

1

Diagnosis of ANCA-associated vasculitis

Diagnosis of AAV must be made as early as possible to decrease the risk of permanent loss of kidney function and life-threatening complications. In case of clinical presentation compatible with small-vessel vasculitis in combination with positive myeloperoxidase (MPO)- or proteinase 3 (PR3)-ANCA serology, waiting for kidney biopsy should not delay starting immunosuppressive treatment, especially in patients who are rapidly deteriorating (Figure 1).

2

Initial treatment

Initial treatment of AAV is glucocorticoids in combination with cyclophosphamide or rituximab. In patients with markedly reduced or rapidly declining kidney function, cyclophosphamide is preferred because of limited experience with rituximab (Figure 2).

3

Rituximab as initial treatment

Rituximab is the preferred initial treatment in children and adolescents, pre-menopausal women and men concerned about their fertility, frail older adults, patients with relapsing disease, patients with PR3-ANCA disease and in patients in whom glucocorticoid-sparing is especially important.

4

Plasma exchange

Plasma exchange should be considered 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 (Figure 2). Plasma exchange should be added to initial treatment for patients with an overlap syndrome of ANCA vasculitis and anti-GBM.

5

Tapering of glucocorticoids

Although high-dose glucocorticoids have traditionally been given during the initial treatment of AAV, recent data demonstrated that lower doses are equally effective but with fewer short- and long-term toxicities.

6

Maintenance treatment

Maintenance therapy with either rituximab or azathioprine and low dose glucocorticoids is recommended after induction of remission (Figure 2). Optimal duration of the maintenance treatment is not known, but should be between 18 months and 4 years.

7

Preferred maintenance treatment

Rituximab as maintenance treatment is preferred in patients with relapsing disease, PR3-ANCA disease, frail older adults, azathioprine allergy, or when glucocorticoid-sparing is especially important.

8

Withdrawal of maintenance therapy

When considering withdrawal of maintenance therapy, the risk of relapse should be factored in, and patients should be informed of the need for prompt attention if symptoms recur.

9

Relapsing disease

Patients with relapsing disease (life- or organ-threatening) should be re-induced, preferably with rituximab.

10

Refractory disease

Patients with 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.

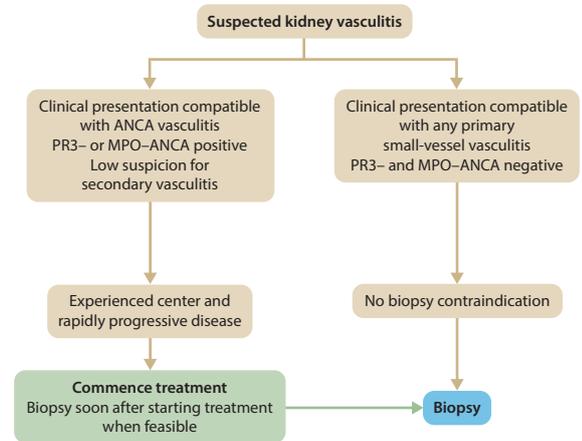


Figure 1

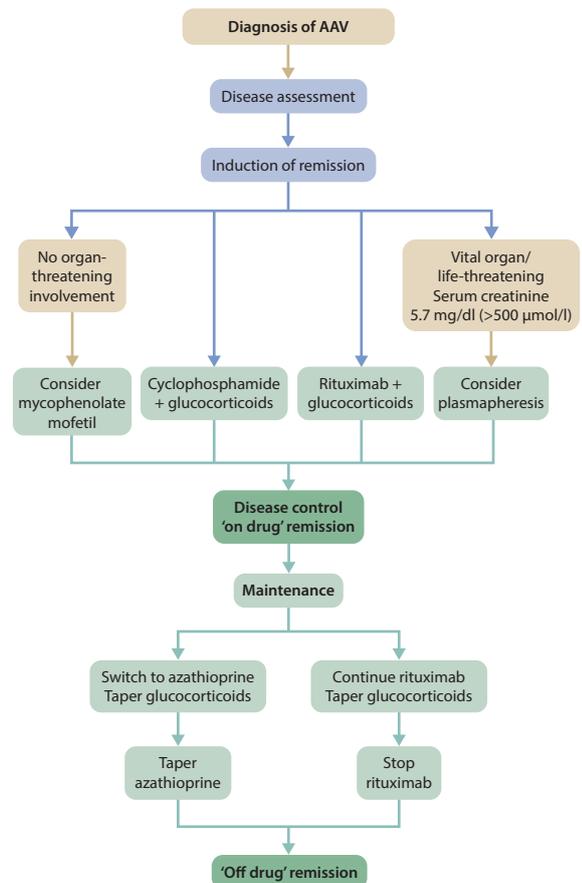


Figure 2

Top 5

Takeaways for Clinicians from the KDIGO 2021 Clinical Practice Guideline for the Management of Anti-GBM Glomerulonephritis



1

Diagnosis

In all patients with a rapidly progressive glomerulonephritis, a diagnosis should be made as quickly as possible, but if anti-GBM disease is suspected, treatment should be started without delay, even if diagnosis has not been confirmed (Figure 1).

