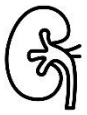
Membranous Nephropathy Management

Diagnosis and secondary causes

Anti-PLA2R blood test
~1 month turnaround
If positive biopsy may be avoidable



Kidney biopsy
If PLA2R –ve or more urgent result required

Screen for **secondary causes:**
ANA - SLE
CXR - sarcoidosis
Drug hx – gold, penicillamine
Malignancy - age/symptoms
BBV screen

Risk stratification and treatment

Low risk	Moderate risk	High risk	Very high risk
Normal eGFR uPCR <350 or >50% reduction at 6/12 Albumin >30	Normal eGFR uPCR >350 & <50% reduction at 6/12 No high risk criteria	eGFR <60 and uPCR >800 for over 6/12 **OR** Normal eGFR, uPCR >350 **and** Albumin <25 or PLA2R>50	Life threatening nephrotic syndrome **OR** Rapid deterioration of kidney function
⬇	⬇	⬇	⬇
Supportive therapy ACE inhibitor Consider SGLT2 inhibitor Consider statin	**Watch and wait with supportive therapy** **OR** **Rituximab** **OR** **Tacrolimus**	**Supportive therapy** **AND** **Rituximab** **OR** **Tacrolimus and Rituximab**	**Supportive therapy** **AND** **Rituximab** **AND** **Tacrolimus**

Rituximab

Initially **2 doses of 1g 2 weeks apart**
SE: Hypogammaglobulinaemia, Hep B reactivation, serum sickness
Further doses based on clinical response
Co-trimoxazole co-prescribed for 6 months

Bloods before commencing rituximab
Immunoglobulins: ideally want IgG >3gL
Hepatitis B serology: HBsAg +ve discuss with GI, if HBcAb +ve and HBsAg -ve consider lamivudine prophylaxis
Screen for TB (CXR and quantiferon) if risk factors

Tacrolimus

Adoport bd (10:00, 22:00), Advagraf OD
Initial dose 0.05mg/kg/day
SE: Hair loss, DM, tremor, TMA, nephrotoxic, HTN, dyslipidaemia
Target level 3-8

Increase levels
Macrolides, antifungals, CCB, doxycycline, amiodarone, metoclopramide, alcohol
Decrease levels
Phenytoin, carbamazepine, rifampicin, isoniazid, St. Johns Wart

Anticoagulation

Anticoagulate when **albumin <20**
Apixaban: most experience but 87% protein bound
Dabigatran: least protein bound 35%, ok eGFR down to 50
Warfarin: ok with all levels of kidney function
Aspirin and low dose LMWH can be considered as an alternative

Vaccinations

Live vaccines contraindicated
Live influenza (Fluenz Tetra), MMR (Priorix, MMRVaxPro), Rotavirus (Rotarix), Shingles (Zostavax), Oral typhoid (Ty21a), Varicella (Varilrix, Varilvax), Yellow Fever, BCG
Inactivated and subunit vaccines ok
COVID (all), Shingles (Shingrex), inactivated influenza, Polio, Hepatitis, Rabies, Japanese encephalitis, HPV, Diptheria, Pertussis
Ideally vaccinate 4 weeks before or 4 weeks after Rituximab

Follow up and ongoing management

If PLA2R +ve monitor 3 monthly
More frequent if >150 U/ml
Changes can predate clinical response

Consider CD19 monitoring if on rituximab; should not be used in isolation to guide future dosing

Generally treat for 6 months
If clinical remission consider tapering immune suppression

Membranous Nephropathy

Diagnosis

The diagnosis of membranous nephropathy has traditionally made by kidney biopsy. The presence of PLA2R antibodies however has a high sensitivity (78%) and specificity (99%) for membranous nephropathy and if positive it may be possible to avoid a biopsy, especially in those with preserved kidney function or lower levels of proteinuria who may not require immune suppressive therapy. [1] Kidney biopsies with features in keeping with membranous nephropathy should be stained for PLA2R. Biopsy staining may be positive in the absence of PLA2R antibodies in blood if there are only low titres of antibody or in the early phase of the disease.

PLA2R antibodies are analysed in Sheffield and are sent on a handwritten immunology form. The turnaround time is approximately 1 month; it may not be practical to delay management until antibody results are available.

It is currently possible to stain kidney biopsies for THSD7A but we are not able to routinely check anti-THSD7A antibodies in blood.

Investigations

Patients with membranous nephropathy should be evaluated for associated conditions, including those with positive PLA2R antibodies. This includes:

- Malignancy screening based on age or symptoms e.g. CT CAP, breast and colon screening
- Chest X ray
- Hepatitis B, Hepatitis C and HIV testing
- ANA
- Any history of associated drug use e.g. penicillamine, gold, NSAIDs

Risk assessment

The risk of progressive loss of kidney function should be assessed in patients with a diagnosis of membranous nephropathy based on blood and urine tests, as shown in Table 1.

Spontaneous remission is relatively common in membranous nephropathy therefore decisions on immune suppression should be based on the patient's risk of progressive decline in kidney function. There is a 45% chance of spontaneous remission in patients with proteinuria <4g/day at 6 months, and 34% chance for patients with proteinuria >8g/day. [2] [3] For most patients it is therefore reasonable to monitor response to conservative management for 6 months before deciding on

immune suppression. If cases where there is heavy proteinuria or high anti-PLA2R levels decisions should be re-evaluated prior to the 6 month timepoint.

The management of patients with secondary membranous nephropathy relating to malignancy is not clear cut, and decisions on immune suppression treatment should be made on an individual patient basis and in conjunction with opinion from other members of the nephrology team.

