

# Nephrology Fellow Clinical Compendium







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Disclaimer- This guide is intended as an overview with salient details only. In order to provide high quality patient care it is important to maintain close and appropriate

supervision.

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### **Chapter 4: Glomerulonephritis and Nephrotic Syndrome**

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As we start this chapter we note that the evidence for therapy in glomerulonephritis is somewhat paradoxical, it moves both quickly and doesn't change at all. We invite our readers to refer to appropriate reviews listed at the end of this chapter as well as resources such as GlomCon in order to keep up with the most current trends in glomerulonephritis.

### Classify based on approach:

**Clinical Phenotype** 

- Is it nephrotic or nephritic?
- · Is it systemic or limited to the kidneys?

Histology

- Mechanism
- · How severe?
- How chronic?

Underlying cause

• Primary or Secondary i.e. FSGS can be secondary to causes such as obesity

### **IgA Nephropathy**

**Epidemiology**: IgA Nephropathy (IgAN) is a systemic disorder with a spectrum of clinical presentations. It is the most common glomerulonephritis (GN) with a peak presentation in the second to third decades of life. Males usually predominate in a 2:1 ratio with the exception of Asian populations in which the sexes are equally affected. IgAN is most common within East Asian populations, and is relatively rare in Black race. IgA deposition may also be found in up to 16% of kidney biopsies in patients with no other features of GN and in other GN processes. The pathological significance of the latter is unclear.

**Clinical presentation**: IgAN can present in a myriad of fashions and ranges from an indolent disease with persistent microscopic hematuria, minimal proteinuria and no evidence of reduced kidney function to a fulminant one with rapidly progressive kidney failure reaching kidney failure.

IgA Nephropathy: Important Statistics

10% will present with rapidly progressive glomerulonephritis (RPGN)

30-40% will present with progressive CKD, microscopic hematuria, hypertension, and proteinuria

40-50% will present with one or more episodes of macroscopic hematuria, typically in a synpharyngitic pattern. This presentation is unusual after the fourth decade, and other causes of macroscopic hematuria should be investigated first.

50% will progress to kidney failure over a prolonged period of monitoring (usually 20 to 25 years) despite IgAN usually being associated with a relatively benign prognosis.

IgAN may also occur in association with other diseases and it is important to screen for these if the clinical picture is suggestive. The most common one is cirrhosis, with a particular predilection for alcohol induced forms but it may occur in any form of cirrhotic liver disease. Up to one third of those with celiac disease will have glomerular IgA deposition, although far fewer than this display evidence of an active GN. Those living with chronic human immunodeficiency virus (HIV) infection may also have an increased incidence of IgA deposition.

**Pathology**: Light microscopy of pathological specimens will often *show matrix expansion and mesangial hypercellularity*. The major finding on immunofluorescence is of course IgA deposition. C3 is often present, but C1q (a marker of the classical complement pathway) is absent. Electron microscopy will show mesangial electron dense deposits.

**Diagnosis**: The diagnosis of IgAN can only be established on kidney biopsy. However, given its prevalence and often benign prognosis a kidney biopsy is usually only undertaken in certain situations;

- A patient with isolated microscopic hematuria, no reduced kidney function, no hypertension and minimal proteinuria < 500 mg/g to 1 g daily would usually just be watched.</li>
- In contrast, those with proteinuria > 500mg to 1 g daily, hypertension and worsening kidney failure usually warrant a biopsy to confirm the diagnosis and exclude other causes.
- Oxford Classification of IgA Nephropathy

**Treatment**: The treatment of IgAN is complex given the clinical spectrum of disease presentation, and there is little agreement on the most appropriate management of those who present with fulminant or rapidly progressive disease. The following points should be noted;

- Those with proteinuria of 500 mg to 1 g/daily have a low risk of progression.
- Clinical indicators of progression include diminished kidney function, hypertension (>140/90) and proteinuria that is > 1g/day.
- As in all patients with CKD, patients should be appropriately screened for cardiovascular disease and placed on lipid lowering therapy with a statin as appropriate.
- Therapeutic choices are thus dictated by the perceived risk for progression of CKD.
- Those with isolated hematuria, minimal proteinuria (<500mg to 1g/day) and a normal estimated glomerular filtration rate (eGFR) are usually subjected to serial monitoring (as there may be progression with time).
- Those with CKD and persistent proteinuria > 1g/daily but with mild disease histologically or an eGFR that is not falling too rapidly are usually managed with non-immunosuppressive (antiproteinuric) strategies as a first instance, such as renin angiotensin system (RAS) inhibition.
- Those with more severe presentations, such as nephrotic range proteinuria, more active disease on biopsy (without much chronic irreparable damage) and little response to an initial trial of 3 to 6 months of non-immunosuppressive therapy may be considered for immunosuppression, although the most recent trials have shown mixed results (STOP-IGA and TESTING). The Low Dose TESTING study was presented at ASN Kidney Week in 2021 and showed that the lower dose arm with addition of PJP prophylaxis led to similar efficacy as higher dose arm with less side effects. However, this study has not been published as of Nov 14, 2021.
- Those with RPGN are often treated with immunosuppression up front in addition to usual antiproteinuric therapy.

**Renin angiotensin system (RAS) inhibition** with with angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are the mainstay of anti-proteinuric therapy in IgAN. There is a paucity of data specifically studying their use in IgAN, and their efficacy is mostly presumed from their use in other forms of proteinuric kidney disease. Their benefit is unclear in those who have < 500 mg of proteinuria per day, and it is unclear at exactly what level of proteinuria (500 mg per day or 1g per day) they should be instituted in.

- The goal proteinuria target should be < 1g / daily.
- The goal blood pressure should be < 130/80 mm Hg.

**Sodium glucose cotransporter (SGLT)-2 inhibitors** are gaining use in IgAN. A prespecified analysis of patients with IgAN in the <u>DAPA-CKD study</u> demonstrated efficacy in this subgroup of 270 randomized to either dapagliflozin or placebo. The primary composite endpoint was a sustained decline in eGFR of 50% or more, end-stage kidney disease, or death from a kidney disease-related or cardiovascular cause. The primary outcome occurred in 6 (4%) participants on dapagliflozin and 20 (15%) on placebo (HR, 0.29; 0.12-0.73).

**Fish oil** has been studied as a potential kidney protective strategy in IgAN. A clear benefit has not been established. The current consensus is that fish oil (at a dose of 3.3g/day) may be considered in those patients who desire to take it and those at risk of progression of their CKD as long as it is not to the exclusion of other therapies such as ACEis/ARBs.

The benefit of **immunosuppression** in IgAN has not been well defined, and the optimal use of immunosuppression is uncertain. It may be reasonable to try immunosuppression in the following circumstances which may suggest active disease and progression:

- A rapidly declining eGFR.
- Persistent proteinuria > 1g/daily after maximal antiproteinuric therapy with an ACE-I or ARB for three to six months.
- Pathological evidence of highly active disease on kidney biopsy (i.e. proliferative or necrotizing glomerular changes).
- Those with crescentic disease are often treated with combination immunosuppressive therapy.
- In contrast, those with fibrotic changes on their biopsy are unlikely to benefit from immunosuppressive therapy. Anti-proteinuric therapies are still appropriate.

There is no consensus on the most appropriate immunosuppressive therapy. In general, one of two major strategies is used;

• 1g daily of intravenous methylprednisolone for 3 days for months 1, 3 and 5, combined with 0.5 mg/kg of oral prednisolone daily on alternate days for a total of six months.

• Alternatively, oral prednisolone at 0.8 to 1 mg/kg daily for two months followed by a slow taper to a total of a six-month course may be considered.

Patients on high dose glucocorticoids or combination immunosuppression should receive appropriate prophylaxis against infection as well as appropriate monitoring of side effects of glucocorticoid therapy.

- Prophylaxis against *pneumocystis jiroveci* (PJP) is given, typically with trimethoprimsulfamethoxazole 160/800 mg three times a week.
- In patients intolerant of this, dapsone at 100 mg daily is an alternative. Patients should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to commencing dapsone.
- Consideration should also be given to stress ulcer prophylaxis with a proton pump inhibitor, frequent blood glucose monitoring and strategies to manage bone mineral density loss such as vitamin D supplementation and measurement of bone density at the completion of glucocorticoid therapy.