2

Treatment

Immunosuppression with cyclophosphamide and glucocorticoids plus plasmapheresis should be initiated in all patients with anti-GBM except those who need dialysis at presentation, have 100% crescents or >50% global glomerulosclerosis in an adequate biopsy sample, and do not have pulmonary hemorrhage (Figure 1). Treatment for anti-GBM disease should start without delay if this diagnosis is suspected, even before the confirmed diagnosis. The patient displays steroid resistance, has an atypical clinical course, or is > 12 years of age at presentation.

3

Length of treatment

Plasma exchange should be performed until anti-GBM antibodies in serum are no longer detectable. Cyclophosphamide should be administered for 2–3 months and glucocorticoids tapered over 6 months. No maintenance therapy of anti-GBM disease is necessary with the exception of patients who are also anti-neutrophil cytoplasmic antibody (ANCA)-positive.

4

Refractory disease

In refractory anti-GBM disease, rituximab may be tried.

5

Kidney transplantation

Kidney transplantation in patients with kidney failure due to anti-GBM disease should be postponed until anti-GBM antibodies remain undetectable for at least 6 months.

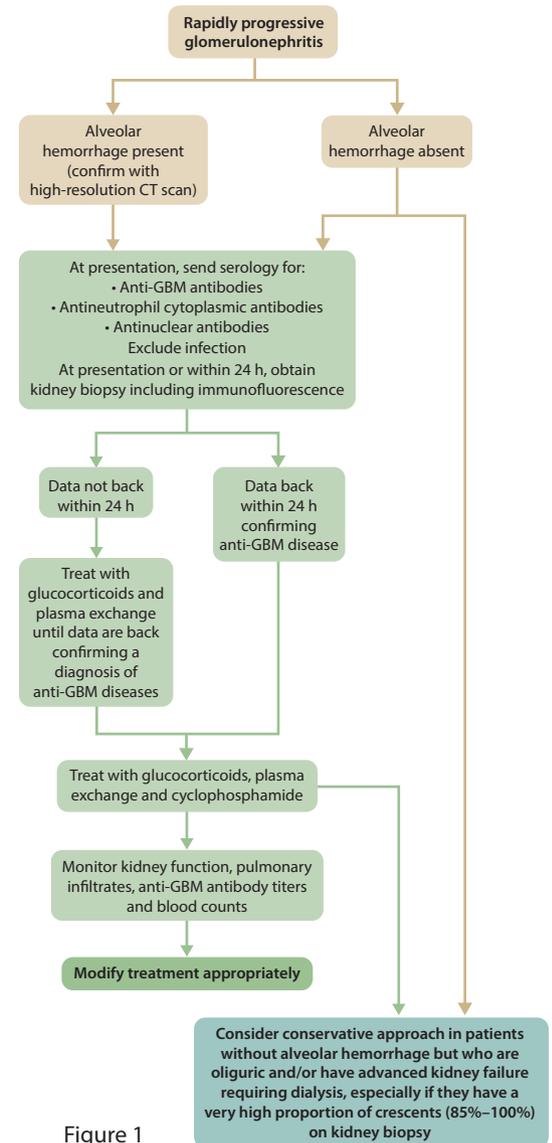


Figure 1

1

MPGN is not a disease

MPGN is not a single, specific disease, but is a light microscopic pattern of kidney injury. The older nomenclature of MPGN types 1–3 should be discarded.

2

Classification of MPGNs

Glomerular injury with an MPGN pattern is now classified by pathobiology and relies on the immunofluorescence examination of the kidney biopsy. These entities may be broadly-defined as immunofluorescence-negative, complement-dominant, or immunoglobulin (with or without complement) positive (Figure 1).

3

Differential diagnosis of MPGNs

The differential diagnosis of glomerular injury with an MPGN pattern is broad and includes infection-related glomerular disease, autoimmune diseases, and complement-mediated diseases (Figure 2).

4

Exclude infection

Infection should be excluded in patients with immune complex-mediated GN, followed by evaluation for an autoimmune disease. If monoclonal immunoglobulin deposits are present, evaluate for a hematologic malignancy.

5

Considerations for idiopathic ICGN in adults

Idiopathic immune complex-mediated GN (ICGN) is not common in adults. If no etiology is discovered, evaluate for complement dysregulation and drivers of complement dysregulation. C3 glomerulopathy (C3G) can masquerade as an immune complex-mediated GN.

6

Considerations for C3G

Prior to assigning a diagnosis of C3G, infection should be excluded, and in patients age 50 or older, a monoclonal gammopathy should be excluded.

7

Treatment of ICGN of known cause

The treatment of immune complex-mediated GN should be directed at the underlying cause.

8

Treatment of ICGN of unknown cause

In the absence of an underlying cause, idiopathic immune complex-mediated GN may be treated with glucocorticoids and/or immunosuppressive therapies, based on the severity and activity of the disease.

9

Treatment of C3G

Patients with C3G who have proteinuria over 1 g/d and/or declining kidney function over 6 months should be treated initially with mycophenolate mofetil plus glucocorticoids, and if this fails, eculizumab may be considered.

