

Management and treatment of glomerular diseases (part 2)

Conclusions from KDIGO Controversies Conference



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MCD & FSGS

- **MCD & FSGS remain relevant**
- **To discriminate between them we need least 20 glomeruli**
- **Primary Dx may show MCD, but the patients may later develop FSGS**
- **Childhood nephrotic syndrome : steroid sensitive vs steroid-resistant**

Primary vs Secondary FSGS

Primary FSGS :

- ▶ Acute-onset heavy proteinuria
- ▶ Diffuse podocyte foot process effacement histologically
- ▶ caused by as yet unknown permeability factors

Secondary FSGS :

- Modest proteinuria & segmental foot process effacement
- Genetic
- Adaptive (reduced nephron mass)
- Drug-induced
- Viral-induced FSGS

Pathogenesis of MCD & Idiopathic FSGS

- ▶ **A role for dysfunctional T cell (over 40 years ago)**
- ▶ **Role for B cells has become evident**
- ▶ **Soluble urokinase-type plasminogen activator receptor**
 - ▶ **Novel prognostic biomarker for chronic kidney disease**
 - ▶ **Not appear to have a role as a diagnostic biomarker**
 - ▶ **Not represent the permeability factor in FSGS**
- ▶ **Cardiotrophin-like cytokine-1 (member of the IL 6 family)**
 - ▶ **May be a candidate FSGS permeability factor**
 - ▶ **Identified in the plasma of patients with FSGS**
 - ▶ **Decrease nephrin expression in podocyte culture**
 - ▶ **100 times plasma concentration in recurrent FSGS vs normal population**

Pathogenesis of MCD & Idiopathic FSGS

- ▶ **Angiopoietin-like-4**
 - ▶ Highly upregulated in the serum and in podocytes (in models of MCD)
 - ▶ Relevant in patients with steroid-sensitive nephrotic syndrome
- ▶ **Podocyte CD80**
 - ▶ May be mediate MCD/FSGS
 - ▶ It's expression induced after an innocuous event such as an infection
- ▶ **Role for glomerular parietal epithelial cells has also been proposed**

Biomarkers and prediction of prognosis

There are no validated biomarkers ready for clinical use

Histological subtype of FSGS:

- ▶ making and help with anticipating response to treatment and prognosis

IHC specimens for parietal epithelial cell activation markers

- ▶ May improve sensitivity for detecting sclerotic lesions & distinguishing primary FSGS from MCD

Proteomic analysis of kidney biopsy :

- ▶ may provide additional insights

Genetic testing

In Pediatric nephrotic syndrome and adult FSGS is controversial

It should be considered for :

- **Congenital and infantile nephrotic syndrome (<1 year of age)**
- **Less than 2 years & steroid-resistant nephrotic syndrome**
- **Nephrotic syndrome associated with other syndromic features**
- **Familial forms of steroid-resistant nephrotic syndrome/FSGS**

Single gene mutations have been found in up to 30% of patients under age 25

Genetic testing

The role of high-risk apolipoprotein L1 genotypes :

- **Is still under investigation**
- **Data are still insufficient to support using this to guide clinical decisions**

Genetic testing may be considered for inclusion and stratification in clinical trials

Biospecimens should routinely be collected

Patients consented for later genetic analysis

Ethical issues should be addressed before recommending genetic analyses

Treatment

Immunomodulatory :

- **First-line treatment in primary/idiopathic FSGS caused by a permeability factor**

Other FSGS subtypes :

- **Respond better to blood pressure control**
- **Correction of abnormal glomerular hemodynamics**

Following identification of causative mutations :

- **Directed therapies for specific mutations (coenzyme Q-10, Vit B12)**
- **Anti proteinuric therapy**
- **Discontinuation of immunosuppressive therapy in those with no early signal of response**

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Treatment :Pediatric

- 80% of children with nephrotic syndrome have MCD on biopsy
- Remaining patients, some will respond to corticosteroid
 - RCT do not support steroid exposure beyond 8 to 12 weeks
 - Use at least 8 weeks of corticosteroids before defining steroid resistance
 - The efficacy of low-dose daily corticosteroids over alternate day for maintaining remission
- So treat all pediatric nephrotic patients with corticosteroids first
 - Alternative immunosuppressive: cyclophosphamide, levamisole,MMF,CNIs,rituximab
- Increase steroid-resistant nephrotic syndrome and FSGS with age
- Consideration to biopsy children >12 years prior to treatment

