Chapter 1: General principles for the management of glomerular disease

The recommendations and practice points on General principles for the management of glomerular disease are summarised in chapter 1, pages S88 to S114 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

1.1 KIDNEY BIOPSY

Practice Point 1.1.1: The kidney biopsy is the "gold standard" for the diagnostic evaluation of glomerular diseases. However, under some circumstances, treatment may proceed without a kidney biopsy confirmation of diagnosis (Figure 2)
Practice Point 1.1.2: The evaluation of kidney tissue should meet standards of biopsy adequacy (Figure 3)
Practice Point 1.1.3: Repeat kidney biopsy should be performed if the information will potentially alter the therapeutic plan or contribute to the estimation of prognosis.

The kidney biopsy remains a key investigation in the diagnostic and prognostic evaluation of adults and children with suspected glomerular disease. It is not required for diagnosis in children aged less than 12 years old with steroid-sensitive nephrotic syndrome (SNSS) and children with post-streptococcal glomerulonephritis (GN). Should contraindications or patient objection preclude kidney biopsy, we agree that it is reasonable to use highly sensitive and specific serologic tests in the diagnostic and therapeutic work-up in certain clinical scenarios (Fig. 2).

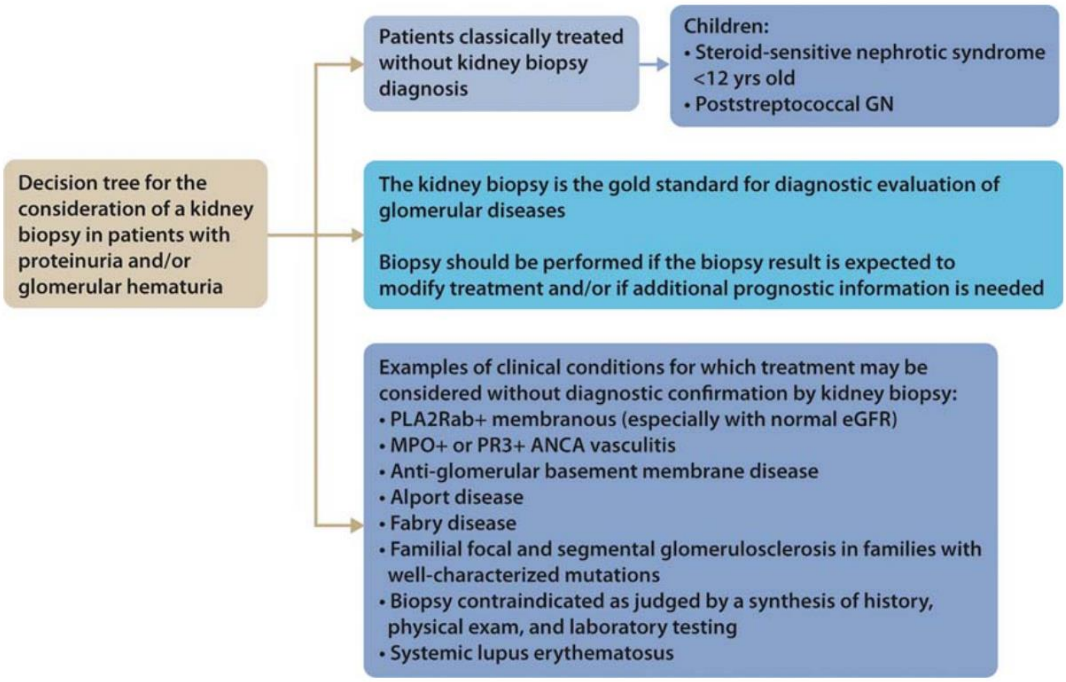

Figure 2. Considerations for a kidney biopsy in patients with proteinuria and/or glomerular haematuria.

1.2 ASSESSMENT OF KIDNEY FUNCTION

Proteinuria

Practice Point 1.2.1: Obtain 24-hour urine collection to determine total protein excretion in patients with glomerular disease for whom initiation or intensification of immunosuppression is necessary, or who have a change in clinical status.
Practice Point 1.2.2: For paediatrics, 24-hour urine collection is not ideal as it may not be accurate and is cumbersome to collect. Instead, monitor first morning protein–creatinine ratio (PCR).

Practice Point 1.2.3: Random “spot” urine collections for PCR are not ideal as there is variation over time in both protein and creatinine excretion.
Practice Point 1.2.4: First morning urine collections may underestimate 24-hour protein excretion in orthostatic proteinuria.
Practice Point 1.2.5: When feasible, a reasonable compromise is to collect an “intended” 24-hour urine sample and measure PCR in an aliquot of the collection.
Practice Point 1.2.6: There is no need to simultaneously and routinely quantify sodium excretion on each timed urinary collection, unless there is reason to suspect a failure to adhere to suggestions regarding dietary sodium restriction (Figure 5 and Practice Points 1.4.2 and 1.5.9).
Practice Point 1.2.7: Quantify proteinuria in glomerular disease, as it has disease-specific relevance for prognosis and treatment decision-making. Qualitative assessment of proteinuria may be useful in selected instances.
Practice Point 1.2.8: In children, quantify proteinuria, but goals of treatment should not be different between disease etiologies. A PCR of <200mg/g (<20 mg/mmol) or <8mg/m^2/hour in a 24-hour urine should be the goal for any child with glomerular disease. Acceptance of a baseline higher than this should come only with kidney biopsy evidence of kidney scarring.

NICE advises against the use of reagent strips for screening of proteinuria in adults, children and young people who are at risk of CKD. We support NICE and recommend using ACR for the initial detection of proteinuria as it is more sensitive for low levels of proteinuria and facilitates the calculation of the 4-variable Kidney Failure Risk Equation (1). Spot uPCR in adults, or first-morning uPCR in children, may be used as an alternative to uACR when the latter is ≥70 mg/mmol, bearing in mind that the result can vary with changes in posture and physical activity which may necessitate repeating for confirmation. Ultimately, 24-hour urine collection for protein quantification remains too cumbersome for routine use in clinical practice, and is mainly reserved for clinical trials.

Target uPCR levels that define clinical response and risk of disease progression in adults vary according to the type of GN. The target uPCR in children with any type of GN must be <20mg/mmol unless there is histological evidence of glomerular sclerosis (1.2.8).

Estimation of GFR

Practice Point 1.2.9: The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR) creatinine equation is preferred in adult patients with glomerular disease, and the modified Schwartz equation is preferred in children. The Full Age Spectrum (FAS) equation may be used in both adults and children (Figure 5).

It is now standard practice to estimate GFR in adults using the creatinine-based CKD-EPI formula. This equation has not been validated in patients with GN. It may overestimate the true GFR in nephrotic patients with hypoalbuminaemia, thus requiring cautionary interpretation. In paediatric cases, the modified Schwartz equation or the FAS formulae should be used. The use of cystatin-c equations to measure GFR are yet to be evaluated in children and adults in the UK, and are not recommended for routine use as yet (1).

1.3 EVALUATION OF HAEMATURIA

Practice Point 1.3.1: Routine evaluation of urine sediment for erythrocyte morphology and the presence of red cell casts and/or acanthocytes is indicated in all forms of glomerular disease.
Practice Point 1.3.2: Monitoring of hematuria (magnitude and persistence) may have prognostic value in many forms of glomerular disease. This is particularly applicable to immunoglobulin A nephropathy (IgAN) and vasculitis (IgAV; Chapter 2).

Dipstick analysis of a fresh voided urine sample is used to detect invisible haematuria in adults and children with suspected glomerular disease. A reading of 1+ or above is considered as a significant result. This is sensitive enough for the work-up of GN, making routine urine microscopy unnecessary to establish the diagnosis.

1.4 MANAGEMENT OF COMPLICATIONS OF GLOMERULAR DISEASE

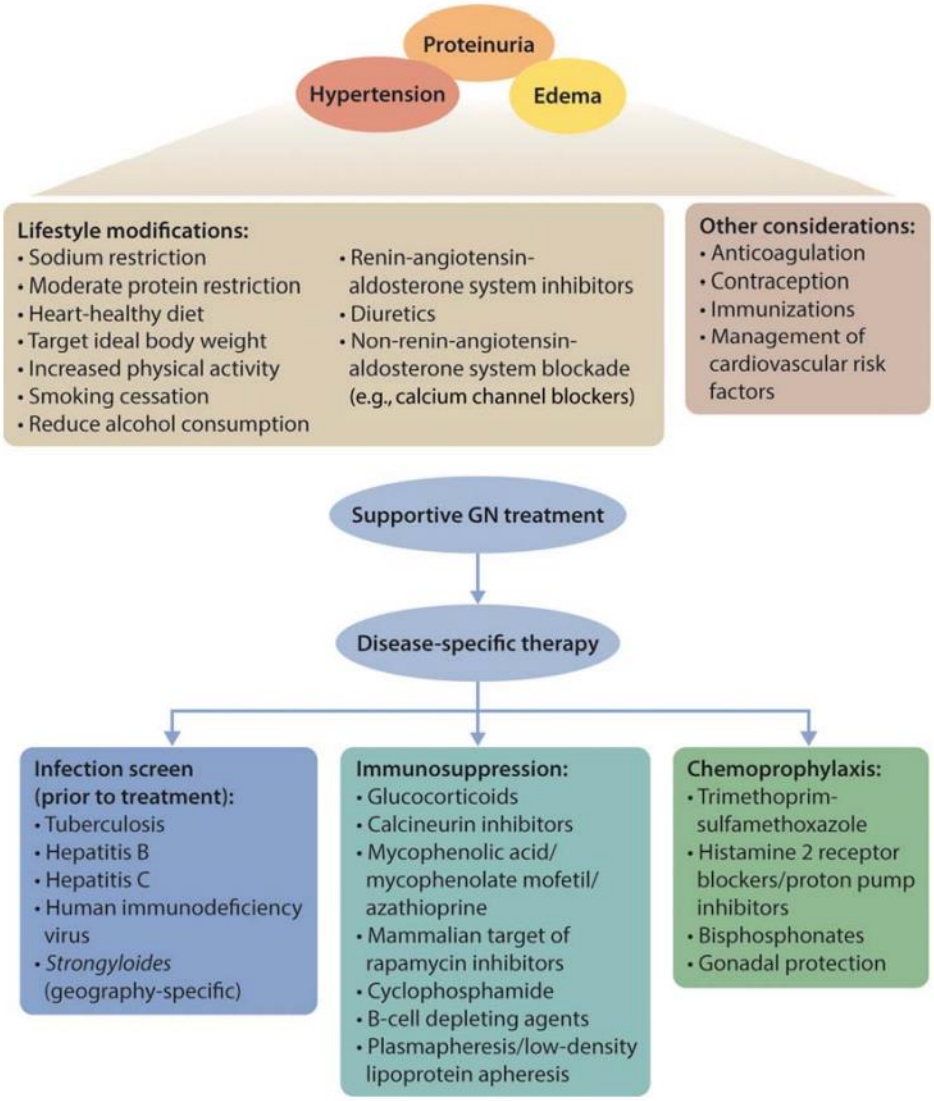

Figure 6. Summary of supportive management of glomerular disease.

Management of glomerular disease comprises a constellation of supportive cardiovascular risk factor modification and disease-specific therapy, comprising immunosuppression and prophylactic therapy. The following chapters discuss this in further detail.

Oedema management in Nephrotic syndrome

Practice Point 1.4.1: Use loop diuretics as first-line therapy for treatment of edema in the nephrotic syndrome
Practice Point 1.4.2: Restrict dietary sodium intake to <2.0g/d (<90 mmol/d)
Practice Point 1.4.3: Use loop diuretics with other mechanistically different diuretics as synergistic treatment of resistant edema in the nephrotic syndrome
Practice Point 1.4.4: Monitor for adverse effects of diuretics
Practice Point 1.4.5: Strategies for diuretic-resistant patients

Diuretic therapy and dietary sodium restriction to <2 g/day (which corresponds to <5 g/day of sodium chloride) are of paramount importance in NS-associated oedema. Treatment-resistant oedema may be addressed by adding synergistic diuretics or ultrafiltration/ haemodialysis in patients with oligo-anuric acute kidney injury (AKI).

1.5 MANAGEMENT OF HYPERTENSION AND PROTEINURIA REDUCTION IN GLOMERULAR DISEASE

Practice Point 1.5.1: Use an ACEi or ARB to maximally tolerated or allowed dose as first-line therapy in treating patients with both hypertension and proteinuria
Practice Point1.5.2: Target systolic blood pressure in most adult patients is <120 mmHg using standardised office BP measurement. Target 24h mean arterial pressure in children is ≤50th percentile for age, sex, and height by ambulatory blood pressure monitoring
Practice Point 1.5.3: Uptitrate an ACEi or ARB to maximally tolerated or allowed daily dose as first-line therapy in treating patients with GN and proteinuria alone
Practice Point 1.5.4: Proteinuria goal is variable depending on primary disease process; typically, <1g/d
Practice Point 1.5.5: Monitor labs frequently if on ACEi or ARB
Practice Point 1.5.6: Counsel patients to hold ACEi or ARB and diuretics when at risk for volume depletion
Practice Point 1.5.7: Use potassium-wasting diuretics and/or potassium-binding agents to reduce serum potassium to normal, in order to use RAS blocking medications for BP control and proteinuria reduction. Treat metabolic acidosis (serum bicarbonate <22mmol/L).
Practice Point 1.5.8: Employ lifestyle modifications in all GN patients as synergistic means for improving control of hypertension and proteinuria
Practice Point 1.5.9: Intensify dietary sodium restriction in those patients who fail to achieve proteinuria reductions, and who are on maximally tolerated medical therapy

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARB) remain the mainstay of treatment of hypertension and/or proteinuria associated with GN. They are known to offer cardiovascular protection and delay CKD progression. The use of such antiproteinuric agents should be in tandem with lifestyle modification (Fig. 6).

The KDIGO recommends a systolic BP of <120mmHg in most adults. This follows the results of the SPRINT trial which revealed a reduction in all-cause mortality in non-diabetic CKD patients with this target (2). This trial excluded patients with GN, proteinuria >1g/day and eGFR of <20 ml/min. We propose a shared-decision making approach to reach a target BP of <130/80mmHg for all patients with CKD/GN, irrespective of level of proteinuria, as long as it is tolerated. We direct the reader to the Renal Association Commentary on NICE Hypertension guideline (NG136) for further advice (3). The goal 24h mean arterial pressure in children should be ≤50th percentile for age, sex, and height.

We emphasise the need for regular monitoring of renal function and electrolytes when using ACEi/ARBs, and advise against combined therapy (4). A rise in serum creatinine of up to 30% and/ or a drop in eGFR by about 25% from baseline may be expected on initiation/ increase in dose. A rapid deterioration in renal function beyond this point, in the absence of other causes of AKI, may indicate underlying renovascular disease and may necessitate the reduction to a previously tolerated dose, or sometimes, withdrawal (1, 5).

Hyperkalaemia is also a common adverse effect of renin-angiotensin-aldosterone system inhibitors (RAASi). With the advent of novel potassium binders, this is now a rare indication for cessation of such therapy. NICE and UKKA recommend the use of patiromer or sodium zirconium cyclosilicate for adults with non-dialysis dependent CKD3b-5 who are unable to take an optimised dose of RAASi due to persistent hyperkalaemia (≥6.0 mmol/L). Patients should be counselled on sick day rules to avoid AKI/ hyperkalaemia during acute illness, particularly in the context of diuretic use or volume depletion. Further advice can be obtained from the UKKA Guideline for Treatment of Acute Hyperkalaemia in Adults (6).

The sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as novel agents in the prevention of CKD progression and reduction in proteinuria in diabetic nephropathy. Their efficacy in IgAN came to light after a subanalysis of the DAPA-CKD trial (7). While such results are extremely promising, the efficacy and safety of these agents in other forms of GN are still to be determined.

Presently, we support NICE in their recommendation on adding an SGLT2i to optimised standard care (ACEi/ARB at maximum tolerated dose) in adult patients if their uACR is ≥25 mg/mmol and eGFR is

>25ml/min, excluding those treated with immunosuppression in the preceding 3 months or anyone on >45 mg prednisolone daily (or equivalent) (8-9).

1.6 MANAGEMENT OF HYPERLIPIDAEMIA IN GLOMERULAR DISEASE

Practice Point 1.6.1: Treatment of hyperlipidaemia may be considered in patients with the nephrotic syndrome, particularly for patients with other cardiovascular risk factors, including hypertension and diabetes

Practice Point 1.6.2: Use lifestyle modifications in all patients with persistent hyperlipidaemia and glomerular disease:

- Heart-healthy diet (avoid red meat, consider a plant-based diet)
- Increased physical activity
- Weight reduction
- Smoking cessation

Practice Point 1.6.3: consider starting a statin drug as first-line therapy for persistent hyperlipidaemia in patients with glomerular disease:

- Assess ASCVD risk based on LDL-C, Apo B, triglyceride and (Lp(a) levels, age group, and ASCVD 'risk enhancers':
    - Chronic inflammatory conditions such as SLE/RA
    - History of preeclampsia
    - Early menopause
    - South Asian ancestry
    - CKD
    - HIV/AIDS (accuracy of ASCVD risk estimators have not been well validated for adults with chronic inflammatory disorders or HIV).
- Align statin dosage intensity to ASCVD risk
- Statins can be initiated in children aged >8 years with concerning family history, extremely elevated LDL-C or Lp(a), in context of informed shared decision-making and counselling with patient and family

Practice Point 1.6.4: Consider initiation of non-statin therapy in those individuals who cannot tolerate a statin, or who are high risk ASCVD risk and fail to achieve LDL-C or triglyceride goals despite maximally tolerated statin dose:

- Bile acid sequestrants
- Fibrates
- Nicotinic acid
- Ezetimibe
- PCSK9 inhibitor
- Lipid apheresis

The aetiology of hyperlipidaemia in the GN population is multifactorial, and is composed of genetic factors, diet, immunosuppressive medications and the presence of NS itself. We consider lifestyle modifications as primary therapy for all patients with GN, irrespective of age. There is a paucity of high-quality data on treatment in this group of patients, but it is sensible to refer to the guidelines that apply to the general population. In adults, NICE CG181 recommends starting atorvastatin at 20mg daily and increasing the dose if <40% reduction in non-HDL cholesterol is achieved (10). Caution is needed if higher doses are required when eGFR <30 ml/min or when statins are administered with calcineurin inhibitors (CNI) due to a potential risk of myalgia/myositis. More RCTs are required to further assess the safety and efficacy of statins, fibrates and ezetimibe for hyperlipidaemia in glomerular disease.

1.7 HYPERCOAGULABILITY AND THROMBOSIS

Practice Point 1.7.1: Full anticoagulation is indicated for patients with thromboembolic events occurring in the context of nephrotic syndrome. Prophylactic anticoagulation should be employed in patients with nephrotic syndrome when the risk of thromboembolism exceeds the estimated patient-specific risks of an anticoagulation-induced serious bleeding event (Figure 11).

Practice Point 1.7.2: Anticoagulant dosing considerations in patients with nephrotic syndrome (Figure 12 and Figure 13)

The NS is well known to be associated with a hypercoagulable state, predisposing patients to both venous thromboembolic events (VTE) and arterial thromboembolic events (ATE). The risk is highest in patients with membranous nephropathy (MN), nephrotic-range proteinuria and hypoalbuminaemia (serum albumin <25g/L or <20g/l when bromocresol purple (BCP) or immunoassays for serum albumin levels are used). Deep venous thrombosis, renal vein thrombosis and pulmonary embolism are more common than arterial thrombosis, and occur at a higher frequency in adults.

Figure 11 summarises the indications and contraindications of full-dose therapeutic and full-dose prophylactic anticoagulation. An online tool has been made available to enable the calculation of bleeding risk versus benefits of anticoagulation in patients with MN, based on a subjective acceptable benefit: risk ratio (https://www.med.unc.edu/gntools/bleedrisk.html).

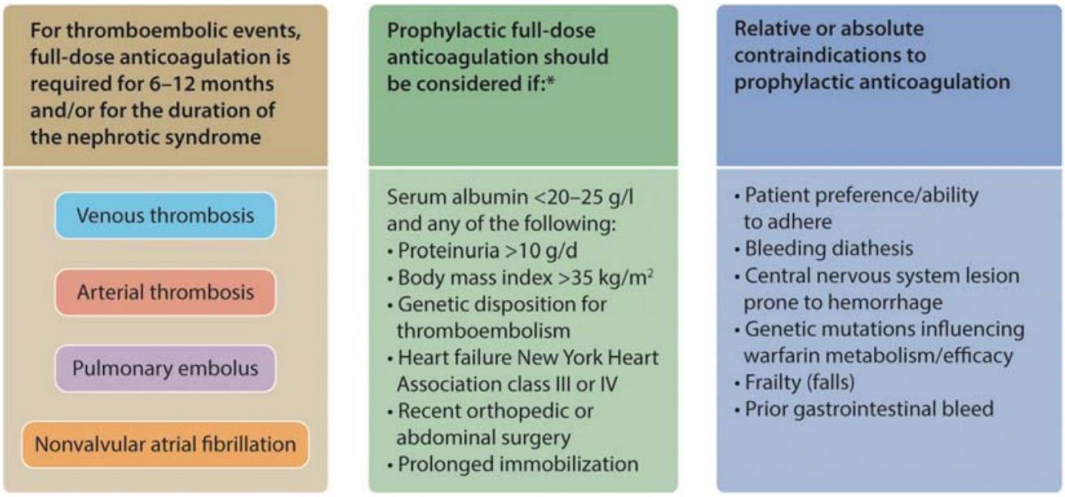

Figure 11. Anticoagulation in NS

Anticoagulation for the prevention and treatment of NS-associated VTE and ATE depends on serum albumin and patient-specific risk factors. The agents of choice for both adults and children are heparin and/or warfarin owing to the long-term experience available. Although DOACs are attractive over warfarin (no requirements for therapeutic drug monitoring and less drug interactions), they are still not approved in NS, in cases of significant renal impairment or in children.

Dabigatran is contraindicated in patients with severe renal impairment (CrCl <30 mL/min), while a lower dose is advised in moderate renal impairment (CrCl 30-50 ml/min). The use of rivaroxaban, apixaban or edoxaban is not recommended in ESKD (CrCl <15 ml/min), but dose reduction is necessary if CrCl 15-50 ml/min. Furthermore, their pharmacokinetics, efficacy and safety for use in nephrotic hypoalbuminaemic patients remains to be ascertained by upcoming studies. We advise the reader to visit www.medicines.org.uk and refer to product literature for further information.

Full anticoagulation with warfarin involves an initial bridging period with lower molecular weight heparin or intravenous heparin (depending on CrCl), until INR is 2 to 3. Frequent INR monitoring is advised due to drug interactions (eg. CNI) and fluctuations in serum albumin during NS treatment, bearing in mind that 99% of warfarin is bound to albumin. Prophylactic low dose aspirin (75mg daily) can be used in patients with a high estimated ATE risk and a serum albumin of 25-31g/L (20-30g/l when bromocresol purple (BCP) or immunoassays for serum albumin levels are used).

A proposed algorithm for patient management is shown in Figure 13. Duration of prophylaxis should be for as long as the NS persists.

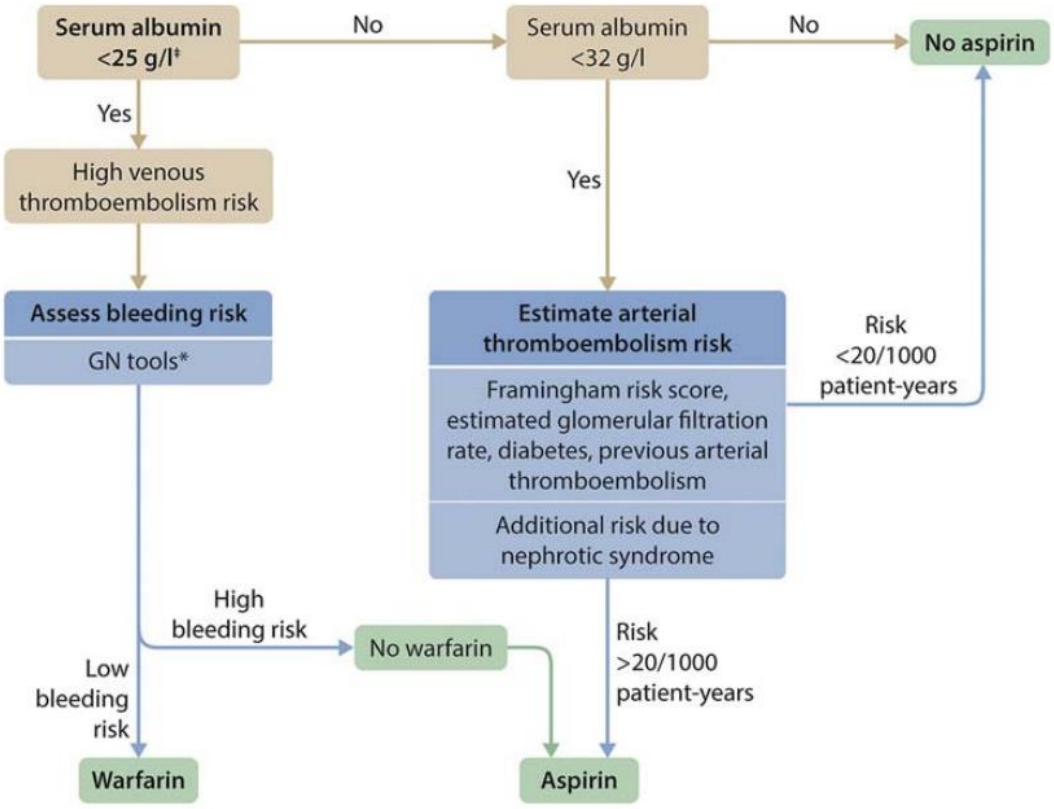

Figure 13. Prophylactic anticoagulation in adults with GN/ Nephrotic syndrome (Reproduced from *Kidney International*, volume 89, issue 5, Hofstra JM, Wetzels JFM.)

*<20g/l should be used when bromocresol purple (BCP) or immunoassays for serum albumin levels are used

**<30g/l should be used (rather than 32) when bromocresol purple (BCP) or immunoassays for serum albumin levels are used

1.8 RISKS OF INFECTION

Practice Point 1.8.1: Use pneumococcal vaccine in patients with glomerular disease and nephrotic syndrome, as well as patients with chronic kidney disease (CKD). Patients and household contacts should receive the influenza vaccine. Patients should receive herpes zoster vaccination (Shingrix).
Practice Point 1.8.2: Screen for tuberculosis (TB), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis in clinically appropriate patients (Chapter 7).
Practice Point 1.8.3: Strongyloides superinfection should be considered in patients receiving immunosuppression who once resided in endemic tropical environments and who have eosinophilia and elevated serum immunoglobulin E (IgE) levels.
Practice Point 1.8.4: Prophylactic trimethoprim– sulfamethoxazole (TMP-SMX) should be considered in patients receiving high-dose prednisone or other immunosuppressive agents (rituximab, cyclophosphamide).

It is widely known that patients with GN are at a heightened risk of infections – opportunistic or not. Screening for latent infections, depending on geographic exposure and lifestyle/occupational risk factors, is recommended before the initiation of immunosuppressive therapy. This should include HIV 1 & 2 antigen and antibody screen, Hepatitis B surface antigen and core total antibody screen, and Hepatitis C antibody screen in the first instance. The detection of infection will require treatment, either prior to, or concurrently with immunosuppressive therapy, depending on the clinical urgency and

severity of GN/NS. While QuantiFERON may be used to screen for TB in high-risk scenarios, one may opt for empirical prophylaxis with isoniazid in patients who come from high incidence countries.

Patients with GN/NS and their household contacts should receive pneumococcal vaccination, annual influenza vaccination and the recently recommended SARS-CoV-2 vaccination series if aged 5 and over. All live attenuated vaccines are contraindicated while on immunosuppressive treatment, or until prednisolone dose is <20mg/day.