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR • Proteinuria <3.5g/day or >50% reduction after 6 months treatment with ACE/ARB • Albumin >30g/L	• Normal eGFR • Proteinuria >3.5g/day and <50% reduction after 6 months treatment with ACE/ARB • No high risk features	• eGFR <60ml/min • Proteinuria >8g/day for >6 months OR • Normal eGFR • Proteinuria >3.5g/day with <50% reduction after 6 months ACE/ARB • Albumin <25g/L • PLA2R >50 RU/ml	• Life threatening nephrotic syndrome e.g. massive PE OR • Rapid deterioration in kidney function not otherwise explained

Table 1. Risk assessment of patients with membranous nephropathy.

Monitoring of anti-PLA2R levels

In patients who are anti-PLA2R positive, PLA2R antibodies should be measured every 3-6 months, or more frequently for patients with levels >150 RU/ml. Falling anti-PLA2R levels can precede clinical remission and so their measurement can be used to guide treatment decisions such as refraining from additional treatment.

Treatment

Supportive treatment

All patients should receive optimal supportive therapy with:

- Maximum tolerated dose of an ACE inhibitor or angiotensin receptor blocker
- Diuretic as required to manage oedema: amiloride can be a helpful adjunct if there is no hyperkalaemia
- SGLT2 inhibitors: depending on the anticipated speed of disease remission. If patients remain nephrotic at 3 months an SGLT2 inhibitor should be considered if not already commenced.

- A statin if evidence of dyslipidaemia, considering the patients overall cardiovascular risk and the anticipated speed of remission. If patients remain nephrotic at 3 months a statin should be considered if not already commenced.
- Dietary salt restriction to under 2g/day: a useful website for patients to refer to is FoodSwitch - Action on Salt

Anticoagulation

Patients with membranous nephropathy have an increased risk of venous and arterial thrombosis. The risk is greatest in the first 6-12 months after diagnosis.

Prophylactic anticoagulation should be commenced in patients with a serum albumin <20g/L and based on the relative risks and benefits if albumin is between 20-25g/L. The risk of thromboembolic disease is greatest in individuals with secondary membranous.

The choice of agent depends on the level of kidney function, patient preference and bleeding risk.

- Warfarin has traditionally been used but there is high INR variability in patients with nephrotic syndrome and low eGFR making its use less straight forward.
- Direct oral anticoagulants have not been systematically studied in patients with nephritic syndrome but can be used for prevention of venous thromboembolism accepting they are variably protein bound and their efficacy may be affected by hypoalbuminaemia. We have most familiarity with apixaban (87% protein bound). Rivaroxaban is the most protein bound (95%) and so other agents should be used in preference to this.
- Aspirin is insufficient to prevent venous thromboembolism, but may be considered for patients with an albumin of 20-30g/L and a high risk of arterial thromboembolic events (>20/1000 patient years) calculated at: https://www.mdcalc.com/calc/38/framingham-risk-score-hard-coronary-heart-disease

Anticoagulation used for the prevention of venous thromboembolism can generally be stopped when serum albumin is consistently greater than 25g/L.

Patients with a known thrombus should be discussed with haematology; warfarin or dalteparin may be chosen in preference to apixaban in this situation.

Patients should not be on apixaban or any other DOAC if they are active on the transplant list.

Immunosuppression

Immunosuppression should be considered for patients with risk factors for disease progression, as outlined in Table 1 and Table 2.

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR • Proteinuria <3.5g/day or >50% reduction after 6 months treatment with ACE/ARB • Albumin >30g/L	• Normal eGFR • Proteinuria >3.5g/day and <50% reduction after 6 months treatment with ACE/ARB • No high risk features	• eGFR <60ml/min • Proteinuria >8g/day for >6 months OR • Normal eGFR • Proteinuria >3.5g/day and <50% reduction after 6 months treatment with ACE/ARB • Albumin <25g/L • PLA2R >50RU/ml	• Life threatening nephrotic syndrome OR • Rapid deterioration in kidney function not otherwise explained
↓	↓	↓	↓
Watch and wait	Watch and wait OR Rituximab OR Calcineurin inhibitor	Rituximab OR Calcineurin inhibitor and rituximab	Calcineurin inhibitor and rituximab

Table 2. Immunosuppression choice based on risk of progressive deterioration in kidney function.

Rituximab

Rituximab is used for patients with moderate to very high risk of progressive CKD. It may be used as a single agent in preference to tacrolimus in patients with moderate risk of disease progression and a low eGFR (e.g. <30ml/min/1.73m^2), or may be used in combination with tacrolimus in patients with high to very high risk disease.

Initial dose regime

1g rituximab IV on day 1 and day 15. This is prescribed on Vital Data and if a stop date is provided can be printed from Crystal Reports. The prescription is sent to pharmacy and rituximab is administered in ambulatory care.

Hepatitis B Screen

- There is a risk of Hepatitis B reactivation in the context of rituximab use. Patients should have HBcAb, HBsAg and HBsAb checked prior to receiving rituximab.
- Patients who are HBcAb positive and HBsAg negative should be considered for treatment with lamivudine. They should start prophylaxis before beginning immune suppression therapy and continue for 6 months after the last dose of rituximab.
- Patients who are HBsAg positive should be discussed with the hepatology team prior to administering rituximab.

Mycobacterium infection

Patients should be assessed for risk of TB through clinical history, examination and CXR.

- A Quantiferon test should be considered in patients with a high risk of latent infection. This comprises:
    - Those with a history of TB
    - Those who are a household contact of someone with previous TB
    - Those born in Africa, Asia, South America, Eastern Europe, the Caribbean, or another country with a TB incidence >40/100,000, or have lived with someone from or spent a significant time in endemic countries as defined above.
    - Have a higher risk of exposure to TB e.g. homeless or in prison.
- If the Quantiferon test is positive or radiological imaging is suspicious for TB, individuals should be referred to a TB specialist. Treatment of organ-threatening membranous nephropathy should not be delayed whilst results of screening tests are pending.