10

Clinical trials

Patients with C3G who do not respond to therapy should be considered for a clinical trial.

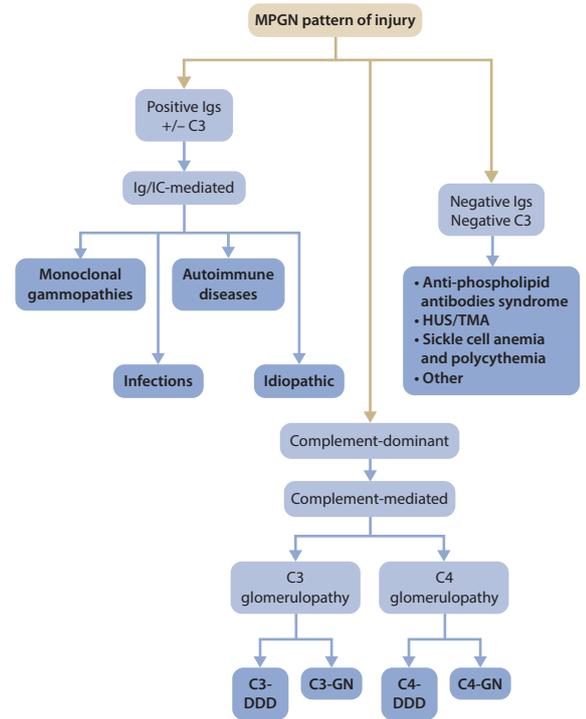


Figure 1

Immunoglobulin-/immune complex-mediated	Deposition of antigen–antibody immune complexes as a result of an infection: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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 <p>Fibrillary glomerulonephritis</p> <p>Idiopathic</p> <ul style="list-style-type: none"> • None of the conditions above are present
Complement-mediated	C3 glomerulonephritis and C3 DDD: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 2

1

Primary FSGS

Primary FSGS will be used to denote the disease entity presumably caused by an as yet unidentified podocyte-toxic factor that is often amenable to immunosuppression. It is a clinical-pathologic syndrome characterized by FSGS lesions on histopathology with diffuse foot process effacement on electron microscopy, presence of nephrotic syndrome as defined by proteinuria >3.5 g/day plus hypoalbuminemia of <30 g/l, without the presence of a genetic or secondary cause. (Figure 1 & 2)

2

FSGS of Undetermined Cause (FSGS-UC)

FSGS can occur in the absence of a genetic or identifiable secondary cause, without nephrotic syndrome nor meeting the criteria for diffuse foot process effacement on electron microscopy and will be ascribed the term FSGS-UC. These individuals should be given supportive therapy and not be started on immunosuppression, with close monitoring of proteinuria and serum albumin. (Figure 1)

3

Genetic testing for FSGS

Genetic testing in adults with FSGS lesions should not be done routinely but may be considered in certain clinical situations, especially when there is a strong family history or resistance to immunosuppression. These individuals should be referred to specialized centers with expertise in genetic counselling and testing. (Figure 3)

4

Secondary FSGS

Adults with FSGS who do not have nephrotic syndrome should be evaluated for a secondary cause. Individuals with secondary forms of FSGS should not be given immunosuppressive treatment.

5

Initial treatment for primary FSGS

High-dose oral glucocorticoids are recommended as the first-line immunosuppressive treatment for primary FSGS. However, in adults with relative contraindications or intolerance to glucocorticoids, calcineurin inhibitors may be considered as an alternative first-line initial therapy in patients with primary FSGS.

6

Duration of high dose glucocorticoid treatment

Initial high-dose glucocorticoids should be continued until complete remission is achieved or as tolerated by patients up to a maximum of 16 weeks, which is used as the definition for steroid resistance. Patients who are likely to respond to therapy will demonstrate some degree of proteinuria reduction before 16 weeks and there is no need to persist with high dose glucocorticoid treatment if the proteinuria shows no signs of reduction, especially when the patient is experiencing side effects.

7

Glucocorticoid-resistant primary FSGS

Cyclosporine or tacrolimus treatment is recommended for adults with steroid-resistant primary FSGS, and should be dosed for at least 6 months before considered resistant.

8

Duration of calcineurin inhibitor therapy

Adults with steroid-resistant primary FSGS who respond to calcineurin inhibitor treatment should receive the drug for a minimum of 12 months, so as to minimize the risk of relapses.

9

Treatment beyond glucocorticoid and calcineurin inhibitors

Adults who have steroid-resistant primary FSGS with resistance or intolerance to calcineurin inhibitors should be referred to specialized centers for consideration of rebiopsy, alternative treatment, or enrollment in a clinical trial.

10

Treatment of relapsing primary FSGS

Adults with previous steroid-sensitive primary FSGS who experience a relapse can be treated using the same approach as that for adults with relapsing minimal change disease.