Should treatment with complement inhibitors be required, protection against *Neisseria meningitidis* must be sought through the administration of both meningococcal conjugate vaccine (MenACWY) and serogroup B vaccine (Bexsero). Measurement of antibody titres is done 4-6 weeks post-vaccination, and annually thereafter, with an aim to provide a booster if titres are low. Patients receiving ravulizumab/ eculizumab should also receive prophylactic antibiotics (eg. penicillin V, or erythromycin if penicillin allergic) as soon as treatment is started and this is to be continued for 8 weeks following cessation.

Pneumocystis jirovecii pneumonia (PJP) prophylaxis with trimethoprim–sulfamethoxazole should be considered in patients receiving prednisolone >20mg/day for at least 4 weeks, triple immunosuppression (anti-metabolite + CNI + prednisolone), rituximab or cyclophosphamide. Dapsone, nebulised pentamidine, azithromycin or atovaquone may be used in sulfa-sensitive patients.

1.9 OUTCOME MEASURES

Practice Point 1.9.1: Goals for proteinuria reduction with treatment vary among the various specific causes of glomerular disease.
Practice Point 1.9.2: A ≥40% decline in eGFR from baseline over a 2–3-year period has been suggested as a surrogate outcome measure for kidney failure.

The composite outcome measures, such as decline in eGFR and proteinuria reduction, vary in different clinical trials, while adverse events and patient concerns are often underreported. The Standardised Outcomes in Nephrology – Glomerular Disease aims to construct a core outcome set common to all glomerular disease that should be reported in all trials (11).

1.10 IMPACT OF AGE, SEX, ETHNICITY, AND GENETIC BACKGROUND

Randomised controlled trials of GN treatment are limited by the small number of patients and lack of representation of ethnic minorities. Additional research is necessary to analyse the impact of ethnicity, age and gender on treatment and outcomes of GN.

1.11 GENOMICS, TRANSCRIPTOMICS, PROTEOMICS, METABOLOMICS

The evolving field of omics technologies has shown to be a highly effective tool in the search for biomarkers involved in several types of GN. Continued research to detect omics patterns which may act as promising therapeutic or prognostic targets is ongoing.

1.12 USE OF GLUCOCORTICOIDS AND IMMUNOSUPPRESSIVE THERAPY

Certain glomerular diseases require the administration of immunosuppressive agents which inevitably lead to adverse effects. The risk:benefit analysis needs to be discussed with the patient and/ or caregiver, taking into account their perspective and wishes. Ultimately, our aim is to prevent or delay ESKD, reduce mortality and improve patient quality of life in the safest way possible.

Figure 14 summarises the measures which can minimise immunosuppression-related adverse effects. The specific adverse effects of individual regimens and the necessary precautionary agents are explained in further detail in the upcoming chapters.

Assessment	Measures
Peptic ulcer disease	H_2 blockers Proton pump inhibitors
Bone health and protection	Individual fracture risk assessment/bone mineral density Calcium and vitamin D supplementation Bisphosphonates Growth hormone (pediatric population)
Infection risk	Assess medical history of herpes zoster infection Screening for hepatitis B virus, hepatitis C virus, human immunodeficiency virus Hepatitis B virus vaccination Zoster vaccination Screening for tuberculosis Screening for strongyloides Pneumocystis prophylaxis Influenza and pneumococcal vaccination* Meningococcal vaccination (if C5 antagonists are used) Monitor gammaglobulin levels and white blood cells levels (rituximab, cyclophosphamide)
Ultraviolet light protection	Limit ultraviolet exposure Broad-spectrum sunscreen
Fertility protection	Gonadotropin receptor hormone agonists (i.e., leuprolide) in cyclophosphamide Sperm/oocyte cryopreservation in cyclophosphamide
Effective contraception	Individual evaluation (preference, thrombosis risk, age)
Cancer screening	Evaluate individual risk factors for malignancy Age-specific malignancy screening Annual dermatology exam Bladder cancer (cyclophosphamide cumulative dose >36 g)

Figure 14. Screening/ prophylaxis for all patients with glomerular disease on immunosuppression.

1.13 PHARMACOLOGIC ASPECTS OF IMMUNOSUPPRESSION

Practice Point 1.13.1: Choose a glomerulonephritis treatment regimen that averts the immediate morbidity of the primary disease process
Practice Point 1.13.2: Choose a glomerulonephritis treatment regimen that prevents disease progression
Practice Point 1.13.3: Choose a glomerulonephritis treatment regimen that minimises harmful side effects from immunosuppression

The choice of the immunosuppressive agent is influenced by the severity of the presenting symptoms, the type of GN, the level of eGFR and patient-specific factors (e.g. age, gender, ethnicity and wishes). The risks and benefits of each therapeutic option and the likelihood of complete/partial remission pertaining to the GN in question ought to be explained, bearing in mind that numerous courses of immunosuppression may be required to prevent/delay CKD. Commissioning arrangements for certain medications are in place.

1.14 DIETARY MANAGEMENT IN GLOMERULAR DISEASE

Practice Point 1.14.1: Restrict dietary sodium to reduce oedema, control blood pressure, and control proteinuria
Practice Point 1.14.2: Restrict dietary protein based on degree of proteinuria
Practice Point 1.14.3: Restrict dietary protein based on kidney function

Practice Point 1.14.4: Restrict caloric intake to achieve normal body mass index and limit central adiposity in order to reduce chronic kidney disease progression, development of kidney failure, cardiovascular events, and mortality
Practice Point 1.14.5: Restrict dietary fats in patients with elevated serum cholesterol to prevent cardiovascular complications

Daily sodium intake must be kept at <2g to control oedema, proteinuria and hypertension. While maintaining a total protein intake between 0.8-1.0g/kg/day may be appropriate in some adults with NS, protein restriction is not recommended in children, and dietary changes should be guided by paediatric dieticians, as this poses a risk of negative nitrogen balance, weight loss and malnutrition. A daily caloric intake of 30-35 kcal/kg consisting of <30% fat is also appropriate for adults depending on BMI and central adiposity.

1.15 PREGNANCY AND REPRODUCTIVE HEALTH IN WOMEN WITH GLOMERULAR DISEASE

Practice Point 1.15.1: Care for the pregnant patient with glomerular disease needs coordination between nephrology and obstetrics, and ideally, such planning should be considered before pregnancy.

A multidisciplinary team approach is essential to care for women with GN who are pregnant, or planning a pregnancy. We recommend referring women to the pre-pregnancy assessment clinic, where they are counselled on the increased risk of progressive deterioration in renal function, pre-eclampsia, intrauterine growth restriction and preterm delivery, the risk of which varies according to type of GN and degree of renal impairment.

Offering contraception to women taking teratogenic drugs (E.g. cyclophosphamide, mycophenolate mofetil) is recommended. Progestogen-only contraceptive agents (pill, implant, and injectable, coil) are all safe effective options, while oestrogen-containing contraceptives are contraindicated due to the risk of worsening hypertension, ATE, VTE and cervical cancer.

The benefits of continued treatment with ACEi/ARB in the presence of significant proteinuria versus the potential risk of teratogenicity should be based on an individualised risk assessment and discussed with the patient. If continuing this treatment is considered to be absolutely necessary, it must be stopped once a positive pregnancy test is achieved. The use of SGLT2i follows similar principles as they are contraindicated in the second and third trimesters, and in breastfeeding.

Women contemplating pregnancy should be switched to safe immunosuppression regimens (consisting of CNIs, azathioprine or prednisolone), allowing sufficient time for washout. Blood pressure control to <140/90mmHg and GN remission for at least 6 months ahead of conception is advised. Low dose aspirin at 75-150 mg daily is recommended after 12 weeks' gestation to reduce pre-eclampsia risk. We refer the reader to the Renal Association guideline on pregnancy and renal disease for further advice on this topic (12).

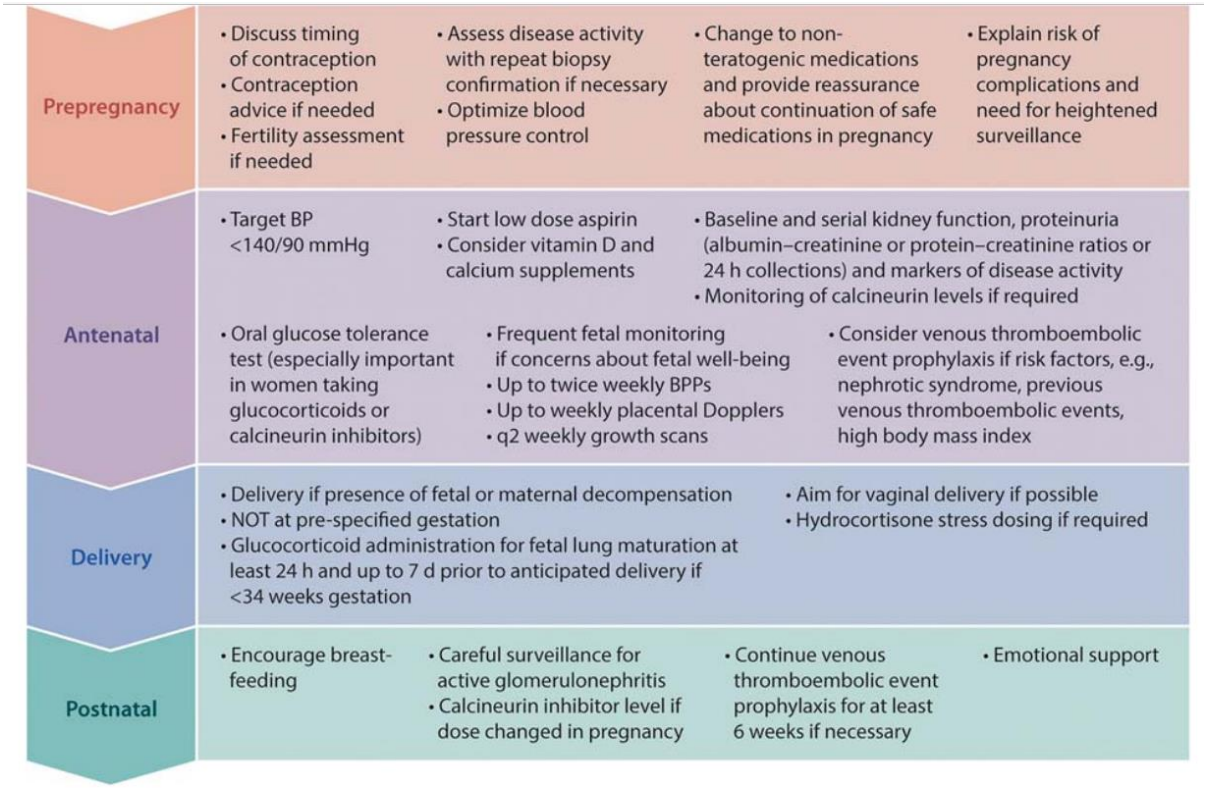

Figure 17. Coordinated care of pregnant patients with glomerular disease.

1.16 TREATMENT COSTS AND RELATED ISSUES

Practice Point 1.16.1: Patients with glomerular disease should be offered participation in a disease registry and clinical trials, whenever available.

When the available standard therapies have failed to achieve remission, we advise caring nephrologists to offer patients the opportunity to enrol into a clinical trial whenever available. We recommend the recruitment of patients with rare GN into the National Registry of Rare Kidney Diseases (RaDaR) in order to facilitate the understanding of such diseases and encourage the development of effective therapies. Further information can be found at https://ukkidney.org/rare-renal/radar.

1.17 GOALS OF GLOMERULAR DISEASE TREATMENT

The management of GN consists of general principles and disease-specific therapy which aim to achieve a prolonged complete or partial remission without incurring significant adverse events. Several factors need to be taken into consideration, including the renal prognosis and extrarenal manifestations of the disease, as well as the likelihood of treatment efficacy, while keeping the patient's safety and quality of life at the forefront.

1.18 POST-TRANSPLANTATION GN

Transplantation is the ideal mode of renal replacement therapy for patients with ESKD secondary to glomerular disease. Nonetheless, recurrent or de novo GN remain leading causes of allograft failure. The risk of recurrence depends on several factors, including type of GN, time from remission to transplantation, and history of previous graft loss due to GN recurrence. The upcoming chapters will describe the preventative measures which are available in certain types of glomerular disease in preparation for transplantation.

Chapter 2: Immunoglobulin A nephropathy (IgAN) / Immunoglobulin A vasculitis (IgAV)

The recommendations and practice points on Immunoglobulin A nephropathy (IgAN) / Immunoglobulin A vasculitis (IgAV) are summarised in chapter 2, pages S115 to S127 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

IMMUNOGLOBULIN A NEPHROPATHY

2.1 DIAGNOSIS

Practice Point 2.1.1: Considerations for the diagnosis of immunoglobulin A nephropathy (IgAN):

- IgAN can only be diagnosed with a kidney biopsy.
- Determine the MEST-C score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) according to the revised Oxford Classification.
- There are no validated *diagnostic* serum or urine biomarkers for IgAN.
- Assess all patients with IgAN for secondary causes.

We agree with all the above points. Staining for glomerular CD68+ve cells of the monocyte-macrophage lineage is being tested and used by many pathology centres in the UK as a more robust way of distinguishing the E score (13).

2.2 PROGNOSIS

Practice Point 2.2.1: Considerations for the prognostication of primary IgAN:

- Clinical and histologic data at the time of biopsy can be used to risk stratify patients.
- The International IgAN Prediction Tool is a valuable resource to quantify risk of progression and inform shared decision-making with patients.
- The International IgAN Prediction Tool incorporates clinical information at the time of biopsy and cannot be used to determine the likely impact of any particular treatment regimen.
- There are no validated *prognostic* serum or urine biomarkers for IgAN other than eGFR and proteinuria.

The prediction tool is available as an online calculator or app, and can be used at the time of the renal biopsy to accurately predict the risk of 50% decline in eGFR or ESRD over the next 5-7 years, to inform shared decision-making (14). The prediction tool has also been updated so it can be used for risk stratification one or two years post-biopsy (15).

2.3 TREATMENT

Practice Point 2.3.1: Considerations for treatment of all patients with IgAN who do not have a variant form of primary IgAN:

- The primary focus of management should be optimized supportive care.
- Assess cardiovascular risk and commence appropriate interventions as necessary.
- Give lifestyle advice, including information on dietary sodium restriction, smoking cessation, weight control, and exercise, as appropriate.
- Other than dietary sodium restriction, no specific dietary intervention has been shown to alter outcomes in IgAN.
- Variant forms of IgAN: IgA deposition with minimal change disease (MCD), IgAN with acute kidney injury (AKI), and IgAN with rapidly progressive glomerulonephritis (RPGN) may require specific immediate treatment.

We agree with all these points. The STOP-IgAN trial demonstrated the effectiveness of comprehensive supportive care, that emphasised addressing cardiovascular risk factors, and titration of an ACEi or ARB to the maximally tolerated dose in patients with proteinuria (see below) (16).

Recommendation 2.3.1: We recommend that all patients have their blood pressure managed, as described in Chapter 1. If the patient has proteinuria >0.5 g/d, we recommend that initial therapy be with either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) (1B).

Recommendation 2.3.2: We recommend that all patients with proteinuria >0.5 g/d, irrespective of whether they have hypertension, be treated with either an ACEi or ARB (1B).

This recommendation differs from the previous KDIGO guideline, with the lowering of proteinuria threshold for treatment to 0.5g/d, as it is recognised that the risk of progressive kidney disease increases above this threshold. Combination of both ACEi and ARB is not recommended. A post-hoc analysis of the STOP-IgAN study showed no benefit from dual blockade (17), and previous studies including ONTARGET have demonstrated potential for harm, with an increased risks of hyperkalaemia and ESKD (4).

Practice Point 2.3.1.1: Considerations for treatment of patients with IgAN who are at high risk of progressive CKD despite maximal supportive care.

- High risk of progression in IgAN is currently defined as proteinuria >0.75–1 g/d despite ≥ 90 days of optimized supportive care.
- Immunosuppressive drugs should be considered only in patients with IgAN who remain at high risk of progressive CKD despite maximal supportive care (The patients enrolled in the only large randomized controlled trial [RCT] suggesting benefit of immunosuppression had an average of 2.4 g/d of proteinuria).
- In view of the current uncertainty over the safety and efficacy of existing immunosuppressive treatment choices, all patients who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to take part in a clinical trial.
- In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient recognizing that adverse treatment effects are more likely in patients with an eGFR <50 ml/min per 1.73 m^2.
- There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining whether immunosuppression should be commenced in IgAN.
- There is insufficient evidence to base treatment decisions on the presence and number of crescents in the kidney biopsy.
- The International IgAN Prediction Tool cannot be used to determine the likely impact of any particular treatment regimen.
- Dynamic assessment of patient risk over time should be performed, as decisions regarding immunosuppression may change.

Practice Point 2.3.1.2: Proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN, and reduction to under 1 g/d is a reasonable treatment target.

- Where appropriate, treatment with glucocorticoid (prednisone equivalent ≥0.5 mg/kg/d) should incorporate prophylaxis against Pneumocystis pneumonia along with gastroprotection and bone protection, according to local guidelines.

Recommendation 2.3.1.1: We suggest that patients who remain at high risk of progressive CKD despite maximal supportive care be considered for a 6-month course of glucocorticoid therapy. The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR <50 ml/min per 1.73 m^2 (2B).

Practice Point 2.3.1.3: Use of glucocorticoids in IgAN:

- Clinical benefit of glucocorticoids in IgAN is not established and should be given with extreme caution or avoided entirely in situations listed in Figure 23:
- There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining when any glucocorticoid therapy should be commenced.
- There are no data to support efficacy or reduced toxicity of alternate-day glucocorticoid regimens, or dose-reduced protocols.

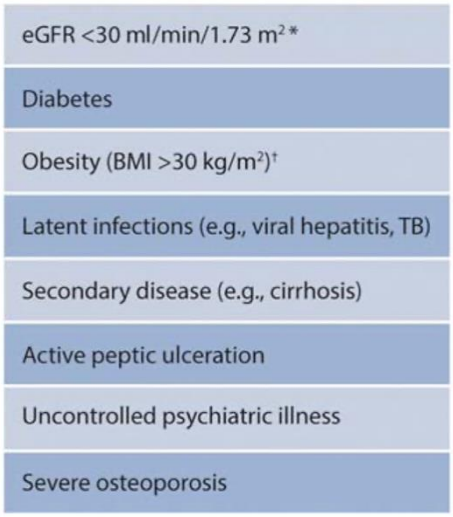

Figure 23. Situations when glucocorticoids should be avoided, or administered with great caution

Use of glucocorticoids in IgAN is a controversial area (for example, see (18)). The recommendation that glucocorticoids are considered for high-risk patients who have persistent proteinuria despite maximal supportive care, is accompanied by the lowest evidence grade in the guideline of 2B. A large randomised controlled trial (STOP-IgAN) conducted in Germany in a primarily white European cohort, found no benefit with immunosuppression (glucocorticoids alone, or in combination with cyclophosphamide then azathioprine) in patients with high-risk IgAN (16).

The TESTING study, conducted mainly in Asia, was terminated early due to an excess of serious adverse events in those randomised to treatment with oral methylprednisolone, including deaths due to sepsis (19). There were however signs of potential improvement in renal outcomes in those treated with methylprednisolone before the study was terminated. Patients in the TESTING study had higher levels of proteinuria and more rapid rates of disease progression compared to the STOP-IgAN population, and this has been postulated to be due to the different ethnicities being studied.

Since publication of the KDIGO guidelines, this study was redesigned to examine the effects of half the previous dose of methylprednisolone with the addition of *Pneumocystis jirovecii* prophylaxis, and this has been recently published (20). Although results demonstrated that those treated with methylprednisolone had a reduction in those reaching the combined renal end point (40% decline in eGFR, ESKD or death due to kidney disease), there were higher rates of adverse events in the methylprednisolone arm and a suggestion that disease progression occurs after steroid treatment is withdrawn.

In the UK, clinical practice is mixed on this issue. We suggest that corticosteroids should not be used in the majority of patients with IgAN, but their use could be considered for patients at high-risk of progression, i.e. with high levels of proteinuria at above 1g/d despite maximised supportive care, after a full discussion of their risks and potential benefits.

Practice Point 2.3.1.4: Management of patients with IgAN who remain at high risk for progression after maximal supportive care (Figure 24)

Practice Point 2.3.1.6: Tonsillectomy in IgAN:

- Tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients.
- Tonsillectomy is suggested in some national guidelines for the treatment of recurrent tonsillitis in patients with IgAN.
- Multiple studies from Japan have reported improved kidney survival and partial or complete remission of hematuria and proteinuria following tonsillectomy alone or with pulsed glucocorticoids (Figure 26)

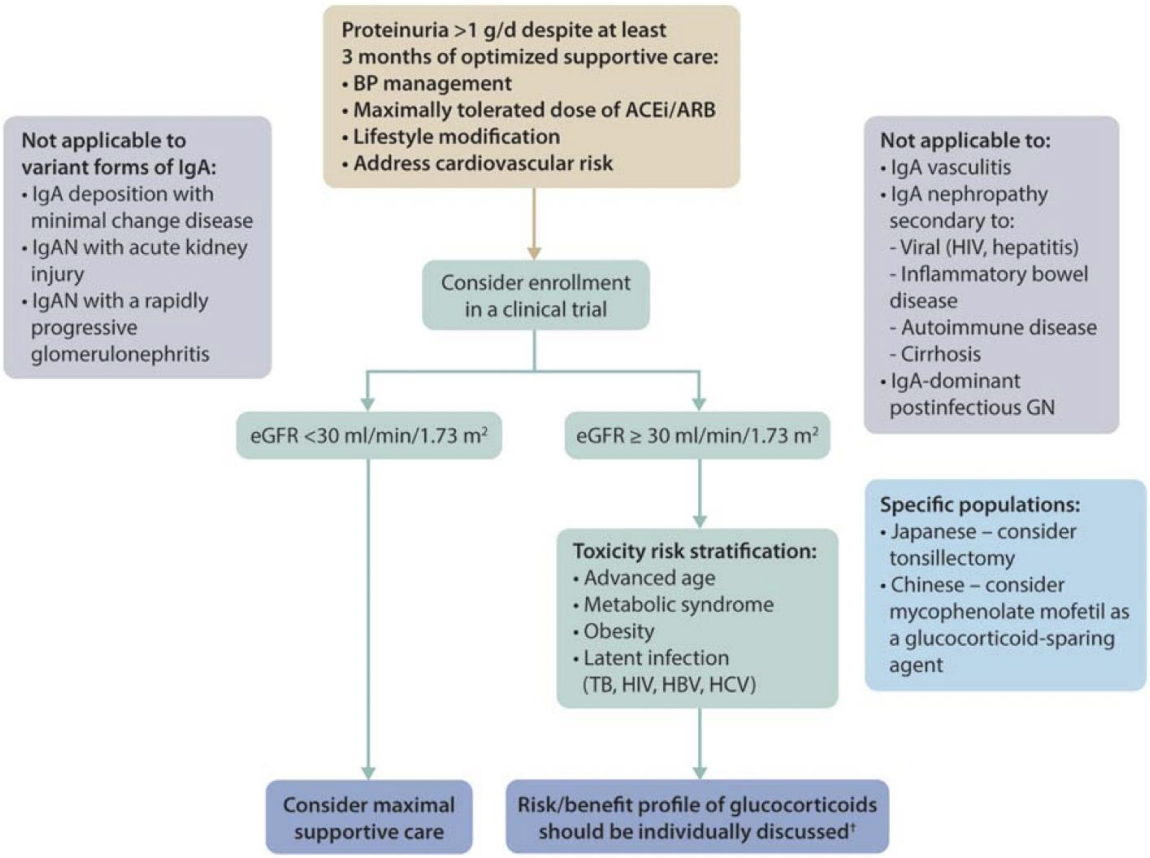

Figure 24. Management of patients with IgAN who remain at high risk for progression after maximal supportive care

There is no consistent evidence to support the use of other forms of immunosuppression (e.g. azathioprine, mycophenolate mofetil (MMF), cyclophosphamide, CNI, rituximab) in IgAN in most populations. Tonsillectomy is not recommended as a treatment for IgAN in the UK, as there is no evidence for benefit outside of small cohort studies within Japan.

2.4 SPECIAL SITUATIONS

Practice Point 2.4.1: IgAN with nephrotic syndrome:

- Rarely, patients with IgAN present with nephrotic syndrome (including oedema and both hypoalbuminemia and nephrotic-range proteinuria >3.5 g/d).
- In these cases, mesangial IgA deposition can be associated with light and electron microscopy features otherwise consistent with a podocytopathy resembling MCD.
- It is unclear whether this is a specific podocytopathic variant of IgAN or the existence of MCD in a patient with IgAN.
- Patients with a kidney biopsy demonstrating mesangial IgA deposition and light and electron microscopy features otherwise consistent with MCD should be treated in accordance with the guidelines for MCD (Chapter 5).
- Patients with nephrotic syndrome whose kidney biopsy has coexistent features of a mesangioproliferative glomerulonephritis (MPGN) should be managed in the same way as those patients at high risk of progressive CKD despite maximal supportive care.
- Nephrotic-range proteinuria without nephrotic syndrome may also be seen in IgAN, and this commonly reflects coexistent secondary focal segmental glomerulosclerosis (FSGS) (e.g., obesity, uncontrolled hypertension) or development of extensive glomerulosclerosis and tubulointerstitial fibrosis.

Practice Point 2.4.2: IgAN with AKI:

- AKI can occur in patients with IgAN in the context of severe visible hematuria, commonly in association with an upper respiratory tract infection. A repeat kidney biopsy should be considered in patients who fail to show improvement in kidney function within 2 weeks following cessation of the hematuria. Immediate management of AKI with visible hematuria should focus on supportive care for AKI.
- IgAN may also present with AKI either de novo or during its natural history due to an RPGN with extensive crescent formation, commonly in the absence of visible hematuria. In the absence of visible hematuria and when other causes of an RPGN (e.g., antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis [AAV], anti-glomerular basement membrane [GBM] disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded, a kidney biopsy should be performed as soon as possible.

Practice Point 2.4.3: IgAN with RPGN:

- Rapidly progressive IgAN is defined as a ≥ 50% decline in eGFR over ≤ 3months, where other causes of an RPGN (e.g., AAV, anti-GBM disease) and reversible causes (e.g., drug toxicity, common pre- and post-kidney causes) have been excluded.
- A kidney biopsy is essential in these cases and will commonly demonstrate mesangial and endocapillary hypercellularity, and a high proportion of glomeruli affected by crescents with areas of focal necrosis.
- The presence of crescents in a kidney biopsy in the absence of a concomitant change in serum creatinine (SCr) does not constitute rapidly progressive IgAN; however, these patients require close follow-up to ensure prompt detection of any GFR decline. If this occurs, a second kidney biopsy may be considered.
- Patients with rapidly progressive IgAN should be offered treatment with cyclophosphamide and glucocorticoids in accordance with the guidelines for AAV (Chapter 9).
- Prophylactic measures that should accompany immunosuppression are discussed in Chapter 1.
- There is insufficient evidence to support the use of rituximab for the treatment of rapidly progressive IgAN.

We agree with these points. Cyclophosphamide and glucocorticoids may be considered for rapidly progressive IgAN according to the definition above, in a treatment regimen analogous to AAV, although treatment outcomes are often poor, and the evidence for this approach is based on limited case series only.

Practice Point 2.4.4: IgAN and pregnancy planning:

- IgAN is a disease predominantly of young adults, and all women of childbearing potential should be offered preconception counselling when appropriate.
- Preconception counselling should include a discussion on cessation of renin–angiotensin system (RAS) blockade.
- Blood pressure control should be optimized with alternative antihypertensive medications prior to conception.
- In those women at high risk of progressive CKD (Recommendation 2.3.1.1) despite maximal supportive care, a trial of immunosuppression to optimize immunologic activity and reduce proteinuria prior to conception may be preferable to emergent initiation of immunosuppression during pregnancy.