PCP prophylaxis

- Co-trimoxazole 480mg daily or 960mg 3x weekly should be prescribed for patients receiving rituximab. This should be continued for 6 months after their last dose.

Rituximab side effects

- Hypersensitivity
- Late onset neutropenia
- Hepatitis B reactivation
- Progressive multifocal leukoencephalopathy

Contraception advice

Female patients of childbearing age should be recommended on potential risks of pregnancy and contraception advice should be given. Advice is to avoid pregnancy for 1 year after rituximab treatment.

B cell monitoring on rituximab

B cell depletion is insufficient to judge the efficacy of rituximab and extra doses may be considered even if peripheral blood B cells are absent or low. B cells monitoring should be considered in selected cases only e.g. if there is a lack of clinical response to treatment. This involves sending blood for CD19 levels on a handwritten form to WGH.

Tacrolimus

In contrast to Rituximab, tacrolimus can be stopped rapidly if required. There is a moderate rate of relapse when treatment is stopped and therefore tacrolimus is only recommended as a single agent in patients at moderate risk of disease progression.

Initial dose regime

- Initial dose of 0.05-0.1mg/kg/day, aiming for a trough level of 3-8 ug/L.
- Treatment should be continued for at least 1 year and then be reassessed.

Tacrolimus side effects

- Hair loss
- Diabetes mellitus
- Tremor
- Thrombotic microangiopathy
- Reduction in kidney function
- Hypertension
- Dyslipidaemia

A patient information leaflet on tacrolimus side effects is available online. Whilst designed for transplant patients it remains applicable to those requiring tacrolimus for glomerulonephritis:

Adoport (Tacrolimus) - Information for Transplant Patients (RIE) (nhslothian.scot)

Cyclophosphamide

Cyclophosphamide can be used as an alternative agent to rituximab and tacrolimus for patients at high or very high risk of disease progression, but its side effect profile means it is less frequently selected. Studies using cyclophosphamide have favoured its oral use as opposed to intravenous, [4] though intravenous use may be used to minimise cumulative cyclophosphamide exposure.

Oral cyclophosphamide has been given cyclically as per the Ponticelli regimen (alternate months of oral prednisolone and oral cyclophosphamide) or as a continuous oral treatment for 6 months. In our experience, cyclophosphamide has been used as 2 intravenous pulses 2 weeks apart alongside rituximab therapy for patients at high risk of disease progression.

The cyclophosphamide regime based on age, ideal body weight and renal function is shown in Table 3. The maximum dose is 1.2g and should be rounded down to the nearest 20mg.

Age (years)	**Creatinine <300umol/L**	**Creatinine≥300umol/L**
<60	15mg/kg	12.5mg/kg
60-70	12.5mg/kg	10mg/kg
>70	10mg/kg	7.5mg/kg

Table 3. Intravenous Cyclophosphamide dosing

Patients receiving IV cyclophosphamide should also:

- Be advised to be well hydrated to dilute the metabolites in the urine.
- Consider being prescribed MESNA to reduce the risk of haemorrhagic cystitis.

Cyclophosphamide side effects

- Bone marrow suppression
- Increased risk of infections
- Infertility and early menopause (approx. 50%): dependent on cumulative dose and age. The highest risk is in pre-menopausal women over the age of 30 years.
- Teratogenicity: contraception advice must be given where appropriate and a negative pregnancy test in women of childbearing age should be seen prior to commencing treatment.

- Malignancy: the malignancies with the greatest increased relative risk are listed below, although the absolute risk remains small. These are generally related to a cumulative dose of cyclophosphamide over 30g.
    - Lymphoma
    - Skin cancer
    - Bladder cancer: 3% at 10 years. Surveillance with regular urinalysis should be continued indefinitely after a course of cyclophosphamide. De novo non-visible haematuria without other cause should prompt urological investigation.
- Hair loss
- GI upset

Immunisations for patients on immunosuppression

A vaccination history should be sought from patients at baseline. Live vaccinations should be avoided until immune suppression has been stopped for over 3 months. These include:

- MMR
- Varicella
- BCG
- Yellow fever

Non-live vaccines should be given before treatment if feasible, although this will often not be the case. For patients receiving rituximab, vaccines should be given at least 4 weeks before rituximab or postponed until 4 weeks from the last dose of rituximab. Non-live vaccines include:

- Tetanus/diphtheria/inactive polio
- Hepatitis B
- Influenza
- Typhoid (inactive polysaccharide vaccine)
- Pneumococcal/Meningococcal/Hib
- Combined Hepatitis A/B
- SARS-CoV-2 vaccines (all formulations)
- Non-live Shingles vaccine (Shingrix)

All patients with nephrotic syndrome or on immune suppression should be advised to have an annual influenza vaccine and the pneumococcal vaccine every 5 years.

Patients can be referred for unscheduled vaccinations by completing the following form available on the intranet: Search Results (scot.nhs.uk)

Duration of immunosuppression

The duration of immunosuppression varies depending on clinical response.

For patients who are PLA2R antibody positive, a PLA2R antibody level taken after 6 months of treatment can be used to guide ongoing therapy:

- Absent PLA2R: if on rituximab – no additional dose and monitor; if on tacrolimus – taper tacrolimus dose.
- Positive PLA2R >50RU/ml: if on rituximab – continue dosing; if on tacrolimus – consider adding rituximab and tapering tacrolimus dose.
- Positive PLA2R <50RU/ml: if on rituximab – continue dosing; if on tacrolimus – continue for another 6 months and re-evaluate.