In a similar fashion, there is limited data on the use of combined immunosuppressive therapy with cyclophosphamide and prednisolone in severe IgAN or crescentic IgAN. The limited data does suggest a potential benefit, and it may be reasonable to trial such therapy in a patient with a RPGN type pattern. One regime that may be used includes;

- Pulse methylprednisolone (15 mg/kg per day for three days intravenously)
- Oral prednisolone (1 mg/kg daily for two months, followed by a gradual taper over six months)
- Monthly intravenous cyclophosphamide (0.5 g/m2) for six months.
- Cyclophosphamide is associated with a number of toxicities.
  - The complete blood count should be monitored weekly to monitor for leukopenia
    - Aim of a total white cell count > 3500 and neutrophil count > 1500.
    - Isolated lymphopenia is tolerated as long as the total white cell count remains > 3500.
    - Dose reduction is needed if leukopenia occurs.

- Elevations of AST/ALT may occur, and liver function should be monitored.
- Cyclophosphamide may induce a cystitis with hematuria.
- Longer term, cyclophosphamide is associated with the development of bladder cancer and this complication must be kept in mind with the longer term follow up of a patient treated with cyclophosphamide who develops new hematuria.
- Both men and women of childbearing age are at risk for infertility as well as premature ovarian failure in women. We suggest the involvement of a reproductive endocrine and fertility specialist preferably before the commencement of therapy.
  - Appropriate contraception must be used during therapy.
- Cyclophosphamide is teratogenic and pregnancy must be excluded.

### **Granulomatosis with Polyangiitis and Microscopic Polyangiitis**

**Epidemiology**: Granulomatosis with PolyAngiitis (GPA) and Microscopic PolyAngiitis (MPA) form part of the Anti-Neutrophil Cytoplasmic Antibody (ANCA) vasculitis spectrum. These are typically aggressive GNs that commonly present with a rapidly progressive decline in kidney function and may have a variety of non-kidney manifestations. The two conditions most commonly occur in older adults. There is no sex predisposition. Caucasians are more likely to be affected.

**Clinical Presentation**: GPA and MPA will commonly (although not always) present with the classical features of a GN, with variable proteinuria, microscopic hematuria with an active sediment, hypertension and a progressive decline in kidney function. Patients will often report constitutional type symptoms, sometimes for months prior to the time of presentation.

It is important to note that both GPA and MPA can present with a variety of extra-kidney manifestations. Upper respiratory tract involvement is far more likely to occur in GPA (90% vs 35%). Manifestations may include;

- Chronic rhinosinusitis
- Interstitial lung disease

- Pulmonary nodules
- Alveolar hemorrhage due to pulmonary capillaritis
- Tracheal or bronchial stenosis
- Hearing loss (conductive or sensorineural)

Both GPA and MPA may have other extra-kidney manifestations. These include:

- Mononeuritis multiplex (MPA more common than GPA 70 vs 15%)
- Central nervous system (CNS) vasculitis
- · Cutaneous lesions, most commonly a leukocytoclastic vasculitis
- Orbital lesions, including conjunctivitis, episcleritis/scleritis, corneal ulceration and uveitis

**Diagnosis**: In general, a biopsy of the affected organ is preferred to establish the diagnosis of an ANCA vasculitis. However, given the aggressive and potential life and organ threatening nature of the disease a biopsy may not be feasible. In these settings a presumptive diagnosis may be made on serological testing (see below) and a compatible clinical picture given the need to institute prompt therapy, although a biopsy is still favorable in order to guide therapy and establish the degree of chronic damage (if any).

The ANCA vasculitis syndromes have two major immunofluorescence patterns on review of stained neutrophils;

- Cytoplasmic ANCA (C-ANCA), most commonly associated with GPA.
- Perinuclear ANCA (P-ANCA), most commonly associated with MPA.

In addition to this cytoplasmic staining, there are two target antigens present within the neutrophil that are commonly associated with the ANCA vasculitides;

- Proteinase 3 (PR3), most commonly associated with GPA.
- Myeloperoxidase (MPO), most commonly associated with MPA.

It is important to note that up to 10% of patients will be ANCA negative, and 20% of patients will have the alternative ANCA pattern.

The ANCA vasculitides may be drug induced (mostly MPO pattern) and induced by the following medications;

- Minocycline
- Propylthiouracil
- Hydralazine

A positive ANCA does not necessarily imply a diagnosis of an ANCA vasculitis, and these tests may be positive in a number of other clinical conditions. As always, they must be interpreted in the correct clinical context. Other diseases associated with a positive ANCA include;

- Cystic fibrosis
- Ulcerative colitis (particularly in association with primary sclerosing cholangitis, and P-ANCA). Crohn's disease is much less commonly associated
- · Bacteremia include subacute bacterial endocarditis
- Adulterated cocaine (cut with levamisole).

**Treatment:** Click <u>here</u> for a review. Prompt immunosuppressive therapy is needed in GPA/MPA with organ threatening manifestations (which includes all active GN presentations) in order to attempt to save those threatened organs. It is important to realize there are a subgroup of patients with non-organ threatening disease (i.e. those with arthritis, rhinosinusitis or pulmonary nodules alone) that may undergo less intensive induction therapy but kidney disease is not considered amongst this category.

 Therapy for ANCA vasculitis consists of induction therapy followed by maintenance. There is disagreement in the literature about the best options for both of these measures. In general, induction therapy will consist of corticosteroids and either cyclophosphamide or rituximab. The use of plasma exchange is controversial and covered in further detail below.

With **cyclophosphamide** based regimes there is the option of both oral and intravenous dosing. They probably induce remission at a similar rate. Intravenous dosing appears to have a higher relapse rate, but fewer adverse events. All induction regimens receive glucocorticoids in addition to cyclophosphamide.

- Oral cyclophosphamide is dosed at 1.5 to 2.5 mg/kg daily. It is dose reduced in patients with reduced kidney function. Those with very severely reduced kidney function (i.e. eGFR < 15 or dialysis dependent are often dosed at a lower amount (0.8mg/kg daily). An eGFR of 15 to 30 usually warrants 1mg/kg daily. This is usually continued for three to six months until a stable remission is induced. The white cell count (wbc) should be closely monitored (see below).</li>
- Intravenous cyclophosphamide is dosed at 15mg/kg every two weeks for three doses and then every three weeks (regime in the <u>CYCLOPS trial</u>). Alternatively, 0.5g/m2 every two weeks may be used. Whichever regime is chosen, the total length of therapy is around three to six months.

Cyclophosphamide is associated with a number of toxicities (see section above on cyclophosphamide toxicities).

**Rituximab** is an alternative to cyclophosphamide for induction therapy. There are two dosing options for rituximab.

- 375 mg/m2 per week for four weeks (the dose used in the <u>RAVE trial</u>).
- 1g as a single dose followed by a further 1g 14 days later.

Rituximab is usually well tolerated, however many toxicities are noted below

- Infusion reactions can occur and can be serious including anaphylaxis.
- Hepatitis B (HBV) viral reactivation, sometimes with fatal hepatitis, is well documented with rituximab use and **HBV must be excluded prior to the use of rituximab**.
- Neutropenia and hypogammaglobulinemia may occur.

In addition to either cyclophosphamide or rituximab, all patients receive concomitant **glucocorticoid** therapy. In general this consists of pulse methylprednisolone followed by a prolonged glucocorticoid wean.

- Methylprednisolone is pulsed at a dose of 500 mg to 1g daily for three days as an intravenous dose.
- This is followed by oral prednisolone at 1mg/kg (maximum 60 to 80mg daily). There is no consensus for tapering schedules. The PEXIVAS trial demonstrated that reduced dose of steroids is non-inferior to high dose.

**Plasma exchange** is now considered to be a controversial field in the ANCA vasculitides. Previously this technique was often employed in those who presented with severe active disease with a rapid deterioration in kidney function, dialysis dependence or concurrent pulmonary hemorrhage on the basis of meta-analysis data (including the previously largest trial MEPEX) which suggested that plasma exchange in severe disease decreased the risk of ESKD or death. However, PEXIVAS suggests that there is no benefit to plasma exchange within the ANCA vasculitis syndromes.

• The one exception to this is those with concurrent anti-glomerular basement membrane (GBM) antibodies which are treated as if they have anti-GBM disease. These should be checked at the time of ANCA presentation.

As with all patients on high dose immunosuppression, appropriate risk reduction strategies should be used to prevent opportunistic infections as well as the adverse effects of glucocorticoids.

This is covered here under the <u>appropriate prophylaxis section</u>.

**Treatment (maintenance):** Following induction therapy, the ANCA vasculitides require a period of maintenance immunosuppression to reduce the risk of relapse. There are several choices for maintenance therapy; - azathioprine, methotrexate, mycophenolate mofetil, and rituximab.