It should be noted that maternal and foetal outcomes do not appear to be different or any worse in those with IgAN, compared to other forms of CKD (21). The point about a trial of immunosuppression to optimise immunologic activity prior to conception is controversial (see earlier).

Future directions

We agree that patients with IgAN who are at high risk of progression CKD should be offered the opportunity to take part in a clinical trial. There are several ongoing Phase 2 and Phase 3 clinical trials in IgAN, that are exploring novel disease-specific therapies in IgAN. A number of treatments for IgAN

are now in the late stages of clinical development, and one treatment (Nefecon / targeted release budesonide) has been granted conditional approval by the US FDA, EMA and UK MHRA for the treatment of high risk IgAN. A second treatment (Sparsentan) was recently granted accelerated approval by the US FDA.

Since the KDIGO guidelines were published, a pre-specified post-hoc analysis of the DAPA-CKD trial reported benefit from the use of SGLT2i in IgAN, and in the UK, the use of SGLT2i in IgAN has become more commonplace (7). The interpretation and generalisability of these results have been debated, with arguments that this cohort of IgAN patients within the DAPA-CKD trial had fairly advanced CKD (mean eGFR 43.8ml/min), some had co-existing diabetes mellitus, that RAS blockade was not optimised by a specific run-in period, and that the number of patients receiving placebo who reached the primary endpoint (composite of decline in eGFR of at least 50%, ESKD, or death from renal or cardiovascular cause) was higher than what might be expected (22). Further analysis of data from the EMPA-Kidney trial, which included a large number of patients with IgAN, may help to clarify these issues (23).

IMMUNOGLOBULIN A VASCULITIS

2.5 DIAGNOSIS

Practice Point 2.5.1: Considerations for the diagnosis of immunoglobulin A vasculitis (IgAV):

- Unlike children, there are no internationally agreed upon criteria for the diagnosis of IgAV in adults, although a clinical diagnosis of IgAV is often made based on the criteria described for children.
- In adults with a vasculitic rash typical of IgAV, a kidney biopsy should be performed in the setting of features consistent with a persistent and/or significant nephritis, RPGN, proteinuria >1g/d, and/or impaired kidney function.
- Assess all adult patients with IgAV for secondary causes.
- Assess all adult patients with IgAV for malignancy, with age- and sex-appropriate screening tests.

It should be noted that inflammatory renal lesions are more common in IgAV compared to IgAN, emphasising the importance of performing a renal biopsy in the above settings.

2.6 PROGNOSIS

Practice Point 2.6.1: Considerations for the prognostication of IgAV:

- Retrospective data from a limited number of small registries have identified uncontrolled hypertension and the amount of proteinuria at presentation, and hypertension and mean proteinuria during follow-up, as predictors of a poor kidney outcome in adults with IgAV.
- The Oxford Classification has not been validated for IgAV.
- The International IgAN Prediction Tool is not designed for prognostication in IgAV.

2.7 TREATMENT

2.7.1 Prevention of nephritis in IgAV

Recommendation 2.7.1.1: We recommend not using glucocorticoids to prevent nephritis in patients with isolated extrarenal IgAV (1B).

Practice Point 2.7.1.1: Considerations for the treatment of all patients with IgAV-associated nephritis (IgAVN) who do not have an RPGN:

- Assess cardiovascular risk and commence appropriate interventions as necessary.
- Give lifestyle advice, including information on smoking cessation, weight control, and exercise, as appropriate.
- No specific dietary intervention has been shown to alter outcomes in IgAVN.

- Treat to nationally agreed-upon blood pressure targets. KDIGO suggests treating to an SBP target of <120 mm Hg measured using standardized office blood pressure measurement (Figure 8).
- Treat with maximally tolerated dose of ACEi or ARB if proteinuria >0.5 g/d.
- Offer participation in a clinical trial if one is available.

These practice points align to those for IgAN.

2.7.2 Patients with IgAVN who are at high risk of progressive CKD despite maximal supportive care
Practice Point 2.7.2.1: Considerations for the treatment of patients with IgAVN who are at high risk of progressive CKD despite maximal supportive care:

- There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining whether immunosuppression should be commenced in patients with IgAVN.
- The presence of crescents in the kidney biopsy is not in itself an automatic indication for commencement of immunosuppression.
- In all patients in whom immunosuppression is being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient with a recognition that adverse treatment effects are more likely in patients with an eGFR <50 ml/min per 1.73 m2.
- In those patients who wish to try immunosuppressive therapy, treatment with glucocorticoids is as described above for IgAN.

In the UK, it is more commonplace to use glucocorticoids or other forms of immunosuppression for IgAVN compared to IgAN, but clinical practice regarding this is highly variable, with little clinical evidence to help to guide choice of therapy.

2.8 SPECIAL SITUATIONS

Practice Point 2.8.1: IgAV with RPGN:

- The potential risks and benefits of immunosuppression should be evaluated at the individual patient level and discussed with the patient.
- Patients agreeing to treatment should be treated in accordance with the guidelines for AAV (Chapter 9).
- IgAV with RPGN as well as other IgAVN may be associated with significant extrarenal involvement (pulmonary, gastrointestinal, and skin), which may dictate alternative immunosuppressive strategies.
- There are insufficient data to determine the efficacy of plasma exchange in IgAVN with RPGN. However, uncontrolled case series describe the potential role for the addition of plasma exchange to glucocorticoid therapy to accelerate recovery in patients with life- or organ-threatening extrarenal complications of IgAV. Clinicians are referred to the guidelines of the American Society for Apheresis regarding recommendations regarding plasma exchange for IgAV.

There is little evidence to help guide immunosuppression choice or the use of plasma exchange in IgAVN with RPGN. Some clinicians would use cyclophosphamide, rituximab or MMF in this setting, in combination with corticosteroids. We suggest that such cases, with organ or life-threatening disease, are discussed in an MDT setting and/or with an expert centre.

Chapter 3: Membranous nephropathy

The recommendations and practice points on Membranous Nephropathy are summarised in chapter 3, pages S128 to S139 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

3.1 DIAGNOSIS

Practice Point 3.1.1: A kidney biopsy is not required to confirm the diagnosis of membranous nephropathy (MN) in patients with nephrotic syndrome and a positive anti-PLA2R antibody test.

Practice varies amongst UK centres on this point. The KDIGO guideline details that a biopsy is not required in the presence of a positive anti-PLA2R antibody test and nephrotic syndrome, if the patient has normal kidney function and if immunosuppression is not being considered. Some authors suggest that a kidney biopsy may be required if considering immunosuppression i.e. with rituximab or cyclophosphamide to confirm the diagnosis, or if other conditions are present such as diabetes mellitus that could also be contributing to the clinical picture.

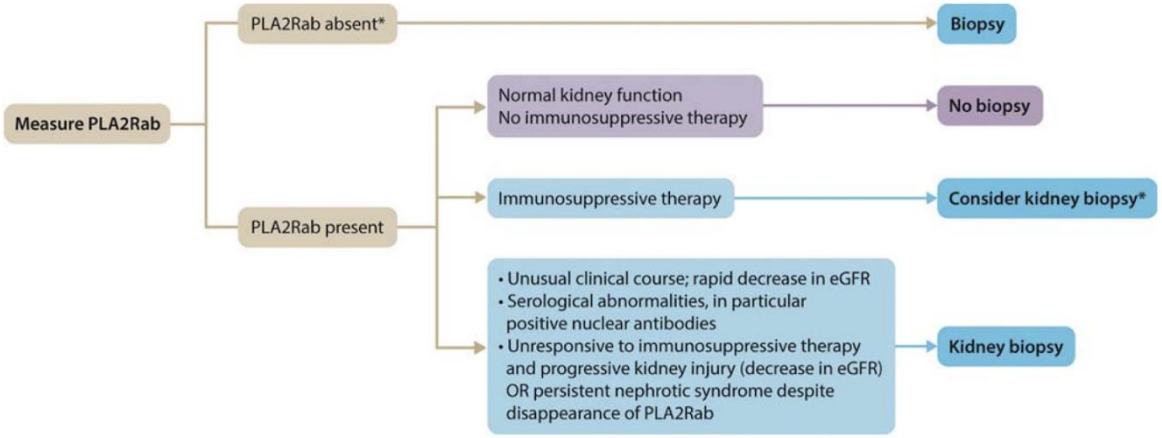

Figure 28. When to consider a kidney biopsy in a patient who is anti-PLA2R antibody-positive.

Practice Point 3.1.2: Patients with MN should be evaluated for associated conditions, regardless of whether anti-PLA2R antibodies and/or anti-THSD7A antibodies are present or absent.

We agree with the practice point, that non-invasive investigations should be considered for associated conditions according to the clinical history.

3.2 PROGNOSIS

Practice Point 3.2.1: In patients with MN, use clinical and laboratory criteria to assess the risk of progressive loss of kidney function.

As spontaneous remission occurs in MN and due to the potential adverse effects of immunosuppression, it is important to assess the risk of progressive loss of kidney function before deciding whether to start immunosuppressive treatment.

For most patients it would be reasonable to wait for 6 months before considering immunosuppression. The KDIGO guidelines suggest re-evaluation earlier than 6 months in cases at high-risk for progressive loss of kidney function, e.g. those with declining kidney function, high levels of proteinuria, anti-PLA2R antibodies or low-molecular weight proteinuria. Some biomarkers mentioned in Figure 30 are not available in many UK centres, such as urinary biomarkers, or measurements of proteinuria selectivity index.

Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and serum albumin >30 g/l OR • Normal eGFR, proteinuria <3.5 g/d or a decrease >50% after 6 months of conservative therapy with ACEi/ARB	• Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND • Not fulfilling high-risk criteria	• eGFR <60 ml/min/1.73 m^{2}* and/or proteinuria >8 g/d for >6 months OR • Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND at least one of the following: • Serum albumin <25 g/l† • PLA2Rab >50 RU/ml‡ • Urinary α_1 -microglobulin >40 µg/min • Urinary IgG >1 µg/min • Urinary β_2-microglobulin >250 mg/d • Selectivity index >0.20§	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained

Figure 30. Clinical criteria for assessing risk of progressive loss of kidney function.

3.3 TREATMENT

Practice Point 3.3.1: Considerations for treatment of patients with primary MN:
- All patients with primary MN and proteinuria should receive optimal supportive care.
- Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury (Figure 31).

A flow chart is shown in Figure 31. Treatment with CNI is associated with a high relapse rate on withdrawal, but the KDIGO guidelines note that their use could be considered in moderate risk patients as many will develop spontaneous remission, and CNI could shorten the duration of proteinuria. The combination of CNI followed by rituximab is suggested in high-risk patients. In very high-risk patients, the guidelines advise cyclophosphamide plus glucocorticoids, as currently there is insufficient evidence that rituximab prevents the development of kidney failure.

Following release of the KDIGO guidelines, two trials have been published in MN. Firstly, the STARMEN trial demonstrated that treatment with cyclical corticosteroids and cyclophosphamide was superior to the combination of CNI followed by a single 1g rituximab dose at 6 months (to maintain remission), in inducing complete or partial remission and in maintaining patients in remission (24). The number of serious adverse events did not differ significantly between the two groups, although the number of non-serious adverse events was higher in the corticosteroid-cyclophosphamide group. Secondly, the RI-CYCLO pilot study compared cyclical corticosteroids-cyclophosphamide with two doses of 1g rituximab 2 weeks apart, and found no significant difference in remission rates or adverse events between the two groups (25). This was a descriptive study that recruited a small number of patients, and therefore was not powered to show superiority. Leucopoenia and infectious complications were more common in the corticosteroid-cyclophosphamide arm, and infusion reactions were more common in the rituximab arm. Therefore, this recent evidence confirms the efficacy of cyclical corticosteroids-cyclophosphamide in high-risk MN and that rituximab is a viable alternative (26). We refer the readers to the recent NHS England commissioning policy published in October 2022 (27).

CNI remain a 3rd line treatment in high risk patients, due to the high rates of relapse on withdrawal and nephrotoxicity associated with long-term use. Based on the above, we do not recommend use of CNI followed by rituximab in high risk patients with MN.

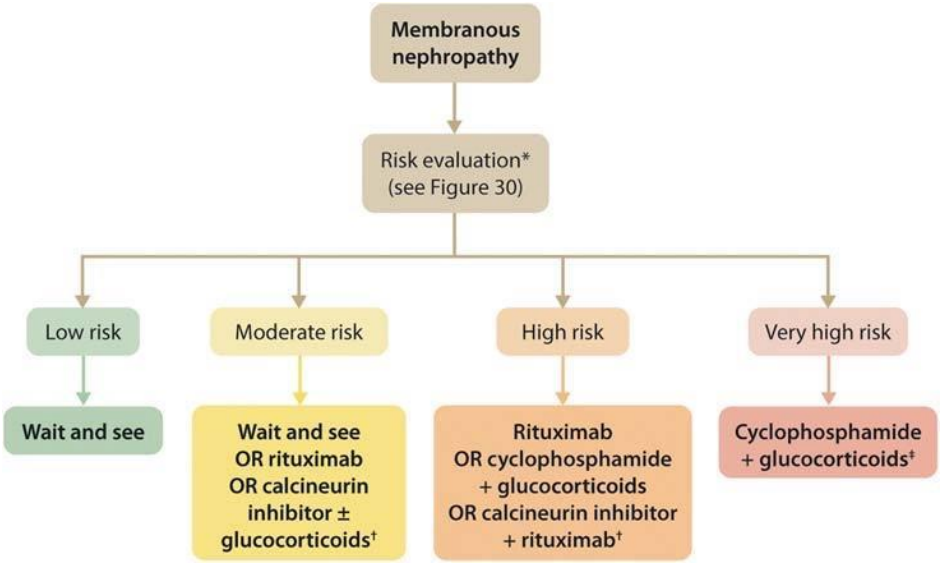

Figure 31. Risk-based treatment of MN.

Practice Point 3.3.2: Immunosuppressive therapy is not required in patients with MN, proteinuria <3.5 g/d, serum albumin >30 g/l by bromocresol purple (BCP) or immunometric assay, and eGFR >60 ml/min per 1.73 m^2.

It is noted that patients who have MN with normal eGFR who have non-nephrotic proteinuria generally have good outcomes. Burden of symptoms and complications are low, and therefore immunosuppression may add risks without providing any additional benefit.

Practice Point 3.3.3: Immunosuppressive therapy is not required in patients with MN, nephrotic syndrome, and normal eGFR, unless at least one risk factor for disease progression is present or serious complications of nephrotic syndrome (e.g., AKI, infections, thromboembolic events) have occurred.

Since many patients (approximately 40%) with MN will have a spontaneous remission, immunosuppression is not recommended for those with no risk factors for disease progression apart from in the above circumstances.

Recommendation 3.3.1: For patients with MN and at least one risk factor for disease progression, we recommend using rituximab or cyclophosphamide and alternate month glucocorticoids for 6 months, or CNI-based therapy for ≥6 months, with the choice of treatment depending on the risk estimate (Figure 30 and Figure 31) (1B).

A balance between preventing progressive kidney function decline and reducing the complications and risks associated with nephrotic syndrome, and the risks of immunosuppression should be made. In the UK, first line therapy in most centres for high-risk patients is either rituximab or cyclical prednisolone and oral cyclophosphamide (modified Ponticelli regimen). Some UK centres use IV cyclophosphamide as a means to reduce its overall cumulative dose (28), but there are currently no RCTs that evaluate IV cyclophosphamide according to kidney endpoints. Rituximab was demonstrated to be superior to CNI monotherapy in the MENTOR study (29). Withdrawal of CNIs in MN is associated with a high relapse rate, and long-term use may lead to nephrotoxicity. Mycophenolate mofetil is not discussed in the KDIGO guideline, and its use as monotherapy did not lead to increased remission in a single previously published RCT (30).

Practice Point 3.3.4: Longitudinal monitoring of anti-PLA2R antibody levels at 6 months after start of therapy may be useful for evaluating treatment response in patients with MN, and can be used to guide adjustments to therapy (Figure 33).

The below figure discusses a suggested treatment schedule regarding this. It is noted that measurement of B cell depletion is insufficient to judge the efficacy of rituximab treatment, and extra

doses may be considered even if peripheral B cells are absent or very low. In most patients, response occurs within 3 months of starting treatment. It should be noted that immunological remission may precede clinical remission, sometimes by several weeks.

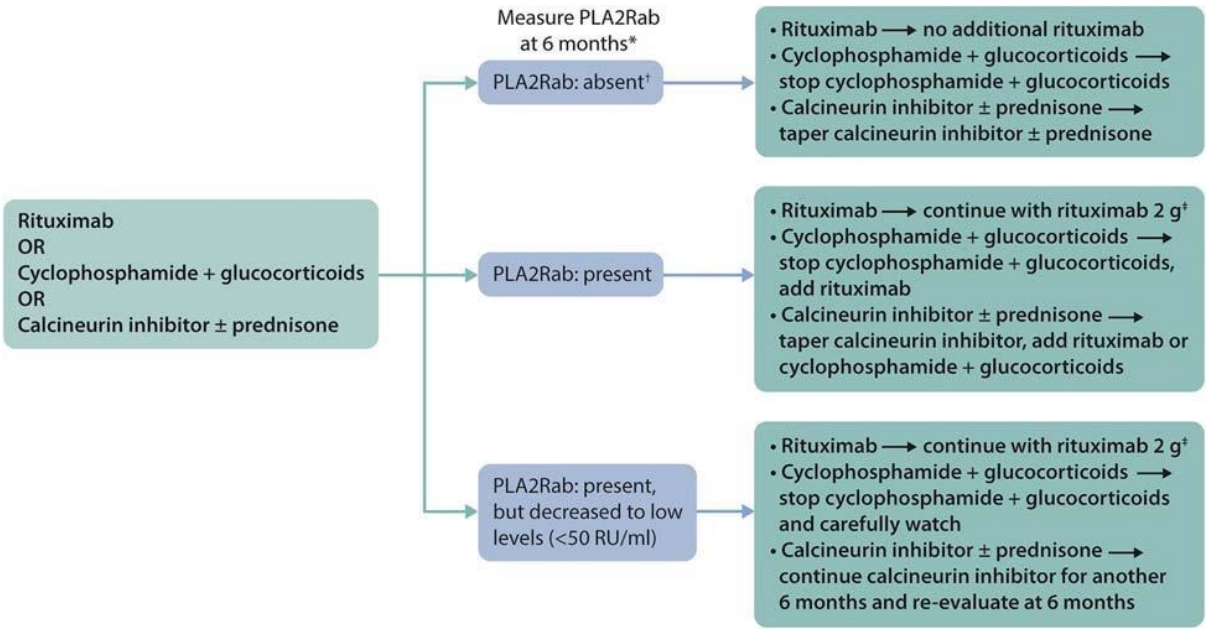

Figure 33. Immunologic monitoring in MN after start of therapy.

3.4 SPECIAL SITUATIONS

Practice Point 3.4.1: Algorithm for the treatment of patients with MN and initial relapse after therapy (Figure 34)

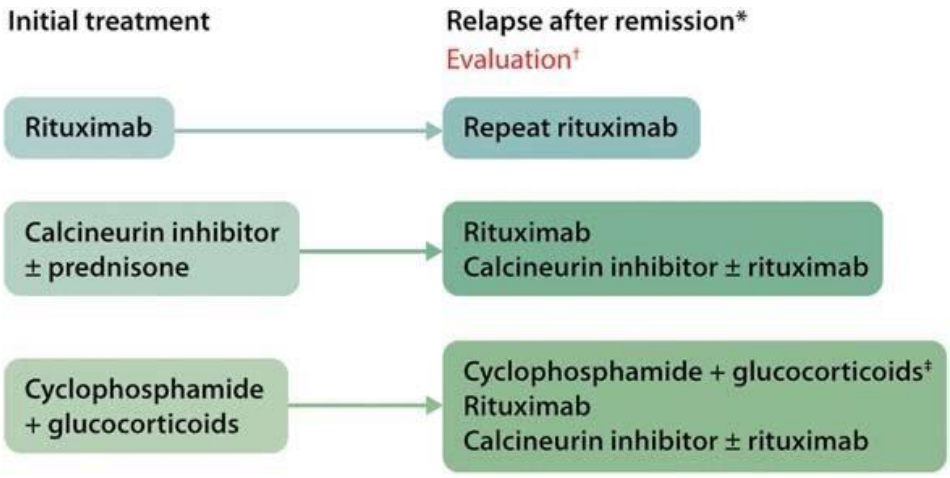

Figure 34. Management of initial relapse after therapy in MN.

Repeated courses of cyclophosphamide should be avoided, given its cumulative toxicity.

Practice Point 3.4.2: Algorithm for management of patients with treatment-resistant MN (Figure 35)

An algorithm is displayed in Figure 35. The KDIGO guidelines suggest that in patients with resistant disease, compliance should be checked and efficacy monitored (e.g. B cell response, anti-rituximab antibodies, IgG levels, leukocytopenia during cyclophosphamide, CNI levels). Persistent proteinuria is

not sufficient to define resistance. If proteinuria persists, while serum albumin has increased, one should consider secondary focal segmental glomerulosclerosis (FSGS). This would be further supported by the disappearance of anti-PLA2R antibodies. In patients with persistent proteinuria with normal or near-normal serum albumin levels or patients with persistent proteinuria despite loss of anti-PLA2R antibodies, a kidney biopsy should be considered to document active MN.

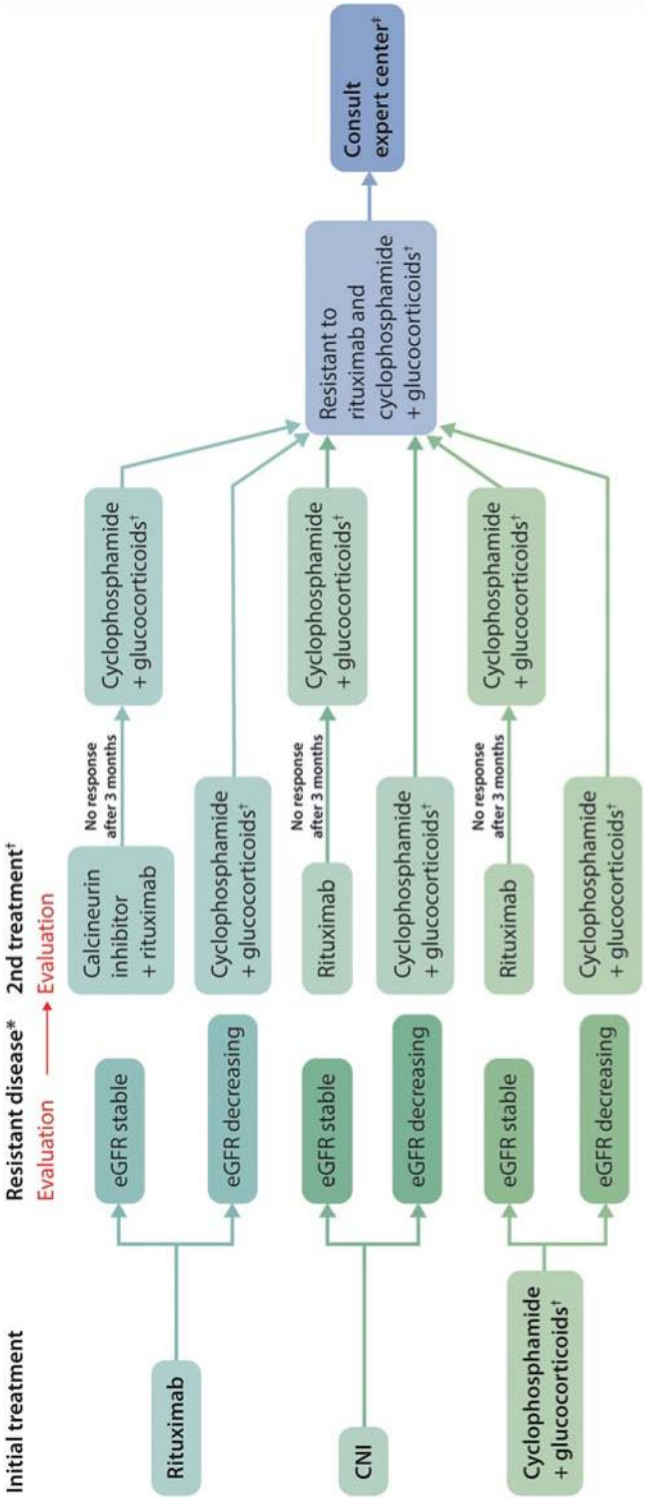

Figure 35. Management of resistant disease in MN

Practice Point 3.4.3: Evaluation of a kidney transplant recipient with MN (Figure 36)

Limited data are available, and a suggested treatment algorithm is displayed in Figure 36:

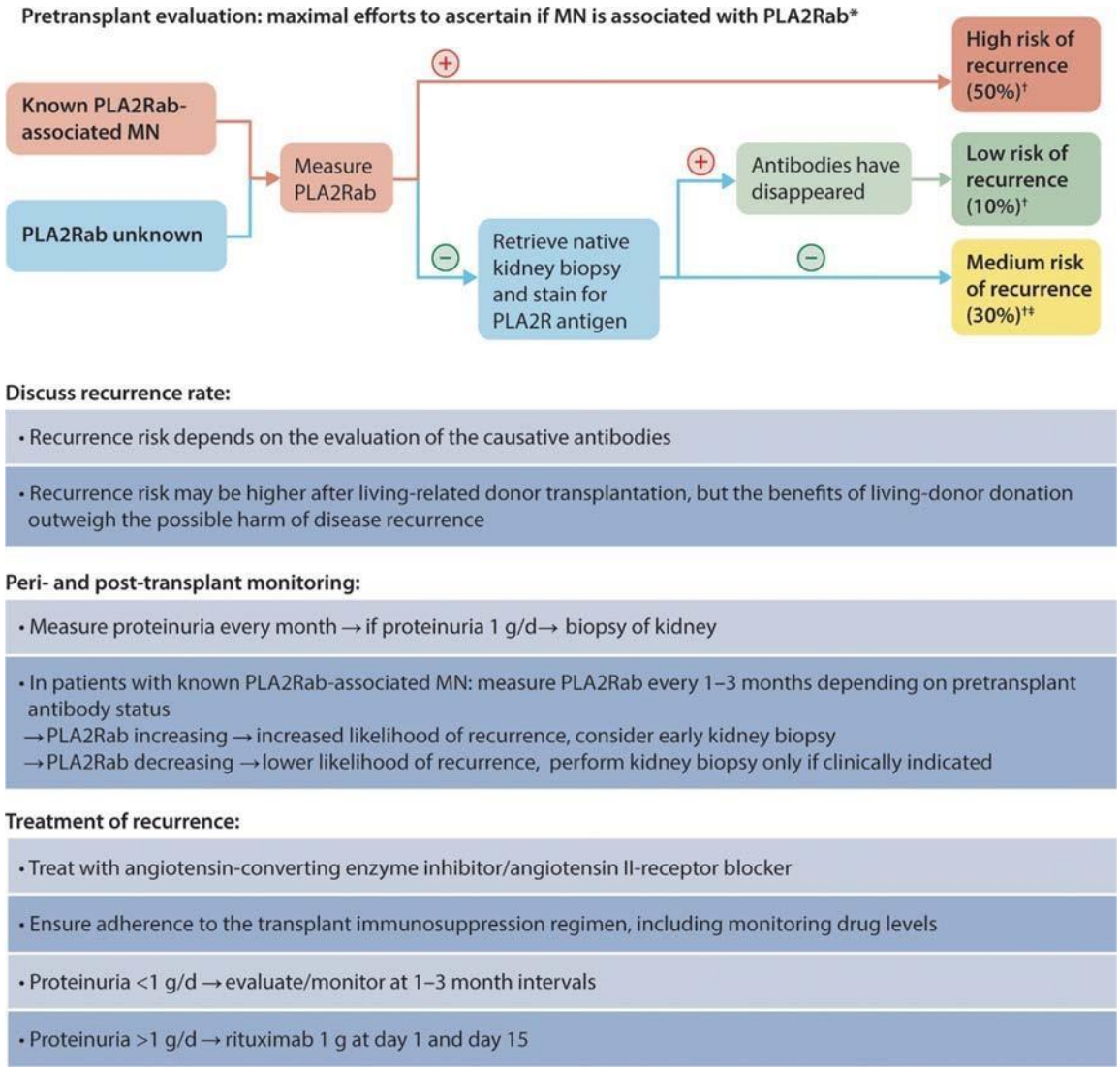

Figure 36. Evaluation of a kidney transplant recipient with MN.