Treatment :Adult

- Previous guideline : Minimum 16 weeks of high-dose corticosteroids for FSGS or MCD (It felt to be controversial -Given its potential for toxicity)
- Alternative first-line agents or combination & lower doses of corticosteroids :
No supporting data
- CNIs or CYC should remain as **second-line** agents in relapsing or steroid-dependent MCD
- RTX is an emerging **second-line therapy** in MCD in adults (evidence is observational only)
- CNIs and MMF as **second- and third-line treatments**, respectively, for FSGS should be maintained
- New agent: CD80 inhibitor abatacept, , in MCD and FSGS (RCT ongoing)

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Histologic descriptor of glomerular injury

- Increasing understanding of C3 glomerulopathy (C3G)
- Monoclonal gammopathies of renal significance (MGRS) (paraprotein-associated kidney diseases)

Overlapping disease mechanisms

- Common kidney biopsy features
- Some cases will remain “idiopathic” in nature

In understanding the pathogenesis

- C4d staining to distinguish C3G from Ig-mediated and post infectious GN
- Staining for the DNA J homolog subfamily B member 9 protein in fibrillary GN

C3 Glomerulopathies

Abnormal complement activation, deposition and/or degradation

- **Single nucleotide changes**
- **C3 nephritic factors in the majority of cases**
- **Heterogeneity in the kidney biopsy criteria used for diagnosis**
- **Targeted anticomplement agents are available**

C3 Glomerulopathies

Biomarkers and prediction of prognosis

Soluble C5b-9 levels for predicting treatment response → unclear

Use of serial complement testing requires further study

Testing for paraproteins in C3G has also received increased attention

C3 Glomerulopathies Treatment

- ❑ Optimal duration of therapy remains unclear**
- ❑ Current treatment : inhibiting definable pathways**
 - Inflammation or terminal complement**
 - Antiproliferative or terminal complement blockers**
- ❑ Treatment with MMF and corticosteroids**
 - Has shown promise in 2 retrospective case series**
 - But was not found to be effective in a third case series**
 - Not effective in in patients with more severe baseline kidney disease**
- ❑ For patients with C3G and monoclonal gammopathy**
 - Superior hematologic and renal response rates**
 - Higher renal survival**
 - In whom treated with clone-directed chemotherapy compared with conservative or immunosuppressive treatment**

Monoclonal Gammopathies of Renal Significance

Pathogenesis:

- Heavy chain deposition disease
- Truncated Ig heavy chain that lacks the first constant domain (CH1 deletion)
- Most patients have an underlying plasma cell clone that does not meet criteria for multiple myeloma
- Evidence of the truncated heavy chain can be found in the serum and bone marrow
- Igs are from plasma cell or B-cell clones
- Targeting these clones may improve outcomes
- The clones are often undetectable

Monoclonal Gammopathies of Renal Significance

The International Kidney and Monoclonal Gammopathy Research Group :

- All patients with paraprotein-associated kidney disease
- Undergo hematology evaluation, including a bone marrow biopsy
- Utility of the bone marrow is not clear in patients without a detectable circulating paraprotein

Monoclonal Gammopathies of Renal Significance

Biomarkers and prediction of prognosis

In Myeloma and light chain amyloidosis:

- **Achieving hematologic response (improvement in levels of circulating paraprotein) Associated with improved overall and renal survival**
- **Stabilization or improvement in kidney function & proteinuria may be linked with long-term renal survival**
- **Emerging data regarding the importance of hematologic response in MGRS**
- **It is not clear how to monitor patients without a detectable circulating paraprotein**

Monoclonal Gammopathies of Renal Significance

Treatment

- Risk stratification: based on kidney dysfunction and proteinuria
- Treatment strategies : clone-directed approach similar to MM & lymphomas (chemotherapeutic regimens, autologous stem cell transplant)

A large retrospective case series found that using bortezomib-based therapy:

- Higher hematologic and renal response rates
- Prolonged renal survival

Controversy :

- In treatment of patients without a detectable underlying clone
- Recent uncontrolled data suggest benefit from empiric

Hepatitis C-associated glomerulonephritis

Table 2 | KDIGO clinical practice guideline on the treatment of HCV-associated glomerulonephritis