- If oral cyclophosphamide is used for induction therapy then maintenance is started once the total white cell count is > 4000 and neutrophil count > 1500. This may be the following day if these criteria are met.
- If intravenous cyclophosphamide is used, maintenance is commenced two to four weeks after the last dose of cyclophosphamide (provided the hematological parameters above are met).
- If rituximab is used, then maintenance begins four to six months after the last induction dose.

The dosing of maintenance regimes is as follows:

- Azathioprine is usually begun at 2 mg/kg daily. Patients should be considered for thiopurine methyltransferase (TPMT) testing in order to guide dosing prior to the commencement of azathioprine.
- Rituximab dosing is variable. One option is that used in <u>MAINRITSAN</u>, where rituximab is given as two 500 mg doses separated by 14 days to start maintenance, followed by 500 mg at months 6, 12 and 18.
- Alternatively 1000 to 2000 mg every six months may be given.

• Mycophenolate mofetil is often dosed at 2,000 mg daily followed by a reduction to 1,500 and 1,000 mg daily at 12 and 18 months respectively.

Maintenance therapy is typically given for 12 to 24 months. There is no clear data as to the appropriate duration of maintenance therapy.

It is also unclear if maintenance therapy should be ceased in those who have had one or more relapses. Many experts would continue maintenance therapy indefinitely, particularly if a relapse would be poorly tolerated or organ-threatening.

**Treatment (relapse)**: Those who have a relapse of GPA or MPA are re-treated with induction therapy with cyclophosphamide or rituximab. These patients carry a higher risk of subsequent relapse than those with newly diagnosed disease. There is no clear guide as to the most appropriate agent for reinduction therapy. Rituximab may be preferred in those previously exposed to cyclophosphamide to limit cumulative dose exposure. Those who relapse during maintenance therapy may be considered to switch to an alternative maintenance agent. There is no good evidence that a rise in ANCA titer predicts a disease flare. Patients who do have persistently high or rising titers of PR3 or MPO are typically monitored closely for evidence of recurrence of active disease.

### Anti-Glomerular Basement Membrane (Anti-GBM) Disease

Anti-GBM disease is a rare but explosive RPGN (see below for RPGN algorithm from NephSIM) that often presents severely impaired kidney function and may present with concurrent pulmonary hemorrhage. Younger patients (<30) are more likely to present with a concurrent pulmonary-kidney syndrome. Males usually predominate.

The antibodies produced are directed against the alpha 3 chain of collagen IV, a component of both the GBM and pulmonary membranes. Antibody production is usually short lived, and relapses are uncommon.

**Clinical Presentation**: The clinical presentation of kidney involvement is similar to that of other forms of GN. There is progressive decline in kidney function, hypertension, usually subnephrotic proteinuria and dysmorphic red cells.

Pulmonary involvement occurs in up to 40 to 60% of patients. They may present with dyspnea, overt hemoptysis, radiological infiltrates, or an increase in the diffusion capacity for carbon monoxide

(DLCO). Those who are smokers are more likely to have pulmonary involvement (thought to be due to exposure of the underlying epitope within the alveolar basement membranes).



**Diagnosis**: The diagnosis of anti-GBM disease requires the presence of anti-GBM antibodies either in the serum or kidney biopsy. In general a kidney biopsy is preferred to assess for the activity and chronicity of background damage that may help guide immunosuppressive therapy.

On light microscopy the kidney biopsy will often show a crescentic GN. Immunofluorescence typically reveals linear deposition of IgG directed against the GBM.

Note there are only two other disorders which can produce linear staining in a similar fashion

- diabetic nephropathy
- fibrillary GN.

## These should be readily distinguishable from the history and other clinical/pathological findings.

Serum samples will often have anti-GBM antibodies. It is important to concurrently test for the ANCA antigens (and vice versa) given there is an appreciable crossover of between 10 to 50% of patients. See this <u>post</u> on RFN.

It is imperative that the diagnosis is made in a timely fashion so immunosuppression can be commenced. Those patients presenting with a creatinine level >5.7 mg/dL have poor kidney survival. The avoidance of maintenance dialysis is rare amongst those who require dialysis within 72 hours of presentation or those who present with 100% crescents on biopsy.

**Treatment**: Most of the recorded data for the treatment of anti-GBM disease is uncontrolled. Therapy is typically started with high dose glucocorticoids, cyclophosphamide and plasma exchange.

- Glucocorticoids are typically begun with a pulse of intravenous methylprednisolone (15 to 30 mg/kg to a maximum of 1000mg) daily for three days followed by 1mg/kg (to a maximum of 60 to 80 mg) of oral prednisolone daily.
- **Cyclophosphamide** is typically given orally at a dose of 2 mg/kg daily. Intravenous cyclophosphamide has been used, but the relative efficacy is unknown.
- For those in whom cyclophosphamide is contraindicated or not tolerated, there is no clear evidence as to an alternative agent. **Rituximab or mycophenolate mofetil** are typically used.
- In addition to immunosuppression patients are usually treated with plasma exchange. There is a
  relative lack of evidence of benefit. Despite this, patients receive plasma exchange usually as an
  alternative day regime with 4L exchanges for two to three weeks. Albumin is usually used as a
  replacement fluid, with the exception of a recent kidney biopsy or active pulmonary hemorrhage
  in which fresh frozen plasma should be used. Plasma exchange may be considered to continue
  beyond two to three weeks if there is ongoing active pulmonary disease or of antibody titers are
  not decreasing substantially.

The optimal duration of therapy is unknown. Most patients end up on the aforementioned regimen of plasma exchange, cyclophosphamide for three months and prednisolone alone for the subsequent six to nine months in a slowly tapering regime.

Anti-GBM antibody titers are typically measured every one to two weeks until they are negative on two occasions. They are often recommended to be checked for an additional six months to confirm maintenance of remissions or at any time there are symptoms suggestive of a relapse.

Davis and Patel- GN Cyclophosphamide is associated with a number of toxicities.

See section on cyclophosphamide toxicities.

See section on prophylaxis with immunosuppression.

**Prognosis**: Anti-GBM disease is usually a self-limited syndrome. Patient and kidney survival correlates closely with the degree of kidney function at presentation. Those who are dialysis dependent within 72 hours of presentation often continue to need maintenance dialysis despite therapy.

Recurrence is extremely rare, both in native kidneys and transplants. Note that the disease can occur de novo in those with Alport syndrome who receive a transplanted kidney (with approximate rates of 3%).

### Lupus nephritis

Kidney disease in systemic lupus erythematosus (SLE) is common, and up to 10% of those with lupus nephritis will end up developing kidney failure.

**Epidemiology**: Clinically evident kidney disease occurs in approximately half of those with SLE, and is more common in Asian, Black, and Hispanic populations. kidney involvement typically begins early within the first 6 months to three years. It typically affects younger patients.

**Clinical Features**: Those with SLE should undergo regular urinalysis (with spot protein/creatinine ratio) and assessment of kidney function, looking for elevations in serum creatinine, hematuria or proteinuria. Depressed complement levels (of C3 and C4) and elevated anti-DNA antibody titers also suggest active disease.

Those with evidence of kidney involvement should undergo a kidney biopsy to confirm the diagnosis, as the class of lupus nephritis and the degree of activity may sometimes be more severe than that indicated by the clinical picture. The indications for a kidney biopsy in those with suspected lupus nephritis include:

- Proteinuria > 500 mg per day
- · An active urinary sediment- dysmorphic red cells or red cell casts
- Decreasing kidney function of unclear cause.

Those with an inactive sediment and < 500 mg per day of proteinuria are usually monitored closely with repeat testing at three to six month intervals. These patients are likely to have underlying class I or class II disease (see below) which does not warrant immunosuppressive therapy. Any evidence of progressive disease during follow up may suggest a transformation into a more aggressive subtype and usually warrants a biopsy at this time.

Those with lupus nephritis will often need to undergo a repeat biopsy at a later time in their disease course. The indications for this are discussed below.

**Pathological classification**: Currently lupus nephritis is classified according to the kidney pathology society / International Society of Nephrology (RPS/ISN) classification into six different classes. There is an appreciable degree of overlap within an individual patient, and patients may evolve from one subtype to another.