Practice Point 3.4.4: Algorithm for management of children with MN (Figure 37)

We would agree that the observation strategy is generally not adopted in children with MN, and treatment typically starts with prednisolone and then follows adult practice due to a lack of specific evidence in childhood onset disease. In the UK, children should be managed in one of the 13 paediatric nephrology centres.

Practice Point 3.4.5: Prophylactic anticoagulant therapy in patients with MN and nephrotic syndrome should be based on an estimate of the risk of thrombotic events and the risk of bleeding complications (Figure 38).

Please refer to Chapter 1.

Chapter 4: Nephrotic Syndrome in Children

The recommendations and practice points Nephrotic syndrome in children are summarised in chapter 4, pages S140 to S152 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

Nephrotic syndrome is the most frequent glomerular disease in children with an incidence of 1-17 per 100,000 children (31). The introduction of glucocorticoids in the 1950's changed the natural history of this disease. This chapter makes recommendations for children with nephrotic syndrome (NS) who are aged 1-18 years. A summary of the management of a newly presenting child with nephrotic syndrome is illustrated in Figure 40.

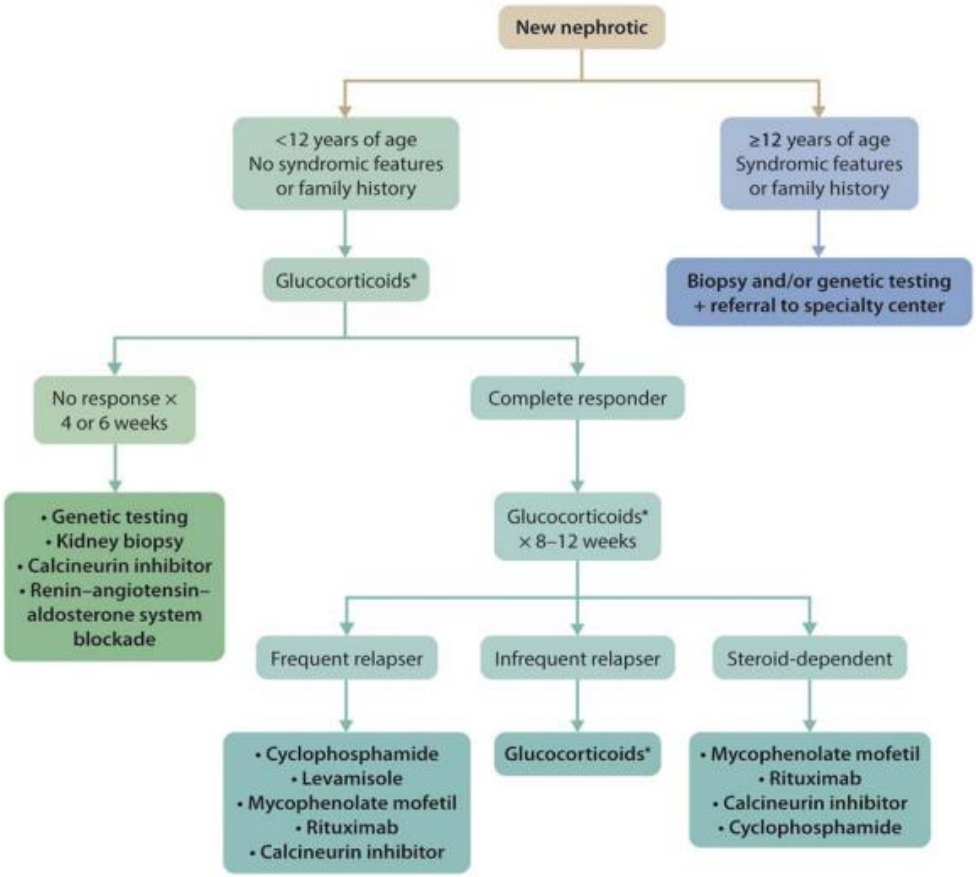

Figure 40. Treatment algorithm for NS in a newly nephrotic child.

4.1 DIAGNOSIS

Practice Point 4.1.1: The definitions relating to nephrotic syndrome in children are based on the clinical characteristics outlined in Figure 39.

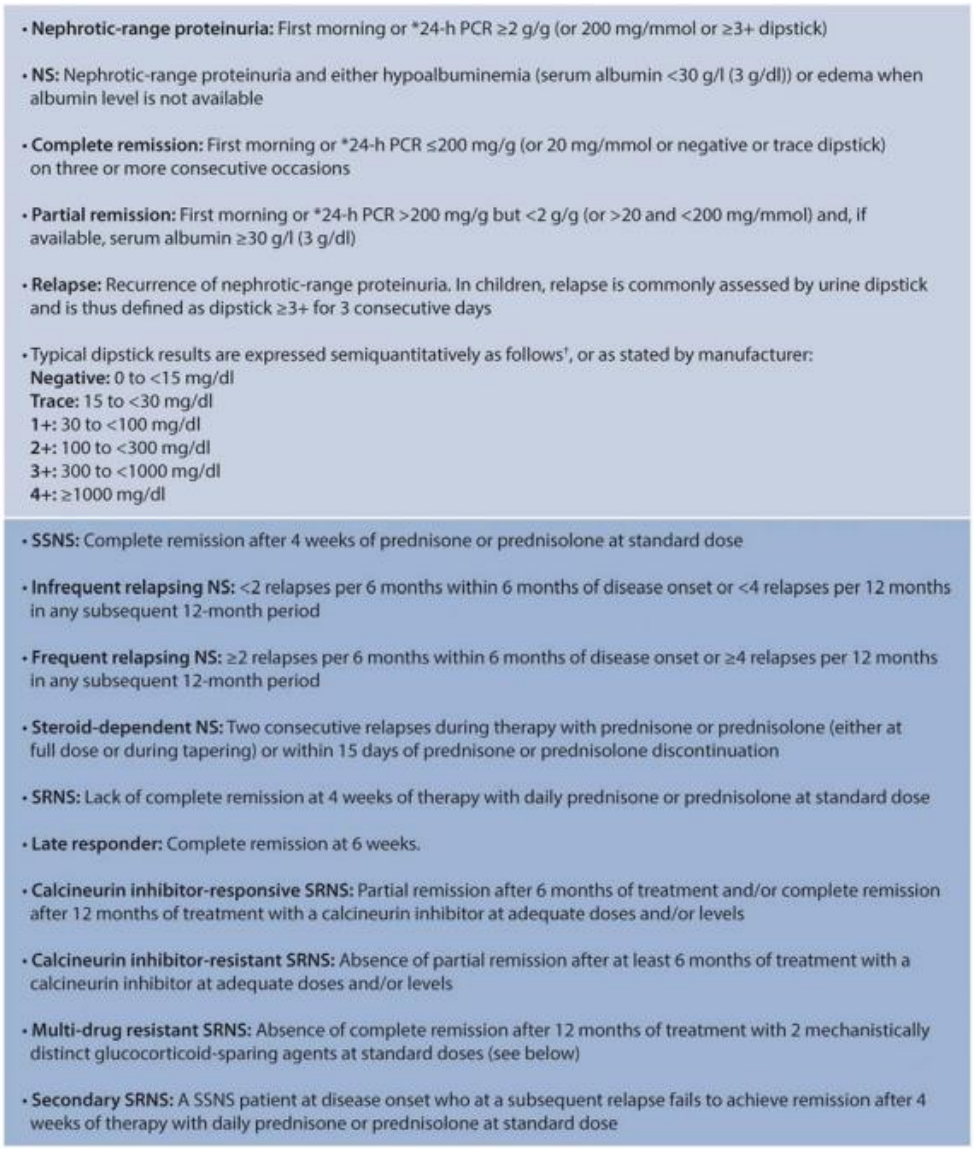

Figure 39. Definitions relating to NS in children aged 1-18 years.

The clinical characteristics defined within this chapter are summarised in figure 39 and most of the terminology should already be familiar with paediatric nephrologists. They include the definitions of nephrotic syndrome (nephrotic range proteinuria, hypoalbuminaemia with serum albumin <30g/l and/or oedema), nephrotic range proteinuria (24 hour urine PCR >2g/g or 200 mg/mmol or ≥3+ on urine dipstick), complete remission (no proteinuria for three or more consecutive occasions), partial remission (24 hour urine PCR >200mg/g but <2g/g or >20 and <200 mg/mmol and serum albumin >30g/L) and relapse (recurrence of nephrotic range proteinuria with ≥3+ on urine dipstick testing for 3 consecutive days). Apart from the threshold definition of hypoalbuminaemia changing from <25g/l in the previous edition of the KDIGO guideline to <30g/l in this current guideline and the time period of 4 weeks of prednisolone used to define steroid resistant disease (reduced from 8 weeks previously), the rest of the thresholds and definitions are unchanged.

In order to capture the 40-45% of patients with SRNS who will respond to CNI (32), the guideline now includes a definition of CNI responsive SRNS. These are defined as patients achieving partial remission after 6 months of treatment and/or complete remission after 12 months of CNI treatment and it includes a definition of CNI resistant SRNS, which is defined as the absence of partial remission after at least 6 months of treatment with a CNI. Multi-drug resistant SRNS is defined as the absence of complete remission after 12 months of treatment with 2 mechanistically distinct glucocorticoid-sparing agents at standard, age appropriate doses. A late responder is defined as someone who achieves complete remission at 6 weeks. The definition of steroid dependent NS (SDNS) remains the same as previously, describing a patient who has two consecutive relapses during prednisolone (or equivalent) therapy or

within 15 days of discontinuation. Other familiar definitions include infrequently relapsing NS, defined as disease with less than 2 relapses per 6 months in the first 6 months after disease onset or less than 4 relapses per 12 months subsequently and frequently relapsing NS (FRNS) is greater than or equal to 2 relapses per 6 months within 6 months of disease onset or greater than or equal to 4 relapses per 12 months. These new definitions are important to standardise the way we cohort patients with SRNS.

4.2 PROGNOSIS

Practice Point 4.2.1: The prognosis for childhood nephrotic syndrome is best predicted by the patient's response to initial treatment and the frequency of relapse during the first year after treatment. Therefore, a kidney biopsy is not usually needed at initial presentation, and instead is reserved for children with resistance to therapy or an atypical clinical course.

With regards to prognosis, this chapter continues to support the concept that the response to glucocorticoids and the disease course over the subsequent year(s) allows disease classification and this is the best predictor of future prognosis. The clinical response therefore continues to hold more value than routinely performing a kidney biopsy at disease onset and the kidney biopsy continues to not be recommended in patients presenting with 'typical' features. The authors continue to support the assumption that the majority of patients with SSNS, if biopsied, would be found to have minimal change disease. In SSNS, the prognosis is mostly related to glucocorticoid exposure and the use of steroid sparing agents. A kidney biopsy would be indicated at the time of disease onset if there were atypical features (≥12 years of age at disease onset, syndromic features, positive family history), in children classified with SRNS and in children who have a prolonged (>2-3 years) exposure to CNI's. The aim of treatment in SSNS and CNI responsive SRNS is to use the lowest cumulative doses of glucocorticoids and the safest, most effective glucocorticoid sparing agents to maintain disease remission. In all cases of SRNS genetic analysis is mandatory.

4.3 TREATMENT

Recommendation 4.3.1.1: We recommend that oral glucocorticoids be given for 8 weeks (4 weeks of daily glucocorticoids followed by 4 weeks of alternate-day glucocorticoids) or 12 weeks (6 weeks of daily glucocorticoids followed by 6 weeks of alternate-day glucocorticoids).
Practice Point 4.3.1.1: The standard dosing regimen for the initial treatment of nephrotic syndrome is daily oral prednisolone 60mg/m^2/day or 2mg/kg/day (maximum 60mg/day) for 4 weeks followed by alternate-day prednisolone, 40mg/m^2 or 1.5mg/kg (maximum 50mg) for other 4 weeks, or prednisolone 60mg/m^2/day (maximum 60mg/day) for 6 weeks followed by alternate day prednisolone, 40mg/m^2, or 1.5mg/kg (maximum 50mg/day) for other 6 weeks.
Recommendation 4.3.2.1: For children with frequently relapsing and steroid-dependent nephrotic syndrome who are currently taking alternate-day glucocorticoids or are off glucocorticoids, we recommend that daily glucocorticoids 0.5mg/kg/day be given during episodes of upper respiratory tract and other infections for 5-7 days to reduce the risk of relapse.
Practice Point 4.3.2.1: The initial approach to relapse should include oral prednisolone as a single daily dose of 60mg/m^2/day or 2mg/kg/day (maximum 60mg/day) until the child remits completely for ≥3 days
Practice Point 4.3.2.2: After achieving complete remission, reduce oral prednisolone to 40mg/m^2 or 1.5 mg/kg/day (maximum 50mg) on alternate days for ≥4 weeks
Practice Point 4.3.2.3: For children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome without glucocorticoid toxicity, the same glucocorticoid regimen may be employed in subsequent relapses
Practice Point 4.3.2.4: For children with frequently relapsing nephrotic syndrome without serious glucocorticoid-related adverse effects, low-dose alternate-day oral prednisolone (optimally ≤0.5mg/kg/day) can be prescribed to prevent relapse
Recommendation 4.3.2.2: For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse effects and for all children with steroid-

dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents be prescribed, rather than no treatment or continuation with glucocorticoid treatment alone.
Practice Point 4.3.2.5: Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid-sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs). Coadministration of glucocorticoids is recommended for ≥2 weeks following initiation of glucocorticoid-sparing treatment.
Practice Point 4.3.2.6: Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and CNI is a decision that requires careful consideration of specific patient-related issues such as resources, adherence, adverse effects, and patient preferences. Oral cyclophosphamide and levamisole may be preferable glucocorticoid-sparing therapies in frequently relapsing nephrotic syndrome. MMF, rituximab, CNIs and to a lesser extent, oral cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome.

With regards to initial treatment, KDIGO has an evidence-based recommendation that all patients are treated with a course of 8-12 weeks of once daily oral glucocorticoids, namely prednisolone, after initial presentation using doses as detailed above. This is based on moderate-quality evidence on equivalent clinical outcomes and the reduced risk of adverse effects when compared to longer courses (>12 weeks). This recommendation is based on the findings from 4 RCT's that have evaluated glucocorticoid dosage for the initial episode of SSNS in children since the last KDIGO guideline review (33-35). These demonstrated that extending the initial treatment from 8-12 weeks up to 6 months may reduce the time to first relapse but it did not prevent frequent relapses or change the overall disease course. The evidence from these studies, and recognised in other conditions, strongly suggests that the risk of adverse effects associated with glucocorticoid treatment is proportional to the cumulative dose and therefore KDIGO recommend the shorter duration course as recommended initial treatment. Following the completion of the PREDNOS study (36), UK practice has been aligned and general clinical practice is to opt for the 4 weeks of daily dose prednisolone at disease presentation followed by 4 weeks of alternate days.

The recommendation 4.3.2.1 detailed above that proposes that children with nephrotic syndrome are treated with prophylactic prednisolone during an intercurrent viral upper respiratory tract infection to prevent infection may now be disputed following the recent completion of the PREDNOS 2 study (37). This KDIGO recommendation put a high value on the low-quality evidence that suggested that pre-emptive prednisolone reduces the risk of a SSNS relapses in children during an intercurrent infection and a low value on the low-quality evidence of the potential adverse effects of such intervention. The PREDNOS 2 randomised clinical trial was published online in December 2021 and therefore outside the scope of this current updated guideline. The study was an evaluation of daily low-dose prednisolone during an upper respiratory tract infection to prevent the onset of a relapse in children known to have relapsing SSNS (defined as having experienced 2 or more relapses in the preceding 12 months). This double-blind, placebo-controlled randomised clinical trial recruited 365 children from multiple UK paediatric departments between February 2013 to January 2020. At the start of an upper respiratory tract infection, children received 6 days of prednisolone at a dose of 15mg/m^2 daily or a matching placebo preparation and 271 children were evaluation on an intention-to-treat basis demonstrating no significant difference in the number of children experiencing a relapse (42.7% in the prednisolone arm, 44.3% in the placebo arm). The authors found no evidence that the treatment effect differed according to ethnicity or background immunosuppression and no difference in any of the secondary outcomes. No specific differences were found in the serious adverse events, corticosteroid adverse effects or behaviour scores between the groups. These findings do not support the previously published small, low quality clinical trials which reported a benefit of daily prednisolone at the time of an upper respiratory tract infection, however these studies suffered from methodological flaws, including samples sizes of 36-100 patients, and as this is now the largest, most robust, multi-centre RCT published in this area, it seems likely that future recommendations will change and it may be clinically appropriate to conclude that the routine use of low-dose prednisolone at the start of an intercurrent illness to prevent SSNS relapse offers no benefit to the majority of patients. However, as the adverse effect profile of this intervention did not appear to be significant, and the study was not powered for subgroup analysis, it is of our opinion that there may be some patients for which adopting this measure is necessary on a case by case individual basis.

The recommendation 4.3.2.2 states that for children with FRNS who develop serious glucocorticoid-related adverse effects, and for all children with SDNS, glucocorticoid-sparing agents should be

prescribed, rather than no treatment or continuation with glucocorticoid treatment alone, and this remains best clinical practice. The practice points state that patients should ideally be in remission through the use of glucocorticoids prior to the initiation of a glucocorticoid-sparing agent and suitable agents include oral cyclophosphamide, levamisole, MMF, rituximab or calcineurin inhibitors (CNI's). They suggest the co-administration of glucocorticoids for at least 2 weeks following the start of a glucocorticoid-sparing agent. KDIGO suggest that the choice of glucocorticoid sparing agent requires consideration of patient specific issues such as local resources, adherence, adverse effects experienced and patient preference. For FRSSNS, oral cyclophosphamide and levamisole may be preferred as the second line therapy and for SDNS, then MMF, rituximab and CNI's are preferable. The doses and helpful clinical tips in using each of these agents are summarised in Figure 41.

Treatment	Dose and duration	Clinical tips
First line:		
• Oral cyclophosphamide	2 mg/kg/d for 12 weeks (maximum cumulative dose 168 mg/kg)	Cyclophosphamide should not be started until the child has achieved remission with glucocorticoids. Moreover, second courses of alkylating agents should not be given. Weekly CBCs are recommended during the treatment course to assess for severe leukopenia or overall bone marrow suppression prompting dose reduction or treatment cessation
• Oral levamisole	2.5 mg/kg on alternate days, with a maximum dose of 150 mg	Monitor CBC every 2–3 months and alanine and aspartate aminotransferases every 3–6 months during therapy with levamisole. Check ANCA titers every 6 months, if possible, and interrupt treatment in case of ANCA positivity, skin rash or agranulocytosis. Maintaining low-dose alternate-day glucocorticoid dosing on the days not taking levamisole may be effective in some children. Levamisole should be continued for at least 12 months
Alternative agents:		
• Mycophenolate mofetil	Starting dose of 1200 mg/m²/d (given in two divided doses)	Target area under the curve >50 µg•h/ml.* Mycophenolate mofetil should be continued for at least 12 months, as most children will relapse when it is stopped. In children experiencing significant abdominal pain on mycophenolate mofetil, other mycophenolic acid analogs (MPAAs), such as sodium mycophenolate, may be employed at equivalent doses (360 mg of sodium mycophenolate corresponds to 500 mg of mycophenolate mofetil)
• Rituximab	375 mg/m² i.v. × 1–4 doses	Rituximab may be used as a treatment for steroid-sensitive nephrotic syndrome in children who have continuing frequent relapses despite optimal combinations of prednisone and glucocorticoid-sparing oral agents, and/or who have serious adverse effects of therapy. Current trials report 1 to 4 doses of rituximab. There are insufficient data to make a recommendation for specific number of needed doses. Where available, CD20 levels should be monitored. Hepatitis B surface antigen, hepatitis B core antibody, and a QuantiFERON test for tuberculosis must be checked prior to rituximab administration. Monitoring IgG levels both before and after rituximab therapy may allow for earlier identification of risk for developing significant infection and identify patients who may benefit from immunoglobulin replacement
• Calcineurin inhibitors‡		CNI should be continued for at least 12 months as most children will relapse upon discontinuation. Monitor CNI levels during therapy to limit toxicity
– Cyclosporine	4 to 5 mg/kg/d (starting dose) in two divided doses	Cyclosporine may be preferable in patients at risk for diabetic complications. Target 12 hour trough level of 60–150 ng/ml [50–125 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity
– Tacrolimus	0.1 mg/kg/d (starting dose) given in two divided doses	Tacrolimus may be preferred over cyclosporine in patients for whom the cosmetic side effects of cyclosporine are unacceptable. Target 12 hour trough level of 5–10 ng/ml [6–12 nmol/l] aiming for lowest levels to maintain remission and avoid toxicity

Figure 41. Glucocorticoid-sparing therapies in children with SSNS.

STEROID RESISTANT NEPHROTIC SYNDROME (SRNS)

Practice Point 4.4.1: We recommend using cyclosporine or tacrolimus as initial second-line therapy for children with steroid-resistant nephrotic syndrome

As defined at the start of this chapter, SRNS is a more challenging clinical entity and it should be suspected in patients who do not respond to glucocorticoids after 4 weeks of treatment. This cohort of patients will require genetic analysis to exclude a monogenic cause that may be far less likely to respond to immunosuppression. The guidelines mention early use of RAASi and to continue glucocorticoid administration. The only recommendation within this section relates to the use of CNI's as second line therapy for SRNS. The working group placed high value on the likelihood of achieving remission using large registry data including the Europe-based PodoNet Registry (1174 children) and a meta-analysis of 790 children included in clinical trials (38,39), and a lower value on the risk of long-term nephrotoxicity related to CNI use. This high value stance was taken due to the risk of progressive kidney failure and complications associated with untreated NS and it was felt that all patients would accept the risk of treatment-associated nephrotoxicity in these circumstances. The quality of evidence relating to this area was low with few, small trials that are not of sufficient size to determine differences between treatments. Among the children with SRNS where no genetic form is found, a substantial proportion will respond to a CNI after weeks to months of treatment. These children who demonstrate CNI responsive SRNS will either remain in stable remission with no or infrequent relapses or develop steroid dependent forms of NS as previously discussed. MMF may be considered in patients with SRNS who have an eGFR <30ml/min/1.73m^2 or as an alternative agent to the CNI after remission and stability has been achieved for greater than 1 year. There is no evidence to support a specific type of CNI with most data related to either the use of cyclosporine or tacrolimus. In terms of nephrotoxicity, the rates appear similar between these two agents, however the rates of gingival hyperplasia and hypertrichosis are more common with cyclosporine and the rates of glucose intolerance are more common with tacrolimus. UK clinical practice preferentially uses tacrolimus in this situation due to its favoured side effect profile, however individual risk factors may guide clinicians to select an alternative CNI. There is no evidence to support a role for oral cyclophosphamide in SRNS.

Rarely, children who initially respond to glucocorticoids experience a subsequent relapse that then does not respond and these are termed secondary SRNS. In these cases, multi-drug resistance, including CNI-resistance, can develop leading to eventual kidney failure and a high risk of post-transplant recurrence. The working group conclude that there may be a limited or no role for the use of rituximab in patients with multi-drug resistant secondary SRNS, however this conclusion was made based on low quality data, mainly a small cohort of 31 children with CNI-resistant NS who were randomised to receive rituximab (n=16) and they reported no difference in the levels of proteinuria at 3 months (40). This data is very limited as it was a small cohort of children all of whom had primary SRNS without genetic screening to rule out those with monogenic disease. The other paper referenced involved 10 children with SDNS who received rituximab and these are not comparable to the complex secondary SRNS, CNI resistant patients (41). Shortly after the literature gathered for this guideline, data from the UK National Registry of Rare Kidney Diseases (RADAR) was published (42). This data represented a large, national cohort of patients with SRNS (n=271) who underwent extensive baseline genetic testing identifying 81 children with monogenic disease and 190 who tested negative for recognised genetic mutations. In the genetically negative CNI resistant SRNS group, the complete response rate to rituximab was reasonably good at 39% and this increased to 65% when evaluating the subgroup of patients with secondary onset SRNS disease. Importantly, 97% of those patients who achieved complete response did not progress to kidney failure over a median follow up period of 5.2 years. As this information that has direct translation to our UK population, rituximab does seem to be a useful medication in this group of highly complex patients. Due to the limited evidence and risk of disease progression in patients who fail to respond to the conventional treatments suggested, these patients should be entered into a clinical trial if at all possible and they are a cohort where the use of new adjunctive agents, such as Sparsentan, a dual endothelin and ARB, may be considered.

4.5 SPECIAL SITUATIONS

Practice Point 4.5.1: Figure 43 outlines the general principles in children with nephrotic syndrome

The chapter outlines special situations that should be considered as general principles in the management of children with NS as shown in Figure 43.

Indication for kidney biopsy*	• Children presenting with nephrotic syndrome ≥ 12 years of age • Steroid-resistant nephrotic syndrome or subsequent failure to respond to glucocorticoids in steroid-sensitive nephrotic syndrome (secondary steroid-sensitive nephrotic syndrome) • A high index of suspicion for a different underlying pathology (macroscopic hematuria, systemic symptoms of vasculitis, hypocomplementemia, etc.) • At onset, kidney failure not related to hypovolemia. Subsequently, decreasing kidney function in children receiving calcineurin inhibitors or prolonged exposure to calcineurin inhibitors (2 to 3 years)
Genetic testing	• Steroid-resistant nephrotic syndrome • Congenital and infantile forms of nephrotic syndrome (<1 year of age) • Nephrotic syndrome associated with syndromic features • Family history of steroid-resistant nephrotic syndrome or focal segmental glomerulosclerosis
Vitamin D/calcium	In patients with steroid-sensitive nephrotic syndrome and normal vitamin D levels, supplementation is not required. However, in frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome in children or in the presence of a known vitamin D deficiency, a reduction in bone mineral content can be prevented by oral supplementation with oral calcium and vitamin D.[1,2]
Gastroprotection	There is insufficient evidence of benefit to recommend prophylactic use of proton-pump inhibitors in children with nephrotic syndrome in the absence of risk factors for gastrotoxicity or of gastric symptoms.

Figure 43. General principles in children with NS.

Research recommendations

KDIGO highlights the need for RCT's to compare the initial duration of oral prednisolone for disease induction and ways to further shorten this using combination therapy with a glucocorticoid-sparing agent at disease onset. They suggest research is needed to optimise the treatment of relapses, especially in patients with FRNS and/or SDNS and to evaluate the optimal duration of glucocorticoids in SRNS. Further suggestions include the stratification of patients and the exploration of quality of life measures as clinical trial endpoints.

Chapter 5: Minimal Change Disease (MCD) in adults

The recommendations and practice points on minimal change disease (MCD) in adults are summarised in chapter 5, pages S153 to S160 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

5.1 DIAGNOSIS

Practice Point 5.1.1: MCD in adults can be diagnosed only with a kidney biopsy.

The KDIGO guidelines on MCD generally reflect practice in the UK. We agree that a kidney biopsy is essential for a diagnosis of MCD in adults and adequate sampling is necessary as FSGS lesions can be missed if the biopsy sample is small.

5.2 PROGNOSIS

Practice Point 5.2.1: Long-term kidney survival is excellent in patients with MCD who respond to glucocorticoids, but less certain for patients who do not respond.

10-20% of patients with MCD are steroid resistant and a repeat biopsy may show FSGS. This is associated with a worse prognosis. See Chapter 6 discussion for steroid-resistant FSGS recommendations.

