Use of CNIs in Nephrology

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Outlines

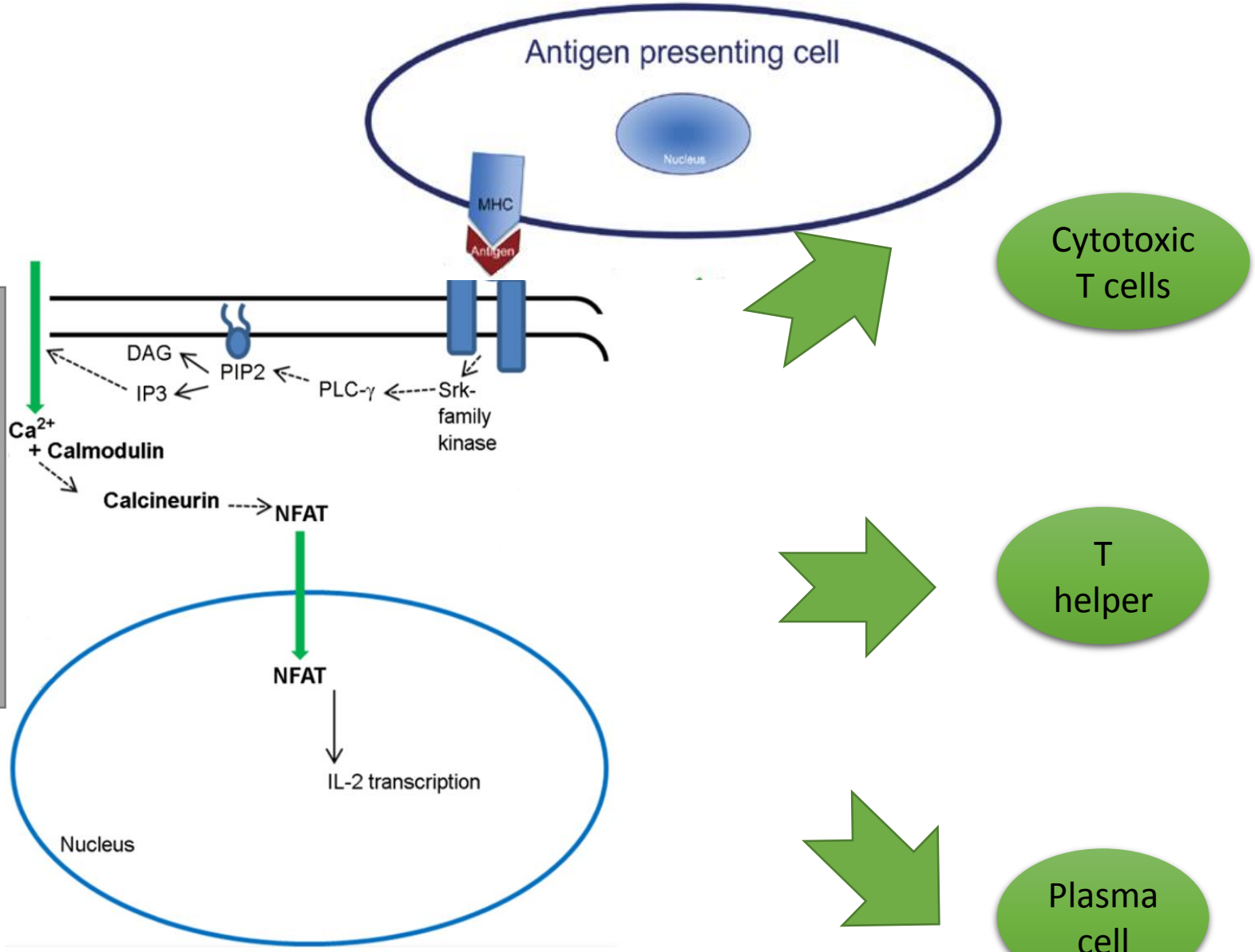
- Mechanisms of CNIs
- Use of CNIs in Kidney diseases
  - Idiopathic Membranous Nephropathy
  - Minimal Change Disease/FSGS
  - Lupus Nephritis
  - BK virus Nephropathy
- CNI in Pregnancy
- One of the unusual complications of CNI

Mechanism of function

- The calcineurin inhibitors cyclosporin A (CsA) and FK506 are among the most potent immunosuppressant drugs that are used for the treatment of many kidney diseases.
- Mechanistically, the immunosuppressive potency of both drugs is achieved mainly through an inhibition of the protein phosphatase calcineurin, which is critically involved in IL-2 production by T lymphocytes by the action of the nuclear factor of activated T cells

