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 at 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
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
Treatment

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Treatment: Pediatric

- 80% of children with nephrotic syndrome have MCD on biopsy
- Remaining patients, some will respond to corticosteroids
  - 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 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
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>
<thead>
<tr>
<th>Renal presentation</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Stable kidney function and/or nonnephrotic proteinuria</td>
<td>Direct-acting antiviral therapy</td>
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<tr>
<td>Cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure</td>
<td>Direct-acting antiviral therapy with immunosuppressive treatment, with or without plasma exchange</td>
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<tr>
<td>Histologically active HCV-associated glomerulonephritis that does not respond to direct-acting antiviral therapy</td>
<td>Rituximab as first-line immunosuppressive treatment</td>
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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. Verify adherence (check mycophenolic level if on MMF/check infusion records if on CYC)

2. Repeat biopsy if concern for chronicity or other diagnosis (e.g., TMA)

3. Switch from MMF to CYC or vice versa

4. Consider regimen with combined MMF/CNI “multi-target” therapy or
   - Addition of rituximab or
   - Consider prolonged course of i.v. pulse CYC

5. Consider i.v. Ig or 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
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

New diagnosis or relapse of ANCA-associated vasculitis

For new diagnosis, biopsy to investigate the extent of kidney involvement

CYC with corticosteroids

RTX with corticosteroids

Rapidly progressive ANCA-associated vasculitis

> 4 mg/dl (354 μmol/l) serum creatinine or crescentic GN

+ Pulmonary hemorrhage

CYC with corticosteroids

CYC + RTX with corticosteroids

PLEX

Remission

Yes

No
ANCA-ASSOCIATED VASCULITIS

Maintenance

Remission

Yes

AZA for at least 18 months

RTX on demand*

RTX on a fixed schedule for at least 18 months

Taper after 24–48 months

No

Refractory disease:
- No improvement in 4 weeks
- Improvement of less than 50% in 6 weeks of treatment (as measured by BVAS/WG)
- Chronic persistent disease after more than 12 weeks

Change in therapy‡:
- Switch to RTX if previously treated with CYC (especially in PR3–ANCA patients) or vice versa
- Oral CYC if previous i.v. CYC failure (and RTX unavailable)
- i.v. Ig 0.4 g/kg for 5 days especially if persistent low disease activity
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
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\textsuperscript{171,172} or 2 biweekly doses of 750 mg/m² (maximum dose 1000 mg)\textsuperscript{182}
Four weekly i.v. doses of 375 mg/m² and 1 monthly infusion 1 and 2 months apart\textsuperscript{179,186}

**Maintenance**
750 mg/m² (maximum dose 1000 mg) every 6 months\textsuperscript{180–183}
750 mg/m² (maximum dose 1000 mg) every 4 months\textsuperscript{181}
750 mg/m² (maximum dose 1000 mg) every 6 months for 24 months\textsuperscript{184}
750 mg/m² (maximum dose 1000 mg) every 12 months\textsuperscript{183}
375 mg/m² every 6 months\textsuperscript{183}
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 months\textsuperscript{185}