Resistant disease

There is no consensus on the definition of resistant disease. Usually resistant disease refers to a failure of normalisation of serum albumin after 6 months of treatment, or the persistence of PLA2R antibodies despite clinical remission. Persistent proteinuria is not sufficient to define resistant disease as proteinuria can persist for 1-2 years from start of treatment. In patients with an improved serum albumin but persistent proteinuria, secondary FSGS should be considered. A repeat kidney biopsy may be considered in patients with persistent proteinuria and improved but not normalised serum albumin to determine if there is active membranous nephropathy, signified by the presence of small dense deposits on electron microscopy.

Concordance with treatment should be considered and treatment efficacy measured if possible in cases of resistant disease e.g. evidence of B cell depletion, IgG levels, tacrolimus levels or presence of anti-rituximab antibodies.

Alterations to treatment should be based on whether kidney function is stable or deteriorating (Figure 1). In patients with low anti-PLA2R levels and partial remission of proteinuria, close follow-up without additional immune suppression can often be considered.

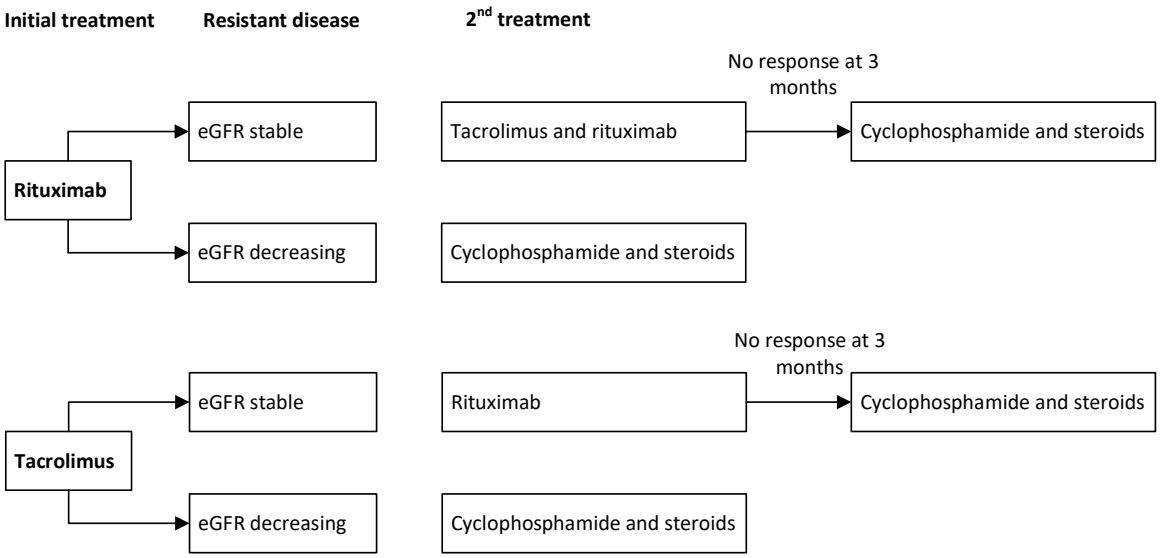


Figure 1. Management of resistant membranous nephropathy.

Relapsing disease

A relapse is defined as an increase in proteinuria with parallel fall in serum albumin levels. Disease relapses are generally treated with rituximab, or a combination of rituximab and calcineurin inhibitor as outlined in the earlier sections.

Transplantation

For patients with PLA2R positive membranous nephropathy, the absence of antibodies at the time of transplant predicts a lower risk of disease recurrence. Higher anti-PLA2R levels (>45RU/ml) are associated with an increased risk of disease recurrence but there is insufficient data to define a cut off value.

Post-transplant there is insufficient data to suggest that protocol biopsies or pre-emptive treatment with rituximab are indicated unless there is a history of multiple disease recurrences and positive PLA2R antibodies.

In patients with PLA2R-positive disease, PLA2R antibodies should be monitored regularly in the first 6-12 months after transplant. A relapse may be predicted if there are high or rising titres, and in this setting a biopsy may be considered.

In PLA2R negative patients, proteinuria should be quantified monthly for 6-12months post-transplant. A biopsy is indicated if proteinuria is over 1g/day.

Recurrence of membranous nephropathy post-transplant should be treated with maximal conservative therapy. Rituximab should be considered if there is over 1g/day proteinuria.

References

1. Du Y, Li J, He F, et al. The Diagnosis Accuracy of PLA2R-AB in the Diagnosis of Idiopathic Membranous Nephropathy: A Meta-Analysis. *PLOS ONE*. 2014;9(8):e104936. doi:10.1371/journal.pone.0104936

2. Seitz-Polski B, Debiec H, Rousseau A, et al. Phospholipase A2 Receptor 1 Epitope Spreading at Baseline Predicts Reduced Likelihood of Remission of Membranous Nephropathy. *J Am Soc Nephrol*. 2018;29(2):401. doi:10.1681/ASN.2017070734

3. Pei Y, Cattran D, Greenwood C. Predicting chronic renal insufficiency in idiopathic membranous glomerulonephritis. *Kidney International*. 1992;42(4):960-966. doi:10.1038/ki.1992.374

4. Falk RJ, Hogan SL, Muller KE, Jennette JC. Treatment of Progressive Membranous Glomerulopathy. *Ann Intern Med*. 1992;116(6):438-445. doi:10.7326/0003-4819-116-6-438

Minimal Change Disease

Diagnosis

Renal Biopsy:
LM – normal
EM – diffuse effacement of foot processes
IF – negative (currently…)

Consider **secondary causes:**
Drugs – NSAIDs, bisphosphonates, lithium
Malignancy – esp. haematological
Infection – TB, syphilis, HIV
Immunisations

Supportive Therapy

Fluid balance management
- Loop diuretic first line
- Documented weights

Dietary sodium restriction <2g/d
AKI relatively common
- Withold ACEi if anticipate quick improvement