How Does it Work

1- IL2 production Inhibition

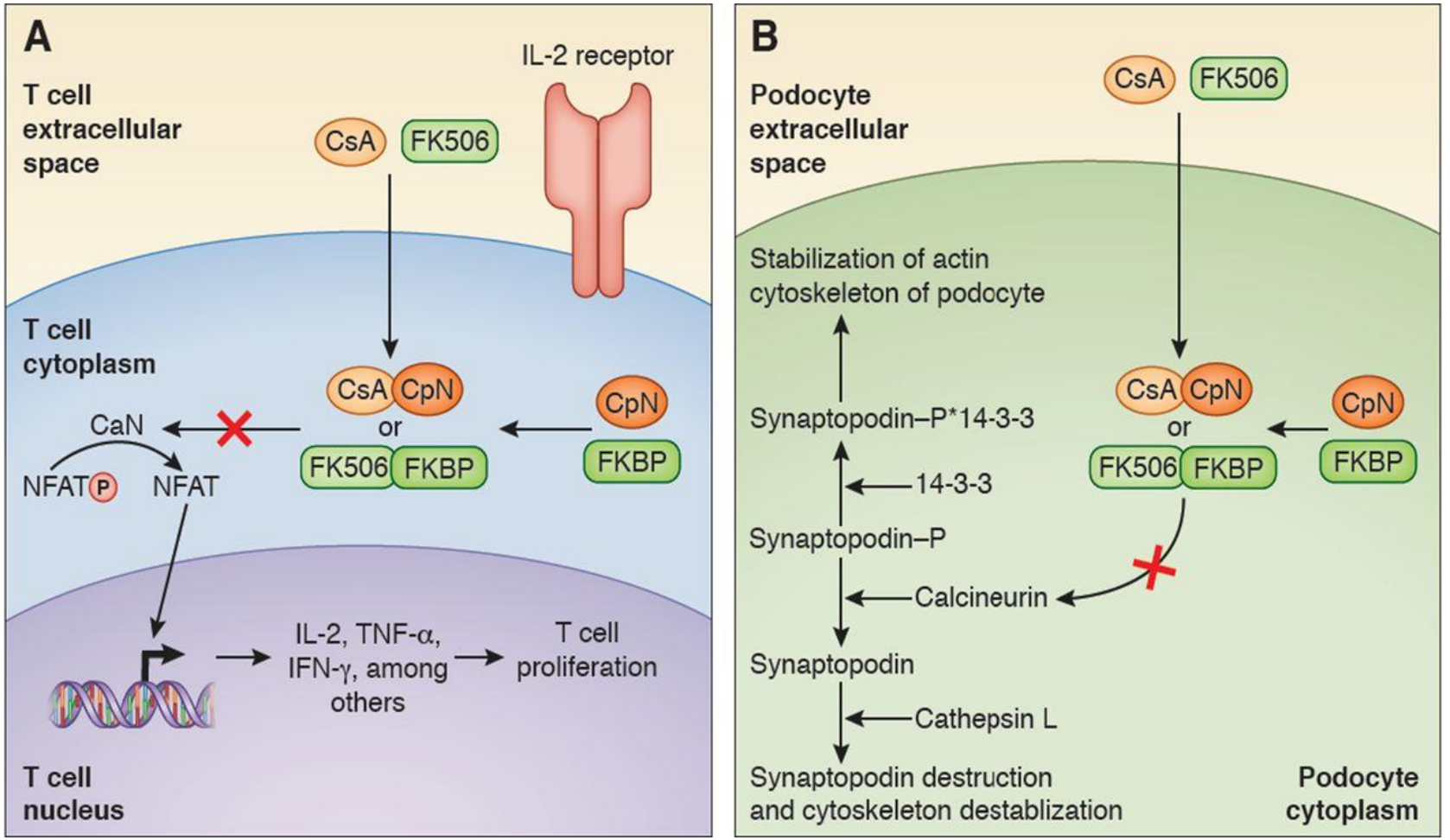


Cytotoxic T cells

T helper

Plasma cell

How Does it Work



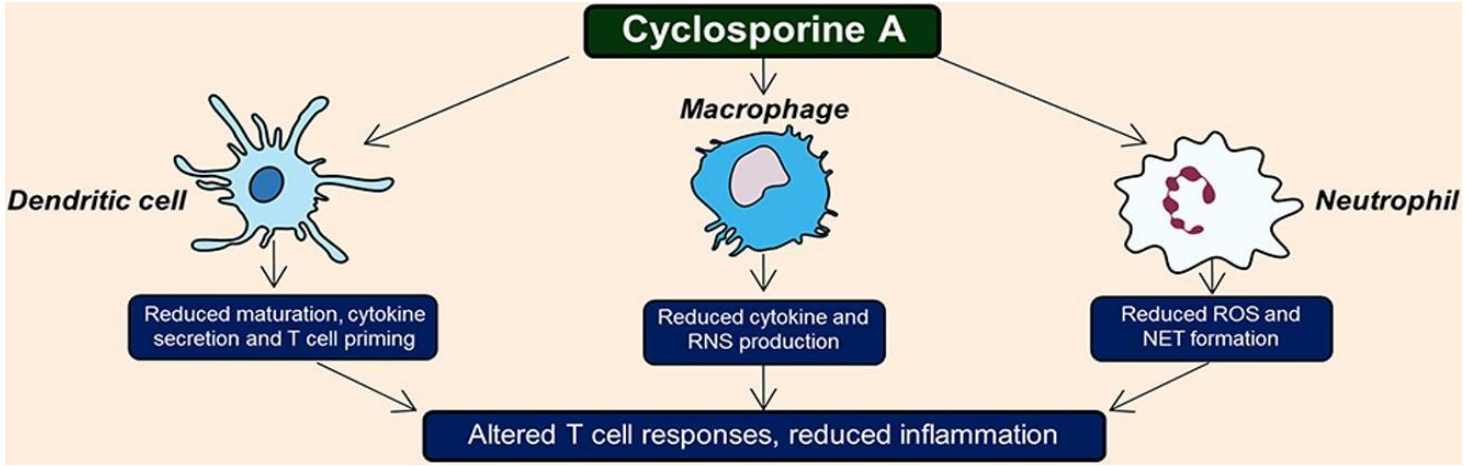
2- cytoskeleton stabilization

The Evolving Role of Calcineurin Inhibitors in Treating Lupus Nephritis

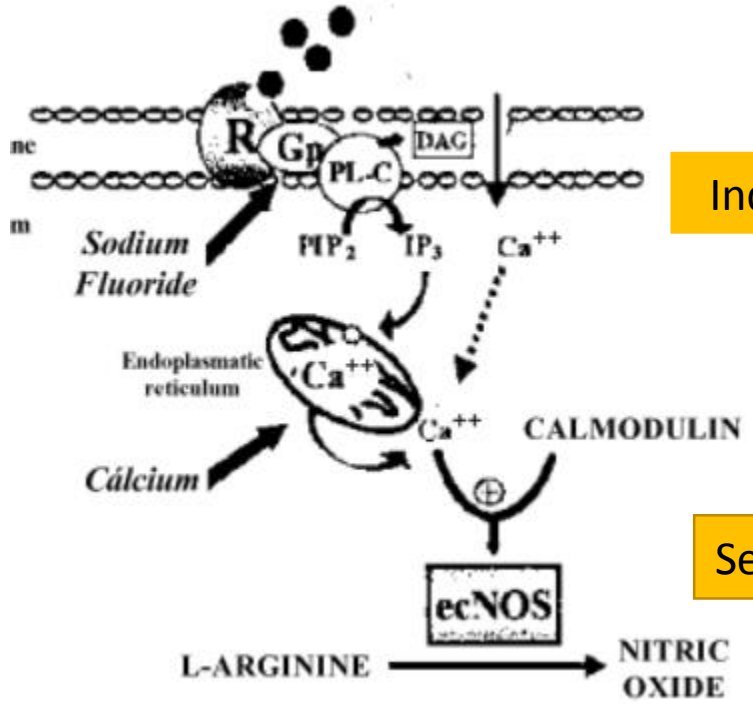
Yonatan Peleg, Andrew S. Bomback and Jai Radhakrishnan

CJASN July 2020, 15 (7) 1066-1072; DOI: https://doi.org/10.2215/CJN.13761119

How Does it Work



3- anti-inflammatory/ Pro-inflammatory



Inducible cyclooxygenase II

Secretory phospholipase type A2

Inducible nitric oxide synthase

Degradation of ECM proteins:
-the action of matrix metalloproteinases (MMP)
-Intrinsic inhibitors, **the tissue inhibitors of MMP**
****In Cs-induced fibrosis: inhibitors>>MMP**
MMP9

How Does it Work

- Pharmacologically, the immunosuppressive activity of FK506 has been reported to be 50 to 100 times higher than CsA but exerts a lower fibrogenic influence on glomeruli.
- Therefore, the renal dysfunctions that accompany FK506 treatment in some cases were less severe than those that were observed under CsA treatment

Membranous nephropathy

- Calcineurin inhibitors are often employed in patients with MN.
- These agents have significant antiproteinuric effects.
- While their mechanism(s) of action are not fully understood, recent studies have suggested that inhibition of calcineurin phosphatase activity stabilizes cell cytoskeletal structures and improves slit-pore function

When do I use CNIs for IMN?

- All patients with primary MN and proteinuria should receive optimal supportive care.
- Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury.

Risk assessment in IMN

Low risk

- Normal eGFR, proteinuria < 3.5 g/day and/or serum albumin > 30 g/L

Moderate risk

- Normal eGFR, proteinuria > 4 g/day and no decrease > 50% after 6 months of conservative therapy with ACE/ARB
- PLA2Rab < 50 RU/ml[b]
- Mild LMW proteinuria
- Selectivity index < 0.15
- U IgG < 250 mg/day

High risk

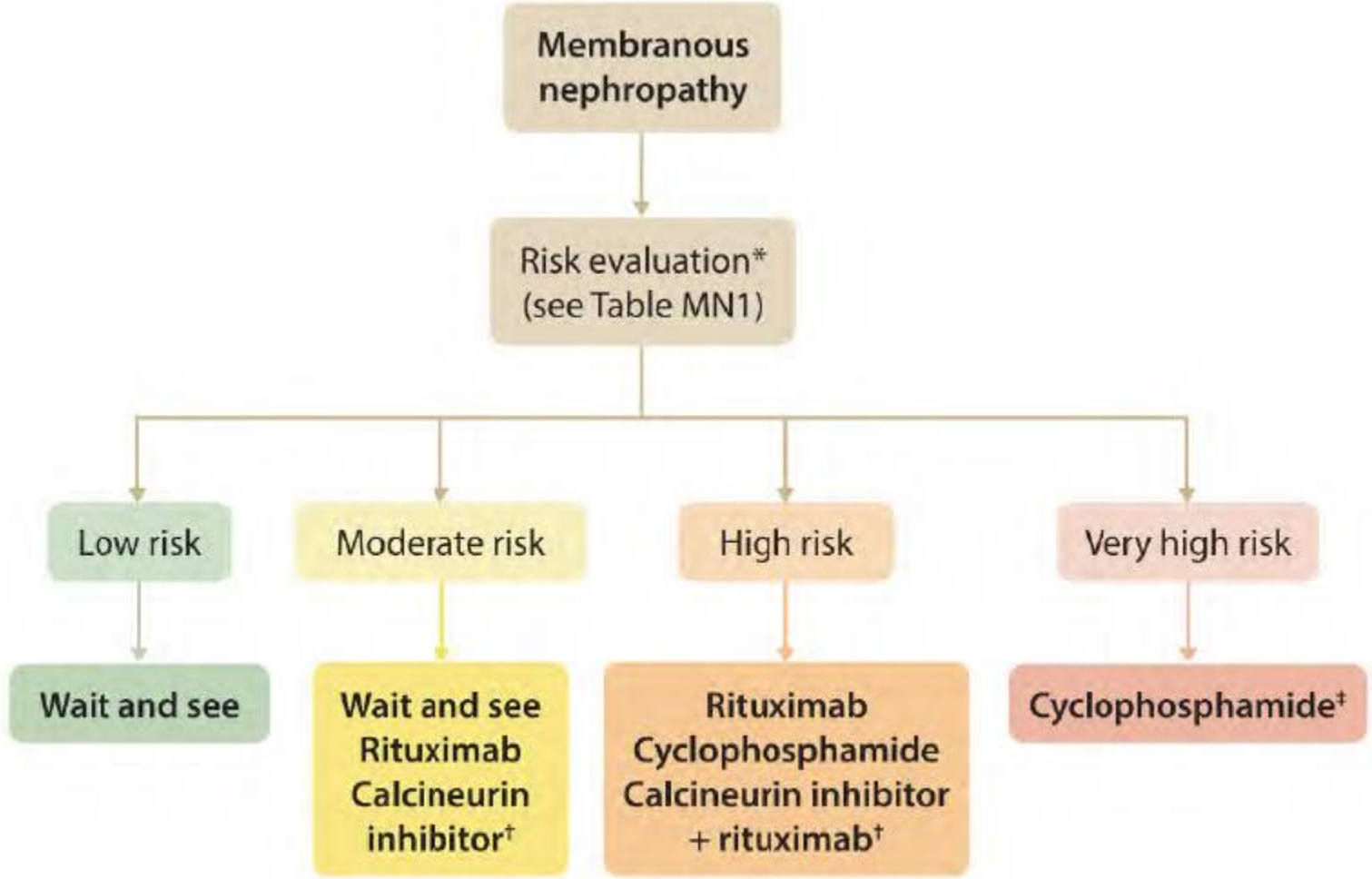
- eGFR < 60 ml/min/1.73 m^2 [a]
- Proteinuria > 8 g/day for > 6 months
- PLA2Rab > 150RU/ml[b]
- High LMW proteinuria
- U IgG > 250 mg/day
- Selectivity index > 0.20