- **Class I** (Minimal mesangial lupus nephritis). These patients have no light microscopic abnormalities, and mild mesangial immune complex deposition only. They rarely have an abnormal urinalysis (and are thus not biopsied).
- Class II (mesangial proliferative lupus nephritis). Light microscopy will reveal mesangial hypercellularity or matrix expansion. There are mild subepithelial or subendothelial deposits on immunofluorescence or electron microscopy. Whilst these patients present with microscopic hematuria and proteinuria, the kidney prognosis is usually benign unless the patient progresses to a more advanced kidney lesion.
- Class III (focal lupus nephritis). On light microscopy less than 50% of glomeruli are involved, and endocapillary or extracapillary GN is usually almost always segmental. Despite this immunofluorescence often reveals close to 100% deposition of immunoglobulins / complement. Class III is further subdivided into A, A/C or C depending on the activity or chronicity of the lesions noted.
- Class IV (diffuse lupus nephritis). Class IV is the most severe form. On light microscopy more than 50% of glomeruli are involved. There is endo and extracapillary GN that may be segmental or global. Proliferative, necrotizing and crescentic lesions may all be present. Wire loops may be seen. Immunofluorescence will reveal the typical 'full house' pattern of immunoglobulin/ complement deposition. Subendothelial deposits may be seen on electron microscopy. Class IV is similarly divided into segmental (S), global (G), active (A) or chronic (C) based on pathology findings.

- Class V (lupus membranous nephropathy). Those with class V disease typically present with features of the nephrotic syndrome. Class V disease may also commonly be seen with mixed class III/IV lesions. On light microscopy there is thickening of the glomerular capillary wall, and there are subepithelial immune deposits on immunofluorescence or electron microscopy. It is important to note that those with class V lupus nephritis may present with no other features of SLE. Distinguishing features on pathology from primary membranous nephropathy may include;
   the 'full house' immunofluorescence pattern, tubular basement membrane immune deposits, tubuloreticular structures within the endothelial cells on electron microscopy or electron dense subendothelial or mesangial deposits similar to the proliferative forms of lupus nephritis.
- Class VI (advanced sclerosing lupus nephritis). Class VI disease is associated with >90% of glomeruli showing global sclerosis, and is the advanced form of classes III through V. These patients typically have a bland sediment together with proteinuria and progressive CKD.
   Immunosuppressive therapy is unlikely to be helpful.
- In addition to the classical presentations of lupus nephritis, kidney manifestations may be noted. These include a tubulointerstitial disease in which the glomeruli are relatively spared, which may be accompanied by signs of distal renal tubular acidosis (RTA) or electrolyte abnormalities.

Risk factors for progression at the time of initial clinical presentation include:

- Black or Hispanic ethnicity
- Anemia
- Nephrotic range proteinuria
- Hypertension
- Decreased kidney function

**Treatment (induction)**: In addition to immunosuppressive therapy for certain classes of lupus nephritis, all those with evidence of CKD benefit from non-immunosuppressive therapy as dictated for all proteinuric CKD.

- This includes RAS inhibition with either ACE inhibitor or ARBs.
- It also includes an assessment for CVD and lipid lowering therapy with a statin as appropriate.

Immunosuppressive therapy for lupus nephritis consists of induction and maintenance phases. It is indicated in all those with focal or diffuse proliferative nephritis (classes III and IV). Induction therapy consists of glucocorticoids together with either cyclophosphamide or mycophenolate mofetil. There are a number of reasons why one particular regime may be chosen over another;

- Younger patients, and in particular women of childbearing age, may wish to avoid the potential gonadal toxicity that is associated with cyclophosphamide.
- There is limited evidence that Hispanic and black populations may be more likely to respond to mycophenolate mofetil, although long term data is limited.

There is no consensus on the most appropriate glucocorticoid dosing in lupus nephritis. In severe active lupus nephritis, such as rapidly progressive acute kidney injury (AKI), cresentic disease or severe extra-kidney manifestations, therapy may be begun with an intravenous pulse dosing of methylprednisolone given as 250 to 1000 mg daily for three days.

This is followed by oral prednisolone at a dose of 60 mg daily tapered to 40 mg over around a months-time and followed by a slower wean typically over six months (similar to that used in the <u>ALMS trial</u>). Another option is the regime used by the Lupus Nephritis Collaborative Study Group which involves alternate day dosing once three months have passed.

If cyclophosphamide is used for induction, the most common dosing regimes are usually taken from the more recent <u>ACCESS</u> and <u>Euro-Lupus trials</u>, as opposed to the older and higher dose used in the original NIH trial.

- The lower-dose regime consists of intravenous cyclophosphamide 500mg every two weeks for a total of six doses.
- The higher dose regime, which may be considered in those of Hispanic or black ancestry as
  there are some concerns that the trial data for the lower dose regimes was inadequate to draw
  conclusions about these patient populations given their low numbers within the trials
  themselves. This regime is usually given at 0.5 to 1g/m2 monthly for six to seven months. Like
  all uses of cyclophosphamide, the white cell count must be monitored. If the leukocyte nadir
  (at 10 to 14 days post dose) is < 4000 and the neutrophil count is < 1500, the dose is reduced
  by 0.25g/m2. In contrast if the counts are normal the dose may be increased by 0.25g/m2. The
  total dose should not exceed 1g/m2.</li>
- Alternatively, oral cyclophosphamide may be used. The starting dose is usually 1mg/kg daily, and may be uptitrated to 1.5 mg/kg daily and continued for two to four months.

Cyclophosphamide is associated with a number of toxicities.

### See cyclophosphamide toxicity section

Mycophenolate mofetil is an acceptable alternative to cyclophosphamide for induction therapy in lupus nephritis. It may be a particularly attractive option for young women who wish to preserve fertility. The two regimes appear to be equally as efficacious as each other in inducing remission.

 If mycophenolate is used, the most common dosing regime mirrors that used in the ALMS trial. Mycophenolate is started at 0.5g twice daily for the first week, 1g twice daily for the second week, and 1.5g twice daily thereafter. This dose is typically continued for six months.

Mycophenolate is teratogenic, and patients must be informed of this and counseled on appropriate contraception strategies. Mycophenolate may also cause a leukopenia and particularly neutropenia which can be dose limiting.

#### See prophylaxis for immunosuppression section.

**Treatment (maintenance)**: Following successful induction therapy, maintenance therapy is required to reduce the risk of relapse. The relapse rate is approximately 8 per 100 patient years for the first five years of follow up. It is more likely to occur with a partial as opposed to complete response to therapy (where a complete response is typically defined as a substantial reduction in protein excretion (variably defined as < 0.33g/day to <1g/day), an improvement or stabilization in the serum creatinine, and improvement of the urinary sediment to < 10 red cells per high power field.

There are two main options for maintenance therapy, mycophenolate mofetil and azathioprine. Mycophenolate is usually the preferred agent, with the exception of pregnancy where it is contraindicated and azathioprine is used. Transitioning from mycophenolate to azathioprine is unlikely to produce a flare of nephritis. The duration of maintenance therapy is typically 12 to 24 months.

Mycophenolate is preferred on the basis of meta-analysis data which suggests a lower relapse rate with mycophenolate with no significant difference in adverse events or mortality/risk of ESKD.

In those patients who received intravenous cyclophosphamide as induction therapy, maintenance is started at two to four weeks after the last dose of cyclophosphamide when the total white cell count is > 3000 and the neutrophil count is > 1500. In those who received oral cyclophosphamide maintenance may begin straight away provided the white cell parameters mentioned above are satisfied.

- The typical dose of mycophenolate mofetil for maintenance is 1 g twice daily.
- Azathioprine is usually given as 2mg/kg to a maximum of 150/200 mg daily.
- Such therapy is usually continued for 24 months.
- Low dose glucocorticoids are often continued during extended maintenance therapy, and may be required for symptomatic control of other features of SLE. Patients who remain asymptomatic may be considered to be weaned off their prednisolone.

**Treatment (relapse)**: Relapse of lupus nephritis is not uncommon, and are typically manifest by recurrent disease activity with worsened proteinuria, dysmorphic hematuria and worsening serum creatinine. Patients who have a rise in their anti-dsDNA titers or new hypocomplementemia (in the absence of active features of nephritis) after achieving a complete response should be closely monitored for relapse, but therapy changes are not solely based on these serological parameters alone.

Relapses can be mild or moderate/severe.

- A mild relapse is usually defined by new hematuria and modest (<50%) increase in proteinuria but with a stable kidney function.
- A moderate to severe relapse however is associated with a decrease in kidney function and worsened proteinuria.

There is minimal data available to guide therapy for a mild relapse, but typically an augmentation in immunosuppression is given. Those with moderate to severe disease however are typically given re-induction therapy.

- If cyclophosphamide was the initial induction therapy patients are often switched to mycophenolate for induction given the concern about toxicity with cyclophosphamide with increasing exposure. If mycophenolate if not tolerated then cyclophosphamide may be considered.
- If mycophenolate was used for induction and the patient is off immunosuppression after a period of maintenance, either agent may be used for re-induction.
- Those who relapse on mycophenolate maintenance are often switched to cyclophosphamide.