Renal presentation	Treatment
Stable kidney function and/or nonnephrotic proteinuria	Direct-acting antiviral therapy
Cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure	Direct-acting antiviral therapy with immunosuppressive treatment, with or without plasma exchange
Histologically active HCV-associated glomerulonephritis that does not respond to direct-acting antiviral therapy	Rituximab as first-line immunosuppressive treatment

Fibrillary GN

- ▶ IHC on kidney biopsy for the DNA J homolog subfamily B member 9 protein
- ▶ Role of DNA J homolog subfamily B member 9 in disease pathogenesis is unknown
- ▶ The data on treating fibrillary GN consist of small studies using a variety of therapies
- ▶ None of which have been conclusive

LUPUS NEPHRITIS

International Society of Nephrology/Renal Pathology Society system classification :

Does not consider

- ▶ Tubulointerstitial injury
- ▶ Vascular lesions
- ▶ Podocytopathies

Patients with tubulointerstitial injury, thrombotic microangiopathy (TMA), and renal vasculitis have worse outcomes

LUPUS NEPHRITIS

Systemic Lupus International Collaborating Clinic diagnostic criteria for SLE

- Immune complex GN
- Consistent with LN
- In the setting of a positive ANA or anti-ds DNA

Sufficient for diagnosing SLE



LUPUS NEPHRITIS (Pathogenesis)

Genetic (African ancestry / APOL1)

Epigenetic

Immunoregulatory

Hormonal

Environmental phenomena

LUPUS NEPHRITIS (Biomarkers & prognosis)

Proteinuria, hematuria, urinary sediment, and estimated GFR

- ▶ No single biomarker predicts the development
- ▶ The diagnosis of LN should be confirmed by biopsy
- ▶ Clinically stable patient may have activity on biopsy
- ▶ Proteinuria at 1 year was the best predictor of long-term renal outcome

Anti-double-stranded DNA, complement C3, C4, anti-C1q testing

Combination of elevated anti-ds DNA, low complement level, & anti-C1q Ab

- ▶ Strongly associated with renal involvement
- ▶ Should be monitored in patients at risk for LN or LN flare

LUPUS NEPHRITIS (Treatment)

Antimalarials :

- Recommended for all patients with LN
- Reduce the odds of developing LN
- Higher likelihood of a complete renal response to treatment
- Reduced likelihood of developing end-stage kidney disease

Corticosteroids:

- Adverse effect in moderate and high dose
- Dose minimization (<5mg/day)

LUPUS NEPHRITIS (Treatment: Induction)

Immunosuppressive therapy

- ❑ **CYC- or MMF-based induction → gold standard**
- ❑ **CNI-based → studied in Asia (combine MMF & corticosteroids)**
 - **Cumulative effect was similar**
 - **Risk of CNI toxicity**
 - **Protocol biopsies**

LUPUS NEPHRITIS (Treatment: Maintenance)

MMF or azathioprine (AZA) with or without low-dose corticosteroids

- ▶ It is not clear how long to continue maintenance
- ▶ In recent trials: the duration of maintenance has been 3 to 5 years
- ▶ Many patients remained on maintenance therapy for 10 years
- ▶ **A minimum of 3 years of maintenance is suggested**
- ▶ Slowly withdrawing immunosuppression
- ▶ Repeat biopsy : to exclude persistent clinically silent

Preliminary studies : intensive B-cell depletion with a RTX plus

- ▶ May avoid the need for maintenance therapy

LUPUS NEPHRITIS (Treatment: Refractory)