Very high risk

- Life-threatening nephrotic syndrome
- Rapid deterioration of kidney function not otherwise explained
- High LMW proteinuria in two urine samples collected with interval of 6–12 months

-Most studies have used SCr values to guide management, and SCr values >1.5 mg/dl are often used to define kidney insufficiency.
-An eGFR value of 60 ml/min/1.73 m2 defines kidney insufficiency in a young adult.
-It is important to realize that eGFR decreases with age, and an SCr value of 1.5 mg/dl reflects an eGFR of 50 ml/min/1.73 m2 in a 60-year-old male patient and 37 ml/min/1.73 m2 in a 60-year-old female patient.
-Thus, when using eGFR in risk estimation, age should be taken into account.

Use of CNI in IMN



Use of CNI in IMN

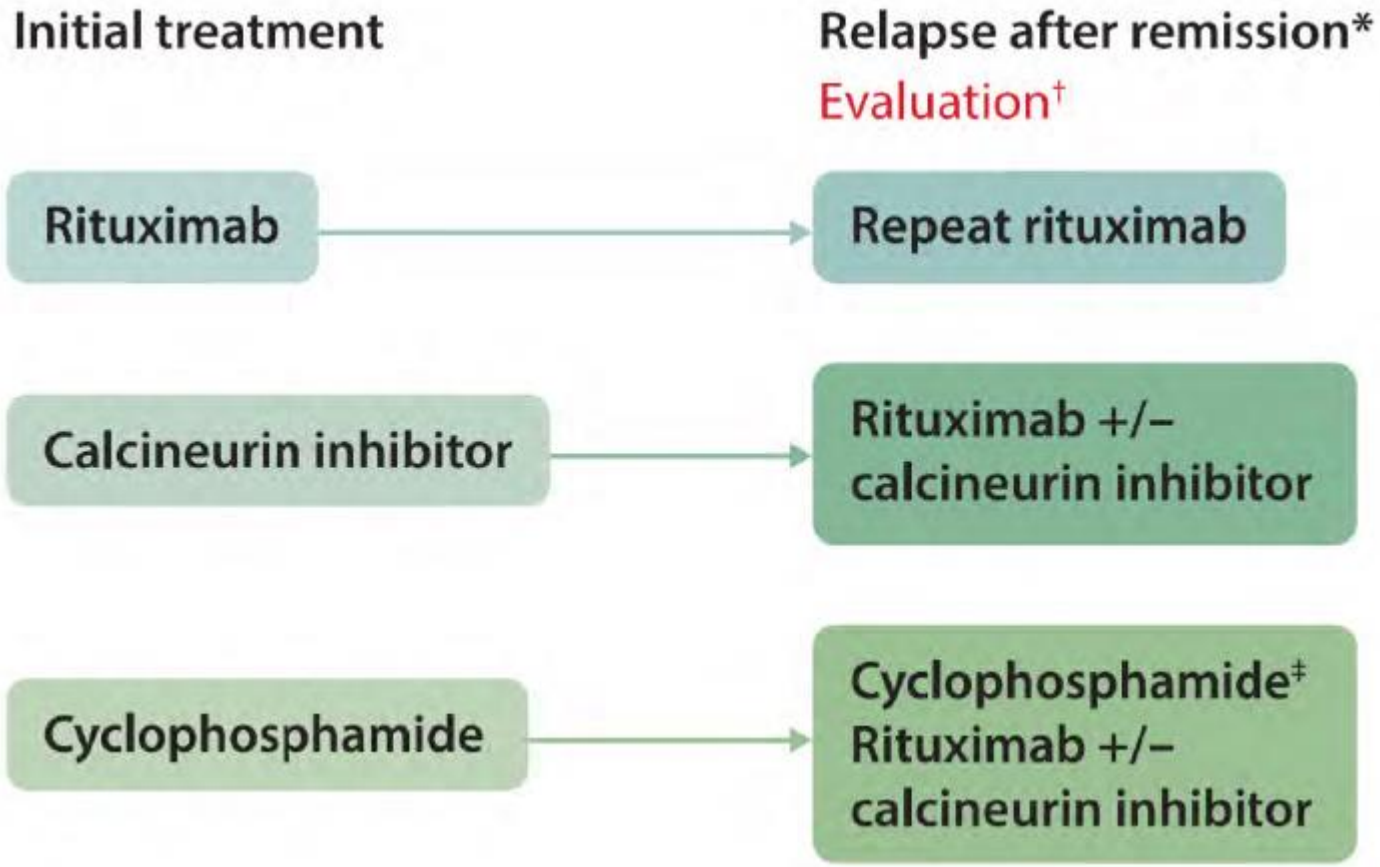
- In patients with high risk of progression, addition of rituximab after six months of treatment with CNI is advised, with the possible exception of patients with documented disappearance of PLA2Rab after CNI treatment.
- **Immunosuppressive therapy is not required in patients with MN, proteinuria <3.5 g/d, and eGFR >60 ml/min/1.73 m2**

Use of CNI in IMN

- **Immunosuppressive therapy is not required in patients with MN, nephrotic syndrome, and normal eGFR unless at least one risk factor for disease progression is present or unless serious complications of nephrotic syndrome (e.g., AKI, infections, thromboembolic events) have occurred**
- **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**