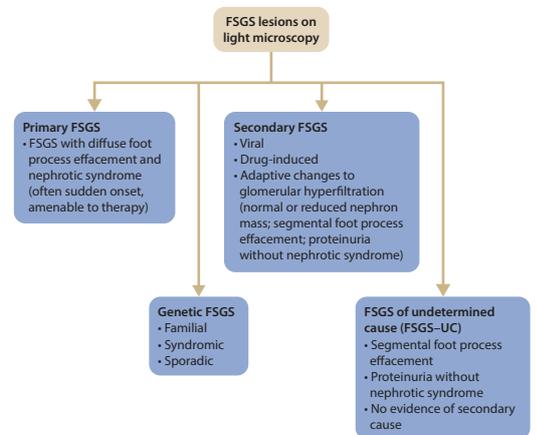


Figure 1

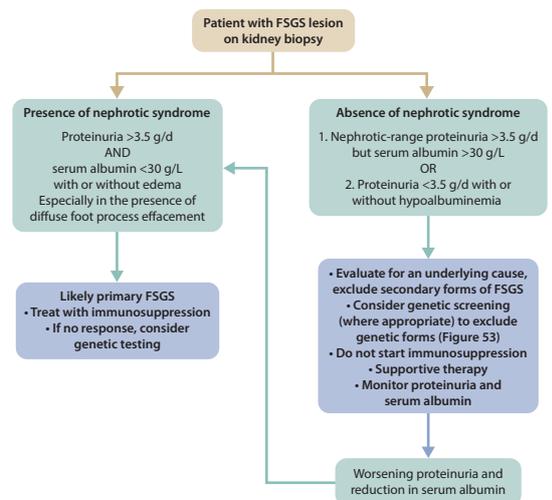


Figure 2

Genetic forms of FSGS	
Genetic mutations of podocyte and glomerular basement membrane proteins	<ul style="list-style-type: none"> • Familial • Sporadic • Syndromic
Considerations for genetic testing in adults with FSGS	
<ul style="list-style-type: none"> • When there is a strong family history and/or clinical features suggestive of a syndromal disease • Aiding in diagnosis, especially if the clinical features are not representative of a particular disease phenotype • Limiting immunosuppression exposure, especially in situations where patients appear to be resistant to treatment • Determining the risk of recurrent disease in kidney transplantation • Allowing for risk assessment in living-related kidney donor candidate, or where there is a high suspicion for <i>APOL1</i> risk variants • Aiding in prenatal diagnosis 	

Figure 3

1

Kidney biopsy

The kidney biopsy is the “gold standard” for the diagnostic evaluation of glomerular diseases to facilitate the initiation or modification of treatment and/or to provide prognostic information. Under some circumstances, treatment may proceed without a kidney biopsy. (Figure 1)

2

Proteinuria evaluation

In adults, the measurement of protein and creatinine on a 24-hour urine collection is the optimal way to determine total protein excretion; a reasonable compromise is to collect an “intended” 24-hour urine sample and calculate a PCR in an aliquot of the collection. For pediatrics, monitoring first morning PCR is an alternative. Random “spot” urine collections are not ideal due to variation over time in both protein and creatinine excretion.

3

Examination of the urine

Proteinuria should be quantified and followed sequentially. Hematuria should be assessed microscopically for acanthocytes and red blood cell casts in all forms of glomerular disease.

4

Treat edema, hypertension, and proteinuria

Dietary sodium restriction and loop diuretics should be first-line therapy. For resistant edema, add diuretics with actions on other tubule segments, and rarely intravenous albumin. In severe cases, hemodialysis or kidney replacement therapy for ultrafiltration may be needed. Use ACEi or ARBs titrated to maximal tolerability to reduce proteinuria and control hypertension, while monitoring frequently for safety. Consider facilitating their use with the judicious addition of potassium wasting diuretics and oral K binders. (Figure 2)

5

Treat metabolic acidosis and hyperlipidemia

Maintain serum bicarbonate >22 mmol/l. Consider starting a statin as first-line therapy for persistent hyperlipidemia.

6

Treat thrombotic complications

Prescribe full-dose anticoagulation for pulmonary embolus, arterial and venous thrombosis, and non-valvular atrial fibrillation for at least 6–12 months or until the nephrotic syndrome is resolved. Consider full-dose anticoagulant prophylaxis for serum albumin <20–25 g/l. In patients with absolute and relative contraindications to anticoagulants or at high bleeding risk, aspirin may be a reasonable alternative. A risk calculator is available at <https://www.med.unc.edu/gntools/bleedrisk.html>

7

Glomerular disease treatment

Choose a glomerular disease treatment that minimizes immediate morbidity of the primary disease, prevents disease progression, and minimizes treatment side effects.

8

Prevent infection during immunosuppressive treatment

Screen for and treat underlying latent infections prior to administering immunosuppression. Vaccinate against infectious agents avoiding live attenuated vaccines. Use prophylaxis against agents of concern generally including pneumocystis (trimethoprim-sulfamethoxazole, atovaquone, dapson) and meningococcus specifically when using complement inhibition (vaccines for meningococcal serotypes a, c, w, y and b; concomitant penicillin or ciprofloxacin for the penicillin-allergic).