Considerations

Infection
- Consider cover encapsulated bacteria
- Vaccination

Thrombosis risk
- Renal vein thrombosis / PE
- Consider prophylaxis

Hyperlipidaemia
- Statin

Bone prophylaxis

First line Treatment

Glucocorticoids

Prednisolone : 1mg/kg/d (max 80mg)
- Min. 4 weeks, max. 16 weeks
- Begin tapering 2 weeks after complete remission
- Taper over at least 24 weeks

SE: DM, Osteoporosis, Adrenal insufficiency, HTN, Cushingoid appearance, Psychosis

Contraindication to glucocorticoid:
- Obesity
- Diabetes
- Pre-existing serious psychiatric disorder
- Osteoporosis
- Patient preference

Tacrolimus

Adoport bd (10:00, 22:00), Advagraf OD
Initial dose 0.05mg/kg/day
Target level 6-8; increase 9-12 at week 8 if inadequate response
- Begin tapering 12 weeks after complete remission
- Taper over 8 weeks

SE: Hair loss, DM, tremor, TMA, nephrotoxic, HTN, dyslipidaemia
*Check drug interactions

Other drug options:
- Cyclophosphamide
- MPAA
- Rituximab

Ongoing Management

Infrequent relapse

Oral prednisolone 1mg/kg for 4 weeks (or until remission)
- Taper by 5mg every 3-5 days
- Aim disontinuation within 1-2 months

Frequent relapse / Steroid Dependent

Induce remission with glucocorticoid
- Wean off over 2-4 weeks

Cyclophosphamide
- 12 week / single course

CNI
Rituximab
MPAAs

Resistant Disease

Repeat biopsy - ? FSGS
Optimise supportive management
Monitor for complications
? Genetic testing
? Clinical trial

Minimal Change Disease

Diagnosis

Minimal change disease accounts for 10-25% of nephrotic syndrome in adults. In adults the diagnosis is dependent on renal biopsy which typically shows normal glomeruli on light microscopy and extensive glomerular podocyte foot process effacement on electron microscopy without dense deposits. Immunofluorescence is typically negative. The heavy proteinuria results from disruption of the slit-diaphragm protein complexes linking the interdigitated glomerular foot processes.

Secondary causes should be considered in the initial history and examination. These include:

- Drugs: NSAIDs (most commonly), antimicrobials, lithium, bisphosphonates.
- Malignancy: Most commonly haematological malignancies
- Infection: TB, syphilis, HIV, mycoplasma, HCV
- Recent immunisation

Investigations

Standard investigations include:

- Confirm proteinuria >3.5g/d (urine PCR) and hypoalbuminaemia
- Lipid profile
- BBV testing – hepatitis B, C, HIV
- ANA, Anti ds-DNA, C3/4
- Serum electrophoresis, urine Bence Jones, serum free light chains
- Anti-PLA2-R if membranous nephropathy in differential
- Renal biopsy. In young adults presenting with nephrotic syndrome the risks and benefits of kidney biopsy versus empirical treatment for a presumptive diagnosis of minimal change disease should be considered taking the above investigation results, and subsequently initial response to treatment, into account.

Treatment

Untreated nephrosis is associated with an increased risk of infection, thromboembolic disease, complications of hyperlipidaemia, and acute kidney injury. The majority of data around treatment for minimal change disease is extrapolated from trials in children.

Supportive therapy

Initial supportive management largely relates to management of extracellular volume expansion and typically comprises:

- Diuretic as required to manage oedema: amiloride can be a helpful adjunct if there is no hyperkalaemia
- ACE inhibitors: in general, if a therapeutic response to treatment is anticipated to occur rapidly it is reasonable to hold off initiating ACEi/ARB but this should be kept under review in association with the clinical response to treatment.
- SGLT2 inhibitors: depending on the anticipated speed of disease remission. If patients remain nephrotic at 3 months an SGLT2 inhibitor should be consider if not already commenced.
- A statin if evidence of dyslipidaemia, considering the patients overall cardiovascular risk and the anticipated speed of remission. If patients remain nephrotic at 3 months a statin should be consider if not already commenced.
- Dietary salt restriction to under 2g/day: a useful website for patients to refer to is FoodSwitch - Action on Salt

Anticoagulation

Patients with nephrotic syndrome are at a higher risk of venous and arterial thrombosis. The degree of proteinuria and a serum albumin of <25g/L are associated with increased thrombosis risk. In general, the threshold for anticoagulation is higher in minimal change disease given the hope for rapid clinical improvement with treatment. Further information on anticoagulation can be found by following this hyperlink: Anticoagulation

Vaccination and infection risk

The loss of immunoglobulins in the urine predisposes to infection, and consideration of atypical infection (including encapsulated bacteria) is important if patients are unwell.

Vaccination against influenza and pneumococcal disease should be offered.

Further information on vaccinations and how to refer for these can be found by following this hyperlink: Immunisations for patients on immunosuppression

Corticosteroids

The management of minimal change disease has traditionally been with high dose glucocorticoids, with evidence largely from studies in the paediatric population. Over 80% of patients achieve remission with steroids during their first presentation. [5] Local practice typically uses glucocorticoids as first line therapy, unless contraindicated in which case tacrolimus is used.

Treatment involves high dose prednisolone (typically 1mg/kg/d to a maximum of 80mg/d) for a minimum of 4 weeks and up to a maximum duration of 16 weeks. With this treatment it would be expected that 50% of patients will respond by 4 weeks and 75% by 16 weeks.

Patients should receive a steroid safety card when commencing prednisolone. Prednisolone should be co-prescribed with a PPI, bone protection and co-trimoxazole (see below).