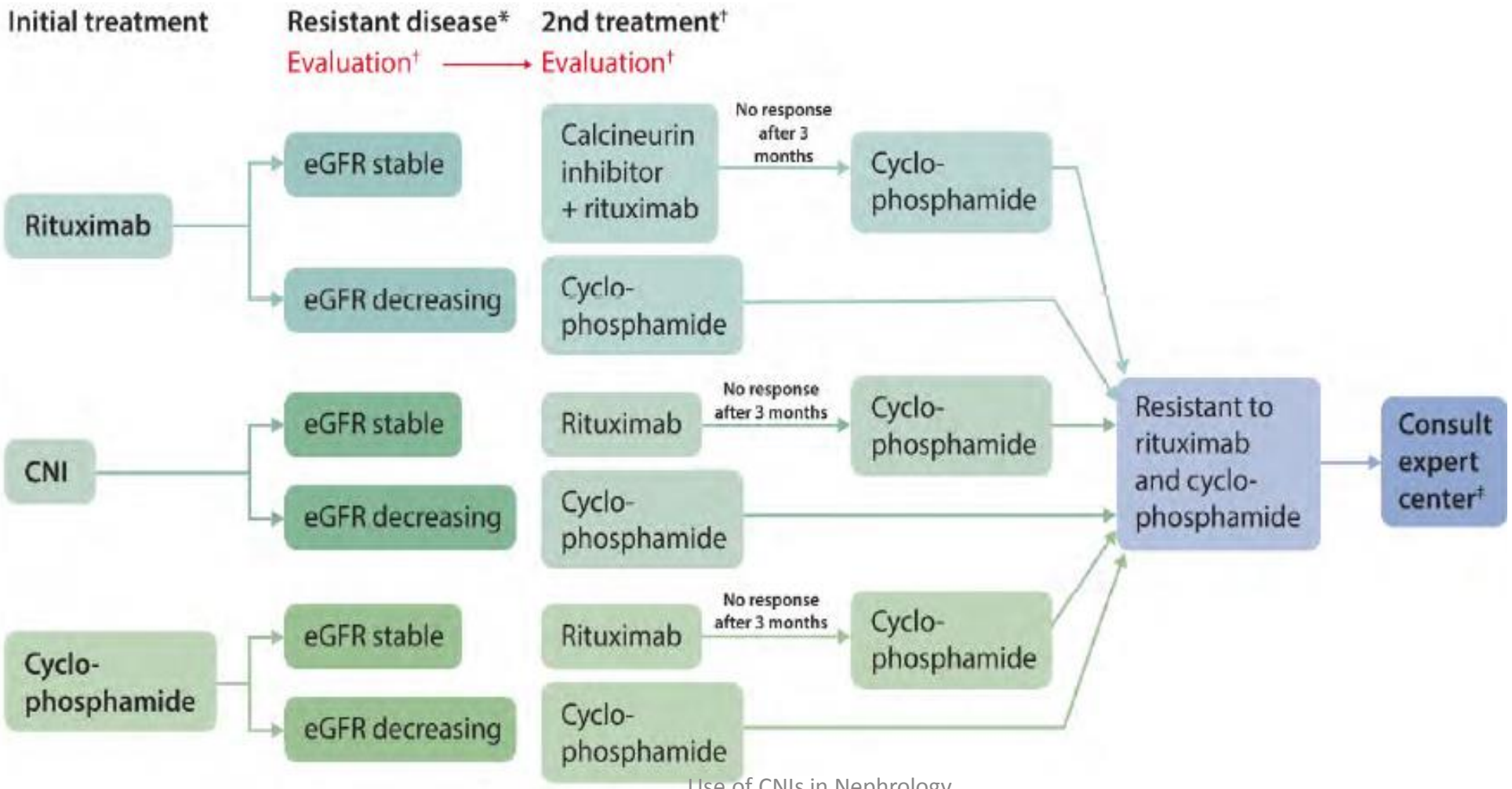
Management of initial relapse after therapy

- Relapse after remission: an increase in proteinuria >3.5 g/day in patients who developed a partial or complete remission.
- KDIGO: If PCR decreased to values between 2 and 3.5 g/day without an increase of serum albumin to normal, the subsequent rise in PCR should be considered a resistant disease rather than relapse after remission.
- In patients with a partial remission (characterized by normalization of serum albumin), a relapse should be defined by an increase of proteinuria paralleled by a decrease in serum albumin levels.



Cyclophosphamide can be repeated; however, physicians must take into account the maximal tolerable dose: the cumulative dose should not exceed 10 g if preservation of fertility is required.
The cumulative dose should not exceed 25 g to limit risk of malignancies.

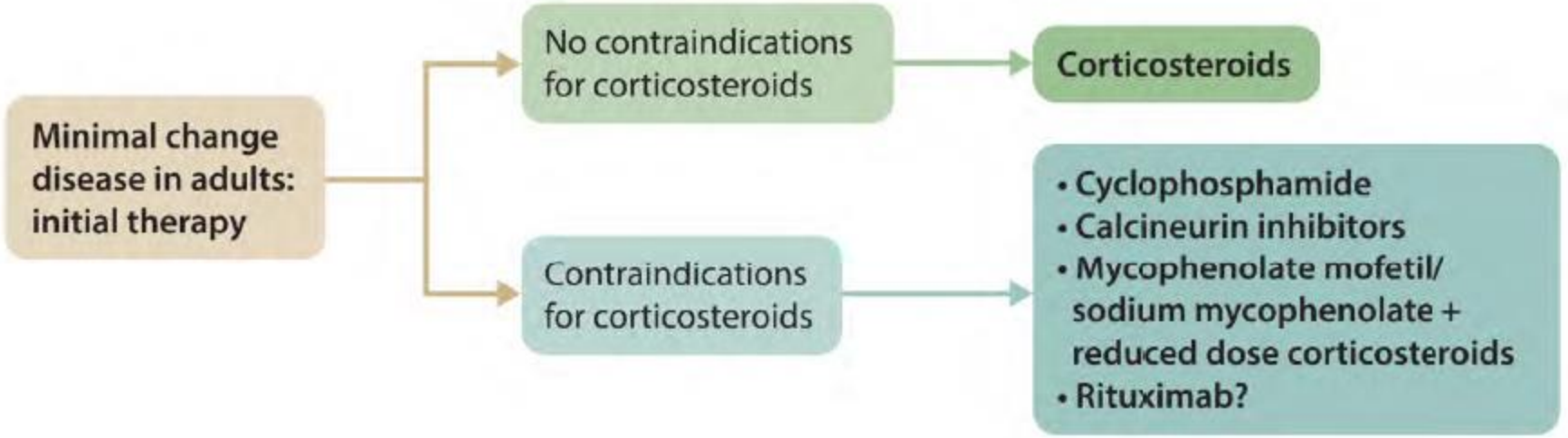
Management of initial relapse after therapy



Management of initial relapse after therapy

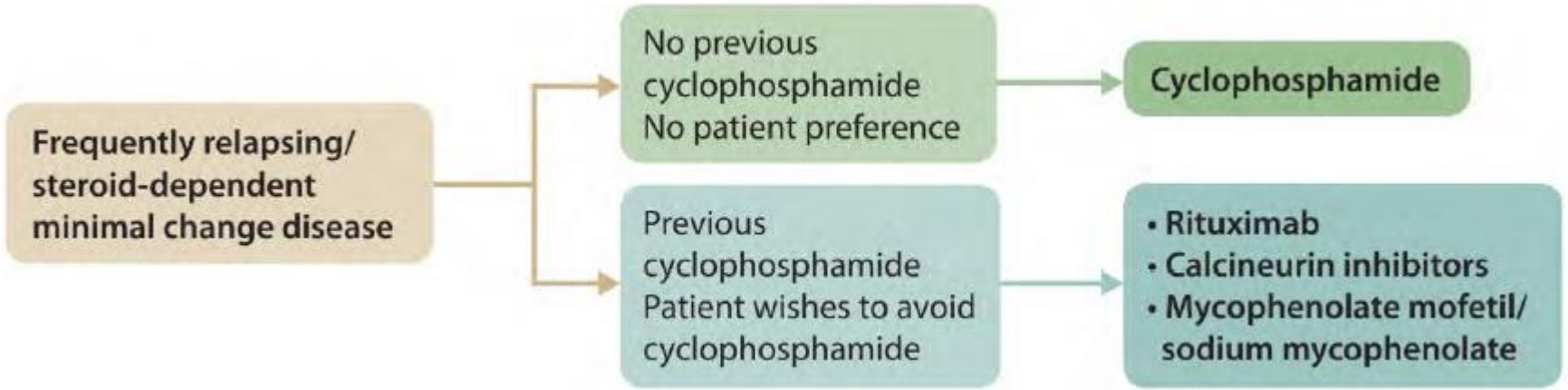
- Persistent proteinuria is not sufficient to define resistance.
- If proteinuria persists, while serum albumin has increased, one should consider secondary FSGS.

When do I use CNIs for MCD?

