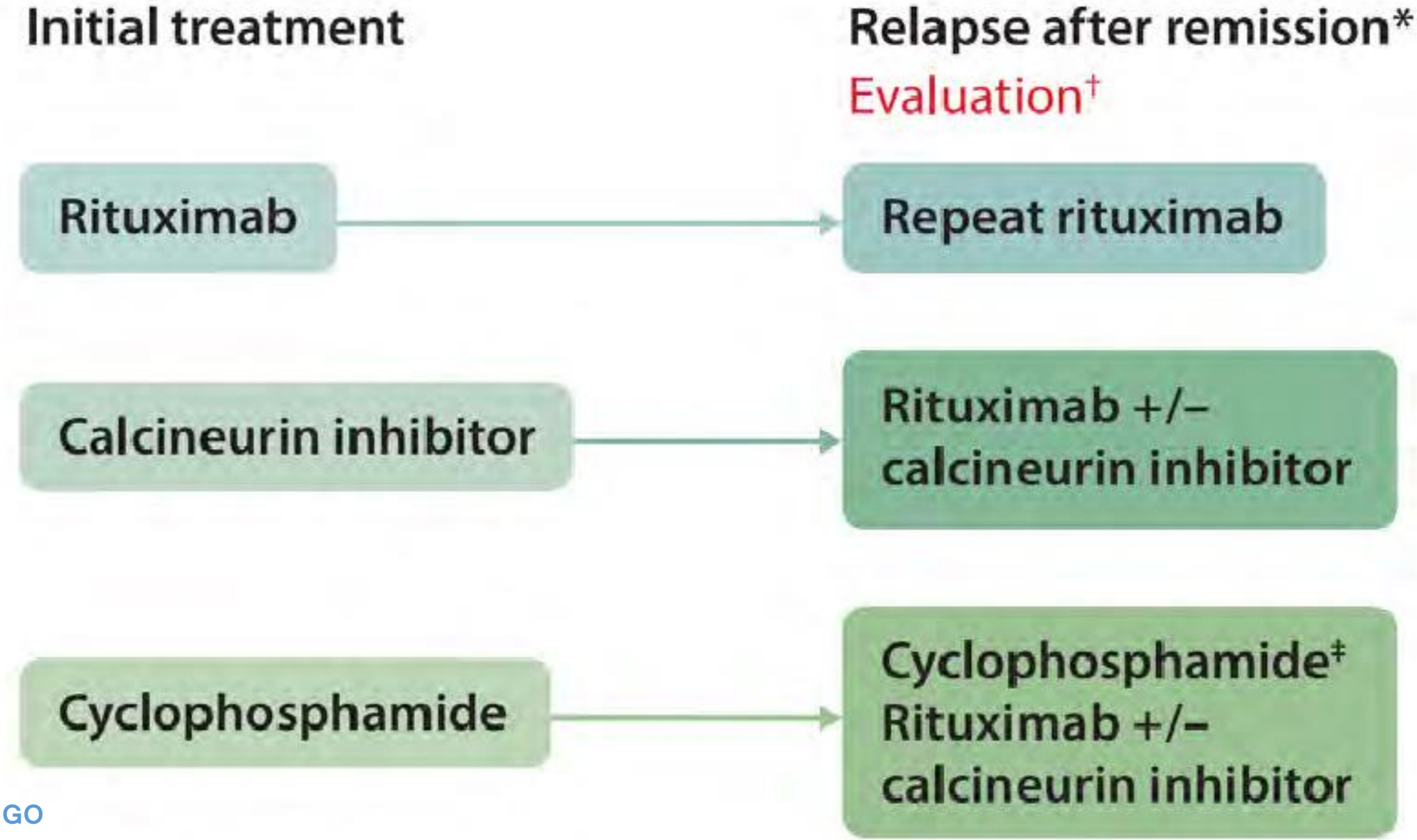
Cyclophosphamide (cyclical)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d in months 1, 3, and 5 • Cyclophosphamide 2.5 mg/kg/d in months 2, 4, and 6‡
Cyclophosphamide (continuous)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d every other day in months 1–6, with taper thereafter • Cyclophosphamide 1.5 mg/kg/d in months 1–6‡
Rituximab	• Rituximab 1 g i.v. administered twice within 2 weeks* • Rituximab 375 mg/m^2 given 1–4 times at weekly intervals
Tacrolimus	• Tacrolimus 0.05–0.1 mg/kg/d, target trough level 3–8 µg/ml, duration 12 months†
Cyclosporine	• Cyclosporine 3.5 mg/kg/d, target trough level 125–225 µg/ml†