There are many ways to taper steroids. Generally tapering can begin after being in remission for 2 weeks with steroids being stopped by around 24 weeks. There is no standard prednisolone weaning regime and the rate of reduction may vary depending on clinical response. The PEXIVAS trial outlines a steroid weaning regime that reduces prednisolone to 5mg by 6 months; this is not designed to be used in nephrotic syndrome but can provide an example of steroid reduction intervals. [6]

Guidance on how to withdraw steroids, including assessing the risk of adrenal insufficiency, can be found at the following link: Lothian+Steroid+Safety+Bundle+approved.pdf (squarespace.com)

Contraindication to steroids

There are few absolute contraindications to steroids. Relative contraindications reflect patients at a higher risk of complications from treatment including obesity, poorly controlled diabetes mellitus, pre-existing serious psychiatric disorder, pre-existing osteoporosis and patient refusal or concern.

Steroid side effects

Patients should be counselled on the side effects of steroids prior to commencing therapy. This should include:

- Precipitation / worsening of diabetes
- Deterioration of pre-existing psychiatric conditions (especially psychosis)
- Osteoporosis
- GI bleeding

- Cushings syndrome
- Obesity / weight gain
- Cataracts

A patient information leaflet on steroid side effects is available online and whilst designed for transplant patients it is applicable to those requiring steroids for glomerulonephritis:

Prednisolone - Information for Transplant Patients (RIE) (nhslothian.scot)

Bone prophylaxis whilst on steroids

Patients should be prescribed calcium and vitamin D supplementation when starting steroids.

A DEXA scan should be considered if patients have a ≥10% 10 year fracture risk and taking prednisolone at a dose of 7.5mg/day or over for at least 3 months, as calculated at the following link: QFracture

Infection prophylaxis whilst on steroids

There is no local consensus on whether patients should receive PCP prophylaxis with co-trimoxazole if receiving high dose steroids alone. The British Columbia Renal Glomerulonephritis Committee recommends patients receive co-trimoxazole if they are on prednisolone at a dose of 20mg/day or more for at least 4 weeks as demonstrated in Figure 2 below.

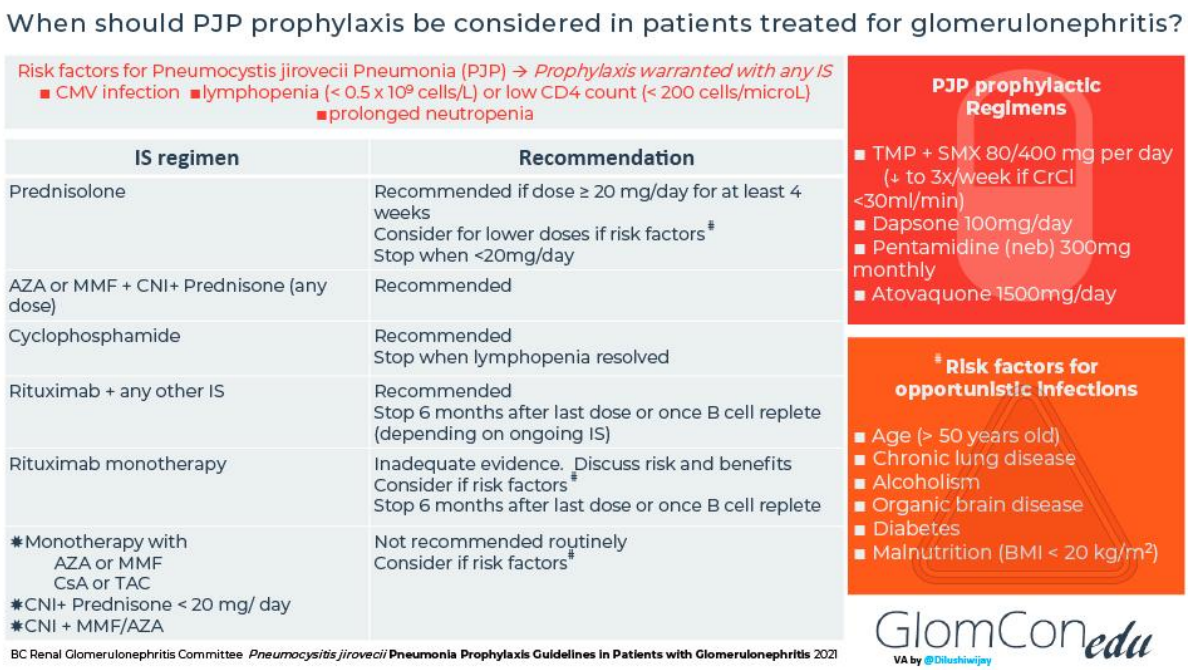


Figure 2. When to consider PCP prophylaxis with immune suppression.

Calcineurin Inhibitors

Calcineurin inhibitors induce remission of minimal change disease in 70-90% of patients. The MINTAC trial (2019) suggests that tacrolimus is a suitable alternative therapy to glucocorticoids. [7]

Adoport (tacrolimus) is the CNI of choice and should be started at a dose of 0.05-0.1mg/kg/day, aiming for a trough level of 6-8 ug/L. If an inadequate response is achieved, the target tacrolimus trough should be increased to 9-12 at week 8. Tacrolimus doses can be titrated down once in clinical remission for 8-12 weeks with a view to discontinuing therapy around 6 months to 1 year after diagnosis depending on clinical response.

There is a risk of nephrotoxicity with long term CNI use, and biopsy should be considered if there is progressive renal dysfunction that cannot otherwise be explained.

Other therapeutic options

Rituximab : 1g/dose for 2 doses, 2 weeks apart.

- The long term efficacy and role of re-dosing unclear. For more information on monitoring, side effects and prescribing rituximab follow the hyperlink to: Rituximab

Cyclophosphamide : oral dosing 2-2.5mg/kg/d for 8-12 weeks.