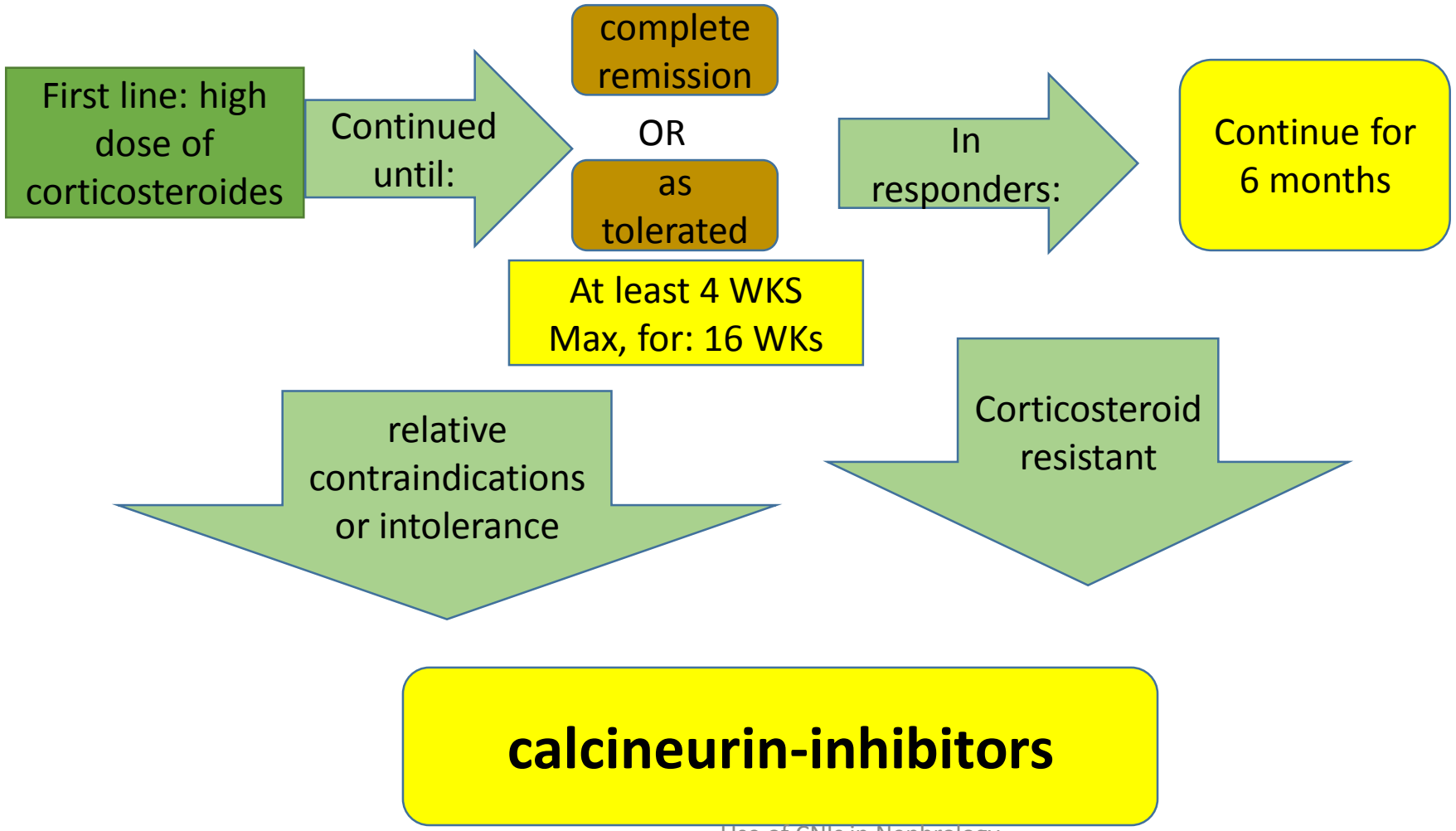


High-dose corticosteroid treatment for MCD should be given for no longer than 16 weeks.
Begin tapering of corticosteroids two weeks after remission.

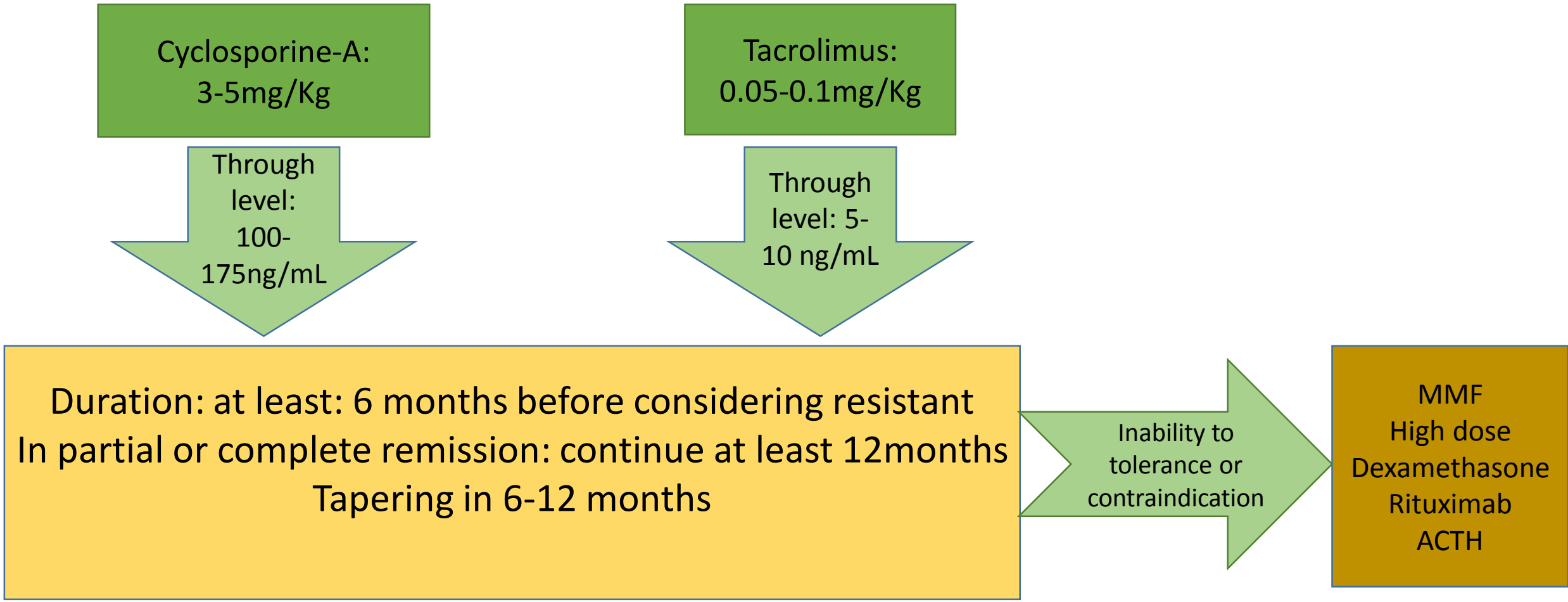
Treatment of FR/SD MCD in adults



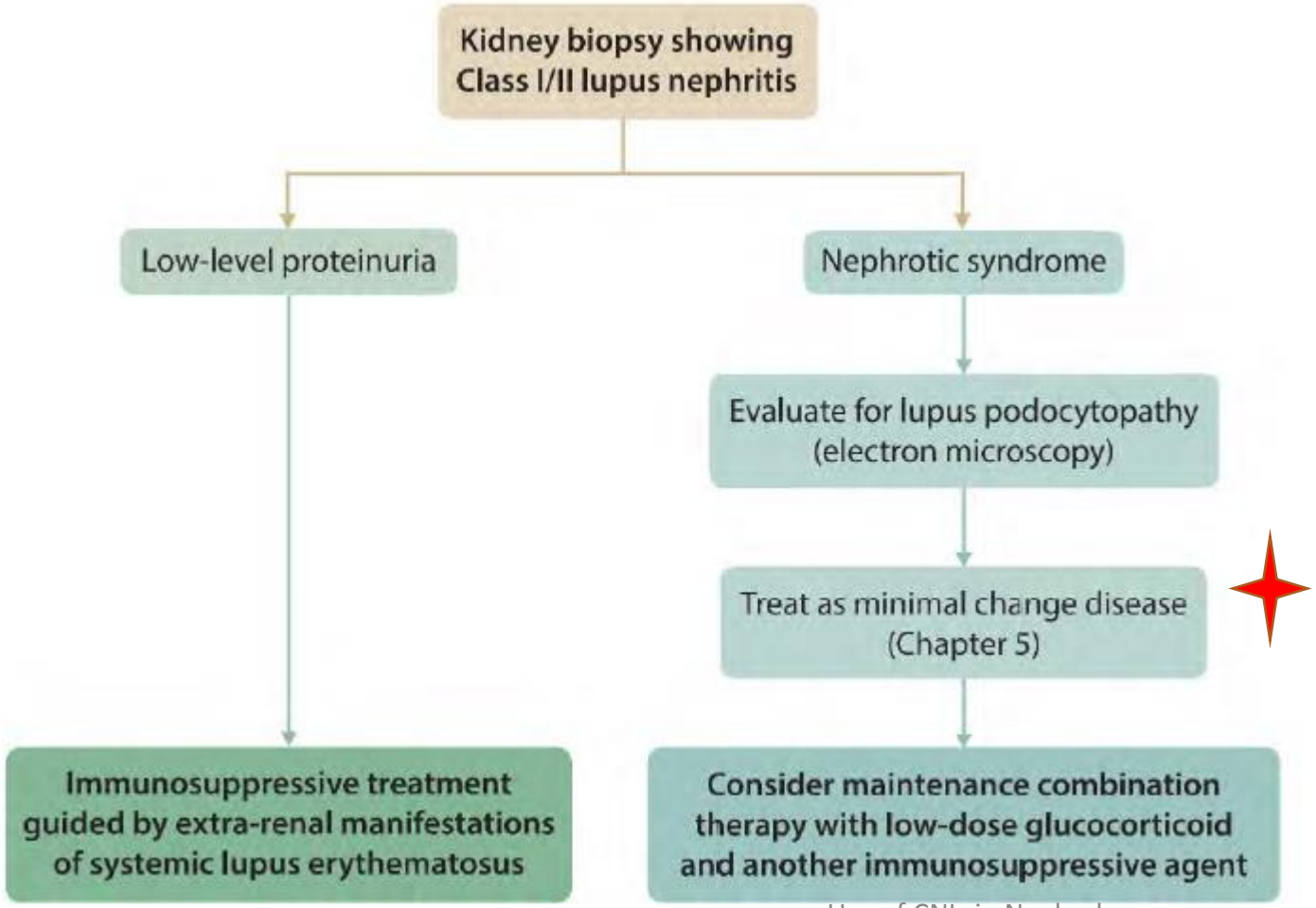
When do I use CNIs for MCD?