9

Optimal pregnancy outcomes require planning

(ideally pre-natal) among the patient, obstetrician, and nephrologist. Prevent fetotoxicity during immunosuppressive treatment with effective contraception. Optimal pregnancy outcomes are achieved if pregnancy is delayed until glomerular disease remission.

10

Employ lifestyle modification synergy

to enhance antihypertensive and antiproteinuric strategies. Normalize weight, undertake regular exercise, consume a heart-healthy diet avoiding dietary protein excess, and avoid smoking. (Figure 2)

Decision tree for the consideration of a kidney biopsy in patients with proteinuria and/or glomerular hematuria

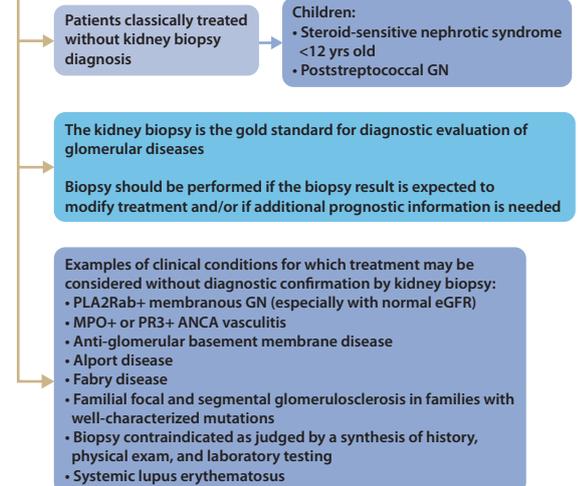


Figure 1

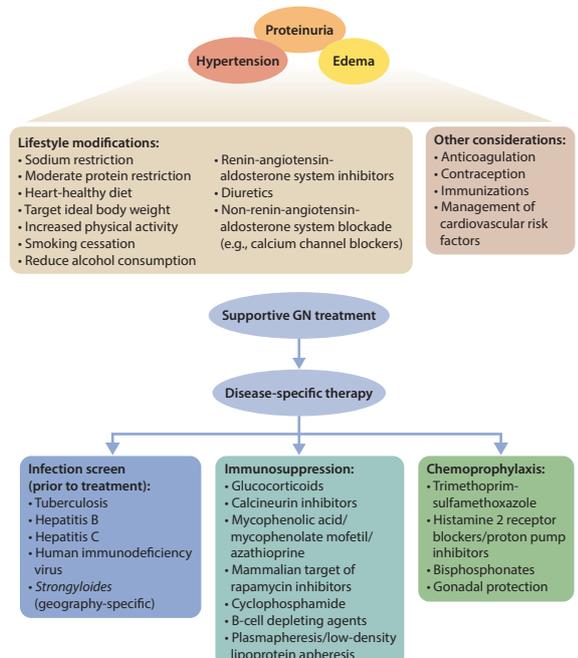


Figure 2

1

Diagnosis of IgA nephropathy (IgAN)

IgAN can only be diagnosed with a kidney biopsy. There are no validated diagnostic serum/urine biomarkers. The differential diagnosis of IgA dominant glomerulonephritis includes primary IgAN, IgA vasculitis, cirrhosis, inflammatory bowel disease and infection-related GN. (Figure 1)

2

Prognosis

The International IgAN Prediction Tool helps determine the risk of a 50% decline in eGFR or progression to kidney failure up to 6.7 years from the time of kidney biopsy to inform shared decision-making with patients (available at QxMD¹). (Figure 2) There are no validated prognostic serum/urine biomarkers other than eGFR and proteinuria.

3

Treatment for all patients with primary IgAN

Initial management is supportive care including lifestyle modification (smoking cessation, weight control, regular exercise and dietary sodium restriction), blood pressure control and maximum tolerated RAS blockade.

4

Identification of patients at high risk of progression

Assess risk of progression regularly in all patients with IgAN. High risk is currently defined as persistent proteinuria >1 g/d despite 3 months of stable, optimized supportive care. While proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcome in IgAN, persistent proteinuria 0.5–1 g/d is also likely to increase the risk of progression. (Figure 3)

5

Management of high-risk patients on optimized supportive care

Neither the International IgAN Prediction Tool nor the Oxford Classification MEST-C score alone can be used to determine the likely impact of any particular treatment regimen. Unless inclusion in a clinical trial is possible, glucocorticoid therapy may reduce the risk of kidney failure in IgAN. If glucocorticoids are considered, the risk of treatment-emergent toxicity, in particular serious infectious complications, must be discussed with the patient, particularly those with an eGFR <50ml/min/1.73 m². (Figure 3)

6

Ethnicity-specific alternative treatment options

There are data to support the use of mycophenolate mofetil (MMF) in Chinese patients as a glucocorticoid-sparing agent. Tonsillectomy is widely performed in Japan with supportive data for Japanese patients. (Figure 3)

7

IgAN variants – rapidly progressive glomerulonephritis

Rarely patients with IgAN can develop a rapidly progressive glomerulonephritis (RPGN) associated with extensive crescent formation. These cases should be treated with cyclophosphamide and glucocorticoids in the same way as ANCA-associated vasculitis. The presence of crescents in a kidney biopsy without a concomitant change in serum creatinine does not constitute a RPGN.