### Immunoglobulin/complement-mediated glomerulonephritis (formerly membranoproliferative, MPGN)

Immunoglobulin (Ig)/complement-mediated GN describes a histological pattern of injury and has a number of different causes. On histology specimens, an Ig/complement-mediated GN pattern typically refers to a thickened glomerular basement membrane (GBM) due to the deposition of immune complexes and complement, and endocapillary and mesangial hypercellularity. Given the scope of disorders which may cause this pattern of injury a full discussion on all of the various topics is outside the scope of this book, and the author directs readers to appropriate topic reviews for such disorders.

There are two major categories of Ig/complement-mediated GN:

- Immune-complex mediated
- · Complement mediated

Hypocomplementemia is common in all types of Ig/complement-mediated GN. Immune complex disease typically has complement activation via the classical pathway causing a low C4 and normal or mildly depressed C3, whereas complement mediated diseases typically have low C3 and normal C4 due to alternative pathway involvement. A normal serum complement does not exclude an Ig/ complement-mediated GN.

There are three major causes of immune-complex mediated Ig/complement-mediated GN – infection, autoimmune disease and monoclonal gammopathies.

- Infectious Ig/complement-mediated GN is often seen in association with chronic HBV and hepatitis C (HCV) infection.
- HCV-associated Ig/complement-mediated GN is often associated with mixed cryoglobulinemic disease.
- Infection associated Ig/complement-mediated GN may also be seen with chronic bacterial or fungal infections such as endocarditis or shunt nephritis, and chronic schistosomiasis or echinococcosis infection may also cause this pattern.
- Autoimmune Ig/complement-mediated GN is seen with rheumatoid arthritis, Sjogren syndrome or (far more commonly), SLE (<u>see above</u>).

 Monoclonal gammopathies can not infrequently cause an Ig/complement-mediated GN pattern of injury.

Complement associated Ig/complement-mediated GN in contrast, is associated with the deposition of complement (typically C3, but C4 glomerulopathy may also occur) within the mesangium and capillary walls of the glomerulus. Complement mediated Ig/complement-mediated GN is typically split into dense deposit disease (DDD) or C3 glomerulopathy (C3GN) depending on the pattern of complement deposition. These disorders can be caused by inherited defects in complement regulatory proteins such as complement factor H or I, or acquired through the development of a C3 convertase stabilizing antibody known as a C3 nephritic factor (C3NeF). Rarely a monoclonal gammopathy may drive complement activation.

- DDD has electron dense deposits that are characteristically wavy, sausage shaped and dense within the GBM and mesangium on electron microscopy.
- C3GN in contrast will have an electron microscopy pattern similar to that of immune complex deposition driven MPGN without immune complexes.

**Treatment**: Given the diverse range of causes of lg/complement-mediated GN there are a number of different therapeutic approaches depending on the underlying driving process. A full discussion of each individual cause and its therapy is outside the scope of this book, and instead general principals will be put forth.

There are three major components to any Ig/complement-mediated GN therapy;

- Treatment of the underlying cause (if possible)
- Assessment of the factors that guide kidney prognosis (with worse outcomes predicted by the nephrotic syndrome, an elevated creatinine, crescentic kidney disease on biopsy and hypertension)
- Treatment of the Ig/complement-mediated GN itself, often with immunosuppression.

If an obvious underlying cause is present, and particularly in the case of infection, resolution of the lg/ complement-mediated GN may occur with effective therapy of the underlying infection. The mixedcryoglobulinemic syndrome is an exception to this and is often treated with immunosuppression in addition to treatment of the underlying inciting factor.

The optimal therapy in those with an Ig/complement-mediated GN due to a monoclonal gammopathy is unclear. Patients in this category often get therapy that would be used to treat multiple myeloma,

with the exception of IgM driven disease which is typically treated with Waldenstrom macroglobulinemia regime. Close liaison with hematology colleagues is important.

Sometimes even after an appropriate workup the underlying cause of the Ig/complement-mediated GN may not be immediately apparent. Such patients have an idiopathic immune complex mediated Ig/complement-mediated GN. There are no randomized trials in which to base treatment decisions.

- In patients with non-nephrotic range proteinuria, a normal creatinine and normal blood pressure (ie those with mild disease) it may be appropriate to simply treat with RAS inhibition alone given the lack of evidence of benefit of immunosuppression in these patients.
- In those who present with the frank nephrotic syndrome and relatively preserved creatinine, one suggestion is the use of an immunosuppression regime similar to that for focal segmental glomerulosclerosis (FSGS). This would typically involve prednisolone 1 mg/kg (to a maximum of 60 to 80mg daily) for 12 to 16 weeks. In those that respond this dose is usually tapered down for a six to eight month total course. All patients should receive standard concurrent non-immunosuppressive therapy with RAS inhibition. Those who fail to respond may be considered for a calcineurin inhibitor.
- In those that present with an elevated creatinine with nephritic features prednisolone at a dose of 1 mg/kg (to a maximum of 60 to 80 mg daily) is typically used first. If there is a poor response then oral cyclophosphamide at a dose of 2 mg/kg daily would be added for a three to six month total course.
- Those who present with an RPGN picture with crescentic disease are typically treated with a combined cyclophosphamide and prednisolone regime similar to other RPGN presentations.

#### See section on prophylaxis on immunosuppression

### Minimal change disease

Minimal change disease (MCD), whilst being the classical cause of the nephrotic syndrome in pediatric populations where it accounts for 90% of cases, accounts for only 10% of cases in adults. The disease is known for its unremarkable appearance on light microscopy but foot process effacement causing disruption of the podocyte filtration barrier on electron microscopy.

The majority of cases are primary (idiopathic), although an appreciable number may be secondary to another process including; drugs, allergy, malignancy, and infection.

- Drugs that are classically associated with MCD include the non-steroidal anti-inflammatory (NSAIDs), antibiotics, lithium, d-penicillamine and pamidronate.
- Malignancies that may cause MCD are usually hematological, such as Hodgkin or non-Hodgkin lymphoma. They are usually apparent at the time of the MCD diagnosis.
- A history of allergy may be noted in up to 30% of cases, and relapses may be triggered by an allergic reaction.
- MCD may rarely be associated with infectious etiologies such as syphilis, mycoplasma and tuberculosis.

Clinical Features: MCD is usually characterized by the abrupt onset of the nephrotic syndrome over a few days to a week, often following a systemic or upper respiratory tract infection. The nephrotic syndrome itself is characterized by nephrotic range proteinuria (>3.5 g/day), edema, hypoalbuminemia and hyperlipidemia. This relatively sudden onset is in contrast to the other major causes of nephrotic syndrome – membranous nephropathy and FSGS which are typically more subacute (with the notable exception of the glomerular tip variant of FSGS).

Patients may also have microscopic hematuria and can have a mild decrease in kidney function.

**Treatment**: Glucocorticoids are the mainstay of therapy in MCD, and lead to a complete remission in up to 90% of cases. In contrast to pediatric cases, adult cases of MCD remit more slowly, and up to 25% of cases may take three or four months to fully remit.

Remissions are typically abrupt with patients having no proteinuria within a few weeks of the response to therapy. Partial responses are unusual in MCD, and suggest a possible misdiagnosis of FSGS (with the notable exception of the tip lesion of FSGS which remits in a similar fashion to MCD).

Kidney failure is unusual in MCD, and is usually only seen in steroid resistant cases. It is unclear if these cases are truly MCD or FSGS that was missed due to sampling error.

Relapse is not uncommon, with around 50 to 75% of glucocorticoid responsive patients suffering from a relapse at some point in their disease. Frequent relapses occur in up to 25%. Dependence on steroids to maintain a remission may be seen in up to 30%. Relapses may be triggered by allergic reactions or infections. They typically occur within a year of discontinuation of therapy, but can occur multiple years later.

As with all proteinuric kidney disease, RAAS inhibition should be used (in addition to immunosuppression). Those with markedly elevated lipids may benefit from statin therapy.

Glucocorticoids are first line therapy in MCD.

- Prednisolone at a dose of 1 mg/kg (to a maximum of 80 mg) is given daily. This dose is usually continued for eight weeks. For those who have not responded by eight weeks, prednisolone tapering is commenced two weeks after the attainment of remission.
- Tapering then occurs slowly, with a total duration of therapy being approximately six months.
- See prophylaxis section for patients on immunosuppression.

Patients who do not respond by 16 weeks are considered to be steroid resistant. In this situation there are a few things that must be considered.