CNI dosing


Cyclosporine-A:
3-5mg/Kg
Through level:
100-175ng/mL
Tacrolimus:
0.05-0.1mg/Kg
Through level: 5-10 ng/mL
Duration: at least: 6 months before considering resistant
In partial or complete remission: continue at least 12months
Tapering in 6-12 months
Inability to tolerance or contraindication
MMF
High dose Dexamethasone
Rituximab
ACTH

Lupus nephritis and CNI



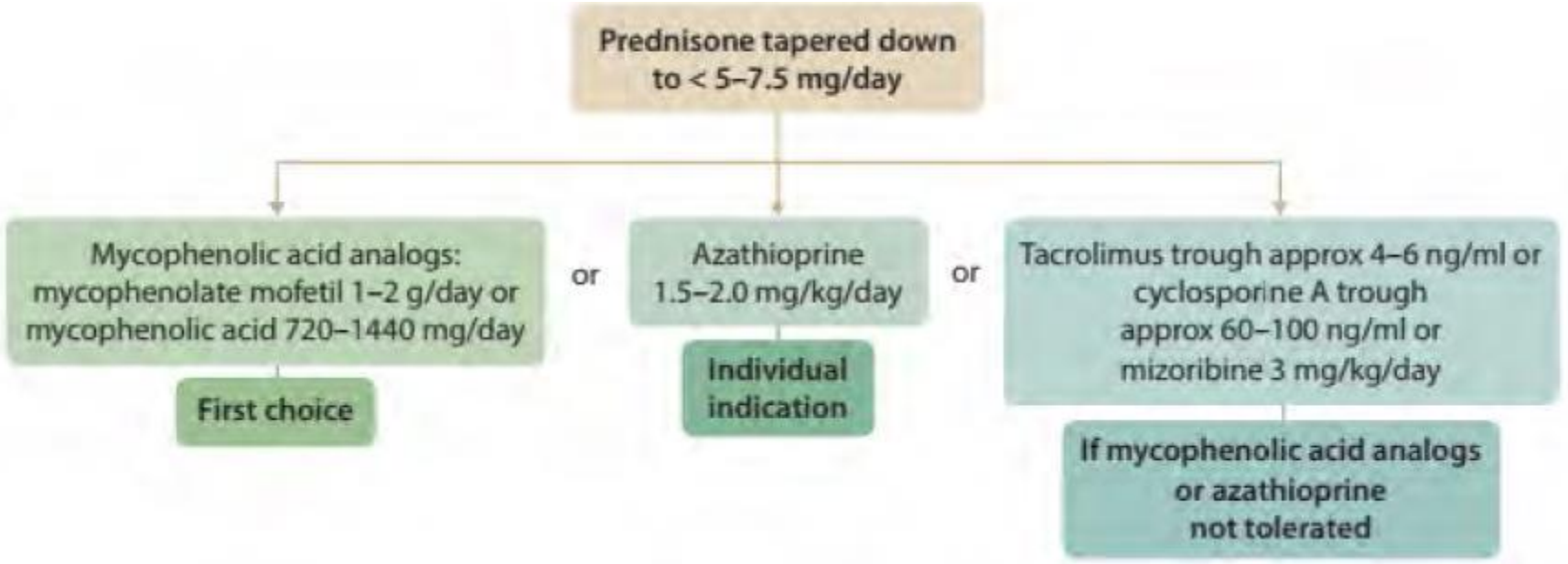
Lupus nephritis and CNI

- **Patients with active Class III or IV LN ± membranous component, be treated initially with corticosteroids plus either low-dose intravenous cyclophosphamide or MPAA.**
- **Initial therapy with triple immunosuppressive regimen that includes a calcineurin inhibitor, reduced-dose MPAA, and corticosteroids should be reserved for patients who cannot tolerate standard-dose MPAA and are unfit for or will not use cyclophosphamide-based regimens.**

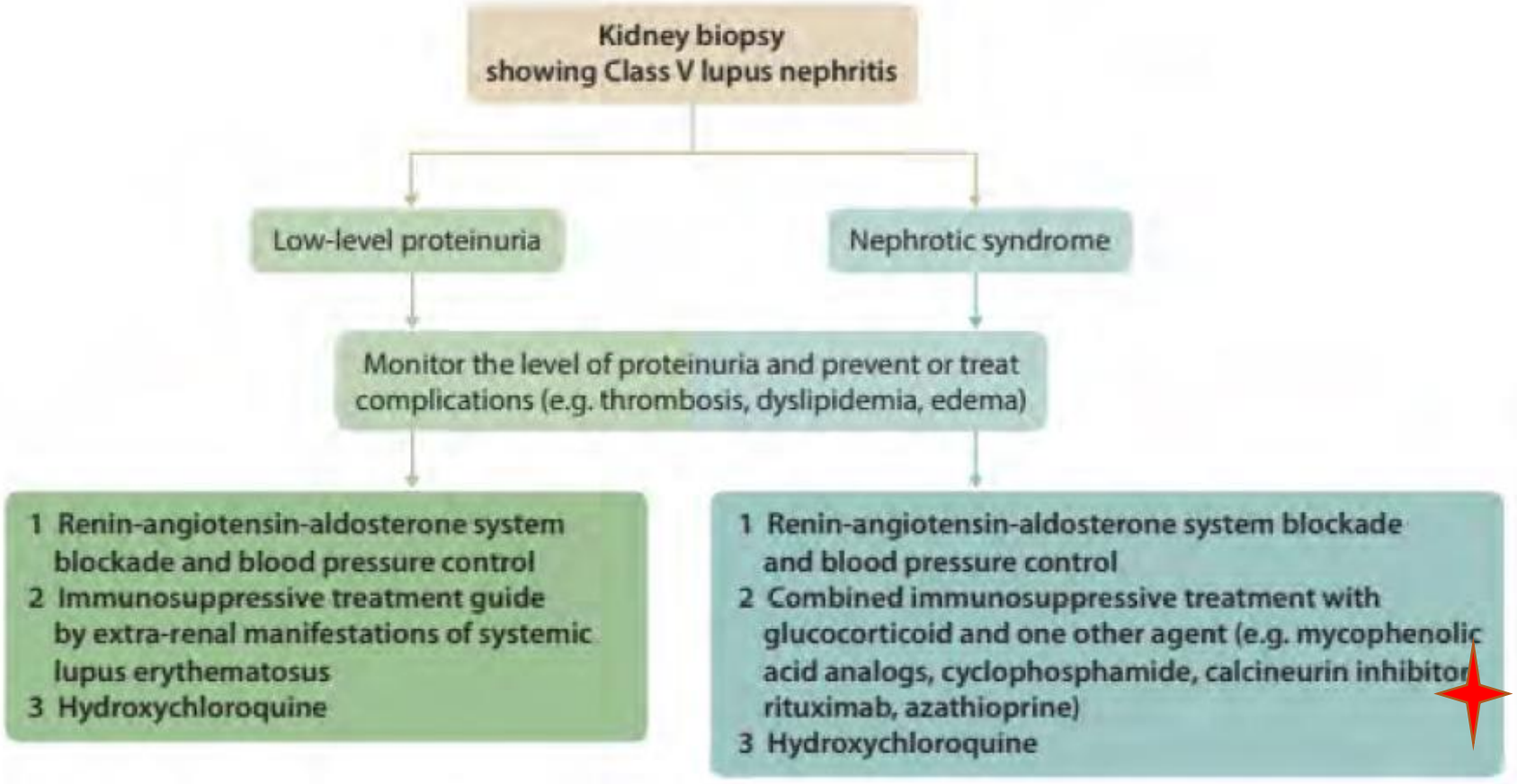
Maintenance therapy

- **After completion of initial therapy, patients should be placed on MPAA for maintenance.**
- **If MPAA and azathioprine cannot be used for maintenance, CNIs or mizoribine should be considered**
- **The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should not be less than 36 months.**

Lupus nephritis and CNI



Management of patients with pure Class V LN



Case

- A 32 years-old woman was referred for management.
- She was healthy until doing check up laboratory examination that was reported Cr= 3.7 mg/dL and proteinuria 2056mg/24h.
- Her autoimmune exams was within normal range and no Dysmorphic RBC or cast was seen in urine analysis.
- In abdominal sonography: kidney size: 82 mm and 86 mm (Rt and Lt side).