- Extrapolated from data in children and not frequently used in our clinical practice.

Mycophenolate Mofetil : 1g BD.

- Not frequently used in our clinical practice.

Contraception

Advice around conception must be provided to women on ACE inhibitors/ARBs, rituximab and MMF. Contraception should generally be non-oestrogen containing, and ideally long-acting methods are preferred given their significantly better real life efficacy data.

Treatment response definitions

- **Complete remission:** reduction of proteinuria to <0.3g/d or PCR <30mg/mmol; stable serum creatinine and stable serum albumin >35g/l
- **Partial remission:** Reduction of proteinuria to 0.3-3.5g/d and a decrease of >50% from baseline
- **Relapse:** Proteinuria of >3.5g/d after complete remission has been achieved. 50-75% of patients will experience a relapse.
- **Steroid-resistant MCD:** Persistence of proteinuria >3.5g/d with <50% reduction from baseline despite prednisolone 1mg/kg/d for > 16 weeks. 10-20% of adults with MCD have steroid-resistant disease.
- **Frequently relapsing MCD :** >= 2 relapses per 6 months or >= 4 relapses per 12 months. Up to 33% of patients have frequently relapsing MCD.
- **Steroid dependent MCD:** Relapse occurring during, or within 2 weeks of completing glucocorticoid therapy. 15-30% patients develop steroid dependent MCD.

Relapse

Up to 75% of patients will experience a relapse of MCD with recurrence of nephrotic syndrome. Patients should be encouraged to utilise home urine dipsticks assessing for albuminuria to allow prompt reassessment with escalation of therapy.

For infrequent relapses then re-initiation of previously successful therapy (typically glucocorticoids if they have been used as first line) is appropriate, with regular monitoring to assess response.

Appropriate infection and bone prophylaxis should be started at the same time. It is recommended that patients receive at least 4 weeks of therapy for a disease relapse but treatment should be tapered more rapidly, with the aim of discontinuation over around 2 months. [8]

For frequently relapsing or steroid dependent disease the recommendation is for CNIs, rituximab, cyclophosphamide or mycophenolic acid analogues rather than prednisolone alone.

References

5. Palmer SC, et al. Interventions for minimal change disease in adults with nephrotic syndrome (Review). Cochrane Database of Systematic Reviews. 2008:1;CD001537

6. Walsh M et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med 2020; 382:622-631

7. Medjeral-Thomas NR, Lawrence C et al. Randomized, Controlled Trial of Tacrolimus and Prednisolone Monotherapy for Adults with *De Novo* Minimal Change Disease: A Multicenter, Randomized, Controlled Trial. Clin J Am Soc Nephrol. 2020 Feb 7;15(2):209-218. doi: 10.2215/CJN.06180519. Epub 2020 Jan 17.

8. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

Focal Segmental Glomerulosclerosis (FSGS) Management

Diagnosis and consideration of secondary causes

Duration of symptoms, degree of nephrotic syndrome and family history can help

Kidney biopsy essential

Supportive management should be considered for all:
RAS blockade
Target BP<120/70

Consideration of aetiology to guide treatment

Primary FSGS
Usually sudden onset
Typically >3.5g proteinuria/day and serum albumin <30

Secondary FSGS
Gradual onset
Usually not nephrotic

Viral infections
Drugs
Maladaptive glomerular changes

Genetic FSGS
Variable presentation of progression and proteinuria
Family history suggestive
Resistant to immunosuppressive treatment

FSGS of undetermined cause
Gradual onset
Variable degree of proteinuria
Resistant to immunosuppressive treatment

Immunosuppression
Corticosteroids (1mg/kg prednisolone) first line unless contraindicated CNI if so

Supportive therapy
Treat underlying cause (if possible)

Supportive therapy
Genetic testing
Family support

Supportive therapy

Prednisolone

1mg/kg (maximum 80mg)
SE: hyperglycaemia, weight gain, hypertension among others
Duration: At least 4 weeks until remission achieved, maxiumum 16 weeks of high dose
Wean thereafter to complete a minimum of 6 months of therapy

Additional treatments with steroid
- **Co-trimoxazole** prescribed for PJP prophylaxis
- **Bone protection** – Adcal D3 or equivalent
- **Lanzoprazole 30mg od** gastric protection

Tacrolimus – 2nd line

Adoport bd (10:00, 22:00), Advagraf OD
Initial dose 0.05mg/kg/day
SE: Hair loss, DM, tremor, TMA, nephrotoxic, HTN, dyslipidaemia
Target level 5-10
6 months of treatment required prior to calling condition CNI resistant
Duration of at least 12 months to minimise relapse

Anticoagulation

Anticoagulation should be considered if albumin <20 or if there are other additive risk factors

Genetic testing

Consider genetic testing if:
There is a family history of renal disease
Insidious onset with no other secondary causes
Concerns about transplant listing
Refractory to treatment

Other options

Mycophenolate mofetil or Rituximab would be 3rd line options

Follow up and ongoing management

Monitor for side effects including hyperglycaemia

Consideration of recurrence important in transplant assessment

Focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is a pattern of injury for which there are many potential causes. It is diagnosed based on the presence of the characteristic FSGS lesion on kidney biopsy.

Investigations

Treatment depends upon the likely underlying cause, which can be divided into 4 categories:

1. Primary FSGS (presumed permeability factor affecting podocytes)
2. Genetic FSGS
3. Secondary FSGS
4. FSGS of undetermined cause

In the presence of sudden onset nephrotic syndrome: proteinuria >3.5g/daily and serum albumin <30g/L the underlying diagnosis is most likely primary FSGS, therefore immunosuppression should be considered with genetic testing if there is limited response to treatment (see Genetic testing).