8

IgAN variants – AKI and nephrotic syndrome

Acute kidney injury can complicate episodes of severe visible hematuria. Treatment is supportive. IgAN rarely presents with nephrotic syndrome. In such cases, electron microscopy may be otherwise consistent with minimal change disease (MCD) and patients should be treated in accordance with the guidelines for MCD.

9

IgAN in children

The International IgAN Prediction Tool has been validated for use in children. Management of children with IgAN is similar to adults except for a lower threshold for the early use of glucocorticoids. Long term follow-up is essential, even after complete remission, as children can relapse after many years of stable disease.

10

IgA vasculitis

Diagnosis is often made on clinical criteria alone but a kidney biopsy should always be considered in patients with an RPGN, proteinuria >1 g/d, and/or impaired kidney function. Glucocorticoids should not be used to prevent nephritis in patients with isolated extrarenal IgAV. Management for adults and children should follow the guidance for IgAN.

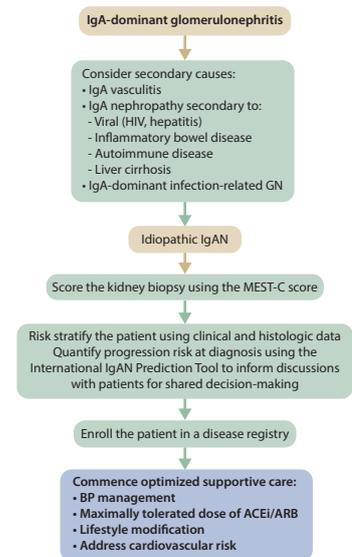


Figure 1

Estimated GFR at biopsy.....ml/min/1.73 m ²
Systolic blood pressure at biopsy.....mmHg
Diastolic blood pressure at biopsy.....mmHg
Proteinuria at biopsy.....g/day
Age at biopsy.....years
Race Caucasian Chinese Japanese Other
Use of ACE inhibitor or ARB at the time of biopsy No Yes
MEST M-score 0 1
MEST E-score 0 1
MEST S-score 0 1
MEST T-score 0 1 2
Immunosuppression use at or prior to biopsy No Yes

Figure 2

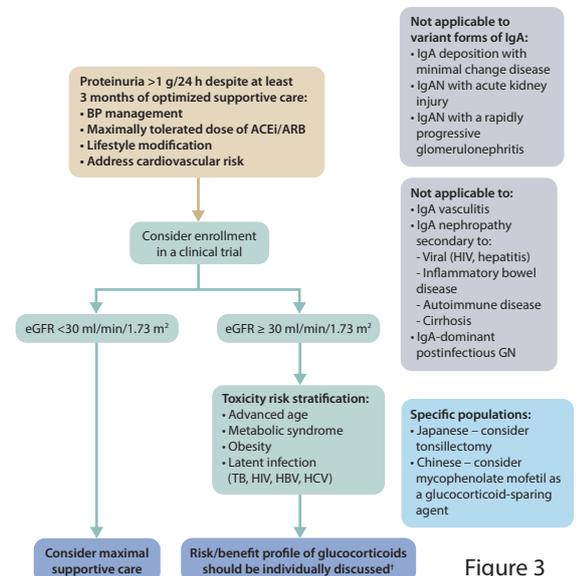


Figure 3

¹ https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool-at-biopsy-adults?branch_match_id=656546875419766679

1

Bacterial infection-related GN

Bacterial infection-related GN may present after a bacterial infection (post-infectious GN), after a latent period, (often days to several weeks after an infection), or in the presence of an ongoing, acute or chronic bacterial infection (infection-related).

2

Clinical diagnosis

The synthesis of history; physical examination; kidney assessments (UA, ACR, PCR, eGFR); cultures of blood, urine, other suspected fluids and tissues; and serological examinations (C3, C4, cryoglobulin, Factor B, Serum IgA level, ASO, antiDNAse B, anti-hyaluronidase antibodies, ANCA) are often sufficient to support a clinical diagnosis in the setting of bacterial infection.

3

Kidney biopsy

Kidney biopsy may be necessary to confirm a diagnosis and/or to provide prognostic information in patients with bacterial infection in uncertain situations.

4

Treatment for infection-related GN

Treatment for post-infectious GN is supportive care to control edema, proteinuria, and hypertension. Immunosuppression is generally inadvisable. For infection-related GN, additional treatment to eradicate the underlying infection should be added.

5

Hepatitis B

Approximately 250–350 million people (5% of the world's population) are chronically infected with HBV, making it one of the most common human pathogens. About 3%–5% of patients with chronic HBV infection develop kidney disease as a complication.

6

Treatment of HBV

Adults with chronic HBV infection are at risk for developing kidney failure. Patients with replicative HBV infection (as denoted by HBV DNA levels >2000 IU/ml) and GN should be treated with nucleos(t)ide analogues as recommended for the general population by standard clinical practice guidelines for HBV infection.