5.3 TREATMENT

Recommendation 5.3.1: We recommend high-dose oral glucocorticoids for initial treatment of MCD (1C).
Practice Point 5.3.2: High-dose glucocorticoid treatment for MCD should be given for no longer than 16 weeks
Practice Point 5.3.3: Begin tapering of glucocorticoids 2 weeks after complete remission.
Practice Point 5.3.4: Although daily oral glucocorticoids are used most often to treat MCD, the route and frequency of administration can be individualized to patient needs.
Practice Point 5.3.5: For patients in whom glucocorticoids may be relatively contraindicated, consider initial therapy with cyclophosphamide, a CNI, or MMF.

Complete remission
Reduction of proteinuria to <0.3 g/d or PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/l)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved
Steroid-resistant MCD
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for >16 weeks
Frequently relapsing MCD
Two or more relapses per 6 months (or four or more relapses per 12 months)
Steroid-dependent MCD
Relapse occurring during, or within 2 weeks of completing glucocorticoid therapy

Figure 46. Definition of remission, relapse, resistance, and dependence for MCD.

Although there is a paucity of high-quality data, steroids are the recommended treatment for most patients with MCD. The use of steroid therapy is based on two randomised controlled trials in adults with MCD, observational studies and experience from large prospective randomised controlled trials in children. Black et al randomised 31 adult patients with MCD to an average of 25mg/day Prednisolone for 6 months then a slow taper or placebo (43). The steroid group showed a rapid decrease in proteinuria. At 2 years both groups had similar outcomes with respect to proteinuria, serum albumin and oedema. Coggins et al randomised 28 patients with adult MCD to alternate day Prednisolone (125 mg/day average dose) for 2 months or placebo (44). Steroid treated patients attained remission more rapidly but at 77 months there was no significant difference in proteinuria. Four patients in the placebo arm had doubling in serum creatinine. The lack of difference in proteinuria is likely due to relapse rates in the treated arm and a significant number of placebo arm patients received steroid therapy. In children, several high quality randomised controlled trials show benefit with steroid therapy and these outcomes have been extrapolated for management in adults.

We would suggest 1mg/kg of Prednisolone at a maximum of 60mg once a day (rather than 80mg once a day as suggested by KDIGO) and begin tapering the steroids 2 weeks after complete remission. The majority of patients respond within 8 weeks. We agree that high-dose steroid treatment should not continue longer than 16 weeks to avoid toxicity.

There are no studies assessing the optimal steroid taper in adults. Generally, steroids are tapered by 5-10mg per week after remission for a total steroid exposure of less than 24 weeks.

Two randomised trials have assessed the effects of initial intravenous Methylprednisolone compared to oral Prednisolone in adult MCD (45,46). Both had limitations of sample size but demonstrated higher remission rates in the oral Prednisolone groups. We would suggest the use of oral Prednisolone in view of the ease of administration. No randomised or prospective trials comparing daily to alternate-day dosing have been performed in adults with MCD. Observational studies show similar remission rates. In the UK, we generally use Prednisolone once daily.

In patients with absolute or relative contraindication to steroids, we agree alternative immunosuppressive agents such as CNI, Cyclophosphamide, MMF or Rituximab should be considered.

In practice the most commonly used steroid sparing regimen is CNI monotherapy. Medjeral-Thomas et al randomised 50 patients with adult MCD to treatment with either oral Tacrolimus at 0.05mg/kg twice daily, or Prednisolone at 1mg/kg daily (maximum 60mg) (47). There were no significant differences in remission rates up to 26 weeks or relapse rates. Similarly a more recent study by Chin et al randomised 144 adults with MCD to tacrolimus 0.05 mg/kg twice daily plus low dose Prednisolone (0.5mg/kg daily) or Prednisolone 1mg/kg daily (48). Complete remission rates were comparable at 8 weeks. Significantly fewer patients in the CNI group experienced a relapse over 24 weeks, and rates of adverse effects were similar between groups.

A multi-centre randomised trial compared Mycophenolate Sodium (720mg twice daily) plus low dose Prednisolone (0.5mg/kg daily) or Prednisolone 1mg/kg daily in 116 adults with MCD. There was no difference in complete remission rates at 4, 8 and 24 weeks. In those who achieved remission in 4 weeks, relapse rates up to 52 weeks were comparable in both groups (49).

If a CNI based regime is used either Cyclosporine 3-5mg/kg/day in two divided doses or Tacrolimus 0.05-0.1mg/kg/day in two divided doses are suggested. If MMF is used, 1g twice daily is suggested.

There are observational studies reporting remission rates of approximately 75% with oral Cyclophosphamide therapy and limited reports of the use of Rituximab during the first presentation of adult MCD.

Treatment of MCD Relapse

Recommendation 5.3.1.1: See algorithm **We recommend cyclophosphamide, rituximab, CNIs, or mycophenolic acid analogs (MPAA) for the treatment of frequently relapsing/steroid-dependent MCD, rather than prednisone alone or no treatment (1C)**
Practice Point 5.3.1.2: Treat infrequent relapses with glucocorticoids

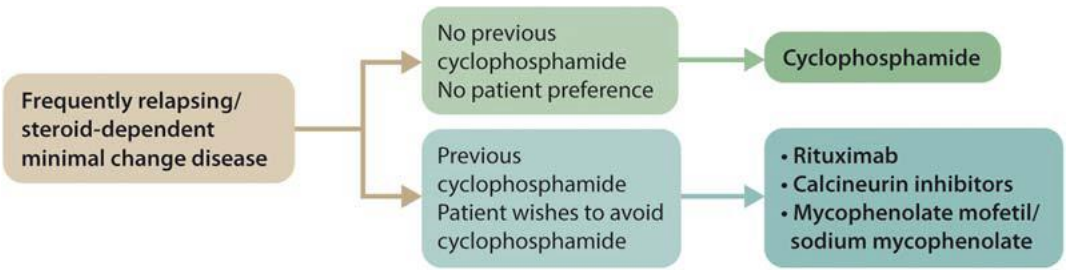

Figure 47. Treatment of FR/SD MCD in adults.

MCD is a relapsing disease. We agree with the suggestion that infrequent relapses can be treated with steroids. The optimal duration of steroid course in relapsing MCD is unknown but regimens similar to the initial treatment are often used.

In frequently relapsing (FR) or steroid-dependent (SD) cases of MCD, CNI, MMF, Rituximab or Cyclophosphamide are recommended based on small RCTs and observational studies. The KDIGO guidelines state that these agents are generally started after inducing remission with steroid or steroid sparing therapy. There is no evidence suggesting use of one class or one regimen is superior to others in FR or SD MCD. We agree the choice is dependent on previous immunosuppression, patient preference as well as resources available.

CNI
The evidence for the use of CNI in FR or SD MCD is limited and come from observational studies and one randomised controlled trial. Although remission rates of 70-90% can be achieved, relapse rates are high and we concur prolonged therapy may be required. The optimal duration however remains unknown.

MMF
Similarly, data on the use of Mycophenolate in FR or SD MCD is limited to observational studies with remission rates of 65-85% reported.

Rituximab
We agree that experience with Rituximab is limited and long-term efficacy or risks remain unknown. A recent meta-analysis of 21 studies involving 382 adults with FR steroid dependent MCD or focal segmental glomerulosclerosis (FSGS) showed that Rituximab was well tolerated and induced complete remission in 91.6% of MCD patients (50). However, 27.4% relapsed during follow-up. Most relapses occurred after 6 months in European studies whilst Asian studies showed relapses often occurred within the first 6 months in those that used 500mg Rituximab 6 months apart. We agree randomised controlled trials to confirm the efficacy of Rituximab are needed.

Cyclophosphamide
Evidence for the use of Cyclophosphamide in adults with FR or SD MCD come from observational studies and one randomised controlled trial of 66 children and adults. The randomised trial included 11 adults with FR or SD MCD, who received oral Cyclophosphamide (2.5mg/kg per day) for 8 weeks or Cyclosporine (5mg/kg per day) for 9 months then tapered by 12 months (51). At 2 years 25% of those who received Cyclosporine and 63% of those given Cyclophosphamide remained in remission. The limited numbers of adults in the study hampers meaningful conclusions.

We agree the risks of infertility need to be discussed with patients of childbearing age and repeated courses or prolonged therapy (>12 weeks) of Cyclophosphamide should be avoided.

Chapter 6: Focal Segmental Glomerulosclerosis (FSGS) in adults

The recommendations and practice points on focal segmental glomerulosclerosis (FSGS) in adults are summarised in chapter 6, pages S161 to S171 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

Definitions

The KDIGO guideline proposes a new subclassification of FSGS. They suggest eliminating the use of the term idiopathic FSGS. FSGS of undetermined cause (FSGS-UC) is added to differentiate those with FSGS lesions on biopsy but do not have any identifiable cause, whilst also not fitting the typical features of primary FSGS.

6.1 DIAGNOSIS

Practice Point 6.1.1.1: Adults with FSGS who do not have nephrotic syndrome should be evaluated for a secondary cause (Figure 51).
Practice Point 6.1.2.1: Genetic testing may be beneficial for selected patients with FSGS who should be referred to specialized centres with such expertise

Distinguishing primary from secondary FSGS can be difficult using histopathological features alone. We agree with the proposed evaluation of patients with FSGS on the kidney biopsy outlined in Figure 51.

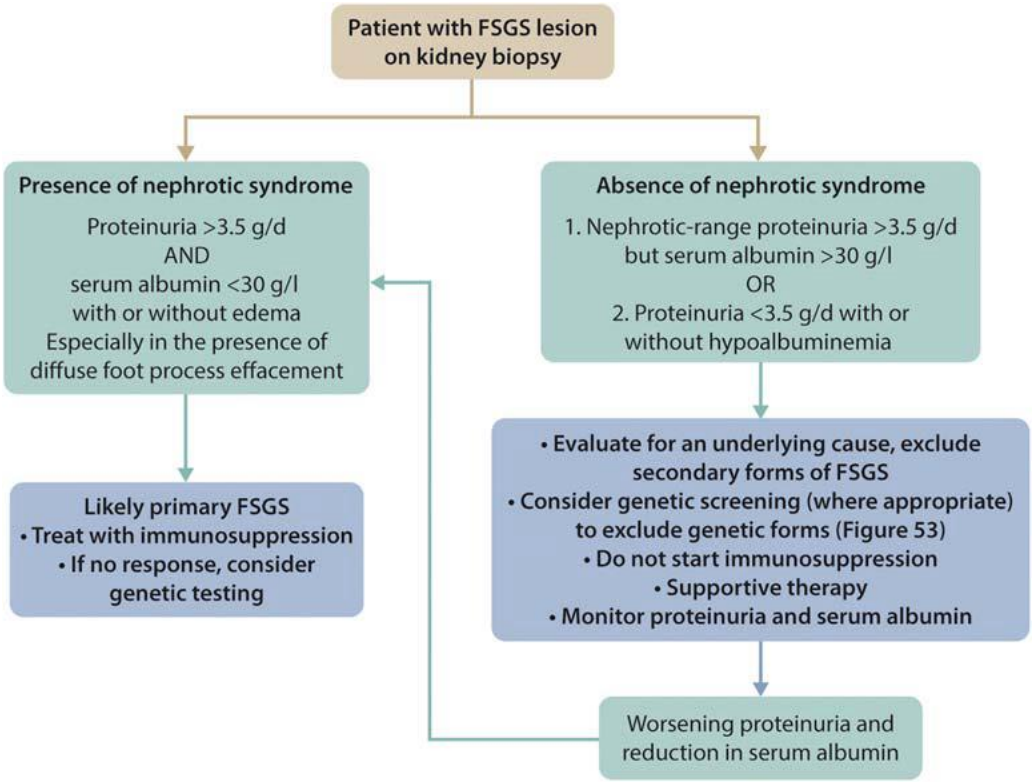

Figure 51. Evaluation of a patient with FSGS lesion on the kidney biopsy and no evidence of other glomerular pathology.

Genetic testing is not as widely available in the UK, however, it should be considered in patients with atypical clinical features, strong family history or resistance to treatment as recommended in practice point 6.1.2.1.

6.2 TREATMENT

Practice Point 6.2.1.1: Immunosuppression should not be used in adults with FSGS of undetermined cause (FSGS-UC), or in those with secondary FSGS.
Recommendation 6.2.2.1: We recommend that high-dose oral glucocorticoids be used as the first-line immunosuppressive treatment for primary FSGS
Practice Point 6.2.2.2: Initial high-dose glucocorticoids should be continued until complete remission is achieved, or as tolerated by patients up to a maximum of 16 weeks, whichever is earlier.
Practice Point 6.2.2.3: Adults with primary FSGS who respond to glucocorticoid treatment should receive glucocorticoids for ≥6 months.
Practice Point 6.2.2.4: In adults with relative contraindications or intolerance to glucocorticoids, alternative immunosuppression with CNIs should be considered as the initial therapy in patients with primary FSGS

We agree that patients with FSGS of undetermined cause, genetic FSGS or secondary FSGS should not receive immunosuppression. The underlying medical issue in secondary FSGS should be managed directly. Furthermore, we acknowledge that patients without nephrotic syndrome are less likely to benefit from immunosuppression. Similarly, those with histologic evidence of extensive glomerulosclerosis and interstitial fibrosis would not benefit from immunosuppression. Supportive management would be more appropriate in these cases.

There are no randomized trials in adults comparing prednisolone or other immunosuppressive agents with placebo for initial therapy of primary FSGS. The recommendations are from observational studies and extrapolations from paediatric studies. Steroids are the recommended treatment for most patients with primary FSGS.

We would suggest 1mg/kg of Prednisolone at a maximum of 60mg once a day (rather than 80mg once a day as suggested by KDIGO) and begin tapering the steroids 2 weeks after complete remission or maximum of 16 weeks as recommended. The optimal steroid therapy duration is unknown. Generally, primary FSGS is less responsive than MCD. The guideline suggests total steroid therapy for 6 months or more. Ponticelli et al treated 53 patients with primary FSGS with steroid therapy (52). The mean treatment duration was for 24.5 weeks. They showed that only 15% of patients who received steroids for a total of 16 weeks or less entered complete remission of proteinuria, whilst 61% of patients treated with steroids for longer obtained complete remission. But given the comorbidities of prolonged steroid therapy, a total of 6 months duration is appropriate.

For patients with absolute or relative contraindication to steroids, we agree that CNI should be considered. However, we recommend CNI treatment should be avoided in those with an eGFR <30 mL/min/1.73 m^2. Laurin et al showed similar outcomes with the use of CNI with or without steroid therapy (n=90) to steroid therapy alone (n=173) in primary FSGS (53). The dosing and duration of CNI in this scenario are similar to those with steroid resistant FSGS.

6.3 SPECIAL SITUATIONS

STEROID-RESISTANT FSGS

Recommendation 6.3.1.1: For adults with steroid-resistant primary FSGS, we recommend that cyclosporine or tacrolimus be given for ≥6 months rather than continuing with glucocorticoid monotherapy or not treating (1C).
Practice Point 6.3.2.1: See Figure 55 - Suggested dosing schedule for cyclosporine and tacrolimus
Practice Point 6.3.3.1: Adults with steroid-resistant primary FSGS who respond to CNI treatment should receive CNIs for a minimum of 12 months to minimize the risk of relapses
Practice Point 6.3.4.1: Adults who have steroid-resistant primary FSGS with resistance to or intolerance of CNIs should be referred to specialized centers for consideration of rebiopsy, alternative treatment, or enrolment in a clinical trial
Practice Point 6.3.5.1: Adults with previous steroid-sensitive primary FSGS who experience a relapse can be treated using the same approach as that for adults with relapsing MCD

We agree with the recommendation that CNI therapy should be used in patients with steroid resistant FSGS. This recommendation is based on two randomised controlled trials and observational studies. Ponticelli et al randomised 45 adults and children with steroid resistant FSGS or MCD to supportive therapy or Cyclosporine (54). Complete or partial response was significantly higher in the Cyclosporine group. In a second trial 49 adults with steroid resistant FSGS were randomised to low dose steroid therapy and Cyclosporine or placebo. The rate of complete or partial remission was significantly higher in the Cyclosporine group (70% versus 4%). Renal function was also better preserved in the CNI group (55). Relapses are common after CNI withdrawal. Hence a minimum of 12 months duration is recommended in those that do respond to CNI therapy, with a taper subsequently.

Although there is more data supporting the use of Cyclosporine, we agree that either Tacrolimus or Cyclosporine can be used. In the UK, Tacrolimus is used more extensively in glomerulonephritis treatment and transplantation, so there is more experience base. Furthermore, Tacrolimus is also associated with reduced cosmetic side effects.

Cyclosporine is started at 3 to 5 mg/kg per day in two divided doses, adjusting the dose to achieve a target trough level between 100 and 175 ng/ml. If Tacrolimus is used, we start with 0.05 to 0.1 mg/kg per day in two divided doses, adjusting the dose to target a trough level between 5 and 8 ng/mL

Figure 55 summarises the proposed KDIGO treatment schedule of CNI therapy.

Treatment	Dose and duration
Calcineurin inhibitors*	**Starting dose:** • Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l) • Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l)
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated • Consider discontinuing cyclosporine or tacrolimus if the eGFR continues to decline to <30 ml/min per 1.73 m^2
Inability to tolerate or contraindications to calcineurin inhibitors	• Lack of quality evidence for any specific alternative agents • Mycophenolate mofetil and high-dose dexamethasone, rituximab, and ACTH have been considered • Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression • Patients should be referred to specialized centers with the appropriate expertise, and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

Figure 55. Treatment of glucocorticoid-resistant primary FSGS.

For patients who are resistant to or intolerant of CNI there is no good quality evidence base to guide treatment. These patients should be enrolled into clinical trials. The risks of further immunosuppression in these groups of patients need to be individualised.

One randomised controlled trial and observational studies suggest benefit of MMF with or without steroid therapy in steroid resistant FSGS. Gipson et al randomised 138 patients (children and adults, although it was initially designed as a paediatric study) to either Cyclosporine or MMF with high dose Dexamethasone (56). At 12 months there was no significant difference in remission rates. However, the trial was underpowered.

Case reports have shown benefit in steroid dependent but not steroid resistant FSGS with Rituximab use (non-commissioned use).

There is little evidence to guide treatment of relapsing FSGS and in general we agree that relapsing FSGS should be managed as relapsing MCD in adults.

Chapter 7: Infection-related Glomerulonephritis

Infection related glomerulonephritis (IRGN) refers to a spectrum of clinical and histopathological presentations best grouped by their precipitating aetiologies. The KDIGO guideline explores these as bacterial, viral, and parasite related GNs (Chapter 7, pages S172-S186).

7.1 BACTERIAL INFECTION-RELATED GN

Diagnosis

Practice Point 7.1.1.1: Kidney biopsy can be useful in suspected bacterial infection-related glomerulonephritis (GN), particularly when culture evidence of infection is elusive or the diagnosis is in doubt, to assess prognosis, and/or for potential therapeutic reasons. In some cases, biopsy may

be critical for arriving at the correct diagnosis, as comorbidities may contribute to confounding effects (Figure 56)

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Risk and risk features	Children, elderly, immuno-compromised hosts, sub-sanitary living conditions	Highest: Ventriculo-atrial Mid: Ventriculo-jugular Least: Ventriculo-peritoneal	Prosthetic valve or structural heart valve lesion; substance abuse; elderly; diabetes mellitus; hepatitis C; HIV; immuno-compromised host	Diabetes mellitus, hypertension, heart disease, malignancy, alcohol or substance abuse, or kidney transplantation
History	Seek evidence of antecedent resolved pharyngitis (1–2 wks) or impetigo (4–6 wks)	May present within months or decades of shunt placement, sometimes after shunt revision. Diagnosis may be confounded and difficult in the 40% with occult infection	Echocardiographic evidence of cardiac valvular vegetations	Demonstration of active blood or tissue infection in a patient with acute GN
Physical exam	In some, active skin or tonsil infections present	Non-specific signs/ symptoms of infection, lethargy, fever, clinical signs of bacteremia	Fever, new or changed cardiac murmur; splenomegaly; characteristic skin lesions	Frequent hypertension. Exam mostly reflects the location/severity of the infection
Laboratory kidney	• Urinalysis (assess for glomerular hematuria and red blood cell casts); ACR; PCR • Measure serum creatinine/eGFR			
Laboratory infection	Culture skin or tonsils if infected Measure anti-streptolysin O, anti-DNAse B, and anti-hyaluronidase antibodies	Organism culture in blood, cerebrospinal fluid, shunt tip (after removal)	Blood culture positive 90%–98%; negative 2%–10%. Fastidious infections, such as *Candida, Coxiella burnetii, Borrelia,* and *Bartonella* may be difficult to culture. Serological tools for diagnosis may be required in such cases	Culture blood/tissues to identify bacterial infection (mostly staphylococcal)
Laboratory immunology	• Assess for low complement (C3, C4), rheumatoid factor, cryoglobulins, factor B antibody levels • Rule out other causes of nephritis if diagnosis in doubt: ANA, ANCA (occasionally PR3-ANCA in shunt nephritis and endocarditis), anti-GBM antibody			
				Serum IgA may be high

Figure 56. Evaluation of classic bacterial infection-related GN syndromes.

Bacterial IRGNs appear to be relatively rare in the UK, but are nevertheless reported (57-60). Suspicion should be raised when kidney dysfunction presents concomitantly with an acute or recent infection. Although most cases are diagnosed clinically through typical presentations (figure 56), a kidney biopsy can contribute to resolving diagnostic doubt. Circumstances for biopsy may include the absence of culture proven infection, rapidly or persistently progressive kidney disease, evidence of persistent complement consumption, or persistent haematuria/proteinuria despite treatment of an underlying infection.

Prognosis and Treatment

Practice Point 7.1.2.1: Prognosis and suggested therapy of bacterial infection-related GN are summarized in Figure 57.

	Postinfectious GN	Shunt nephritis	Endocarditis-related GN	IgA-dominant infection-related GN
Prognosis	Short-term prognosis in children is excellent. In endemic regions, persistent albuminuria may occur and some adults develop low eGFR. In the elderly, kidney prognosis is poor for those who develop persistent albuminuria; mortality may be up to 20%	Outcome is good with early diagnosis and treatment of infection. Most patients recover some kidney function but are left with residual chronic kidney disease	Immediate prognosis is good with prompt infection eradication. Some may require valve replacement	Dialysis is frequently required in the acute setting. Recovery is guarded, with <20% returning to pre-morbid levels of kidney function
Treatment	• No randomized controlled trials guide the treatment in any of these conditions • Antibiotics for underlying infection (although this will not alter GN course in postinfectious GN) per local guidelines. Antibiotics can be given in poststreptococcal GN if streptococci are cultured from any site. This is primarily done to prevent the spread of infection within community sites • Treat edema, hypertension, etc. as well as persistent proteinuria and/or progressive GFR decline as per Chapter 1			
	Value of high dose glucocorticoids remains unproven [1]	Most shunts have been replaced with a shunt with a lesser likelihood of infection. Rarely ventriculocisternostomy has been performed after shunt removal	Utility of glucocorticoids and immunosuppression unproven and carries serious potential risks, even in cases with crescentic GN [2]	For severe kidney functional impairment, weigh risks and benefits of immunosuppression. The risk of infection and glucocorticoid-induced complications in this often elderly population with comorbidities can be substantial. A role for immunosuppression remains unproven and these agents should generally not be used
Course	• Follow kidney function, serum C3 and C4, urinalysis, ACR, and proteinuria at appropriate intervals until complete remission or return to baseline			
	Persistently low C3 beyond 12 weeks may be an indication for kidney biopsy to particularly exclude C3GN.[3] Prevention of epidemic poststreptococcal GN may include socioeconomic interventions and mass antimicrobial use to improve living conditions and limit the spread of infection in populations where Group A streptococcus infection and scabies are highly prevalent	The natural history of the PR3-ANCA seen in some patients is unclear and requires follow-up	If the infection can be identified and promptly eradicated, the prognosis is favorable	The prognosis for recovery is poor, especially in diabetic subjects

Figure 57. Prognosis and therapy of classic bacterial infection-related GN syndromes.

Figure 57 highlights the favourable prognosis associated with most bacterial IRGNs, with the exception of the IgA dominant subtype. Management for bacterial IRGNs is restricted to adequate antimicrobial and symptom directed therapies. KDIGO emphasises the absence of evidence for systemic immunosuppression, including glucocorticoids. We would also add that preventative measures should be undertaken where possible. This may include administering prophylactic antibiotics following device placements if indicated, and alerting the UK health security agency (previously Public Health England) if notifiable aetiologies are identified (postinfectious GN can associate with epidemics).

7.2 VIRAL INFECTION-RELATED GN

KDIGO provides recommendations for the management of hepatitis C, hepatitis B and HIV infection related GNs.

HEPATITIS C VIRUS (HCV) INFECTION RELATED GN

The 2021 guideline concurs with recommendations made in the KDIGO 2018 guideline for the treatment of HCV in CKD (61).

Practice Point (2018 HCV in CKD Guideline): Diagnosis
5.1 We recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease (Not Graded).

The prevalence of HCV infections in the UK is falling, driven by a national drive towards eradication by 2030; with an estimated number of 92,900 cases in 2021 (62). Although a small proportion will develop glomerular disease, the precise risk for this in the UK is unclear. A spectrum of GNs associate with HCV, with mesangioproliferative GN secondary to mixed cryoglobulinemia being most common. GNs can occur independent of liver disease, and KIDGO accordingly recommends all patients with CKD are screened for HCV, and all patients with HCV are screened for kidney dysfunction (urinalysis and eGFR). A biopsy should be considered when kidney dysfunction is present to guide diagnosis and treatment.

Practice Point (2018 HCV in CKD Guideline): Treatment
5.2: We recommend that patients with HCV-associated glomerular disease be treated for HCV (1A). 5.2.1: We recommend that patients with HCV- related glomerular disease showing stable kidney function and/or non-nephrotic proteinuria be treated initially with DAA (1C).

Although no RCTs have evaluated treatments for HCV related GNs, pooled analyses of case, uncontrolled, and retrospective studies demonstrate a benefit to viral load reduction (61). Directly acting anti-virals (DAAs) are thus recommended for all HCV related GNs.

A variety of DAAs are licenced in the UK; specialist hepatology input should be sought when selecting the most suitable agent (63). Interferon based treatments are no longer recommended in the UK (63). DAAs should be commenced in conjunction with generic measures for CKD, including blood pressure and proteinuria control with RAASi if required (61). Commissioning arrangements are in place for DAA treatment options when prescribed by a hepatologist only.

Practice Point (2018 HCV in CKD Guideline): Treatment
5.2.2: We recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or rapidly progressive kidney failure be treated, in addition to DAA treatment, with immunosuppressive agents with or without plasma exchange (1C). 5.2.3: We recommend immunosuppressive therapy in patients with histologically active HCV-associated glomerular disease who do not respond to antiviral therapy, particularly those with cryoglobulinemic kidney disease (1B). 5.2.3.1: We recommend rituximab as the first-line immunosuppressive treatment (1C).

Organ or life-threatening disease, as defined by RPGN, nephrotic syndrome, or cryoglobulinaemic flares (extensive skin disease or severe peripheral neuropathy) warrants rescue therapy with immunosuppression. Suggested regimens include rituximab (four doses of rituximab 375mg/m^2 once per week, or two 1 gram doses given two weeks apart) +/- corticosteroids, or three pulses of methylprednisolone 0.5-1 gram once daily with cyclophosphamide 2mg/kg/day for 2-4 months. Plasma exchange to remove cryoglobulins (3L of plasma, three per week for 2-3 weeks) can also be considered (61). These measures can be instituted before DAA is started. Unfortunately, prognosis in such cases can remain poor even with aggressive treatment (64).

These recommendations are based on the observation that viral load reduction alone may not resolve glomerular damage nor clear cryoglobulins (65). This rationale also informs recommendation 5.2.3, where rituximab is suggested as first line over other immunosuppressants based on two RCTs and

retrospective studies (61). It must be noted however that Rituximab is not commissioned for this indication in the UK.