Initial treatment
Relapse after remission*
Evaluation†
Rituximab
Repeat rituximab
Calcineurin inhibitor
Rituximab +/–
calcineurin inhibitor
Cyclophosphamide
Cyclophosphamide‡
Rituximab +/–
calcineurin inhibitor

Treatment of Secondary MN

In treatment of secondary MN, the general rule is to treat the underlying disease or stop the offending agent.

If the patient subsequently does not show evidence of a remission of proteinuria, a trial of immunosuppression following the algorithm for primary MN is recommended.

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The treatment of class V lupus nephritis will vary depending on whether it exists as a solitary lesion or in combination with a proliferative form (class III/IV lupus nephritis).

Treatment of MN due to chronic HBV infection requires agents directed against the infection, such as pegylated interferon, entecavir, or tenofovir.

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Category	Recurrent MN	De Novo MN
Epidemiology	• 10%-45% recurrence rate (higher rates in centers with protocol biopsies) • Clinically apparent by 13-15 mo, but proteinuria can begin within months of transplantation	• 1%-2% posttransplant with increasing incidence with time; reported as ~5.3% at 8 y • Higher incidence in pediatric population, reaching ~9%
Pathogenesis	• Anti-PLA_2R at time of transplantation is a risk factor • Can appear years later with reemergence of autoantibodies when transplant immunosuppression decreased	• Not fully known • Has been associated with chronic and/or antibody-mediated rejection
Clinical presentation	• Similar to primary MN • May be detected earlier with lower amounts of proteinuria due to heightened surveillance (especially with protocol biopsy)	• Can be asymptomatic or with various degrees of proteinuria many years after transplantation

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Diagnosis	• MN present on biopsy of native kidney • Presence of anti-PLA_2R can support recurrent MN if native diagnosis not known • Positive PLA_2R staining within deposits in 70%-80% • IgG4 is the dominant or codominant IgG subclass	• Diagnosis other than MN in biopsy of native kidney • Typically not associated with anti-PLA_2R antibody or PLA_2R staining of deposits • Evidence of chronic and/or antibody-mediated rejection • IgG1 is predominant IgG subclass
Treatment	• Can closely follow if low titer anti-PLA_2R, subnephrotic proteinuria, stable kidney function • Transplant immunosuppression may cause decrease and disappearance of autoantibodies • Heightened concern warranted as process already resulted in loss of native kidneys • Rituximab for worsening disease in setting of transplant immunosuppression	• Unknown natural history but 50% graft loss has been reported • Treat underlying rejection and implement antiproteinuric therapy • Increase maintenance immunosuppression, consider plasmapheresis if chronic rejection is present • Consider rituximab or cyclophosphamide if kidney function is rapidly declining

Anticoagulation

- The nephrotic syndrome represents a hypercoagulable state with increased risk of venous thromboembolism (VTE)
- The best evidence supporting that the VTE risk starts to increase at a serum albumin level lower than 2.8
- Warfarin and low-molecular-weight heparin can be used for VTE prophylaxis