❑ Medication adherence

❑ Repeated kidney biopsy

➤ Distinguish active LN from scarring

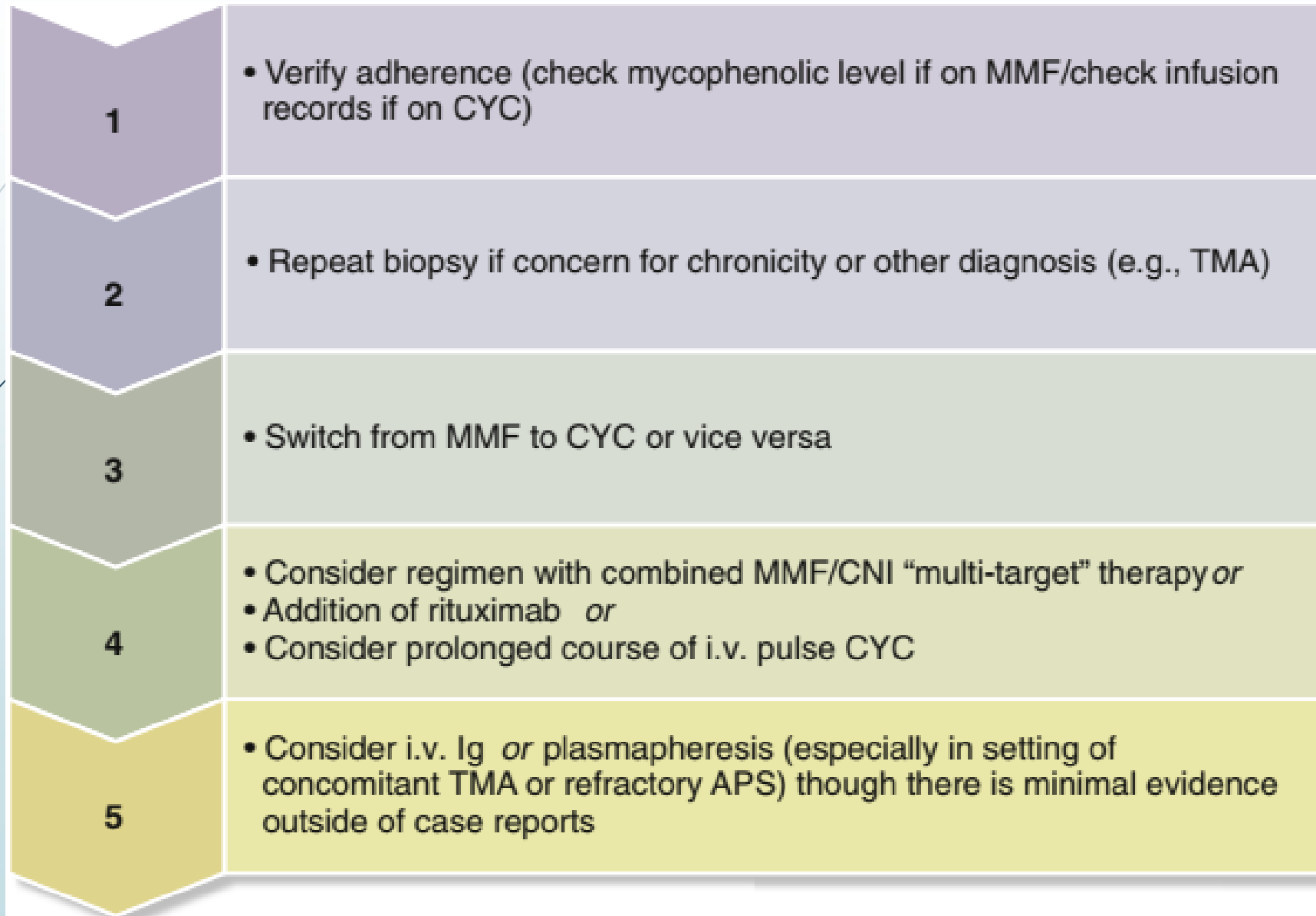
➤ Identify new lesions

For persistently active :

➤ If MMF was used for induction, consider switching to CYC

➤ RTX or CNI-based regimens could be tried

LUPUS NEPHRITIS (Treatment: Refractory)



1	<ul style="list-style-type: none">• Verify adherence (check mycophenolic level if on MMF/check infusion records if on CYC)
2	<ul style="list-style-type: none">• Repeat biopsy if concern for chronicity or other diagnosis (e.g., TMA)
3	<ul style="list-style-type: none">• Switch from MMF to CYC or vice versa
4	<ul style="list-style-type: none">• Consider regimen with combined MMF/CNI “multi-target” therapy <i>or</i>• Addition of rituximab <i>or</i>• Consider prolonged course of i.v. pulse CYC
5	<ul style="list-style-type: none">• Consider i.v. Ig <i>or</i> plasmapheresis (especially in setting of concomitant TMA or refractory APS) though there is minimal evidence outside of case reports

LUPUS NEPHRITIS (Treatment : Special circumstances)

Class V LN:

- Nephrotic proteinuria : should receive immunosuppression
- Some treat patients with lower levels of proteinuria
- Treated initially with MMF , if not effective, CYC may be used
- Some investigators suggest using CNIs for class V LN
- RTX may be considered

LUPUS NEPHRITIS (Treatment : TMA)

Due to antiphospholipid antibodies/syndrome ,TTP, atypical HUS

Plasma exchange :

- **TTP & in cases of refractory APS**

Anti complement therapies

- **In catastrophic APS**
- **TTP**
- **Complement-mediated TMA**
- **Recurrent TMA in an allograft**

Anticoagulation :

- **standard of care for APS**
- **Impact of anticoagulation on renal lesions is unclear**

LUPUS NEPHRITIS (Treatment :Special Condition)

Posttransplant

- ▶ LN have equivalent or better outcomes compared with other primary GN
- ▶ Recurs in <20%
- ▶ Should remain on HCQ and be on MMF/CNI-based immunosuppressive
- ▶ Mild flares → treat with oral corticosteroids alone
- ▶ Moderate flares → treat with i.v. corticosteroids & increased MMF
- ▶ Crescentic disease/severe flare → treated with i.v. corticosteroids & CYC
- ▶ MMF should be held while patient is on CYC therapy

LUPUS NEPHRITIS (Treatment :Special Condition)

Pregnancy

- **MMF to AZA**
- **Consider CNIs if AZA cannot be tolerated**

Pediatric-onset disease

- **Often have few comorbidities**
- **More severe disease with a higher genetic contribution**
- **Class V LN tend to need additional immunosuppression even with subnephrotic proteinuria**

ANCA-ASSOCIATED VASCULITIS

Small vessel vasculitis

- Granulomatosis with polyangiitis (GPA)
- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis
- Renal-limited vasculitis can also occur

Pathogenesis :

- Genetic, epigenetic, immunoregulatory, hormonal, and environmental
- A role for complement activation in the pathogenesis has emerged from therapeutic studies with complement inhibitors