HEPATITIS B VIRUS (HBV) INFECTION RELATED GN

Diagnosis

Practice Point 7.2.2.1: Patients with proteinuric glomerular disease should undergo testing for HBV infection.

A spectrum of GNs associate with HBV, with membranous nephropathy (MN) being the most common. Evidence of glomerular disease should therefore prompt concurrent HBV testing. Although the incidence of HBV in the UK is relatively low, testing serves two purposes; 1) treatment of HBV infections can induce remission of HBV induced GNs, and 2) immunosuppressive treatments for GNs may severely exacerbate occult HBV infections. NICE guidelines for HBV testing are available (66).

Prognosis

Practice Point 7.2.2.2: Adult patients with chronic HBV infection should be considered at risk for the development of kidney failure

Adults with HBV associated MN have an increased risk of kidney failure, and adjunct treatment with systemic immunosuppression (including corticosteroids) carries a risk of HBV reactivation with low rates of therapeutic success. Caution is thus advised when considering treatments beyond those directed at lowering HBV loads for associated GNs. If required and appropriate, calcineurin inhibitors have been suggested as safe treatments in the setting of HBV infections.

Treatment

Recommendation 7.2.2.3: We recommend that patients with replicative HBV infection (as denoted by HBV DNA levels >2000 IU/ml) and GN receive treatment with nucleos(t)ide analogues as recommended for the general population by standard clinical practice guidelines for HBV infection (1C).
Practice Point 7.2.2.3.1: Pegylated interferon regimens should not be used to treat patients with replicative HBV infection and GN

Severe complications associate with untreated HBV infections. NICE recommends commencing pegylated peginterferon alfa-2a as first line treatment for chronic HBV infections (66), but this is not recommended in the context of a GN due to the risk of aggravated kidney disease. Alternatives are nucleoside analogues, which are approved in the UK and include entecavir and tenofovir disoproxil). National guidance and commissioning exists for initiating treatments for HBV infections, which should be followed in consultation with hepatologists (66). Treating HBV may not always induce remission of HBV driven GNs.

Practice point 7.2.2.3.2: Immunosuppressive agents, such as cyclophosphamide or rituximab, may accelerate HBV replication and should be avoided in patients with untreated replicative HBV infection and GN.
7.2.2.4.1: Rituximab and cyclophosphamide should be avoided in patients with simultaneous HBV infection and anti-PLA2R antibody-mediated MN until a sustained virologic remission has been obtained by nucleos(t)ide analogue therapy.
7.2.2.4.2: Plasma exchange may be tried in patients with accompanying cryoglobulinemic vasculitis.

As discussed under practice point 7.2.2.2, the prognosis of HBV driven GNs can be poor and systemic immunosuppressants carries a risk of exacerbating HBV related complications. While calcineurin inhibitors are considered safe, KDIGO recommend liaising with hepatologists to confirm sustained virologic remission prior to initiating any other immunosuppressive treatments for GNs. Based on limited

evidence, plasma exchange could be trialled for symptomatic cryoglobulinaemia, particularly if cryoglobulin levels are high (Crycrit > 5%, 500mg/dl).

Practice Point 7.2.2.4.3: Children with HBV infection and MN should be managed conservatively without immunosuppression due to a high likelihood of spontaneous remission of the kidney disease.

Paediatric MN in association with HBV is relatively rare in the UK. The likelihood of spontaneous remission in this context is high, and warrants the avoidance of immunosuppression. HBV directed treatment should be commenced in conjunction with specialist input.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)-RELATED GN

Diagnosis

Practice Point 7.2.3.1.1: A kidney biopsy should be performed, when feasible, to evaluate the morphology of HIV- related kidney disease. A pathology-based description of HIV-related kidney disease should be used to help define and guide therapy.

Prognosis

Practice Point 7.2.3.2.1: The factors contributing to the long-term outcome of HIV infection associated with GN are numerous and include persistence of viral replication, response to antiviral treatment, genetic predisposition to glomerular injury (e.g., APOL1 risk alleles), coinfection with other viruses, and development of immune complex disease or thrombotic microangiopathy. Thus, the estimation of prognosis in individual patients can be very difficult.

HIV can associate with a spectrum of lesions in the kidney, driven by the virus itself or by treatments for it. Evidence of kidney dysfunction should be evaluated with a biopsy to guide diagnosis, prognosis and management.

Treatment

Recommendation 7.2.3.3.1: We recommend that antiretroviral therapy be initiated in all patients with HIV and CKD, especially biopsy-proven HIV-associated nephropathy (HIVAN), regardless of CD4 count, adjusted to the degree of kidney function (1C).
Practice Point 7.2.3.3.1: A decision for the use of glucocorticoids as an adjunct therapy for HIVAN must be made on a case-by-case basis, as the risks and benefits long-term are uncertain

Viral load has an impact on kidney function, and highly active antiretroviral treatment (HAART) is protective and can improve kidney function and outcomes. Value in the early initiation of HAART is recommended for HIVAN, irrespective of CD4 counts, as demonstrated by the START and TEMPRANO trials. A variety of treatments are licensed and commissioned for HIV treatment in the UK (67). Decisions to start or modify antiretroviral treatments should be made with input from an HIV specialist. All treatments will need to be dose adjusted for CKD stage as needed. Corticosteroids may be used in HIVAN (e.g. uncontrolled proteinuria), but this must be considered on a case by case basis given the risk of adverse events.

7.3 NEPHROPATHIES DUE TO INFECTIONS WITH SCHISTOSOMIASIS, FILARIASIS AND MALARIA

These infections are not endemic to the UK and are not explored in detail here. An index of suspicion should be maintained when evaluating glomerular disease in those who have travelled from abroad. Management is centred around administering appropriate anti-parasitic agents (these are available in the UK and licenced for use), which should be prescribed with infectious diseases specialist input. We

concur with the guideline's emphasis on the lack of immunosuppression for GNs associated with these parasitic infections.

Patients with a history of schistosomiasis who present with haematuria, obstructive uropathy or a raised creatinine should be evaluated for bladder cancer.

A biopsy maybe considered when there is diagnostic uncertainty regarding the aetiology of the glomerular disease.

Chapter 8: Immunoglobulin- and complement-mediated glomerular diseases with a membranoproliferative glomerulonephritis (MPGN) pattern of injury

The recommendations and practice points on immunoglobulin- and complement-mediated glomerular diseases with an MPGN pattern are found in chapter 8, pages S187 to S192 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

Diagnosis

Practice Point 8.1.1: Evaluate patients with immune complex–mediated GN (ICGN) for underlying disease (Figure 68).

Immunoglobulin-/ immune complex-mediated	**Deposition of antigen–antibody immune complexes as a result of an infection:** • Viral: hepatitis C (including HCV-associated mixed cryoglobulinemia), hepatitis B • Bacterial: endocarditis, infected ventriculo-atrial shunt, visceral abscesses, leprosy, meningococcal meningitis • Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis, filariasis, histoplasmosis **Deposition of immune complexes as a result of an autoimmune disease:** • SLE • Sjögren's syndrome • Rheumatoid arthritis • Mixed connective tissue disease **Deposition of monoclonal Ig as a result of a monoclonal gammopathy due to a plasma cell or B cell disorder** **Fibrillary glomerulonephritis** **Idiopathic** • None of the conditions above are present
Complement-mediated	**C3 glomerulonephritis and C3 DDD:** • Mutations in complement regulatory proteins: CFH, CFI, CFHR5 • Mutations in complement factors: C3 • Antibodies to complement factors: C3, C4, and C5 nephritic factors • Antibodies to complement regulatory proteins: CFH, CFI, CFB **C4 glomerulonephritis and C4 DDD**
Membranoproliferative pattern without immune complexes or complement	• Healing phase of HUS/TTP • Antiphospholipid (anticardiolipin) antibody syndrome • POEMS syndrome • Radiation nephritis • Nephropathy associated with bone marrow transplantation • Drug-associated thrombotic microangiopathies • Sickle cell anemia and polycythemia • Dysfibrinogenemia and other pro-thrombotic states • Antitrypsin deficiency

Figure 68. Causes of a membranoproliferative pattern of injury.

Practice Point 8.1.2: Evaluate patients with GN and monoclonal immunoglobulin deposits for a hematologic malignancy.

Practice Point 8.1.3: If no underlying etiology is found for ICGN after extensive workup, evaluate for both complement dysregulation and drivers of complement dysregulation (Figure 70).

Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, and CFHR1-5 MLPA
Plasma cell disorders‡	Serum free light chains, serum and urine electrophoresis, and immunofixation†
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3, negative or minimal Ig, negative C4d)

Figure 70. Evaluation of abnormalities of the alternative pathway of complement

Practice Point 8.1.4: Rule out infection-related GN or post-infectious GN prior to assigning the diagnosis of C3 glomerulopathy (C3G).
Practice Point 8.1.5: Evaluate for the presence of a monoclonal protein in patients who present for the first time with a C3G diagnosis at ‡50 years of age (Figure 69).

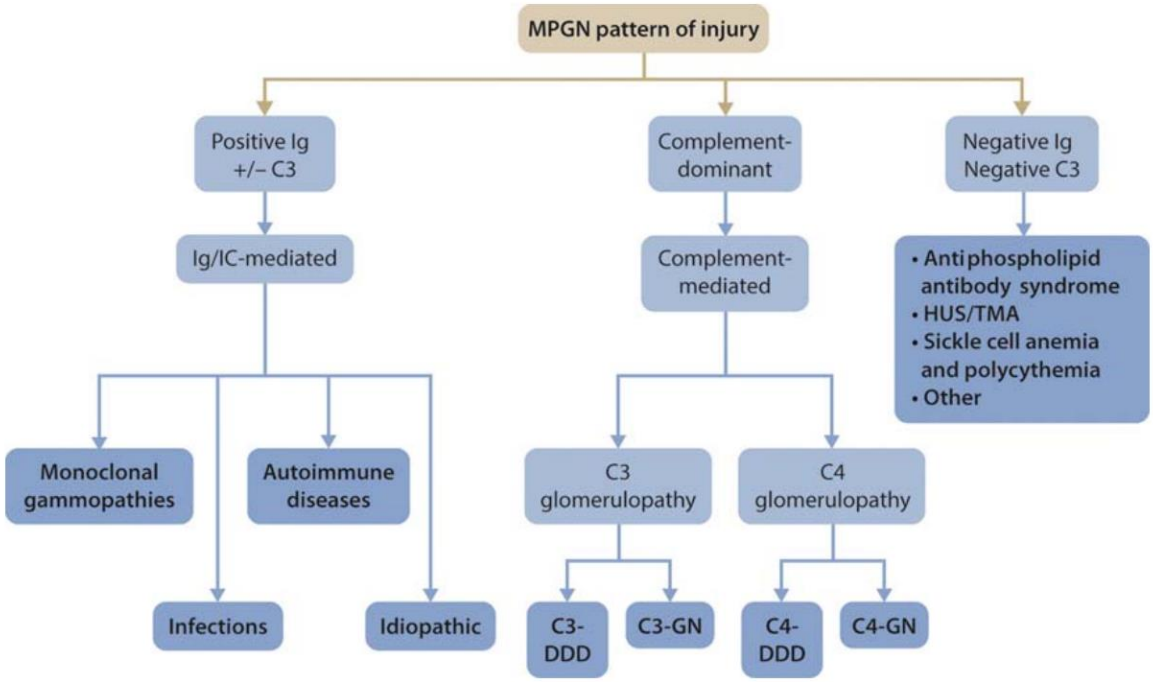

Figure 69. Pathophysiology of membranoproliferative lesions.

The practice points in this section reflect our current understanding and classification when a membranoproliferative (mesangiocapillary) pattern of disease is found on renal biopsy. They emphasise the division into immunoglobulin dominant, C3 dominant, or immunoglobulin and C3 negative aetiologies. A monoclonal protein should be sought in all immunoglobulin positive cases and in older C3 dominant cases.

8.2 TREATMENT

Treatment of Immune Complex-Mediated GN

Practice Point 8.2.1.1: When the cause of ICGN is determined, the initial approach to treatment should focus on the underlying pathologic process.
Practice Point 8.2.1.2: Indolent ICGN, whether idiopathic or linked to a primary disease process, is best managed with supportive care and carefully considered use of immunosuppression.
Practice Point 8.2.1.3: For patients with idiopathic ICGN and proteinuria <3.5 g/d, the absence of the nephrotic syndrome, and a normal eGFR, we suggest supportive therapy with RAS inhibition alone.
Practice Point 8.2.1.4: For patients with idiopathic ICGN, a nephrotic syndrome, and normal or near-normal SCr, try a limited treatment course of glucocorticoids.
Practice Point 8.2.1.5: For patients with idiopathic ICGN, abnormal kidney function (but without crescentic involvements), active urine sediment, with or without nephrotic-range proteinuria, add glucocorticoids and immunosuppressive therapy to supportive care.
Practice Point 8.2.1.6: For patients presenting with a rapidly progressive crescentic idiopathic ICGN, treat with high-dose glucocorticoids and cyclophosphamide.
Practice Point 8.2.1.7: For most patients with idiopathic ICGN presenting with an eGFR <30 ml/min per 1.73 m^2, treat with supportive care alone.
Practice Point 8.2.1.8: Patients who fail to respond to the treatment approaches discussed in 8.2.1.4 and 8.2.1.5 should be considered for a clinical trial where available.

Treatment of an associated infection or autoimmune disease (Figure 68) is clearly indicated (8.2.1.1). If a monoclonal protein due to a B cell disorder is found this is likely to be relevant to pathogenesis. Treatment should often be led by haematologists as they may be more familiar with drugs that may be used and the assessment of treatment response. When there is no likely cause of ICGN then decisions regarding treatment are more difficult as there is no robust evidence base. With normal renal function and sub-nephrotic proteinuria we agree with the suggestion of supportive care (8.2.1.2-3).

Corticosteroids alone are suggested for nephrotic syndrome with normal renal function (8.2.1.4), and immunosuppressive therapy with corticosteroids (8.2.1.5). We are not sure of the rationale for using corticosteroids alone with normal renal function and suggest MMF with steroids in both situations. Even with rapidly progressive GN, we suggest caution in using cyclophosphamide (8.2.1.6) in the absence of evidence of benefit. It would also be reasonable to treat with MMF with steroids in this setting. We agree that initiating a treatment with potential adverse effects and uncertain benefit is not usually advisable when the eGFR is less than 30 (8.2.1.7).

Treatment of C3 Glomerulopathy

8.2.2.1: In the absence of a monoclonal gammopathy, C3G in patients with moderate-to-severe disease should be treated initially with MMF plus glucocorticoids, and if this fails, eculizumab should be considered.
8.2.2.2: Patients who fail to respond to the treatment approaches discussed in 8.2.2.1 should be considered for a clinical trial where available.

There are several case series exploring the effects of immunosuppression. The reported results are detailed in the KDIGO guideline and the results are variable. Overall, they favour a trial of MMF and steroids as the initial treatment.

Given the underlying complement dysregulation there is a clear rationale to using the anti-C5 monoclonal eculizumab. Eculizumab is approved in the UK for the treatment of recurrent C3 glomerulopathy in a renal transplant providing it is authorised by a national expert centre (68). However, data supporting use of eculizumab is relatively weak in C3 glomerulopathy. It is not currently funded by NHS England but may be considered with rapidly progressive crescentic GN (69).

Genetic testing, evaluation of the complement system, and screening for autoantibodies including C3 nephritic factor and C5 nephritic factor may be considered. However, the value of these tests in guiding treatment or prognosis is not defined. This may develop in time, and we encourage the participation in RaDaR and the National Study of MPGN and C3 glomerulopathy.
Children have been omitted from this chapter despite paediatric nephrologists managing these conditions. Management is similar to other forms of GN in that a period of observation is not usually

adopted for children and the proteinuria and renal function goals are much stricter. Treatment would usually consist of supportive management, including use of ACEi or ARB, high dose corticosteroids and MMF.

Chapter 9: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

The recommendations and practice points on ANCA-associated vasculitis (AAV) are found in chapter 9, pages S193 to S206 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

9.1 DIAGNOSIS

We agree that the diagnosis of AAV should be based on 2012 Chapel Hill definitions of primary systemic vasculitis (70). 90% of patients have MPO or PR3 ANCA. High-quality antigen specific immunoassays are the preferred screening method for ANCA.

Practice Point 9.1.1: In the case of a clinical presentation compatible with small-vessel vasculitis in combination with positive myeloperoxidase (MPO)- or proteinase 3 (PR3)- ANCA serology, waiting for a kidney biopsy to be performed or reported should not delay starting immunosuppressive therapy, especially in patients who are rapidly deteriorating.
Practice Point 9.1.2: Patients with ANCA-associated vasculitis (AAV) should be treated at centres with experience in AAV management.

We agree with these statements. Glucocorticoids should not be delayed. The decision to commence rituximab or cyclophosphamide prior to obtaining a tissue diagnosis should be considered on a case-by-case basis. Various factors will influence this decision, such as how unwell the patient is and how long the wait for kidney biopsy will be. Empirical induction immunosuppression should only be started after exclusion of severe intercurrent infection, discussion with a clinician experienced in treating vasculitis and transfer of the patient to an experienced centre should be prioritised.

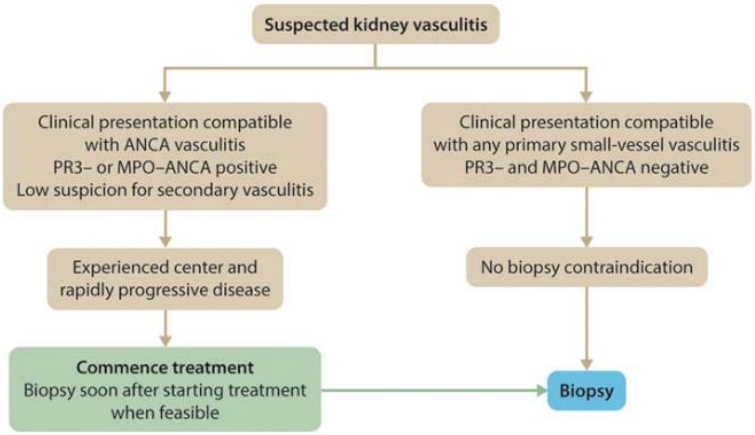

Figure 71. Biopsy strategy in suspected kidney vasculitis.

Relapses

Practice Point 9.2.3.1: The persistence of ANCA positivity, an increase in ANCA levels, and a change in ANCA from negative to positive are only modestly predictive of future disease relapse and should not be used to guide treatment decisions

Detecting relapsing disease in a sensitive and specific manner is one of the most challenging aspects

of AAV management. For relapse detection, ANCA is only one aspect of patient assessment. In patients in whom immunosuppressive treatment has been stopped (particularly after discontinuation of rituximab), a switch from ANCA negative to positive or a rise in ANCA has greater predictive value. In this situation we recommend increased relapse monitoring, and education of patients regarding potential relapse risk.

9.3 TREATMENT

Induction

Recommendation 9.3.1.1: We recommend that glucocorticoids in combination with cyclophosphamide or rituximab be used as initial treatment of new-onset AAV. The best evidence is available for patients with new-onset AAV. In patients with severe (SCr >4 mg/dl [>354 μmol/l]) kidney disease, limited data for induction therapy with rituximab are available.
Practice Point 9.3.1.1: A recommended treatment algorithm for AAV with kidney involvement is given in Figure 76.
Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining GFR (SCr>4mg/dl [>354 μmol/l]), there are limited data to support rituximab and glucocorticoids. Cyclophosphamide and glucocorticoids are preferred for induction therapy. The combination of rituximab and cyclophosphamide can also be considered in this setting.
Practice Point 9.3.1.3: Considerations for choosing between rituximab and cyclophosphamide for induction therapy are given in Figure 77.

We agree with this recommendation, although as per figure 77 in patients with serum creatinine >354 μmol/l, rituximab and cyclophosphamide combination therapy can be considered as an alternative to cyclophosphamide alone (71). NHS England commissioning policy (72) permits rituximab as first line induction therapy when cyclophosphamide is contraindicated; there has had an inadequate therapeutic response to cyclophosphamide; or when cyclophosphamide will impact on family planning and fertility (see Practice Point 9.3.1.3 and figure 77 for relative contraindications to cyclophosphamide).

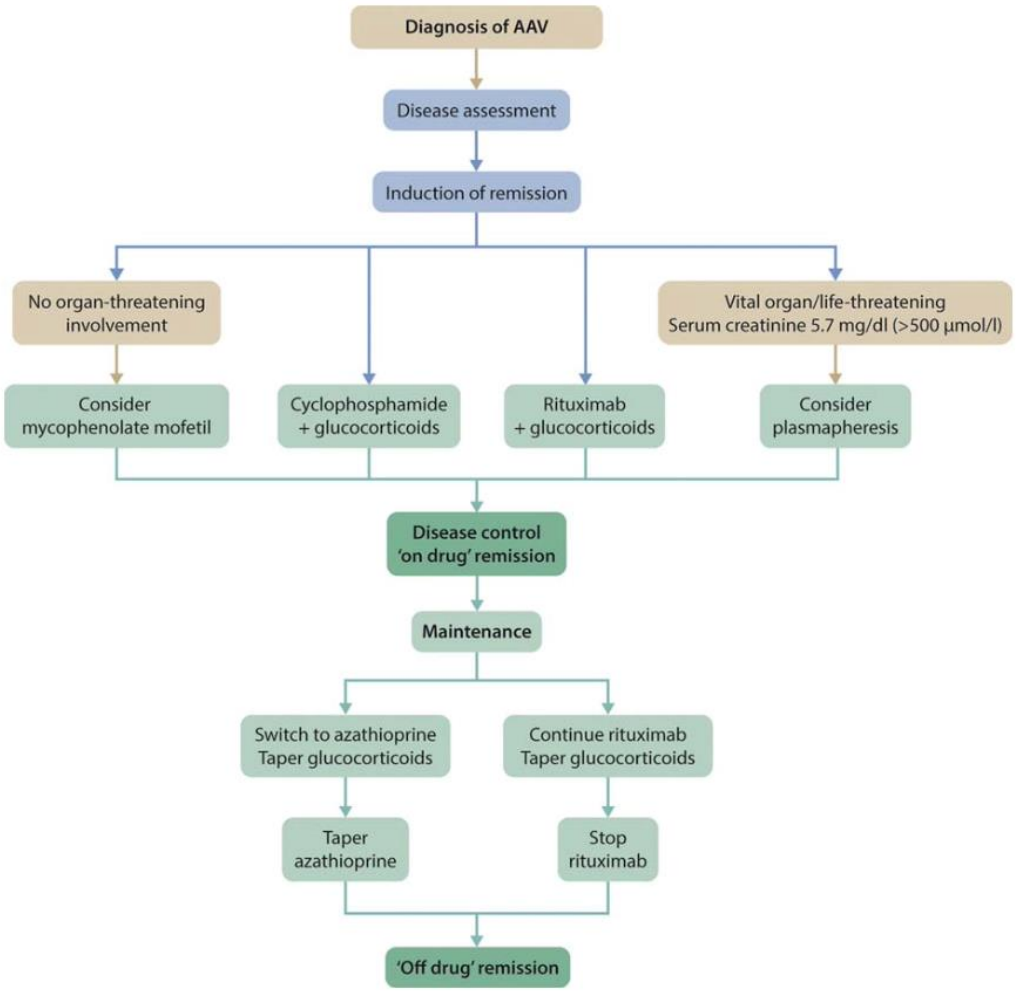

Figure 76. Recommended treatment regimen for AAV.

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered

Figure 77. Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV.

This is the only section in the KDIGO AAV guidelines that considers children. Whilst uncommon, AAV can occur in children and the management is aligned with adult practice.

Practice Point 9.3.1.4: Considerations for choosing the route of administration of cyclophosphamide are given in Figure 78.

We agree and emphasise that with standardised treatment duration for intravenous and oral cyclophosphamide, the cumulative dose of cyclophosphamide is higher with oral dosing. Intravenous cyclophosphamide is associated with reduced rates of leucopenia, but higher relapse rates during follow up.

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

Figure 78. Considerations for the route of administration of cyclophosphamide for AAV.

Practice Point 9.3.1.5: Discontinue immunosuppressive therapy after 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease.
Practice Point 9.3.1.6: Recommendations for oral glucocorticoid tapering are given in Figure 79.

	'Reduced-corticosteroid dose' in PEXIVAS trial		
Week	<50 kg	50–75 kg	>75 kg
1	50	60	75
2	25	30	40
3–4	20	25	30
5–6	15	20	25
7–8	12.5	15	20
9–10	10	12.5	15
11–12	7.5	10	12.5
13–14	6	7.5	10
15–16	5	5	7.5
17–18	5	5	7.5
19–20	5	5	5
21–22	5	5	5
23–52	5	5	5
>52	Investigators' local practice		

Figure 79. Prednisolone tapering regimen for AAV.

Glucocorticoid side-effects and infective complications are associated with substantial morbidity as well as mortality risk. The reduced dose glucocorticoid regimen used in the PEXIVAS trial (73) was non-inferior to a standard glucocorticoid protocol for the primary endpoint of ESKD or death, and serious infections were less frequent. We agree that the PEXIVAS reduced dose regimen should be recommended for patients with severe or life threatening disease. We add that further reductions in glucocorticoid tapering doses can be considered for non-severe disease (74).

Since publication of the KDIGO guidelines, avacopan, an oral C5a receptor antagonist, has received NICE approval for use in severe renal ANCA-associated vasculitis (75). In the phase 3 ADVOCATE trial (76), avacopan 30mg twice daily was non-inferior to prednisolone for remission induction at week 26 and superior at maintaining remission at week 52, with no adverse safety findings (77). Furthermore, avacopan was associated with greater improvements in eGFR compared to prednisolone, particularly in patients with baseline eGFR 15-30ml/min/1.73m^2 (78, 79). Patients with an eGFR <15ml/min/1.73m^2 or dialysis dependence were excluded from the trial. IV methylprednisolone was permitted prior to trial entry, as well as oral prednisolone for the first 4 weeks at investigator discretion. Cumulative oral glucocorticoid exposure in the avacopan group was approximately one third of that in the prednisolone group. Avacopan was found to be associated with improvements in some quality of life outcomes and lower glucocorticoid toxicity index scores. The use of avacopan for 12 months was associated with fewer relapses than prednisolone continued to week 21; however, avacopan has not been compared to azathioprine or rituximab so its role in remission maintenance is not fully established.

ANCA-associated vasculitis (a rare disease) is the first disease indication for avacopan. In accordance, avacopan is an expensive drug. We therefore recommend that avacopan is initially prioritised for

patients at high risk of glucocorticoid side effects and those presenting with a GFR of 15-30ml/min/1.73m^2 (at greatest risk of ESKD). Avacopan also offers a potential additional option for vasculitis patients with treatment resistant disease.

Practice Point 9.3.1.7: Recommendations for immunosuppressive dosing are given in Figure 80.

Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m^2/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m^2/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response
Reduction for age: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m^2	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m^2			

Figure 80. Immunosuppressive drug dosing for AAV.

Practice Point 9.3.1.8: Consider plasma exchange for patients with SCr >5.7 mg/dl (500 μmol/l) requiring dialysis or with rapidly increasing SCr, and in patients with diffuse alveolar hemorrhage who have hypoxemia.

The role of plasma exchange in severe AAV is controversial. The PEXIVAS trial, conducted in 704 patients with a baseline eGFR <50ml/min/1.73m^2, found no benefit in the prevention of ESKD and death (73). Since the KDIGO guidance was published, a meta-analysis of approximately 1000 patients (including the PEXIVAS trial) found plasma exchange has no impact on mortality but was associated with reduced risk of ESKD at 12 months and increased risk of severe infection (80). The estimated absolute risk reduction of ESKD ranged from 0.08% in patients presenting with a creatinine ≤200 μmol/L to 16% in those presenting with a creatinine >500 μmol/L or requiring dialysis (81).

We suggest that decisions regarding the use of plasma exchange in severe AAV are made on a case by case basis in organ or life threatening disease.