7

Avoid immunosuppression for HBV

Chronic untreated HBV infection may flare if immunosuppression is introduced to treat HBV-associated or HBV-independent GN.

8

Prevalence and diagnosis of HIV

Patients with HIV undergoing kidney biopsy show a broad spectrum of kidney pathology, including, in order of prevalence, immune complex GN, diabetic kidney disease, HIV-associated nephropathy (HIVAN), tenofovir toxicity, FSGS, global sclerosis (NOS), acute tubular injury, other tubulointerstitial, glomerular, and vascular diseases. When possible, a kidney biopsy should be performed for accurate diagnosis.

9

Treatment of HIV

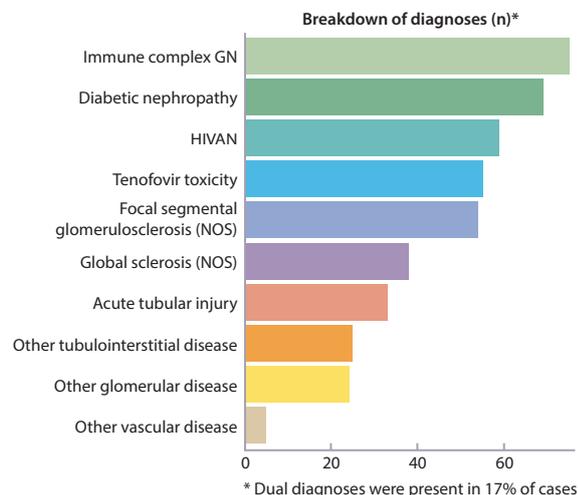
It is recommended that all patients with HIV and CKD receive antiretroviral treatment for HIV with dosing adjustments for CKD, independent of the CD4 count. Early implementation of highly active antiretroviral therapy has been associated with a 60% reduction in the incidence of HIVAN. There are no randomized trials to guide treatment for HIV-associated kidney diseases.

10

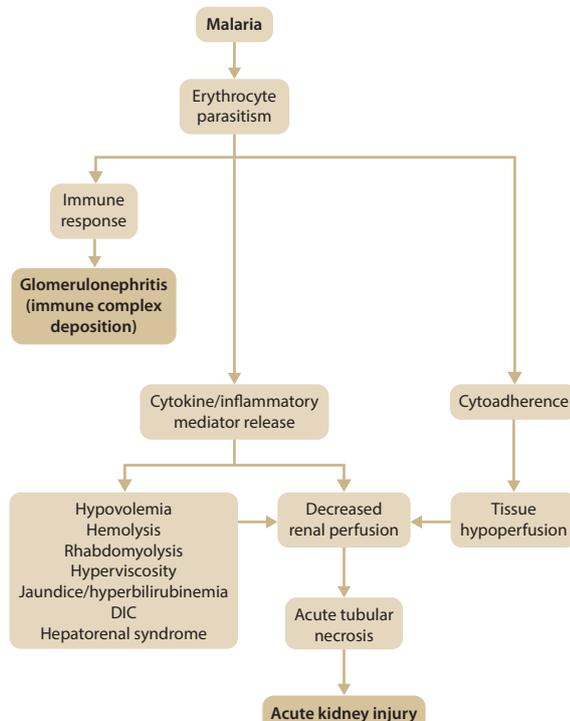
Parasitic infections

Parasitic infections should be treated to eradicate the underlying infectious organism. Monitor patients with hepatic fibrosis from schistosomiasis for the development of kidney disease, and evaluate patients with a history of schistosomiasis and an elevated serum creatinine and/or hematuria for bladder cancer and/or urinary obstruction. Immunosuppression is not indicated for the treatment of GD complicating parasitic infections.

The spectrum of kidney biopsy findings in patients with HIV in the modern era



Pathophysiology of kidney involvement in malaria



Abbreviations: ACR, albumin-creatinine ratio; ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin O titer; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GD, glomerular disease; GN, glomerulonephritis; HBV, hepatitis B virus; HIV, human immunodeficiency virus; PCR, protein-creatinine ratio; UA, urinalysis

1

Diagnosis of lupus nephritis

Early diagnosis and timely treatment of active lupus nephritis are important to preserve nephrons. Changes in kidney function or proteinuria based on serial measurements may suggest lupus nephritis (LN), and this can be confirmed by kidney biopsy.

2

Antimalarial therapy

Hydroxychloroquine is recommended for all patients with LN if there are no contraindications.

3

Class I/II lupus nephritis

Immunosuppressive therapy in patients with Class I/II LN should be guided by extrarenal disease manifestations unless the patients have nephrotic syndrome due to lupus podocytopathy, which is managed as minimal change disease.

4

Initial immunosuppression for active Class III/IV lupus nephritis

The initial treatment of active proliferative (\pm membranous) LN is glucocorticoids plus either mycophenolate mofetil or low-dose (Euro-Lupus) intravenous cyclophosphamide. (Figure 1)

5

Glucocorticoid dosing

Although glucocorticoids have generally been given in high doses for LN, emerging data suggest that lower doses may be equally effective but with fewer short- and long-term toxicities.