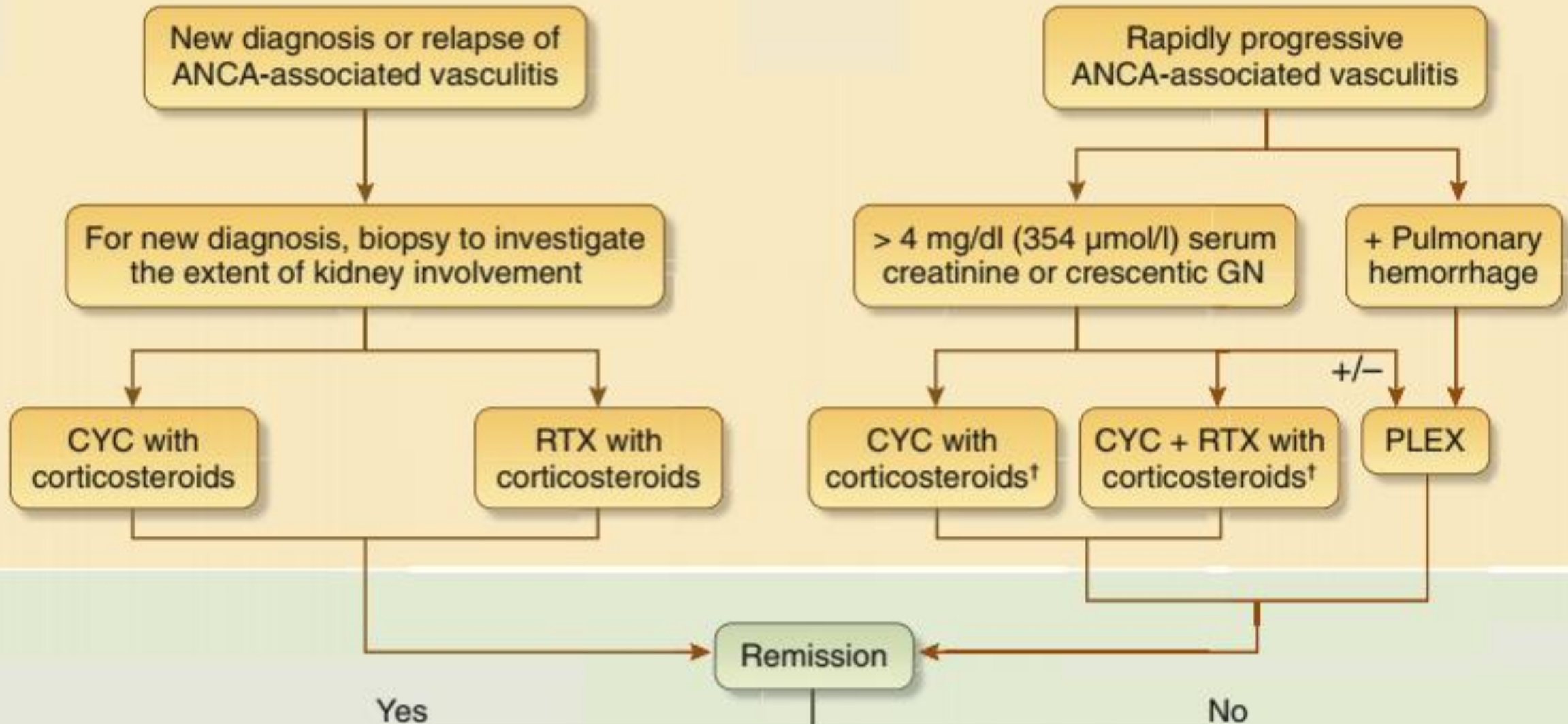
ANCA-ASSOCIATED VASCULITIS

Biomarkers and prediction of prognosis

- ▶ Proteinuria, hematuria, urinary sediment, & eGFR
- ▶ At present, there is no biomarker to predict the development or flares
- ▶ Increase and persistently positive ANCA are modestly but significantly associated with disease relapse
- ▶ Serial ANCA testing is not sufficiently robust to trigger changes in therapy
- ▶ Relapse is more frequent in PR3-ANCA than MPO-ANCA
- ▶ Relapse may be predicted by PR3-ANCA levels