- The initial therapy was inadequate (ie the length of time has not been 16 weeks yet)
- The availability of prednisolone may have been decreased (as may be seen with the concurrent use of aluminium based antacids)
- The diagnosis is incorrect. The most common lesion in this case is FSGS. Patients who are
  resistant to therapy are often re-biopsied at this stage. It is not uncommon for those with
  apparently resistant MCD to actually have FSGS, either due to sampling error in the first sample
  or perhaps progression of the FSGS over time.
- There are other rare causes of the nephrotic syndrome such as IgM nephropathy, C1q nephropathy and idiopathic mesangial proliferation that can be mistaken for MCD.

The next choice of therapy for glucocorticoid resistant MCD is calcineurin inhibitors. This can also be given as first line in patients unable to tolerate glucocorticoids.

- Cyclosporine is begun at 4 to 5 mg/kg daily (3 mg/kg in microemulsion preparations) in two divided doses.
- Tacrolimus is given 0.05 mg/kg twice daily for at least 26 weeks. This was <u>studied</u> in a small RCT of 50 patients compared to steroids.
- It is unclear if patients should be maintained on a small dose of glucocorticoids in addition to the calcineurin inhibitor therapy.

- The length of therapy is unclear. Cyclosporine is often given for 18 months before being tapered to a dose of 2 to 3mg/kg (non-microemulsion preparations). Patients may need to continue on this dose long term to maintain a remission.
- In those who have been relapse free after two years it is not unreasonable to withdraw cyclosporine +/- prednisolone (if used together).

**Treatment (Relapse)**: The majority of patients will relapse at some stage. There is no clear consensus on the best dose of glucocorticoids in this situation. Some would repeat the same initial therapy, whereas others would use the same initial dosing but taper in a more rapid fashion compared to the initial therapy (a typical regime in this case would be 1 mg/kg to a maximum of 80 mg daily for four weeks followed by a taper over one to two months).

Some patients have frequent relapses (defined as three or more per year). There are several therapeutic choices. These are typically begun once remission has been induced with glucocorticoids.

- Occasional patients will have a sustained remission with low dose glucocorticoid therapy but at the cost of continuous exposure to glucocorticoids.
- Cyclophosphamide at a dose of 2 mg/kg daily (orally) for 8 to 12 weeks may be trialed.
   Cyclophosphamide has a myriad of important side effects that are <u>discussed in other sections of</u> <u>this chapter</u>.
- Cyclosporine at similar doses to that used for glucocorticoid resistant disease 4 to 5 mg/kg daily (3 mg/kg in microemulsion preparations) in two divided doses may be given. These are typically given for around 18 months, after which time a reduction in dose and possible cessation after two years of relapse free therapy may be considered.
- Tacrolimus at 0.05 mg/kg twice daily as above.

For those requiring cyclophosphamide and cyclosporine it is unclear if low dose prednisolone should be continued during this period.

### Focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is a histological lesion as opposed to a single disease entity. It can be classified into primary and secondary causes. The underlying reason for the

development of primary FSGS is unknown and suggested to be caused by an as yet unidentified circulating factor. Secondary causes are typically due to hyperfiltration injuries in response to a reduction in nephron mass. FSGS can also occur due to a number of different genetic causes. FSGS is usually thought to cause around 35% of cases of nephrotic syndrome in adults.

Distinction between primary and secondary causes of FSGS is important given the former are typically treated with immunosuppression, whereas the latter represents a maladaptive response to glomerular hyperfiltration and are treated with RAS blockade.

**Clinical Features**: Primary FSGS classically presents with the constellation of features that encompass the nephrotic syndrome. Secondary causes of FSGS however, are much more likely to present without edema, with non-nephrotic range proteinuria and normal serum albumin levels. The noted exceptions to this are pamidronate induced FSGS or classical collapsing FSGS associated with human immunodeficiency virus (HIV) infection.

Histologically, FSGS is characterized into five different underlying lesions. There is some suggestion that differences in histology can be suggestive of prognosis, but the response to initial therapy with glucocorticoids is usually more predictive of the eventual outcome. The differing types include;

- FSGS not otherwise specified (NOS)
- Collapsing
- Tip
- Perihilar
- Cellular

FSGS NOS shows segmental areas of mesangial collapse and sclerosis in some, but not all, glomeruli. There is foot process effacement on electron microscopy. There may be weak and non-specific binding of IgM, C3 or C1q in sclerotic areas. The sclerotic changes occur first in juxtamedullary glomeruli and can be missed with cortical biopsies (giving the classical misdiagnosis of MCD that subsequently does not respond as expected to glucocorticoid therapy).

The collapsing variant has collapse and sclerosis of the entire glomerular tuft. These patients often have rapid progression of their disease to kidney failure. It is classically associated with HIV and other viral infections such as COVID-19. Some have argued that collapsing variant should be considered a distinct entity away from FSGS. Treatment is directed at the underlying cause.

The tip variant shows injury at the tip of the glomerulus near the origin of the proximal tubule. These patients may be more likely to present abruptly with the nephrotic syndrome as well as being potentially more likely to respond to glucocorticoid therapy.

The perihilar variant has perihilar sclerosis and hyalinosis in more than 50% of segmentally sclerotic glomeruli.

The cellular variant is associated with segmental endocapillary hypercellularity that occludes the capillary lumen in at least one glomerulus.

Once a diagnosis of FSGS has been made, it is important to exclude secondary causes that are treated in a markedly different way to primary causes of FSGS.

- Viral infections known to induce FSGS (HIV, parvovirus B19, HCV, cytomegalovirus and Epstein barr, SARS-CoV-2 virus) should be excluded
- A thorough family history should be taken to screen for familial FSGS
- A detailed drug history to exclude drug induced causes (ie bisphosphonates, heroin, interferon and anabolic steroids)
- Prior GN with subsequent FSGS changes in damaged glomeruli
- Factors that may have reduced nephron mass (nephrectomy, low birth weight / prematurity).

Patients who present with the nephrotic syndrome with no obvious causes of a secondary form of FSGS are likely to have primary FSGS. This may additionally be supported by features such as the degree of foot process effacement noted on electron microscopy:

- Those with >80% foot process effacement are more likely to have primary FSGS.
- In contrast, < 60% foot process effacement with a segmental distribution are more likely to have a secondary form of FSGS.
- < 60% foot process effacement may also be seen in genetic causes of FSGS, although this is more variable (see below). Those who fail to respond to therapy appropriately or have a suggestive family history may benefit from genetic testing to identify one of the genetic forms of FSGS.

Genetic variants underlying FSGS are not uncommon and are beginning to be explored in more detail as genetic testing becomes more available. The prevalence can be as high as 30% in pediatric cases

of steroid resistant nephrotic syndrome. A genetic cause should be considered in the following situations;

- Non-response to immunosuppression
- A suggestive family history
- FSGS and a potential syndromic presentation
- Pediatric steroid resistant nephrotic syndrome

The documentation of a genetic cause of FSGS has a number of potential management implications.

- Management decisions pertaining to choice of therapy (as immunosuppression is unlikely to be beneficial in these cases, with the notable exception of mutations in *PLCE1, TRPC6,* or *WT1* that may be responsive).
- Prediction of recurrence post transplant, which is between 0 to 8% with genetic causes of FSGS compared to 30 to 70% with a primary cause.

Common causative genes include: *NPHS1* (nephrin, the classical congenital nephrotic syndrome of the Finnish type), *NPHS2* (podocin, another cause of pediatric FSGS), *TRPC6, ACTN4* and the collagen IV genes (*COL4A3, COL4A4, COL4A5*).

The prognosis of untreated FSGS is generally unfavorable. The spontaneous remission rate is unknown, but is felt to be low and likely <10%. Patients who respond to therapy have a better prognosis than those who do not. Other factors include;

- A worsened outcome with a raised creatinine at presentation.
- Nephrotic syndrome and heavy proteinuria predicts a worse outcome.
- Response to therapy.

**Treatment**: There is a paucity of data for which to guide immunosuppressive therapy for FSGS. Therapy is usually begun in those in whom the underlying cause is felt to be primary FSGS who present with the frank nephrotic syndrome. There is also no clear data as to the most appropriate duration of therapy. Glucocorticoids alone are expected to produce at least a partial remission in 40 to 80% of those treated.

All patients should also be considered for standard risk reducing non-immunosuppressive therapies similar to that used for other forms of proteinuric CKD such as RAS inhibition and the identification and management of CVD risk factors such as treating hypercholesterolemia with statin therapy.