Practice Point 9.3.1.9: Add plasma exchange for patients with an overlap syndrome of ANCA vasculitis and anti-GBM.

Double antibody positive for ANCA and anti-GBM occurs in approximately 5-10% ANCA positive patients, usually presents with renal and/or pulmonary haemorrhage and confers a worse renal prognosis than single positive ANCA-vasculitis. As for patients with anti-GBM disease, double antibody positive patients should usually receive plasma exchange until anti-GBM antibodies are negative. Unlike anti-GBM disease, double antibody positive patients will normally require maintenance immunosuppression.

Maintenance therapy

Recommendation 9.3.2.1: We recommend maintenance therapy with either rituximab or azathioprine and low-dose glucocorticoids after induction of remission (1C). This recommendation places a higher value on prevention of relapses and a relatively lower value on adverse events related to immunosuppressive drugs.
Practice Point 9.3.2.1: Following cyclophosphamide induction, either azathioprine plus low-dose glucocorticoids or rituximab without glucocorticoids should be used to prevent relapse.
Practice Point 9.3.2.2: Following rituximab induction, maintenance immunosuppressive therapy should be given to most patients.

The MAINRITSAN (82) and RITAZAREM (83) trials demonstrated superiority of rituximab fixed interval dosing as maintenance (500mg rituximab every six months in MAINRITSAN and 1000mg rituximab every 4 months in RITAZAREM) therapy over azathioprine in AAV. In the MAINRITSAN trial, patients in both arms received low dose prednislone and some clinicians would give this with Rituximab maintenance (in contrast to Paractice point 9.3.2.4). Rituximab has a significant impact on humoral immunity – with impaired vaccine responses, and long-term hypogammaglobulinaemia with recurrent infections in a subset of patients. Approximately 5% of patients require immunoglobulin replacement therapy following repeat rituximab to prevent infection. Therefore, the use of rituximab as maintenance therapy should be balanced against infection risk and prioritised for those at greatest relapse risk (Figure 82) (84, 85). KDIGO summarise factors that should be considered in balancing rituximab against azathioprine in Practice 9.3.2.7 (Figure 82).

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Lower serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide exposure • Immunosuppressive withdrawal • Glucocorticoid withdrawal

Figure 82. Factors that increase relapse risk for AAV.

Practice Point 9.3.2.3: The optimal duration of azathioprine plus low-dose glucocorticoids is not known but should be between 18 months and 4 years after induction of remission.
Practice Point 9.3.2.4: The optimal duration of rituximab maintenance is not known, but studies to date have evaluated a duration of 18 months after remission. There is no role for the routine use of an oral glucocorticoid or oral immunosuppressive with rituximab maintenance.
Practice Point 9.3.2.5: When considering withdrawal of maintenance therapy, the risk of relapse should be considered, and patients should be informed of the need for prompt attention if symptoms recur (Figure 82).

The current lack of a sensitive and specific biomarker for AAV disease activity, makes relapse timing difficult to predict. Figure 82 concisely summarises the current evidence-based predictors of relapsing disease. The REMAIN (86) trial showed a benefit in terms of relapse prevention by the continuation of azathioprine out to four years. Therefore, in patients deemed to be high risk of relapse, azathioprine maintenance therapy should be continued for at least four years and may need to be continued longer. In the post treatment follow-up phases of MAINRITSAN and RITAZAREM, relapses were greater in the azathioprine groups, however relapses still occured in the rituximab groups. Therefore, careful evaluation of relapse risks, patient education and a plan for monitoring is required before stopping rituximab. In all patients, risks of rituximab withdrawal should be balanced against risks of impact on humoral immunity and infection by continuation of rituximab (87).

Practice Point 9.3.2.6: Consider methotrexate for maintenance therapy in patients, after induction with methotrexate or for those who are intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m2.
Practice Point 9.3.2.7: Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in Figure 83.

Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline IgG <300 mg/dl • Hepatitis B exposure (HBsAg positive) • Limited availability of rituximab

Figure 83. Considerations for using rituximab or azathioprine for AAV maintenance therapy.

The decision between azathioprine and rituximab maintenance is discussed in more detail under Practice Point 9.3.2.2.

Practice Point 9.3.2.8: Recommendations for dosing and duration of maintenance therapy are given in Figure 84.

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at months 6, 12 and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at months 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until one yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yrs
	Extend azathioprine at complete remission until 4 yrs after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yrs after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yrs and then slowly reduced by 1 mg every 2 mo	

Figure 84. Immunosuppressive dosing and duration of AAV maintenance therapy.

Relapsing disease

Practice Point 9.3.3.1: Patients with relapsing disease (life- or organ-threatening) should be reinduced (Recommendation 9.3.1.1.), preferably with rituximab.

We agree with this practice point. NHS England commissioning permits rituximab for relapse after previous cyclophosphamide induction therapy (72). The RAVE trial found that rituximab was more effective than cyclophosphamide for relapsing disease (especially in PR3-AAV) (88). Using rituximab for relapse also avoids repeated courses of cyclophosphamide (reducing malignancy risks associated with high cumulative cyclophosphamide dose).

9.4 SPECIAL SITUATIONS

Refractory disease

Practice Point 9.4.1.1: Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa. Plasma exchange can be considered.

Between 10-20% of patients will not respond adequately to rituximab or cyclophosphamide induction therapy. We agree with practice point 9.4.1.1. Combining rituximab with cyclophosphamide is helpful in achieving disease control in patients with inadequate initial response to one or other agent. For example, 2 doses of rituximab 1g can be combined with 2-3 intravenous 15mg/kg cyclophosphamide pulses: or, 2 doses of rituximab 1g can be combined with fortnightly intravenous cyclophosphamide for 6 doses (10mg/kg for first 2 doses (750mg maximum), followed by 500mg for 4 doses) (71, 89). High dose glucocorticoids and plasma exchange can also be considered for patients with advanced renal involvement (i.e. creatinine >300 μmol/L) and severe refractory disease.

Practice Point 9.4.1.2: In the setting of diffuse alveolar bleeding with hypoxemia, plasma exchange should be considered in addition to glucocorticoids with either cyclophosphamide or rituximab.

The numbers of patients with pulmonary haemorrhage and hypoxia (≤85% oxygen saturation on room air or needing mechanical ventilation) in the PEXIVAS trial were low but plasma exchange did not confer any additional survival benefit. Therefore we do not think plasma exchange should be used in this setting.

Transplantation

Practice Point 9.4.2.1: Delay transplantation until patients are in complete clinical remission for >6 months. Persistence of ANCA should not delay transplantation.

We agree with this recommendation, given the possibility of AAV recurrence after transplantation.

Chapter 10: Lupus Nephritis

The recommendations and practice points on lupus nephritis are found in chapter 10, pages S207 to S230 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

10.1 DIAGNOSIS

Practice point 10.1.1: Approach to the diagnosis of kidney involvement in systemic lupus erythematosus (SLE) (Figure 85)

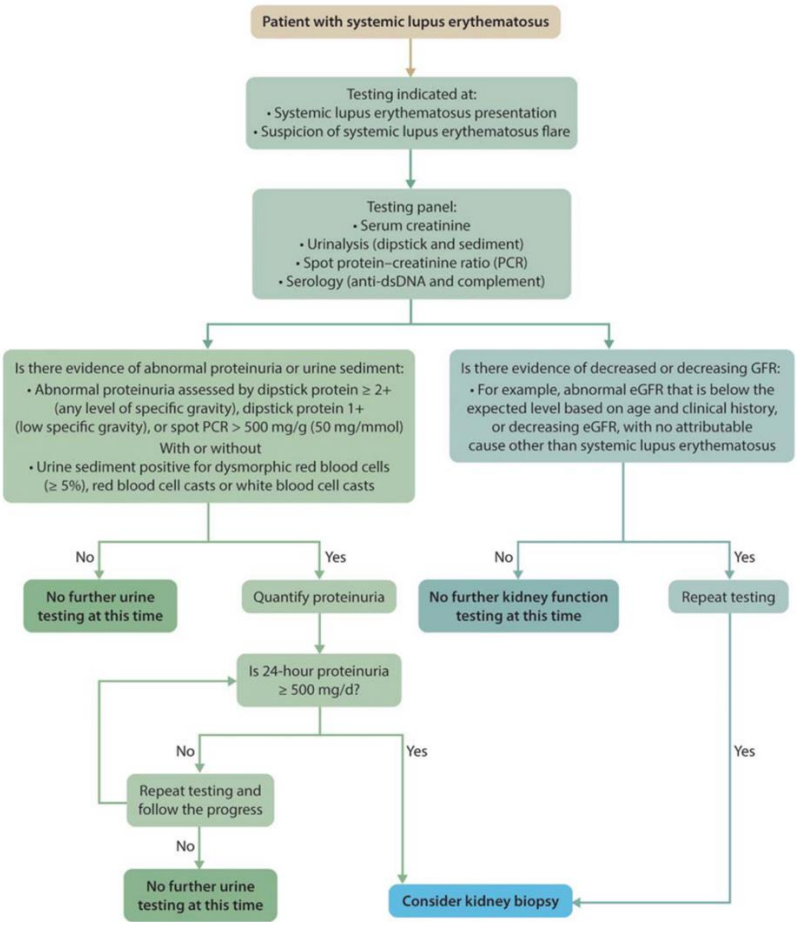

Figure 85. Diagnosis of kidney involvement in SLE.

A 24-hour urine collection to quantify proteinuria is recommended if dipstick protein is 1+ or there is a PCR >50mg/mmol (regardless of haematuria). As assessment of urinalysis may be observer dependent, we suggest sending a urine PCR or ACR every time a patient with SLE is seen, regardless of findings on urinalysis, and at least every 6 months. 24 hour urine collections for proteinuria are rarely performed outside clinical trials in the UK. We suggest confirming an abnormal urine PCR or ACR and referring to a nephrologist if the PCR is >50 mg/ml or ACR > 30mg/mmol) for assessment and consideration of a renal biopsy. We further suggest that in the setting of nephrotic range proteinuria with a decreased serum albumin, treatment with mycophenolate mofetil and prednisolone could be initiated straight away and before a renal biopsy is performed. A diagnosis other than lupus nephritis, such as minimal change disease, is very unlikely especially if there is also active lupus serology.

10.2 TREATMENT

General management of patients with lupus nephritis

Recommendation 10.2.1.1: We recommend that patients with SLE, including those with lupus nephritis (LN), be treated with hydroxychloroquine or an equivalent antimalarial unless contra-indicated (1C).
Practice Point 10.2.1.1: Adjunctive therapies to manage LN and attenuate complications of the disease or its treatments should be considered for all patients, as outlined in Figure 87.

We agree that all patients with SLE including those with LN should receive hydroxychloroquine. There are several observational studies showing a reduction in disease flares and thrombotic events. Although there are no robust trial data, it is unlikely that a large trial that addresses this will ever be performed. Other measures mentioned in 10.2.1.1 include considering cardiovascular risk, RAS blockade for proteinuria, blood pressure control, bone protection, contraception, screening for viruses and vaccination. These are all considerations that apply to any patients with glomerular disease receiving immunosuppression and we agree with them. Considerations more specific to LN include limiting UV light and cyclophosphamide exposure and it is difficult to disagree with these. Measures suggested to preserve fertility, if cyclophosphamide is used, include sperm/oocyte cryopreservation and gonadotrophin-releasing hormone agonists. We agree that sperm cryopreservation should be offered prior to cyclophosphamide administration and refer readers to the UKKA Clinical practice guideline on pregnancy and renal disease (3.2.1 and 3.2.1 and the associated rationale) for recommendations on preserving female fertility.

CLASS I or CLASS II LUPUS NEPHRITIS

Practice Point 10.2.2.1: Approach to immunosuppressive treatment for patients with Class I and Class II LN (Figure 88)

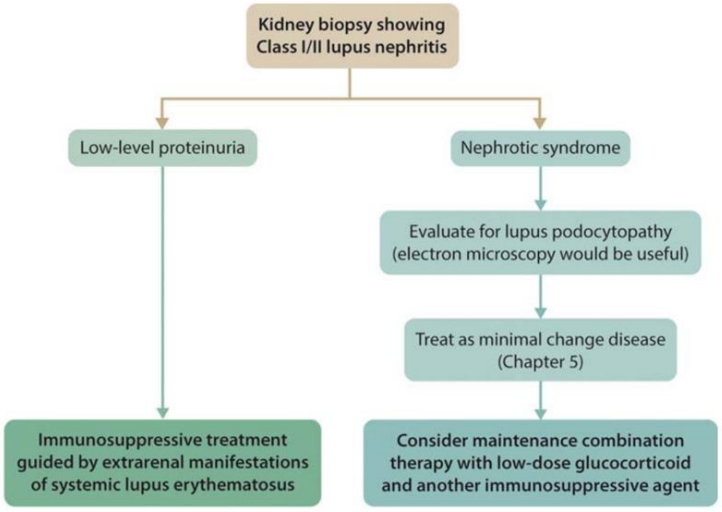

Figure 88 | Immunosuppressive treatment for patients with Class I or Class II LN. LN, lupus nephritis.

We agree with 10.2.2.1, stating that immunosuppression is not indicated with class I/II lupus nephritis and low-level proteinuria, and that nephrotic syndrome should be treated as minimal change disease.

CLASS III OR CLASS IV LUPUS NEPHRITIS

Initial therapy of active Class III/IV lupus nephritis

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with glucocorticoids plus either low-dose intravenous cyclophosphamide or MPPA (1B).
Practice Point 10.2.3.1.1: A regimen of reduced-dose glucocorticoids following a short course of methylprednisolone pulses may be considered during the initial treatment of active LN when both the kidney and extrarenal disease manifestations show satisfactory improvement
Practice Point 10.2.3.1.2: Intravenous cyclophosphamide should be used as the initial therapy for active Class III and Class IV LN in patients who may have difficulty adhering to an oral regimen.
Practice Point 10.2.3.1.3: An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at high risk of infertility, patients who have a moderate to high prior cyclophosphamide exposure, and patients of Asian, Hispanic, or African ancestry.
Practice Point 10.2.3.1.4: Initial therapy with a triple immunosuppressive regimen that includes a CNI (tacrolimus or ciclosporin) with reduced-dose MPAA and glucocorticoids is reserved for patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.
Practice Point 10.2.3.1.5: In patients with baseline eGFR of at least 45 ml/min per 1.73 m^2 , voclosporin can be added to MPAA and glucocorticoids as initial therapy for 1 year. This is not licensed in the UK at the moment or commissioned.
Practice Point 10.2.3.1.6: There is an emerging role for B-lymphocyte targeting biologics in the treatment of LN. Belimumab can be added to standard therapy in the treatment of active LN. Rituximab may be considered for patients with persistent disease activity or repeated flares.
Practice Point 10.2.3.1.7: Other therapies, such as azathioprine or leflunomide combined with glucocorticoids, may be considered in lieu of the recommended initial drugs for proliferative LN in situations of patient intolerance, lack of availability, and/or excessive cost of standard drugs, but these alternatives may be associated with inferior efficacy, including increased rate of disease flares and/or increased incidence of drug toxicities.

We would qualify recommendation 10.2.3.1.1 and suggest that initial treatment for class III or IV LN should be glucocorticoids and MMF in the large majority of patients. Low dose intravenous cyclophosphamide could be used only if MMF is not tolerated or there is another compelling reason such as poor adherence. Several trials have shown that MMF has a similar efficacy to oral or intravenous cyclophosphamide (90-93). The largest trial addressing this was the ALMs study which included 370 patients. Although MMF did not lead to a reduction in infection risk, there is no effect on fertility or haematological malignancy which would occur with cyclophosphamide use. The optimal dose of MMF is uncertain. In the ALMs trial where a target dose of 3g was used (median achieved 2.6g). In transplant patients there are data suggesting that 2g is as effective as 3g per day with less adverse effects (94). However, there are no data on this point in LN and the optimal dose of MMF is uncertain. A trial in 90 predominantly white patients showed that low dose iv cylophosphamide (6 doses of 500mg) was as effective as high dose cyclophosphamide (95), with a follow up report at 10 years (96). Another trial in Asian patients showed that low dose iv cyclophosphamide was as effective as MMF in the short term (97). If cyclophosphamide is used, then 6 doses of 500mg should be given based on these studies, rather than higher doses.

There are no trials that inform the optimal steroid reduction regimen to use (10.2.3.1.1) but there is a growing trend in steroid minimisation both in trials and in clinical practice. It is not known if intravenous methylprednisolone given as up to three daily pulses at the start of induction therapy has a benefit that justifies the inconvenience and potential toxicity. We do agree that there should be some flexibility in the steroid regimen used. This may be modified based on treatment response and patient choice. We consider 10.2.3.1.3 to be unnecessary as we suggest MMF is preferred in all patients.

The use of tacrolimus with reduced MMF (10.2.3.1.4) is based primarily on a trial of 368 Chinese patients showing a superior complete or remission rates to iv cyclophosphamide at 24 weeks months (98). 216 patients in complete or partial remission in this trial were continued on triple therapy or given azathioprine and followed for a further 18 months. The complete remission rates were similar suggesting that some patients initially given cyclophosphamide take longer to respond but eventually this group catches up. It is suggested that voclosporin can be added as initial therapy in patients with an eGFR > 45 (10.2.3.1.5). This is based on the AURORA-1 phase 3 trial of 357 patients (99). Patients received MMF at 2g a day with a rapid steroid taper, with or without voclosporin. At 52 weeks the complete remission rate was superior in the voclosporin group. One could question whether MMF at 2g/day and a rapid steroid taper is standard of care, and whether a benefit for voclosporin was more

likely with this regimen, than with a high dose of MMF and a greater steroid exposure. Voclosporin is not licensed in the UK at the moment or commissioned.

A limitation of trials including CNIs is that proteinuria is assessed whilst patients are still taking a CNI leading to a reduction in the measured proteinuria which is partly due to the direct effect of CNIs on podocytes. This complicates interpretation of most published trials so far. An assessment of proteinuria after a brief period without a CNI would give a more meaningful measure of the effect on disease activity. CNIs have a place in the management of lupus nephritis in patients with preserved renal function. However, we suggest that they are unlikely to be used as initial therapy in the UK based on current evidence. They may be considered as an add on therapy in patients who have not responded to or not tolerated both MPA and cyclophosphamide.

Practice point 10.2.3.1.6 concerns B cell targeting therapies. The BLISS-LN trial compared Belimumab as add on to standard therapy (cyclophosphamide or MPA with steroids) in 448 patients with LN. Belimumab was added to standard care within 60 days of initiation of induction therapy (100). A benefit was suggested based on an endpoint with a PCR threshold that was changed to 0.7 mg/mg (79 mg/mmol) during the trial. If the initial ordinal primary outcome measure had been used - including a PCR of 0.5 mg/mg (56 mg/mmol) – there would have been no difference between groups. There are no trial data showing a benefit for Rituximab, but extensive experience suggesting a benefit in some patients with LN. Obinutuzumab is a long acting B cell depleting monoclonal which has shown promising results, when added to standard care, in a trial of 125 patients (published after the KDIGO guideline), with more patients in complete renal remission at 52 weeks (101). In summary, belimumab, rituximab and obinutuzumab may be considered in patients with an incomplete response to MMF or cyclophosphamide, or a relapse soon after induction treatment. They are unlikely to be used as a routine addition to standard of care based on current evidence. Rituximab and obinutuzumab are not licensed for the treatment of SLE, although rituximab and belimumab are commissioned for this indication. Belimumab is not commissioned for isolated renal disease but may be used if specified criteria are met, and this may include renal disease

Practice point 10.2.3.1.7 concerns treatment inferior options such as azathioprine or leflunamide which would be very rarely used in the UK and would be considered inadequate therapy. Leflunamide is not licensed for this indication.

Maintenance therapy for Class III and Class IV lupus nephritis

Recommendation 10.2.3.2.1: We recommend that after completion of initial therapy, patients should be placed on MPAA for maintenance (1B).
Practice Point 10.2.3.2.1: Azathioprine is an alternative to MPAA after completion of initial therapy in patients who do not tolerate MPAA, who do not have access to MPAA, or who are considering pregnancy.
Practice Point 10.2.3.2.2: Glucocorticoids should be tapered to the lowest possible dose during maintenance, except when glucocorticoids are required for extrarenal lupus manifestations; discontinuation of glucocorticoids can be considered after patients have maintained a complete clinical renal response for ‡12 months.
Practice Point 10.2.3.2.3: The dose of MMF in the early maintenance phase is approximately 750–1000 mg twice daily, and for MPA, approximately 540–720 mg twice daily.
Practice Point 10.2.3.2.4: If MPAA and azathioprine cannot be used for maintenance, CNIs or mizoribine should be considered.
Practice Point 10.2.3.2.5: The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should not be <36 months.

We agree with the recommendation to use MPPA as first line therapy as the maintenance phase of the ALMS trial showed superiority when compared with azathioprine (102). The MAINTAIN trial suggested equivalence, but it was a less robust design given the smaller numbers, lack of blinding, and the fact that not all patients were in remission when randomised (103).

We agree that azathioprine is an alternative and should be used when MMF is not tolerated or pregnancy is planned. CNIs are an alternative but mizoribine is not used in the UK (10.2.3.3). Practice point 10.2.3.2 states that the lowest possible dose of prednisolone should be used in the maintenance phase and we agree that 5mg a day should be used unless extrarenal symptoms necessitate a higher

dose. We also agree that consideration should be given to stopping prednisolone at ≥12 months. The dose of MMF is suggested as 750 – 1000mg bd in the early phase (10.2.3.2).

The total duration of immunosuppression is suggested to be at least 36 months (10.2.3.2.5) and we agree with this. It is uncertain how long immunosuppression should be continued and when it may be stopped. There is a significant risk of relapse if immunosuppression is withdrawn in patients with a history of LN (104).

CLASS V LUPUS NEPHRITIS

Practice Point 10.2.4.1: A suggested approach to the management of patients with pure Class V LN is described in Figure 94.

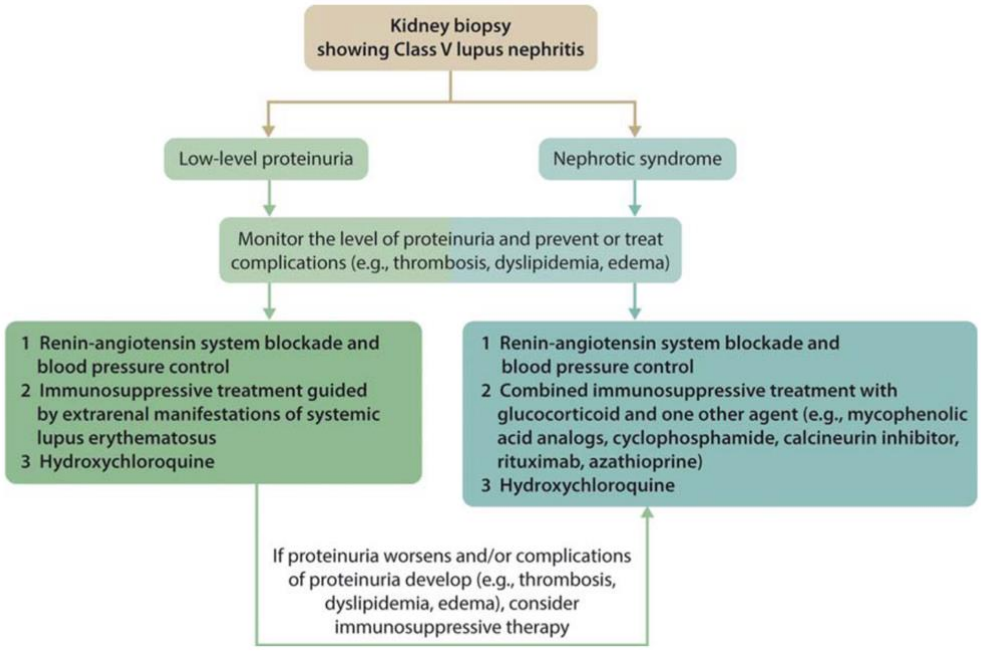

Figure 85. Diagnosis of kidney involvement in SLE.

Class V LN may remit spontaneously and we agree that immunosuppressive treatment should be withheld unless there is nephrotic range proteinuria. This is not always a straightforward decision. There is a borderline area of heavy proteinuria, with no accepted definition of nephrotic. In some cases, the decision to start treatment may be guided by trends in serum albumin and proteinuria, or consideration of a combination of extrarenal symptoms and proteinuria. A further consideration is that it may be difficult to exclude a concurrent class III component, which would indicate a need for treatment, if there is a small renal biopsy sample.

Corticosteroids are suggested with one other immunosuppressive medication but no recommendation is given for and MMF, cyclophosphamide, CNI, rituximab or azathioprine. There are no large clinical trials that include only patients with class V LN and hence no robust evidence on which to base a choice. However, given the efficacy of MMF for class III and IV LN, and the favourable adverse effect profile of MMF compared with cyclophosphamide and CNIs, most nephrologists in the UK would favour MMF as first line therapy for class V LN.

Assessing treatment response in LN

Practice Point 10.2.4.1.1: Definitions of response to therapy in LN as provided in Figure 95.

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

Figure 95. Commonly used definitions of response to therapy in LN.

The definitions of complete and partial response are generally accepted. A PCR from a 24 hour urine collection is rarely used in clinical practice in the UK due to the inconvenience for patients. However, we acknowledge that this would be a more precise measure.

Management of unsatisfactory response to treatment

Practice Point 10.2.4.2.1: An algorithmic approach to patients whose response to therapy is deemed unsatisfactory is provided in Figure 96.

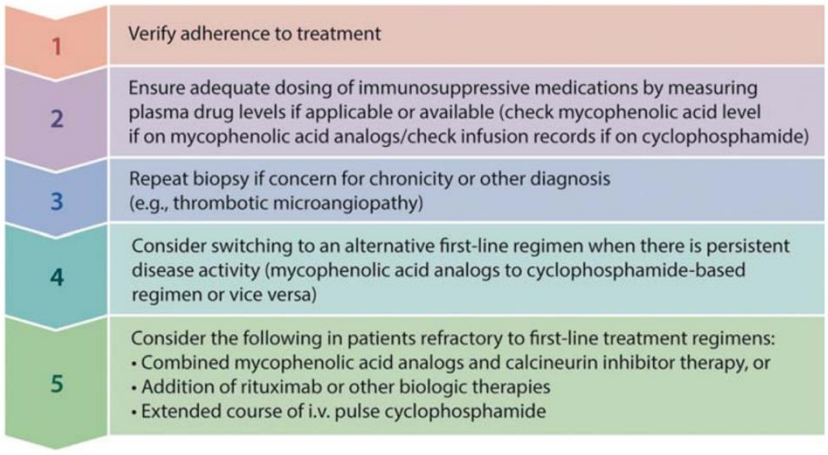

Figure 96. Management of patients who show unsatisfactory response to initial therapy for active LN.

The measures listed for assessing response listed are reasonable. We agree that a discussion on adherence is a priority in patients with an unsatisfactory response as this is a common issue. Additional treatment options include CNIs and B cell therapies as discussed above.

Treatment of LN relapse

Practice Point 10.2.4.3.1: After a complete or partial remission has been achieved, LN relapse should be treated with the same initial therapy used to achieve the original response, or an alternative recommended first-line therapy

Diagnosis and treatment of a relapse is one of the most difficult aspects of managing LN. Issues around adherence and whether to repeat the renal biopsy are complex. MMF is first line therapy in the majority of patients and most would be taking MMF as maintenance therapy at the time of relapse. Therefore, a relapse may be treated with an increase in the dose of MMF with corticosteroids. This approach is effective in most patients. It is essential to discuss adherence at the time of a relapse as poor adherence may be a factor. If adherence has been poor and this is likely to be a continued concern, intravenous cyclophosphamide may be preferred. Cyclophosphamide may also be preferred if adherence had been

good, but the relapse has occurred soon after a course of induction therapy with MMF. An increase in proteinuria may be due to chronic damage or active disease and a renal biopsy may be needed to decide if an increase in immunosuppression is needed. However, if there is heavy proteinuria and active serology, a renal biopsy is unlikely to change treatment. If treatment is given for a presumed relapse without a renal biopsy, but there is no response, it may be appropriate to perform a biopsy at this stage. It is often difficult to decide if a renal biopsy will be useful at the time of a renal relapse.