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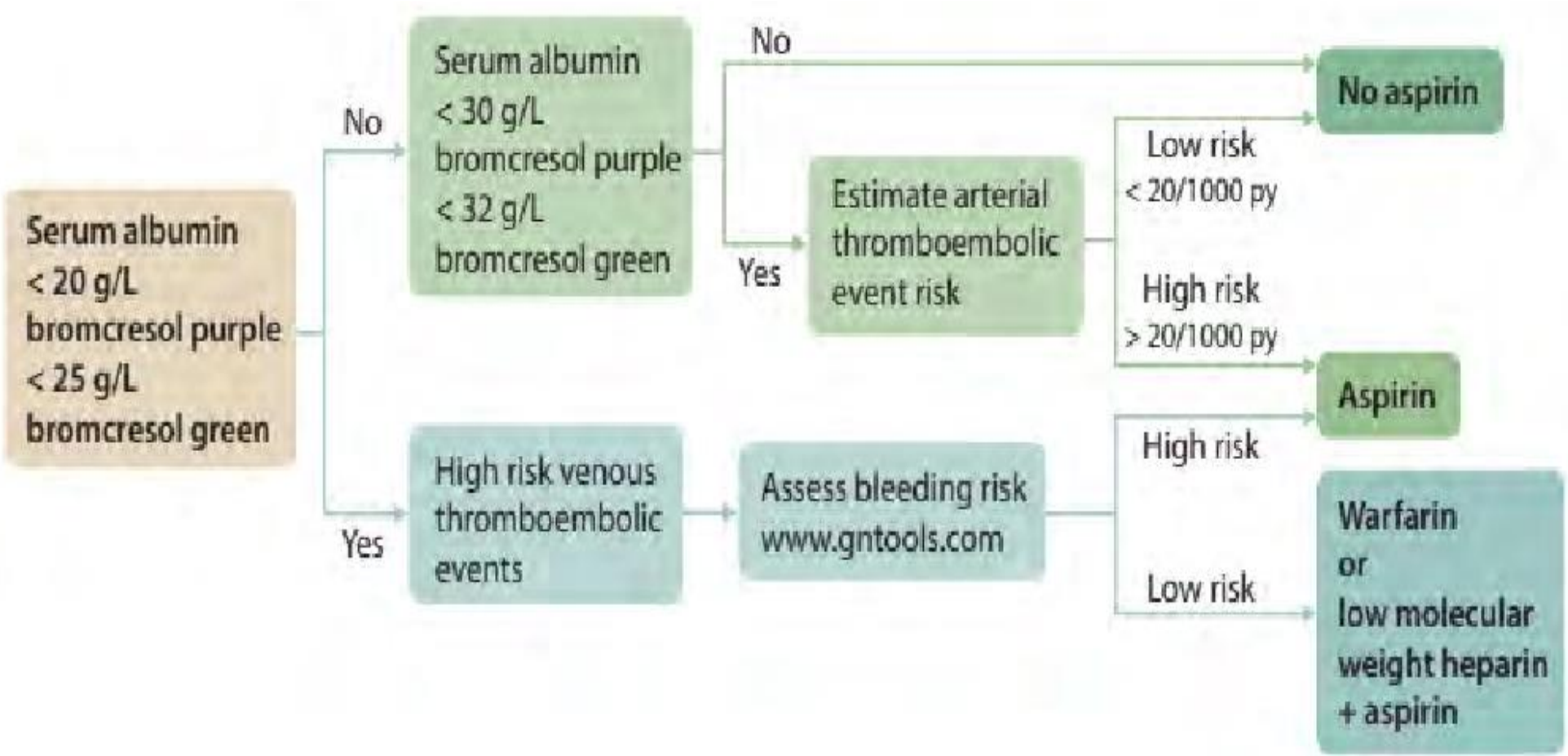
Serum albumin
< 20 g/L
bromcresol purple
< 25 g/L
bromcresol green
No
Serum albumin
< 30 g/L
bromcresol purple
< 32 g/L
bromcresol green
No
No aspirin
Yes
Estimate arterial thromboembolic event risk
Low risk
< 20/1000 py
High risk
> 20/1000 py
Aspirin
Yes
High risk venous thromboembolic events
Assess bleeding risk
www.gntools.com
High risk
Low risk
Warfarin
or
low molecular weight heparin
+ aspirin

Case:

Your patient, despite exhibiting initial remission of her MN with rituximab, has several relapses over the next decade and is ultimately diagnosed with stage 5 chronic kidney disease with no evidence of the nephrotic syndrome. She is deemed an acceptable candidate for preemptive kidney transplantation, and her healthy daughter would like to donate a kidney. As part of the peritransplantation process, your patient is found to have an anti-PLA_2R titer of 43 RU/mL.

Question

How should you proceed in terms of transplantation?

a) Treat with rituximab and await disappearance of anti- PLA2R before proceeding with transplantation

b) Insist on another donor, as a living-related donor is highly likely to lead to recurrence of MN in the allograft

c) Proceed with transplantation and monitor anti-PLA2R and proteinuria closely

d) Perform plasmapheresis in the peritransplantation period

Conclusion

The ability to monitor disease course with circulating autoantibodies, advances in the genetics of this disease, and therapeutic trials identifying effective treatments with fewer adverse effects, such as rituximab.


Thank
you