In the absence of nephrotic syndrome e.g.:

1. Nephrotic range proteinuria >3.5g/day but serum albumin >30g/L or
2. Proteinuria <3.5g/day with/without hypoalbuminaemia

Evaluate for underlying cause (as possible secondary FSGS), consider genetic testing, monitor proteinuria and albumin, and follow supportive therapy in the first instance.

Secondary causes of FSGS

Viral infections

- HIV
- CMV
- Parvovirus B19, EBV,HCV
- Hemophagocytic syndrome

- SARS-CoV-2 (with APOL1 risk genotype)

Drug-induced

- Direct anti-viral therapy
- mTOR inhibitors, CNIs
- Anthracyclines
- Heroin (adulterants)
- Lithium
- Interferon
- Anabolic steroids
- NSAIDs

Maladaptive glomerular changes

Reduced nephron number

- Reflux nephropathy
- Renal dysplasia
- Oligomeganephronia
- Sickle cell disease
- Ageing

Normal nephron number

- Obesity
- Secondary to other glomerular diseases
- Systemic conditions eg diabetic nephropathy, hypertension

Treatment

Supportive measures

- Maximum tolerated RAS blockade, with target BP <120/70
    - Diuretics as required to manage peripheral oedema. Amiloride can be a helpful adjunct if there is no hyperkalaemia.

- SGLT2 inhibitors: depending on the anticipated speed of disease remission. If patients remain nephrotic at 3 months an SGLT2 inhibitor should be consider if not already commenced.
- A statin if evidence of dyslipidaemia, considering the patients overall cardiovascular risk and the anticipated speed of remission. If patients remain nephrotic at 3 months a statin should be consider if not already commenced.
- Dietary salt restriction to under 2g/day: a useful website for patients to refer to is FoodSwitch - Action on Salt

Glucocorticoids

High dose glucocorticoid treatment should be started at 1mg/kg prednisolone (up to 80mg) or alternate day dose of 2mg/kg (maximum 120mg). This should be continued for a minimum of 4 weeks and until complete remission is achieved, up to a maximum of 16 weeks. A shorter course can be considered in patients showing no improvement, particularly if experiencing side effects, with a view to switching to second line therapy.

PPI, co-trimoxazole and bone protection should be prescribed simultaneously. Consider potential corticosteroid side effects including impaired glycaemic control.

Weaning: Continue steroid for 2 weeks after the resolution of proteinuria up to a maximum of 16 weeks. Reduce prednisolone by 5mg every 1-2 weeks thereafter to achieve total duration of 6 months

If partial remission is achieved within 8-12 weeks, continue high dose prednisolone until 16 weeks to determine if a further reduction in proteinuria occurs, followed by weaning prednisolone by 5mg every 1-2 weeks to complete 6 months of treatment.

If the patient is steroid resistant or has intolerable side effects, glucocorticoids should be weaned rapidly and alternative e.g. CNI considered.

For more information on the side effects of steroids and appropriate patient information, please follow the hyperlink to the earlier section on: Corticosteroids

Calcineurin inhibitors

Calcineurin inhibitors are usually second line treatments and can be considered if there are clinical reasons to suggest corticosteroids may carry increased risk e.g. obesity, diabetes, psychiatric illness.

Our local CNI of choice is tacrolimus (adoport), with a starting dose of is 0.05-0.1mg/kg/day in 2 divided doses, target trough 5-10 ug/L.

Duration: Should be at target level for 4-6 months prior to considering FSGS to be resistant to CNI treatment. Treatment should be continued for at least 12 months to minimise the risk of relapse.

Weaning: The dose should then be slowly tapered over 6-12 months as tolerated

Further information on tacrolimus side effects and patient information can be found by following the hyperlink to the earlier section: Tacrolimus

Other considerations

In steroid resistant primary FSGS, CNI should be given for a minimum of 6 months with a target trough 6-12 ug/L, at which point the patient may be considered CNI resistant if no response.

In patients with complete or partial response, CNI should be continued at target range for a minimum of 12 months to reduce risk of relapse. The dose should then be tapered over 6-12 months.

Consider stopping CNI if eGFR <30ml/min/1.73m^2 due to the risk of nephrotoxicity.

Alternative agents

- Rituximab 1g IV, 2 doses 2 weeks apart. For more information on monitoring, side effects and prescribing rituximab follow the hyperlink to: Rituximab
- Mycophenolate mofetil 1g bd

Definitions of treatment response

- **Complete remission**: Reduction of proteinuria to PCR <30mg/mmol, stable serum creatinine and serum albumin >35g/l

- **Partial remission**: Reduction of proteinuria to PCR 30-350mg/mmol and a decrease >50% from baseline
- **Relapse:** Proteinuria >350mg/mmol after complete remission has been achieved or an increase in proteinuria by >50% during partial remission
- **Steroid resistant FSGS**: Persistence of proteinuria >3.5g/day or PCR >350mg/mmol with <50% reduction from baseline despite prednisolone 1mg/kg/d for at least 16 weeks
- **Steroid dependent FSGS**: Relapse occurring during or within 2 weeks of completing glucocorticoid treatment
- **CNI resistant FSGS**: Presence of proteinuria >3.5g/d or PCR >350mg/mmol with <50% reduction from baseline despite tacrolimus trough levels of 5-10ug/l for 4-6 months
- **CNI dependent FSGS**: Relapse occurring during or within 2 weeks of completing tacrolimus therapy for >12 months

Relapse

If patients have previously been steroid sensitive, relapse can be treated as per MCD: Relapse

Genetic testing

Genetic testing is recommended in patients with a family history of renal disease, those with FSGS resistant to treatment, those with syndromic features, and to inform risk of disease recurrence post transplant or in relatives being considered as live kidney donors. There is a set panel of genetic tests that can be performed; suitability for testing should be discussed with the local genetic lead Paul Phelan.