10.3 SPECIAL SITUATIONS

Practice Point 10.3.1.1: Patients with LN and thrombotic microangiopathy (TMA) should be managed according to the underlying etiology of TMA, as shown in Figure 97.
Practice Point 10.3.2.1: Patients with active LN should be counselled to avoid pregnancy while the disease is active or when treatment with potentially teratogenic drugs is ongoing, and for 6 months after LN becomes inactive
Practice Point 10.3.2.2: To reduce the risk of pregnancy complications, hydroxychloroquine should be continued during pregnancy, and low-dose aspirin should be started before 16 weeks of gestation
Practice Point 10.3.2.3: Only glucocorticoids, hydroxychloroquine, azathioprine, and CNIs are considered safe immuno-suppressive treatments during pregnancy
Practice Point 10.3.3.1: Treat pediatric patients with LN using immunosuppression regimens similar to those used in adults, but consider issues relevant to this population, such as dose adjustment, growth, fertility, and psychosocial factors, when devising the therapy plan
Practice Point 10.3.4.1: Patients with LN who develop kidney failure may be treated with hemodialysis, peritoneal dialysis, or kidney transplantation; and kidney transplantation is preferred to long-term dialysis.

These suggestions are not controversial. The points regarding pregnancy are consistent with the UKKA clinical practice guideline on pregnancy and renal disease (5.3). An additional point from the UKKA guideline is that women who are positive for anti-Ro (SSA) or anti-La (SSB) antibodies should be referred for fetal echocardiography in the second trimester (guideline 5.3.4).

The disease is often recognised to be more severe in children and genetic contributors are more common. The treatment of LN in children is similar to the management used in adults, but clinicians must consider issues relevant to this population, such as dose adjustments, growth, fertility, and psychological factors when devising a therapy plan. As lupus is relatively uncommon in children their management should be led by a multiprofessional team that includes paediatric nephrologists and rheumatologists. Consultation with adult colleagues may be helpful.

Chapter 11: Anti-glomerular basement membrane (Anti-GBM) antibody glomerulonephritis

The recommendations and practice points on anti-glomerular basement membrane (anti-GBM) antibody glomerulonephritis are summarised in chapter 11, pages S231 to S234 of the KDIGO guideline. We refer the reader to this for a full statement of practice points discussed in this commentary.

11.1 DIAGNOSIS

Practice Point 11.1.1: Diagnosis of anti-glomerular basement membrane (anti-GBM) disease should be made without delay in all patients with suspected RPGN (Figure 98).

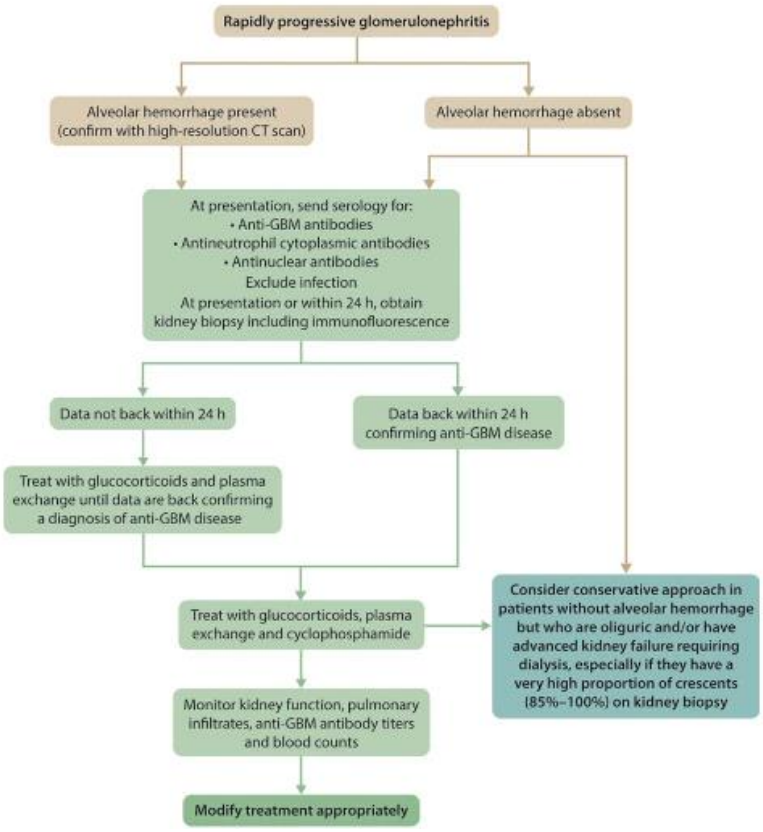

Figure 98. Diagnosis and therapy in anti-GBM disease.

We agree that patients with suspected rapidly progressive glomerulonephritis should be urgently screened for anti-GBM antibodies (as well as ANCA), using enzyme-linked immunosorbent assays (ELISA). The attending clinician should be aware that 10% of anti-GBM cases are seronegative, and these patients will only have a diagnosis made on kidney biopsy. We note KDIGO recommend urgent kidney biopsy at presentation or within 24 hours. We add the caveat that urgent biopsy is not always possible e.g. with severe lung haemorrhage or extreme anaemia. We agree that high-resolution CT is the best modality to diagnose alveolar haemorrhage and that bronchoscopy is not routinely needed.

11.2 TREATMENT

Recommendation 11.2.1: We recommend initiating immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis in all patients with anti-GBM GN except those who are treated with dialysis at presentation, have 100% crescents or >50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary haemorrhage (1C).

Five year mortality is 10-20% and renal survival is 50% with aggressive immunosuppression (105) and renal replacement therapy. Delayed diagnosis and a slow initiation of treatment increases risk of ESKD and death. We agree that, where possible, a diagnosis of anti-GBM disease should be made with either a positive anti-GBM antibody or renal biopsy before commencing immunosuppression. However, initial treatment should not be delayed, and patients with suspected disease should be treated with high dose glucocorticoids and plasma exchange when severe infection (as an alternative diagnosis) has been excluded. We agree that cyclophosphamide should be started after the diagnosis is confirmed with either positive serology or renal biopsy.

KDIGO recommend considering a conservative management approach in patients presenting with oliguria or dialysis dependence, particularly in the presence of >85-100% crescents on renal biopsy, due to the low chance of kidney recovery. We agree that patients with alveolar haemorrhage should receive aggressive immunosuppression, regardless of kidney function.

In addition to the KDIGO treatment recommendations, we recommend that all patients are considered for entry into a clinical trial. Encouraging results were recently published from an international phase II trial, GOOD-IDES-01 with imlifidase (an endopeptidase that cleaves circulating and kidney-bound IgG) (106). The study enrolled 15 patients with eGFR <15 ml/min/1.73m^2 and circulating anti-GBM antibodies who received one infusion of imlifidase, alongside cyclophosphamide and glucocorticoids. Within 6 hours the mean reduction in anti-GBM antibodies was 99%. Plasma exchange was only permitted when anti-GBM antibodies rebounded after imlifidase treatment. At 6 months, 10 of 15 patients were dialysis independent. Imlifidase is being further evaluated in a phase III randomised controlled trial (GOOD-IDES-02) for patients with anti-GBM disease and GFR<20 ml/min/1.73m^2 without anuria.

Practice Point 11.2.1: Treatment for anti-GBM disease should start without delay if this diagnosis is suspected, even before the diagnosis is confirmed.
Practice Point 11.2.2: Plasma exchange should be performed until anti-GBM titers are no longer detectable.
Practice Point 11.2.3: Cyclophosphamide should be administered for 2–3 months and glucocorticoids for about 6 months
Practice Point 11.2.4: No maintenance therapy of anti-GBM disease is necessary.
Practice Point 11.2.5: Patients with GN who are anti-GBM- and ANCA-positive should be treated with maintenance therapy as for patients with AAV.

We agree with practice points 11.2.1-5. We also agree with the recommendation of using azathioprine or mycophenolate (plus glucocorticoids) in the few patients who still have positive serology after 3 months of cyclophosphamide. KDIGO recommends 2-3mg/kg of daily oral cyclophosphamide (reduced to 2mg/kg in patients over the age of 55) for 2-3 months. There is less experience with IV cyclophosphamide which allows reduction in cumulative exposure and bladder toxicity but may increase relapse risk. Relapse of anti-GBM disease is very uncommon, we agree that no maintenance therapy after 6 months is needed; except in cases of concomitant ANCA positivity. We add that patients with lung haemorrhage who continue to smoke are at increased relapse risk and should be advised accordingly and provided with smoking cessation advice.

Practice Point 11.2.6: In refractory anti-GBM disease, rituximab may be tried.
Practice Point 11.2.7: Kidney transplantation in patients with kidney failure due to anti-GBM disease should be postponed until anti-GBM antibodies remain undetectable for ≥ 6 months.

Refractory anti-GBM disease is uncommon and the evidence for rituximab is limited to case-reports. Given the central role of anti-GBM antibodies in the disease pathogenesis, targeting B-cells maybe a reasonable therapeutic approach in refractory disease.

We agree that kidney transplantation should be performed until anti-GBM antibodies have been undetectable for at least 6 months.

References

1. National Institute for Health and Care Excellence. Chronic kidney disease: assessment and management, NICE guideline NG203, 2021. Available from: www.nice.org.uk/guidance/ng203. [Accessed March 2022].

2. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015; 26;373(22):2103-16.

3. The Renal Association. Commentary on NICE guideline (NG136) 'Hypertension in adults: diagnosis and management' including proposals for blood pressure management in patients with chronic kidney disease. 2021. Available from: https://ukkidney.org/health-professionals/guidelines/commentary-nice-guideline-ng136-%E2%80%98hypertension-adults-diagnosis-and?msclkid=685522b9b0eb11ec84711ec398b22fbc [Accessed March 2022].

4. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358(15):1547-1559.

5. Banerjee D, Winocour P, Chowdhury TA, et al. Association of British Clinical Diabetologists and The Renal Association. Management of hypertension and renin-angiotensin-aldosterone system blockade in adults with diabetic kidney disease: Association of British Clinical Diabetologists and the Renal Association UK guideline update 2021. *BMC Nephrol* 2022;23(1):9.

6. The Renal Association. Clinical Practice Guidelines: Treatment of Acute Hyperkalaemia in Adults. 2020. Available from: https://ukkidney.org/health-professionals/guidelines/treatment-acute-hyperkalaemia-adults. [Accessed March 2022].

7. Wheeler DC, Toto RD, Stefánsson BV, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int.* 2021;100(1):215-224.

8. National Institute for Health and Care Excellence. Dapagliflozin for treating chronic kidney disease. NICE technology appraisal guidance TA775, 2022. Available from: https://www.nice.org.uk/guidance/TA775. [Accessed September 2022]

9. UK Kidney Association. Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibition in Adults with Kidney Disease. 2021. Available from: https://ukkidney.org/health-professionals/guidelines/ukka-clinical-practice-guideline-sodium-glucose-co-transporter-2 [Accessed September 2022].

10. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification, NICE guideline CG181, 2014. Available from: www.nice.org.uk/guidance/cg181. [Accessed April 2022].

11. Carter SA, Lightstone L, Cattran D, et al. SONG-GD Initiative. Standardized Outcomes in Nephrology-Glomerular Disease (SONG-GD): establishing a core outcome set for trials in patients with glomerular disease. *Kidney Int* 2019; 95(6):1280-1283

12. The Renal Association. Clinical Practice Guidelines: Pregnancy and Renal Disease. 2019. Available from: https://ukkidney.org/health-professionals/guidelines/pregnancy-and-renal-disease. [Accessed April 2022].

13. Soares MF, Genitsch V, Chakera A, et al. Relationship between renal CD68+ infiltrates and the Oxford Classification of IgA nephropathy. *Histopathology.* 2019;74(4):629-637.

14. Barbour SJ, Coppo R, Zhang H, et al. Evaluating a New International Risk-Prediction Tool in IgA Nephropathy [published correction appears in *JAMA Intern Med*. 2019 Jul 1;179(7):1007]. *JAMA Intern Med.* 2019;179(7):942-952.

15. Barbour SJ, Coppo R, Zhang H, et al. International IgA Nephropathy Network. Application of the International IgA Nephropathy Prediction Tool one or two years post-biopsy. *Kidney Int*. 2022;102(1):160-172.

16. Rauen T, Eitner F, Fitzner C, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med.* 2015;373(23):2225-2236.

17. Lennartz DP, Seikrit C, Wied S, et al. Single versus dual blockade of the renin-angiotensin system in patients with IgA nephropathy. *J Nephrol.* 2020;33(6):1231-1239.

18. Barratt J. Corticosteroids Should Be Used to Treat Slowly Progressive IgA Nephropathy: CON. *Kidney360.* 2021;2(7):1081-1083.

19. Lv J, Zhang H, Wong MG, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *JAMA*. 2017;318(5):432-442.

20. Lv J, Wong MG, Hladunewich MA, et al. Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. *JAMA*. 2022;327(19):1888-1898.

21. Cheung CK, Barratt J. Pregnancy in IgA Nephropathy: An Effect on Renal Outcome?. *Am J Nephrol.* 2019;49(3):212-213.

22. Barratt J, Floege J. SGLT-2 inhibition in IgA nephropathy: the new standard of care?. *Kidney Int.* 2021;100(1):24-26.

23. The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023,12;388(2):117-127.

24. Fernández-Juárez G, Rojas-Rivera J, Logt AV, et al. The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy. *Kidney Int.* 2021;99(4):986-998.

25. Scolari F, Delbarba E, Santoro D, et al. Rituximab or Cyclophosphamide in the Treatment of Membranous Nephropathy: The RI-CYCLO Randomized Trial [published online ahead of print, 2021 Mar 1]. *J Am Soc Nephrol*. 2021;32(4):972-982.

26. Rojas-Rivera J, Fervenza FC, Ortiz A. Recent Clinical Trials Insights into the Treatment of Primary Membranous Nephropathy. *Drugs*. 2022;82(2):109-132.

27. NHS England National Programmes of Care and Clinical Reference Groups. (October 2022) Clinical Commissioning Policy Rituximab for idiopathic membranous nephropathy (Adults) (2012) [201005P]. Available from: https:// www.england.nhs.uk/publication/clinical-commissioning-policy-rituximab-for-idiopathic-membranous-nephropathy/ [Accessed November 2022]

28. Kanigicherla DAK, Hamilton P, Czapla K, Brenchley PE. Intravenous pulse cyclophosphamide and steroids induce immunological and clinical remission in New-incident and relapsing primary membranous nephropathy. *Nephrology (Carlton).* 2018;23(1):60-68.

29. Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. *N Engl J Med*. 2019;381(1):36-46.

30. Dussol B, Morange S, Burtey S, et al. Mycophenolate mofetil monotherapy in membranous nephropathy: a 1-year randomized controlled trial. *Am J Kidney Dis.* 2008;52(4):699-705.

31. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *Lancet*. 2018;392(10141):61-74.

32. Trautmann A, Bodria M, Ozaltin F, et al. Spectrum of steroid-resistant and congenital nephrotic syndrome in children: the PodoNet registry cohort. *Clin J Am Soc Nephrol.* 2015;10(4):592-600.

33. Sinha A, Saha A, Kumar M, et al. Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome. *Kidney Int.* 2015;87(1):217-24.

34. Teeninga N, Kist-van Holthe JE, van Rijswijk N, et al. Extending prednisolone treatment does not reduce relapses in childhood nephrotic syndrome. *J Am Soc Nephrol.* 2013;24(1):149-59.

35. Yoshikawa N, Nakanishi K, Sako M, et al. A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment. *Kidney Int.* 2015;87(1):225-32.

36. Webb NJ, Woolley RL, Lambe T, et al. Sixteen-week versus standard eight-week prednisolone therapy for childhood nephrotic syndrome: the PREDNOS RCT. *Health Technol Assess.* 2019;23(26):1-108.

37. Christian MT, Webb NJA, Mehta S, et al. Evaluation of Daily Low-Dose Prednisolone During Upper Respiratory Tract Infection to Prevent Relapse in Children With Relapsing Steroid-Sensitive

Nephrotic Syndrome: The PREDNOS 2 Randomized Clinical Trial. *JAMA Pediatr*. 2022;176(3):236-43.

38. Trautmann A, Schnaidt S, Lipska-Zietkiewicz BS, Bodria M, Ozaltin F, Emma F, et al. Long-Term Outcome of Steroid-Resistant Nephrotic Syndrome in Children*. J Am Soc Nephrol.* 2017;28(10):3055-65.

39. Li S, Yang H, Guo P, et al. Efficacy and safety of immunosuppressive medications for steroid-resistant nephrotic syndrome in children: a systematic review and network meta-analysis. *Oncotarget*. 2017;8(42):73050-62.

40. Magnasco A, Ravani P, Edefonti A, et al. Rituximab in children with resistant idiopathic nephrotic syndrome. *J Am Soc Nephrol*. 2012;23(6):1117-24.

41. Ruggenenti P, Ruggiero B, Cravedi P, et al. Rituximab in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. *J Am Soc Nephrol.* 2014;25(4):850-63.

42. Mason AE, Sen ES, Bierzynska A, Colby E, Afzal M, Dorval G, et al. Response to First Course of Intensified Immunosuppression in Genetically Stratified Steroid Resistant Nephrotic Syndrome. *Clin J Am Soc Nephrol*. 2020;15(7):983-94.

43. Black DA, Rose G, Brewer DB. Controlled trial of prednisone in adult patients with the nephrotic syndrome. *BMJ* 1970;3:421–426.

44. Coggins CH. Adult minimal change nephropathy: Experience of the collaborative study of glomerular disease. *Trans Am Clin Climatol Assoc* 1986;97:18–26.

45. Yeung CK, Wong KL, Ng WL. Intravenous methylprednisolone pulse therapy in minimal change nephrotic syndrome. *Aust NZ J Med* 1983;13:349–351.

46. Imbasciati E, Gusmano R, Edefonti A, et al. Controlled trial of methylprednisolone pulses and low dose oral prednisone for the minimal change nephrotic syndrome. *Br Med J (Clin Res Ed)* 1985;291:1305–1308.

47. Medjeral-Thomas NR, Lawrence C, Condon M, 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;15:209-218.

48. Chin HJ, Chae DW, Kim YC, et al. Comparison of the efficacy and safety of tacrolimus and low-dose corticosteroid with high-dose corticosteroid for minimal change nephrotic syndrome in adults. *J Am Soc Nephrol* 2021;32:199-210

49. Rémy P, Audard V, MSN Trial Investigators, et al. An open-label randomized controlled trial of low-dose corticosteroid plus enteric-coated mycophenolate sodium versus standard corticosteroid treatment for minimal change nephrotic syndrome in adults (MSN Study). *Kidney Int*. 2018;94:1217-1226.

50. Xue C, Yang B, Xu J, et al. Efficacy and safety of rituximab in adult frequent-relapsing or steroid-dependent minimal change disease or focal segmental glomerulosclerosis: a systematic review and meta-analysis. *Clin Kidney J.* 2021;14:1042-1054.

51. Ponticelli C, Edefonti A, Ghio L, et al. Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: a multicentre randomized controlled trial. *Nephrol Dial Transplant* 1993;8:1326-1332.

52. Ponticelli C, Villa M, Banfi G, et al. Can prolonged treatment improve the prognosis in adults with focal segmental glomerulosclerosis? *Am J Kidney Dis* 1999;34(4):618-625.

53. Laurin LP, Gasim AM, Poulton CJ, et al. Treatment with glucocorticoids or calcineurin inhibitors in primary FSGS. *Clin J Am Soc Nephrol* 2016;11(3):386-394.

54. Ponticelli C, Rizzoni G, Edefonti A, et al. A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. *Kidney Int* 1993;43(6):1377-1384.

55. Cattran DC, Appel GB, Hebert LA, et al. A randomized trial of cyclosporine in patients with steroid-resistant focal segmental glomerulosclerosis. North America Nephrotic Syndrome Study Group. *Kidney Int* 1999;56(6):2220-2226.

56. Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. *Kidney Int* 2011;80(8):868-878.

57. Worthing KA, Lacey JA, Price DJ, et al. Systematic Review of Group A Streptococcal *emm* Types Associated with Acute Post-Streptococcal Glomerulonephritis. *Am J Trop Med Hyg.* 2019;100(5):1066-1070.

58. Harkiss GD, Brown DL, Evans DB. Longitudinal study of circulating immune complexes in a patient with Staphylococcus albus-induced shunt nephritis. *Clin Exp Immunol.* 1979;37(2):228-238.

59. Barnes E, Frankel A, Brown EA, Woodrow D. Glomerulonephritis Associated with Permanent Pacemaker Endocarditis. *Am J Nephrol.* 1995;15(5):436-438.

60. Majumdar A, Chowdhary S, Ferreira MAS, et al. Renal pathological findings in infective endocarditis. *Nephrol Dial Transplant* 2000;15(11):1782-1787.

61. KDIGO 2022 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease. *Kidney Int.* 102 (Suppl 6S), S129–S205

62. Public Health England. Hepatitis C in the UK: 2023 report. February 2023. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1133731/hepatitis-c-in-the-UK-2023.pdf. [Accessed February 2023].

63. National Institute for Health and Care Excellence. Hepatitis C. NICE Clinical Knowledge Summaries. 2020; Available from: https://cks.nice.org.uk/topics/hepatitis-c/.[Accessed November 2022].

64. Tarantino A, Campise M, Banfi G, et al. Long-term predictors of survival in essential mixed cryoglobulinemic glomerulonephritis. *Kidney Int.* 1995 Feb;47(2):618-623.

65. Humphries K, Darling JM, Barritt AS. Membranoproliferative Glomerulonephritis, Type II Cryoglobulinemia and Triple Therapy for Hepatitis C: A Case Series and Review of the Literature. *Dig Dis Sci* 2014;16;59(8):2007-2012.

66. National Institute for Health and Care Excellence. Hepatitis B. NICE Clinical Knowledge Summaries. 2022; Available from: https://cks.nice.org.uk/topics/hepatitis-b/. [Accessed September 2022].

67. National Institute for Health and Care Excellence. HIV infection and AIDS. NICE Clinical Knowledge Summaries. 2021; Available from: https://cks.nice.org.uk/topics/hiv-infection-aids/. [Accessed September 2022].

68. National Institute for Health and Care Excellence. C3 glomerulopathy in the native kidney: eculizumab. NICE Evidence summary [ESUOM49]. 2015. Available from: https://www.nice.org.uk/guidance/esuom49 [Accessed September 2022]

69. Le Quintrec M, Lionet A, Kandel C, et al. Eculizumab for treatment of rapidly progressive C3 glomerulopathy. *Am J Kidney Dis*. 2015;65: 484−9.

70. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*. 2013;65(1):1-11.

71. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010;363(3):211-220.

72. Clinical commissioning policy: Rituximab for the treatment of ANCA associated vasculitis in adults (2015). Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a13-ritux-anca-vascul.pdf [Accessed November 2022].

73. Walsh M, Merkel PA, Peh CA, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. *N Engl J Med.* 2020;382(7):622-631.

74. Furuta S, Nakagomi D, Kobayashi Y, et al. Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial. *JAMA*. 2021;325(21):2178-2187.

75. National Institute for Health and Care Excellence. Avacopan for treating severe active granulomatosis with polyangiitis or microscopic polyangiitis. NICE technology appraisal guidance TA825, 2022. Available from: https://www.nice.org.uk/guidance/TA825. [Accessed November 2022]

76. Jayne D, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the Treatment of ANCA-Associated Vasculitis. *N Engl J Med*. 2021;384(7):599-609.

77. Jayne D, Bekker P. SA-PO696 Integrated Safety of Avacopan in ANCA-Associated Vasculitis. ASN Kidney Week; Nov 2022, Orlando, FL.

78. Jayne D, Merkel PA, Bekker P, et al. POS-444 EFFECT OF AVACOPAN, A SELECTIVE C5A RECEPTOR INHIBITOR, ON KIDNEY FUNCTION IN PATIENTS WITH ANCA-ASSOCIATED VASCULITIS. *KI Reports*. 2022;7(2);S197

79. Jayne D, Merkel PA, Cortazar F, Niles J, Bekker P. Recovery of Renal Function Among ANCA-Associated Vasculitis Patients with Baseline eGFR ≤20 in the Avacopan ADVOCATE Trial [abstract]. *Arthritis Rheumatol.* 2022; 74 (suppl 9).

80. Walsh M, Collister D, Zeng L, et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. *BMJ*. 2022;376:e064604.

81. Zeng L, Walsh M, Guyatt GH, et al. Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis: a clinical practice guideline. *BMJ*. 2022;376:e064597.

82. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med*. 2014;371(19):1771-1780.

83. Smith R, Jayne D, Merkel P. A Randomized, Controlled Trial of Rituximab versus Azathioprine After Induction of Remission with Rituximab for Patients with ANCA-associated Vasculitis and Relapsing Disease [abstract]. *Arthritis Rheumatol.* 2019; 71 (suppl 10).

84. Boekel L, Wolbink GJ. Rituximab during the COVID-19 pandemic: time to discuss treatment options with patients. *Lancet Rheumatol*. 2022;4(3):e154-e155.

85. Jyssum I, Jared H, Tran TT, et al. Humoral and cellular immune responses to two and three doses of SARS-CoV-2 vaccines in rituximab-treated patients with rheumatoid arthritis: a prospective, cohort study. *Lancet Rheumatol*. 2022;4(3):e177-e187.

86. Karras A, Pagnoux C, Haubitz M, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis.* 2017;76(10):1662-1668.

87. McClure ME, Zhu Y, Smith RM, et al. Long-term maintenance rituximab for ANCA-associated vasculitis: relapse and infection prediction models. *Rheumatology (Oxford)*. 2021;60(3):1491-1501.

88. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363(3):221-232.

89. McAdoo SP, Medjeral-Thomas N, Gopaluni S, et al. Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis [published correction appears in *Nephrol Dial Transplant.* 2018 May 1;33(5):899]. *Nephrol Dial Transplant*. 2019;34(1):63-73.

90. Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med* 2000;343:1156-62.

91. Chan TM, Tse KC, Tang CS, Mok MY, Li FK. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. *J Am Soc Nephrol* 2005;16:1076-84.

92. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005;353:2219-28.

93. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009;20:1103-12.

94. Ciancio G, Miller J, Gonwa TA. Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation* 2005;80:S191-200.

95. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;46:2121-31.

96. Houssiau FA, Vasconcelos C, D'Cruz D, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis*; 2010;69(1):61-4.

97. Rathi M, Goyal A, Jaryal A, et al. Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis. *Kidney Int* 2016;89:235-42.

98. Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. *Ann Intern Med* 2015;162:18-26.

99. Rovin BH, Teng YKO, Ginzler EM, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2021;397:2070-80.

100. Furie R, Rovin BH, Houssiau F, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. *N Engl J Med* 2020;383:1117-28.

101. Furie RA, Aroca G, Cascino MD, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2022;81:100-7.

102. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 2011;365:1886-95.

103. Houssiau FA, D'Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis* 2010;69:2083-9.

104. Moroni G, Longhi S, Giglio E, Messa P, Ponticelli C. What happens after complete withdrawal of therapy in patients with lupus nephritis. *Clin Exp Rheumatol* 2013;31:S75-81.

105. Marques C, Carvelli J, Biard L, et al. Prognostic Factors in Anti-glomerular Basement Membrane Disease: A Multicenter Study of 119 Patients. *Front Immunol*. 2019;10:1665

106. Uhlin F, Szpirt W, Kronbichler A, et al. Endopeptidase Cleavage of Anti-Glomerular Basement Membrane Antibodies *in vivo* in Severe Kidney Disease: An Open-Label Phase 2a Study. *J Am Soc Nephrol*. 2022;33(4):829-838.