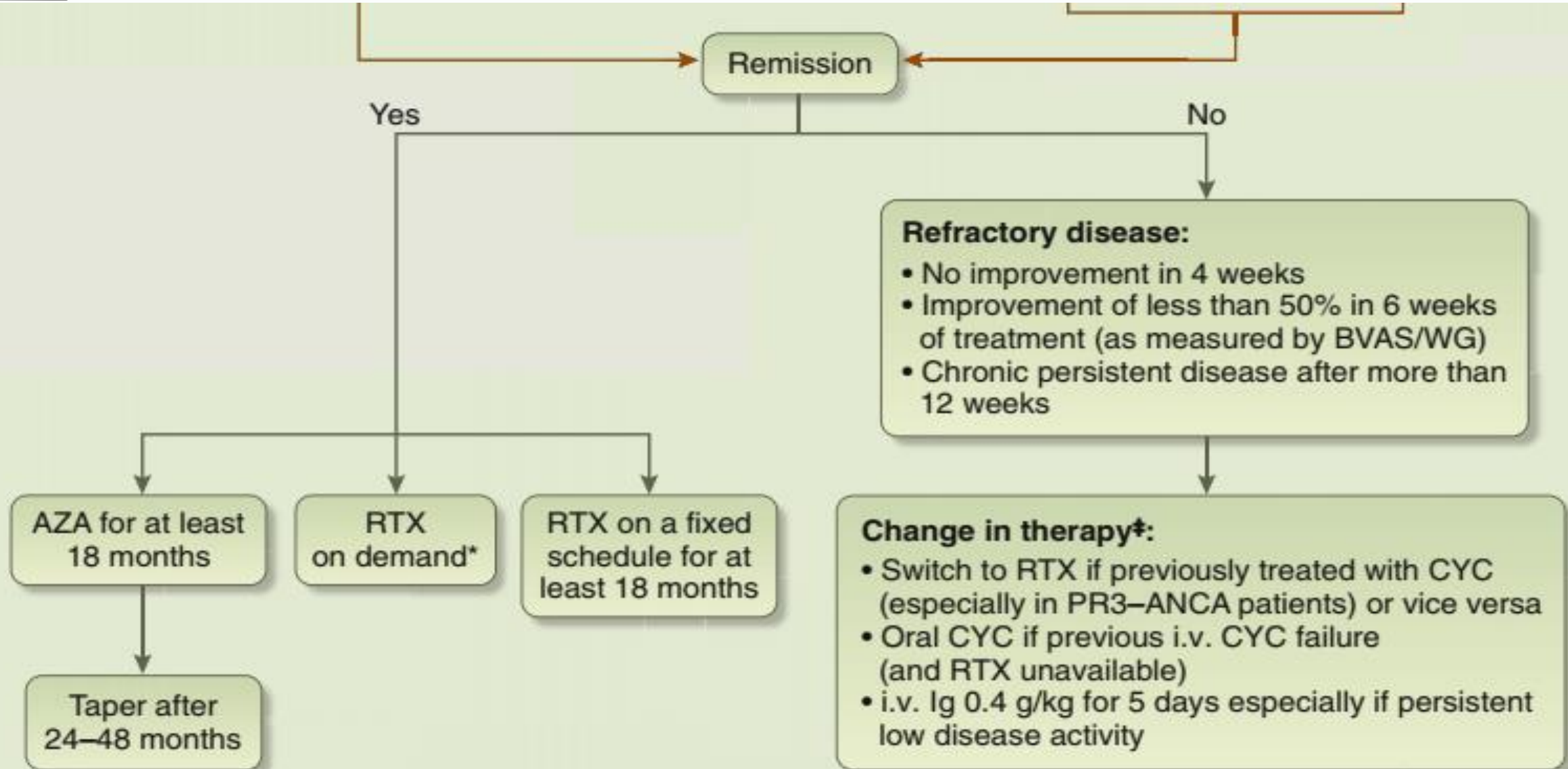
ANCA-ASSOCIATED VASCULITIS

Induction



ANCA-ASSOCIATED VASCULITIS

Maintenance



ANCA-ASSOCIATED VASCULITIS

Treatment

Corticosteroids

- Given as 500- to 1000-mg i.v. pulses daily for 1 to 3 days at initiation
- In patients with a clinical picture of RPGN
- Monotherapy is not effective & have short- and long-term adverse effects

Cyclophosphamide

- Drug of choice for decades
- Despite efficacy its safety require the need for an alternative

ANCA-ASSOCIATED VASCULITIS

- ▶ **RTX effective as CYC induction/AZA maintenance for AAN in patients with serum Cr <4 mg/dl**
- ▶ **Alternative approach :**
 - CYC for the induction & considers RTX for maintenance**
- ▶ **Is treatment should be different for MPO & PR3-ANCA ?**
- ▶ **RTX was superior to CYC for PR3-ANCA and as effective as CYC for MPO-ANCA**
- ▶ **The risk of relapse :associate more closely with disease type than ANCA subset**

ANCA-ASSOCIATED VASCULITIS

Maintenance treatment

- Initiate after remission is achieved, usually 3 to 6 months after induction
- Consists of AZA or RTX (No consensus regarding the length of treatment)

For conventional therapy(CYC induction and AZA maintenance)

- Lower relapse if maintenance be 48 as opposed to 24 months

MPO-ANCA with remission and ANCA negativity at end of induction:

- Might require a shorter course of maintenance

Most patients with MPO–microscopic polyangiitis given a single course of 6 rituximab infusions without any maintenance therapy did not relapse for a mean of 66 months

ANCA-ASSOCIATED VASCULITIS

Role of plasma exchange

- **Considered in AAN with severe renal impairment (serum Cr >5.6 mg/dl and/or diffuse crescents)**
- **May also have a role in AAV with pulmonary hemorrhage**

ANCA-ASSOCIATED VASCULITIS

Table 5 | Examples of various rituximab-based regimens for induction and remission in AAV that have been used in the literature

Induction

Four weekly i.v. doses of 375 mg/m²,^{171,172} or 2 biweekly doses of 750 mg/m² (maximum dose 1000 mg)¹⁸²

Four weekly i.v. doses of 375 mg/m² and 1 monthly infusion 1 and 2 months apart^{179,186}

Maintenance

750 mg/m² (maximum dose 1000 mg) every 6 months^{180–183}

750 mg/m² (maximum dose 1000 mg) every 4 months¹⁸¹

750 mg/m² (maximum dose 1000 mg) every 6 months for 24 months¹⁸⁴

750 mg/m² (maximum dose 1000 mg) every 12 months¹⁸³

375 mg/m² every 6 months¹⁸³

500 mg on days 1 and 15, then 5.5 months later, and again every 6 months for a total of 5 doses over 18 months¹⁸⁵