Case

- What is your plan for patient?

a) Kidney biopsy
b) Start: Cyclosporine 100mg BID + prednisolone 50mg/d
c) Start: MMF 1000mg BID + prednisolone 50 mg/d
d) No specific treatment is needed

Case

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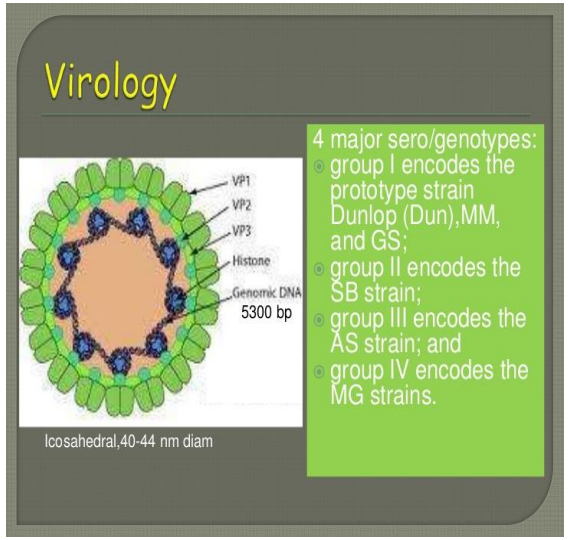
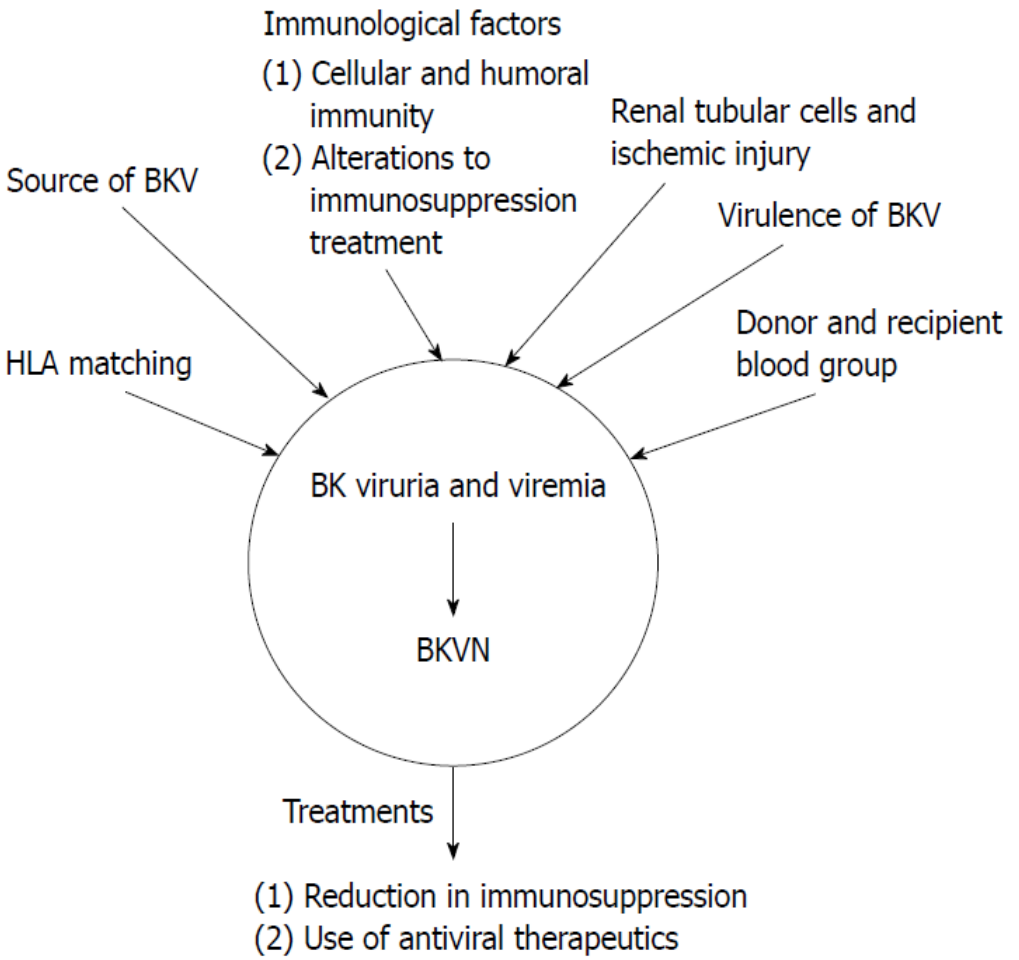


BK virus Nephropathy

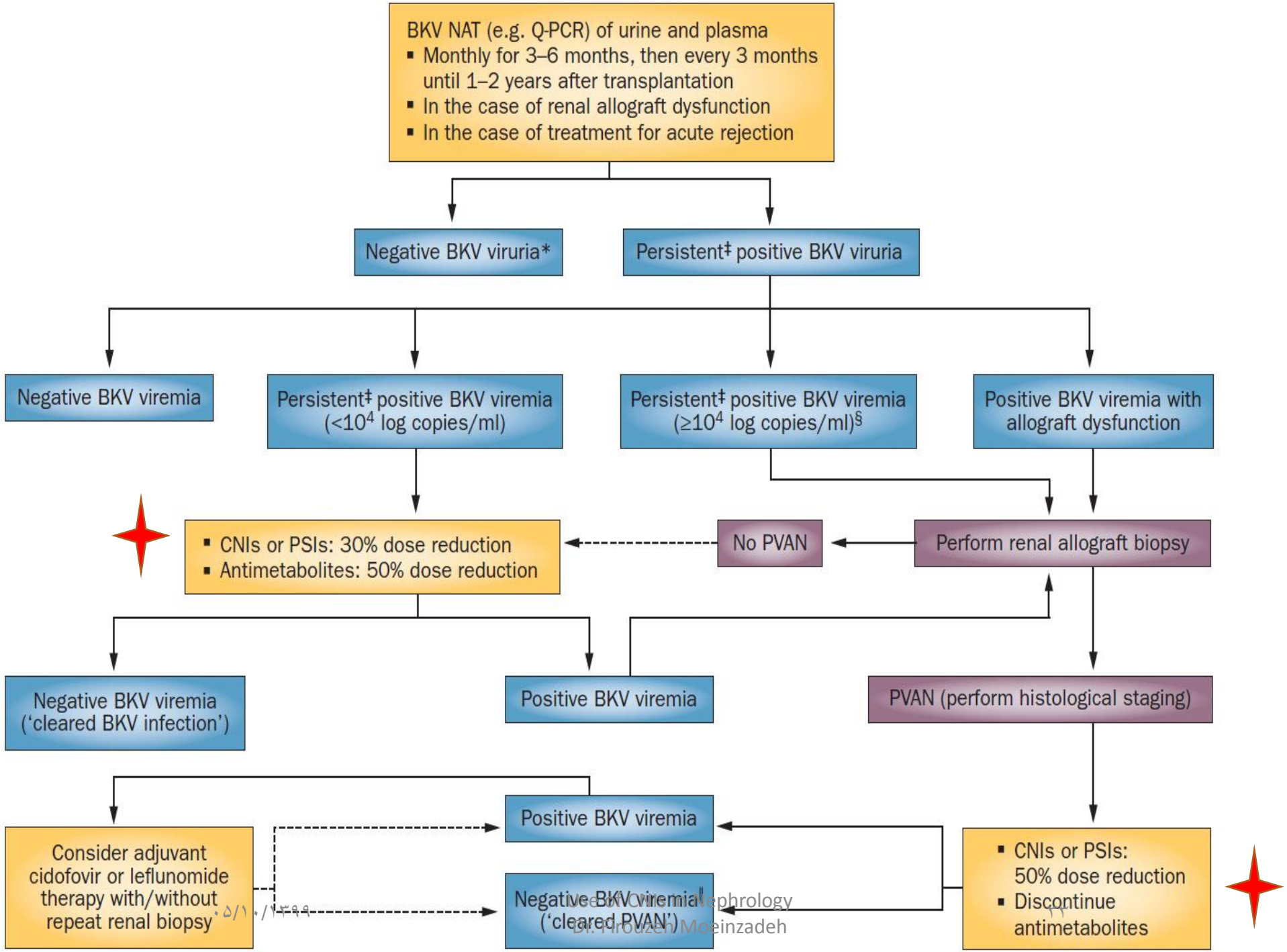
- BK is a circular, double-stranded DNA virus from the polyomavirus family, which includes JC virus and SV40.
- BK can be divided into six subtypes or genotypes(I >IV)(Ia,Ib1,Ib2,Ic)(IV-a1,IVa2, IV-b1, IV-b2, IV-c1, IV-c2)