- Glucocorticoids are typically begun at a dose of prednisolone 1 mg/kg daily (to a maximum of 60 to 80 mg daily) as an oral formulation.
- This initial dose is often continued for 8 to 12 weeks.
- If a response is seen in that time period, this dose is typically continued for another 2 weeks before the dose is slowly tapered down over the ensuring 2 to 3 months, giving a total length of therapy of about 5 to 6 months.
- If a partial response is seen this tapering is often done in a much slower fashion, extending out for around 9 total months of therapy.
- Patients who have a worsening of their proteinuria during glucocorticoid tapering typically have their dose reduction halted with consideration of starting another immunosuppressive agent (usually cyclosporine, but if there is significantly impaired kidney function (eGFR <30ml/min/ 1.73m<sup>2</sup>) then mycophenolate mofetil is often considered

### See prophylaxis for patient in immunosuppression

Those who have little response to prednisolone after 12 to 16 weeks of therapy are considered to be steroid resistant. If secondary or genetic causes have been excluded, then therapy usually consists of adding cyclosporine or mycophenolate if their kidney function is poor.

- Cyclosporine is typically begun at a dose of 2 to 4 mg/kg in two divided doses (usually around 75 to 100mg twice daily). The therapeutic drug level that should be aimed for (as a trough level) is about 100 to 175 ng/ml. In contrast, tacrolimus may be used at a dose of 0.1mg/kg (2 to 4 mg twice daily) with trough levels between 5 to 10ng/ml aimed for.
- It is unclear if prednisolone should be continued in these patients at a low dose. If it is used, the maximum dose is usually 15mg orally daily for approximately six months, followed by a reduction to 5 to 7.5mg orally daily for another six months afterwards.
- Calcineurin inhibitors are typically continued for six months following an attainment of a complete remission and twelve months in cases of a partial remission. Non-responsiveness by six months should lead to consideration of an alternative therapy.

Mycophenolate mofetil has also been evaluated in FSGS and may be considered in those who have not responded to a calcineurin inhibitor or whom have poor kidney function in which a calcineurin inhibitor would be less likely advised.

• The dose of mycophenolate mofetil is usually 750 to 1000mg twice daily for six months. Low dose corticosteroids are often included in this regime.

For those who suffer a relapse of their disease, glucocorticoids are often begun again at similar doses to those used for initial therapy, particularly if they had a good response to therapy in their initial course. Those who relapse frequently or have side effects of glucocorticoids that make such therapy less advisable may benefit from the use of cyclosporine.

FSGS is notorious for recurring in kidney allografts, and the rate of recurrence of primary FSGS may be as high as 30%. A full discussion of FSGS in the kidney allograft is outside the scope of this chapter, and the author invites the reader to appropriate topic reviews.

### **Membranous nephropathy**

Membranous nephropathy is the underlying cause of about 20 to 30% of cases of nephrotic syndrome within a Caucasian population. It can be divided into primary and secondary causes.

Primary causes are often, although not always, associated with antibodies to the phospholipase A2 receptor (PLA2R), which accounts for approximately 70% of cases. Less commonly (perhaps 3%), thrombospondin type-1 domain containing 7A (THSD7A) antibodies may be seen. The remainder of cases of primary membranous are presumed to be idiopathic. A review of each of the antigens can be found <u>here</u> on RFN.

There are a number of secondary causes of membranous nephropathy;

- Drugs, with classical associations being noted for NSAIDs, D-penicillamine, gold-salts and alemtuzumab.
- Infections, with HBV, HCV and syphilis being classically associated. It should also be noted that HBV and lupus nephritis are the only causes of membranous nephropathy that have hypocomplementemia as an association.
- Malignancy may be noted in up to 20% of cases of secondary membranous, particularly in the demographic of patients > 65. Solid tumours are the most common and may include gastrointestinal tract, prostate, lung, bladder and breast.

• Lupus nephritis (class V).

Renal Fellow	Type of protein	Location in kidneys	Mean age (years)	Association	Positivity rate	LM	IF	Type of IgG	EM	Circulating Antibodies	Prognosis
PLA2R	Trans membrane protein	Podocyte	50-60	Primary MN	52-78% of primary MN	Thickened GBM, spikes on methenamine silver stain in the outer surface of capillary wall	Diffuse, uniform finely granular IgG4,C3, C4d deposits along the outer surfaces of capillary wall	lgG4	Sub epithelial deposits	Present	Circulating levels correlate with clinical course, proteinuria, outcomes.
THSD7A	Trans membrane protein	Podocyte	50-60	Malignancy	2-5% of primary MN	Thickened GBM, spikes on methenamine silver stain n the outer surface of capillary wall	Diffuse, uniform, finely granular deposits of IgG4,C3, c4d along the outer surfaces of all capillary wall	lgG4	Sub epithelial deposits	Present	Circulating levels correlate with clinical course, proteinuria, outcomes.
Exostosin 1/2 (EXT1/2)	Glycosyl Transferase	ER of podocyte	36	Autoimmune ANA, dsDNA, Anti Ro/La	50% with class V LN	Thickened GBM, mesangial or endocapillary proliferation	Bright granular staining for IgG, C1q, C3,IgA, IgM along GBM	lgG1	Sub- epithelial, mesangial, sub- endothelial deposits. Tubulo- reticular inclusion in endothelial cells	Absent	Favorable
Nel like protein 1 (NELL 1)	Protein kinase C binding protein.	Cytoplasmic proteins present mostly in tubules	63	Primary MN or malignancy	10-33% with malignancy	Thickened GBM	"Segmental" Bright granular staining for IgG,C3 along GBM	lgG1	Segmental Sub epithelial deposits	Present	Unknown
Semaphorin 3b (Sema3B)	Secreted/ Trans membrane protein	Endothelial cells, podocytes, tubular epithelial cells	7	Family history	Rare, 1-3% of all MN. 15% in pediatric age group	Thickened GBM	Bright granular staining for IgG,C3 along GBM	lgG1	Sub epithelial and TBM deposits	Present	Varied
Protocadherin 7 (PCDH7)	Cadherins - trans membrane proteins on surface	Podocyte	61	Prostate carcinoma	No autoimmune disease or infections	Thickened GBM	Bright granular staining for IgG,C3 along GBM	lgG1 or lgG4	Sub epithelial deposits	Present	Favorable
Human high temperature requirement A1 (HTRA1)	Serine protease	Podocyte	67	Primary MN	4.2% of primary MN	Thickened GBM	Bright granular staining for IgG,C3 along GBM	lgG4	Sub epithelial deposits	Present	Unknown
Contactin 1	Neural cell surface glycoprotein	Podocyte	60	Autoimmune neuropathy	80% Autoimmune neuropathy	Thickened GBM	Bright granular staining for IgG,C3 along GBM	lgG4	Sub epithelial deposits	Present	Circulating levels correlate with clinical course

**Clinical Features:** Membranous nephropathy usually presents with features suggestive of the nephrotic syndrome. This typically develops slowly, particularly in comparison to MCD or FSGS. Microscopic hematuria may be seen. Around 70% of patients will have a normal creatinine at presentation.

Pathologically membranous nephropathy is associated with a diffusely thickened GBM with spikes, representing new GBM developing around the subepithelial immune deposits, appearing in more advanced cases. Immunofluorescence will often reveal diffuse granular IgG and C3 deposition along the GBM. PLA2R or THSD7A deposition may also be seen, typically in association with primary causes.

The value of a kidney biopsy to establish a diagnosis of primary membranous nephropathy in those who have positive PLA2R antibodies in the serum, a normal eGFR, and no overt secondary causes of membranous nephropathy is unclear and opinions vary. The following should be considered.

- Up to 20% of cases of primary membranous will be seronegative at presentation.
- Atypical features, such as a depressed creatinine or red cell casts should probably undergo a biopsy to exclude another cause.
- A positive PLA2R in the serum may also be found in those with other suggestions of a secondary cause (ie HBV antigens or anti-nuclear antibodies) and a biopsy would be indicated to help distinguish between a primary and secondary cause.

Those who also have PLA2R deposits in their kidney biopsy almost always have PLA2R-associated membranous nephropathy. A notable exception may include those with PLA2R and light chain restriction who may have a diagnosis of a membranous with monoclonal antibodies towards PLA2R.

In those with negative staining for PLA2R on immunofluorescence other patterns of staining may suggest a primary or secondary cause. Those with IgG4 deposition are more likely to have a primary cause of membranous, and serological testing for THSD7A should be considered. In contrast, those with IgG1,2 and 3 deposition are more likely to have a secondary cause of membranous.

The use of serum PLA2R to guide the prognosis of primary membranous nephropathy is evolving. A persistently elevated PLA2R titre has been associated with a worse outcome, whereas there is some suggestion that a falling serum titre suggests that a remission may be underway. High PLA2R titres at the time of initial biopsy suggest a lower rate of complete remission.