Pathogenesis



BK virus Nephropathy

- Peak viral loads in the urine precede BKV viremia by 4–6 weeks (range: 2–10 weeks) and precede PVAN by a median of 12 weeks.
- The guidelines stated that if urine viral loads exceeded 10,000,000 copies/mL and/or if plasma viral loads were higher than 10,000/mL for more than 3 consecutive weeks, a renal biopsy should be considered.
- Diagnostic cut-off values for PVAN in urine samples varying between 1,000,000 copies/ml and 2.5 × 107 copies/ml, and plasma cut-off values between 3.0 × 1000 and 1.0 × 104.5 copies/ml



BK virus Nephropathy

- Reduction of immunosuppression is the mainstay of BKVN treatment.
- Management approaches differ and can include discontinuation of the anti-metabolite, dose reduction of the CNI by 25–50% targeting significantly lower levels (tacrolimus 3–4 ng/mL and cyclosporine 50–100 ng/mL, or even less) or switching from tacrolimus to cyclosporine.

Question

- What is the best CNI for retransplantation after kidney graft loss due to polyoma BK virus nephropathy?

a) Avoid any type of CNIs
b) Avoid Tacrolimus
c) Use any type of CNI
d) Use Cyclosporine VS Tacrolimus, ONLY
e) Pre transplantation nephrectomy

Answer

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CNI and pregnancy

- CsA is very lipid-soluble drug, is extensively distributed in the body, and is highly metabolized. High concentrations of CsA metabolites in the placenta can be observed, indicating the presence of CsA metabolizing enzymes in the placenta.
- The FDA classifies CsA as category C, meaning that human risk cannot be ruled out. Theoretically, calcineurin inhibitors might alter the immune status of the infant; however, no reports were found.

Journal of Clinical Medicine

Review

Fetal Toxicity of Immunosuppressive Drugs in Pregnancy

Claudio Ponticelli [1,*] and Gabriella Moroni [2]

CNI and pregnancy

- some investigators found that low-dose CsA treatment can regulate the immune response and increase the live birth rate in mothers with unexplained recurrent miscarriage.
- The lower fetal blood concentrations are likely due to active efflux transport of T**AC** from the fetus toward the mother by placental P-glycoprotein.

CNI and pregnancy

- Tacrolimus has been associated with a higher miscarriage rate, small for gestational age and premature delivery, this may be confounded by the severity of the underlying disease.
- Calcineurin inhibitors are associated with higher rates of hypertension and diabetes, so a glucose tolerance test at 16 and 28 weeks is recommended

Case

- A 22-year-old man received a kidney from a cadaveric donation in 2016.
- He has renal insufficiency due to vesicoureteral reflux and received hemodialysis for 1 year.
- Pre transplantation laboratory variables:
- BUN=75mg/dL Cr= 6.4mg/dL Ca= 7.1mg/dL Alb= 3.6g/L
- Post transplantation laborat

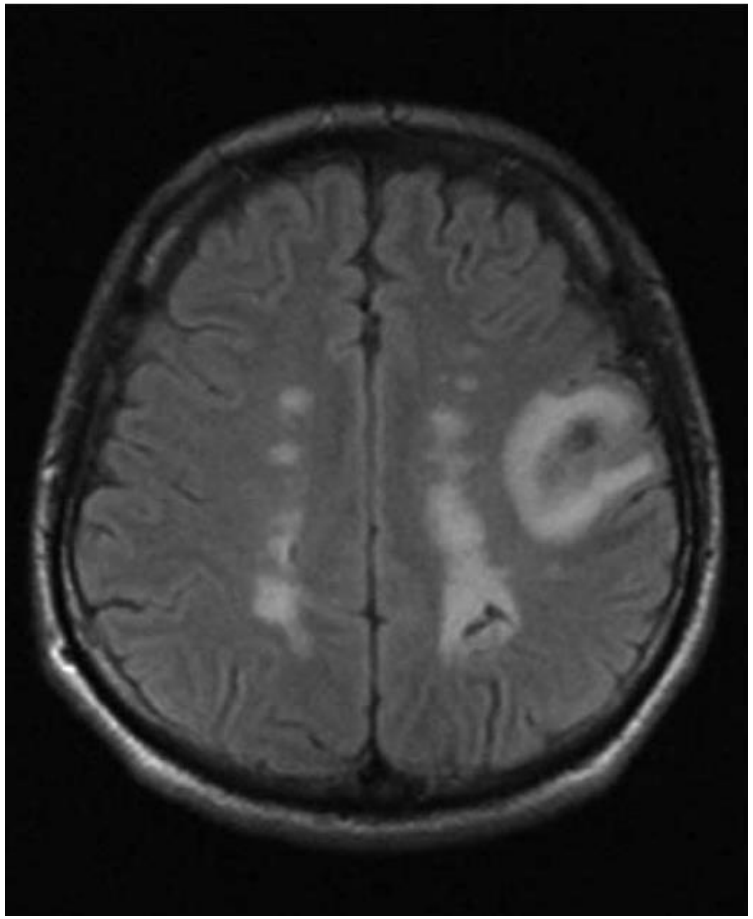
Case

- A 22-year-old man received a kidney from a cadaveric donation in 2016.
- He has renal insufficiency due to vesicoureteral reflux and received hemodialysis for 1 year.

	BUN (mg/dL)	Cr (mg/dL)	Ca (mg/dL)	Alb (g/L)	BP (mmHg)	FK level (ng/mL)
Pre transplantation	75	6.4	7.1	3.6	120/80	-
D1	35	4	6.7	-	130/80	-
D2	20	2.1	6.5	3.5	135/80	-
D3	18	1.8	6.7	-	135/85	6.8
D4	16	1.6	6.7	-	130/80	-
D5	17	1.5	6.7	3.7	140/85	12

- His maintenance immunosuppression therapy included tacrolimus 4.0mg bid, mycophenolate mofetil 1000mg bid, and daily prednisone with an initial dose of 60 mg.
- D5: he had generalized seizure with upward gaze, persist for 2 minutes.
- In Brain MRI: localized subcortical areas of increased T2 signal/edema and markedly increased T2 FLAIR signal in the left temporal lobe with 1 small hypointense area in the center of the lesion, and scattered, small hyperintense areas in the centrum semiovale

Question



What is your diagnosis?

a)Dysequilibrium syndrome

b)Hypocalcemic seizure

c)Underlying neurologic disorder

d)Posterior reversible encephalopathy syndrome

Answer

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b) Hypocalcemic seizure

c) Underlying neurologic disorder

d) Posterior reversible encephalopathy syndrome

CNI- Induced PRES

- PRES-related clinical symptoms and signs can be classified into the following 7 categories: encephalopathy, seizure, headache, visual disturbances, focal neurological deficits, status epilepticus, and nausea/vomiting.
- CNI toxicity is regarded as one of the etiologies of PRES
- CNI associated PRES in the presence of therapeutic drug levels was more likely to occur in patients receiving CsA than in those receiving tacrolimus (40% vs 25.8%)

CNI- Induced PRES

- Most patients have mild symptoms and signs and have a reversible course, if PRES is not recognized and treated early, it can lead to severe and life-threatening situations.
- Management: Substitution of CNIs with other immunosuppressive agents (43.7%) (switching to another CNIs, 26.8%; replacing CNIs with sirolimus, everolimus, mycophenolate mofetil, or hydrocortisone, 16.9%) and lowering the CNI dose (22.5%) were the most commonly applied primary approaches, followed by temporal CNI cessation (19.7%),

Take home messages

Thanks for