A diagnosis of PLA2R associated membranous nephropathy makes it much less likely that the patient has membranous nephropathy associated with a malignant process. Regardless patients should undergo age appropriate cancer screening as recommended for the general population.

**Treatment**: The treatment of primary membranous nephropathy is complex and depends on the perceived risk of progression of the underlying disease. In milder forms of the disease there is a considerable spontaneous remission rate and these patients are unlikely to benefit from a prolonged course of immunosuppression. Regardless all patients should be commenced on appropriate therapies for proteinuric kidney disease such as RAS blockade, CVD risk assessment and reduction, and consideration of anticoagulation in those with hypoalbuminemia.

Patients with secondary causes of membranous often have remission of their disease with either withdrawal of the offending medication, or effective treatment of the underlying condition. Remission in these cases occurs slowly, and may need nine to twelve months for full remission of proteinuria.

The progression of CKD in membranous nephropathy occurs slowly. Therefore a rapid rise in creatinine should prompt consideration of the following complications;

- A superimposed crescentic GN
- Acute interstitial nephritis as a drug reaction
- Bilateral kidney vein thrombosis in those with hypoalbuminemia.

Membranous nephropathy is typically classified into low, moderate and high risk of progression based on presenting clinical characteristics. Such distinctions are important as they inform treatment decisions

- Those with a low risk for progression have subnephrotic proteinuria and a normal eGFR. These patients have a less than 8% risk of progression to CKD over 5 years.
- Those with a moderate risk for progression have proteinuria between 4 to 8 g daily that is persistent for over 6 months. Their eGFR also remains normal (or near normal) during this six month period. Around 50% of these patients will progress to CKD over a five year period.
- Those with a high risk for progression have persistent proteinuria > 8 g / day and a depressed eGFR or an eGFR that decreases over a three month observation period. 75% of these patients will progress over 5 years.

The management of each of these categories is different

- Those with a low risk of progression are usually not treated with immunosuppression. They receive appropriate non-immunosuppressive therapy as for other forms of proteinuric CKD and should be monitored for disease progression.
- Those with a moderate risk of progression still have an appreciable spontaneous remission rate. As such, these patients are often treated with appropriate non-immunosuppressive therapies and monitored over a six month period. In those who achieve sub-nephrotic range proteinuria via spontaneous remission or RAS inhibitor therapy than immunosuppressive is not started. Those who fail to achieve this are usually treated with immunosuppression.
- High risk patients are usually treated with immunosuppressive therapies.

There are a number of therapeutic options available for the treatment of membranous nephropathy. Both cyclophosphamide and calcineurin inhibitor based regimes appear to have similar efficacy, although relapses may be more common with a calcineurin inhibitor based regime. It should be noted that the <u>MENTOR</u> noted that rituximab was non-inferior to cyclosporine for the initial therapy of primary membranous nephropathy and is superior at 24 months in inducing remission. As such it is likely that rituximab may become the preferred initial therapy for those chosen to undergo immunosuppressive therapy, especially in those in whom the side effects of alkylating agents pose a significant concern. Of note, this trial did not compare rituximab to cyclophosphamide.

- Cytotoxic therapy is usually based off the Ponticelli regimen, with chlorambucil being much less used compared to cyclophosphamide given its worse side effect profile. This regime typically consists of oral prednisolone at 0.5mg/kg daily for months 1, 3 and 5 (with intravenous methylprednisolone 1g daily given for 3 days at the start of each prednisolone month) and oral cyclophosphamide 2 to 2.5mg/kg daily for months 2, 4 and 6.
- In comparison a calcineurin inhibitor based regime may be chosen as initial therapy. Cyclosporine is the usual choice, with a dose of 3 to 5mg/kg daily in two divided doses for a (trough) level of 120 to 200mcg/L. It is unclear if low dose prednisolone should also be added to this regime. Cyclosporine is usually continued for one year.
- In those who have a complete response cyclosporine is then tapered slowly over the subsequent two to four months. Those who have a partial remission (to proteinuria < 3.5g daily plus at least 50% reduction from baseline) cyclosporine is usually weaned to 1.5 to 2mg/kg daily (a dose which is felt to be less nephrotoxic) and continued for one to two years.
- Tacrolimus, at a dose of 0.05mg/kg daily to maintain trough levels of 3 to 5 mcg/L is an alternative to the use of cyclosporine.

Those with resistant disease were previously treated with rituximab as the next step, however as noted above since the publication of MENTOR the authors predict that it will become the preferred first line therapy as opposed to the use of calcineurin inhibitors in those in whom the Ponticelli regimen is not chosen.

- Rituximab is dosed in one of two fashions, 1g intravenously as an initial dose followed by a further 1g intravenously two weeks later, or weekly doses at 375mg/m<sup>2</sup> for four weeks. There does not appear to be a difference between the two regimes. Check <u>MENTOR</u> trial
- Those who fail to have an appreciable response to this regime may be considered for a repeat dose at six months time.
- A fall in PLA2R titres appears to predict the response to rituximab.

• Rituximab has been known to cause severe reactivation of HBV with potentially fatal hepatitis and patients must have infection with this agent excluded prior to its use.

### See the section on prophylaxis in patients on immunosuppression

#### See section on cyclophosphamide toxicities.

The relapse rate after successful therapy appears to be in the order of 30%. Repeat therapy with a course of cytotoxic therapy may be appropriate for some patients, but in those in whom exposure to cyclophosphamide is wished to be limited the use of a calcineurin inhibitor may be appropriate. Rituximab is associated with a lower relapse rate compared to calcineurin inhibitors at 24 months. At the time of writing it has not been directly compared to the Ponticelli regimen.

### **Glomerulonephritis post transplant**

A full discussion of the spectrum of GN recurrence post transplant is outside the scope of this chapter. A link to the appropriate topic review is provided for the reader here;

A flowsheet for the workup of the nephrotic syndrome from NephSIM may be found below;



### Davis and Patel- GN Associated testing:

HbA1C	DM				
ANA	SLE				
Anti-ds DNA	SLE				
Anti-PLA2R autoantibody	Membranous Nephropathy, + in 70-80%, does not exclude secondary causes, about 100% specific				
Serum free light chains (sFLC's) 3.3 to 19.4 mg/L kappa free light chains 5.71 to 26.3 mg/L lambda free light chains Normal ratio is 0.26 to 1.65 kappa/lambda *Note that CKD can complicate the interpretation of these values as FLC are cleared by the kidneys and values rise in CKD - however despite this rise the ratio should still be (relatively) within the normal limit above	Light Chain Disease/Myeloma/Amyloid *< 0.26 means high # of lambda chains so can be monoclonal gammopathy or Amyloid				
Serum protein immunofixation	Myeloma				
Anti-GBM Antibodies	Anti-GBM disease (Goodpasture syndrome) or Anti-GBM glomerulonephritis (Goodpasture disease)				
Cytoplasmic-Anti-Nuclear Antibody (C-ANCA) Against neutrophil proteinase 3 (PR3)	Active Granulomatosis with Polyangitis (GPA)				
Perinuclear-Anti-Nuclear Antibody (P-ANCA) Against myeloperoxidase (MPO)	Active Microscopic Polyangiitis (MPA, systemic and kidney limited) Eosinophilic Granulomatosis with Polyangiitis (EGPA)				

Cryoglobulins (sign of B cell dysregulation)	Type I (B cell lymphoma), II, III Cryoglobulinmia, associated with myeloma, Waldenstrom macroglobulinemia, viral infection (Hep B and Hep C), and connective tissue disease (eg. SLE, Sjogren syndrome, or rheumatoid arthritis)
Hepatitis B PCR	Ig/complement-mediated GN, IgA nephropathy, Polyarteritis Nodosa, Cryoglobulinemia
Hepatitis C PCR	MPGN, Cryoglobulinemia
HIV PCR	HIV-associated nephropathy (HIVAN) and HIV immune complex disease of the kidney (HIVICK)
Parvovirus	FSGS

### Low Complement Acronym (CHAMPS)

Cryoglobulinemia (C4 drop to undetectable levels compared to a lesser drop in C3)

Heavy chain deposition

Arthero-embolic disease (also cholesterol emboli notice)

\*hx of cardiac cath or vascular intervention

\*see eosinophilia

#### MPGN

Post-infectious GN (low C3 and CH50 and near normal or normal C4)

Infectious Endocarditis

#### SLE

IgG4 related diseases (AIN) (lymphocytic infiltrates/plasma cell in lung and kidney maybe with masses with eosinophilia, low grade ANA)

#### **Other Resources:**

**<u>Glomcon</u>** is a fantastic resource for those who wish to learn more about glomerulonephritis.

Other potential topic reviews may be found in the following list of manuscripts:

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