6

Long-term immunosuppression for Class III/IV lupus nephritis

Following initial therapy of proliferative LN, mycophenolate mofetil is the preferred immunosuppressive and should be continued for at least 36 months. (Figure 2)

7

Class V lupus nephritis

Class V lupus nephritis is managed with RAS blockade, blood pressure optimization, and hydroxychloroquine, and the addition of immunosuppression in patients who develop nephrotic range proteinuria.

8

Unsatisfactory response to treatment

Unsatisfactory treatment responses can be due to non-adherence, inadequate immunosuppressant dosing, or significant chronic kidney damage that preclude complete resolution of kidney abnormalities. Patients in whom these factors are excluded may have treatment-resistant LN. (Figure 3)

9

End stage kidney disease

Kidney transplantation is the preferred form of kidney replacement therapy for LN patients who develop end-stage kidney disease.

10

Pregnancy in patients with lupus nephritis

Good pregnancy outcomes require pre-pregnancy counselling and planning. Pregnancy should be avoided when LN is active or when patients are exposed to potentially teratogenic medications.

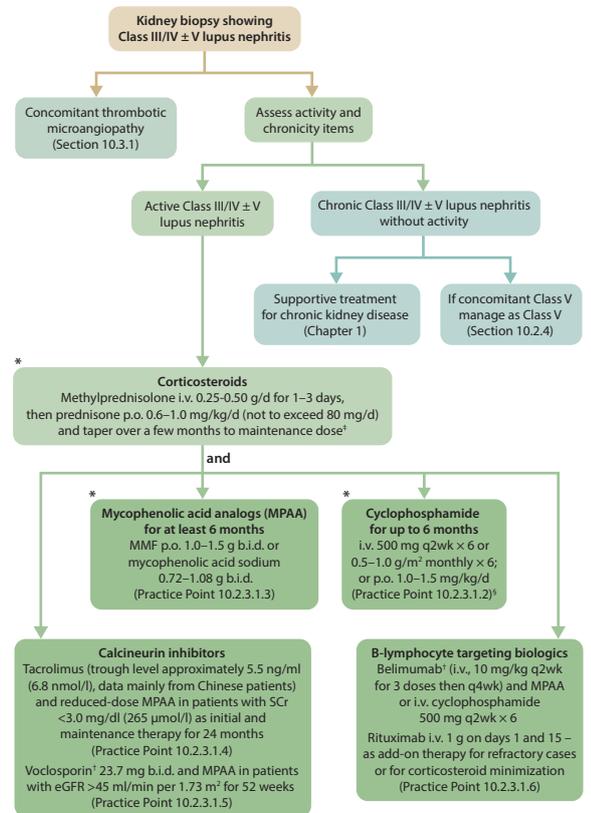


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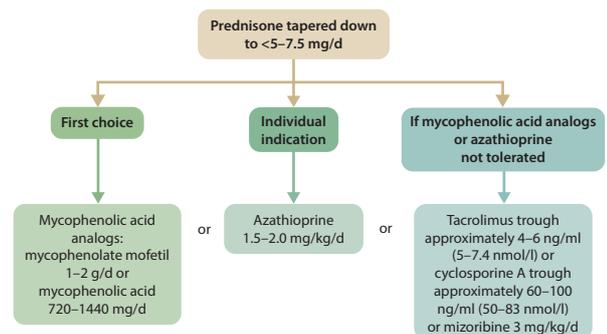


Figure 2

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)
4	Consider switching to an alternative first-line regimen when there is persistent disease activity (mycophenolic acid analogs to cyclophosphamide-based regimen or vice versa)
5	Consider the following in patients refractory to first-line treatment regimens: <ul style="list-style-type: none"> • Combined mycophenolic acid analogs and calcineurin inhibitor therapy, or • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide

Figure 3

1

Diagnosis of membranous nephropathy (MN)

A kidney biopsy is not required to diagnose membranous nephropathy in a patient with nephrotic syndrome and a positive PLA2Rab test, but may help in determining prognosis and treatment decisions. (Figure 1)

2

Added value of kidney biopsy staining

A negative PLA2Rab test does not rule out PLA2R-associated MN. PLA2Rab can be absent in early disease. A positive glomerular staining of a kidney biopsy for PLA2R defines PLA2R-associated MN.

3

Be aware of new antigens

Identification of new antigens might help in defining the underlying cause in PLA2Rab negative patients.

4

Exclude secondary causes of MN

Evaluate all patients with MN for secondary causes such as infections, systemic diseases, malignancies, certain drugs (NSAIDs) or nutritional supplements (lipoic acid).

5

Prophylactic anticoagulant therapy

Patients with MN are at high risk of arterial and venous thromboembolic events. Prophylactic anticoagulant therapy is advised in patients with low serum albumin levels taking into account bleeding risk. (Figure 2)

6

Conservative therapy

All patients should receive optimal supportive therapy targeting edema, blood pressure, dietary salt intake, and lipid profile. Monitor the patient regularly, whilst evaluating risk parameters (see below). The duration of conservative therapy might vary with risk levels and response.

7

Risk-based immunosuppressive therapy

Start of and the choice of immunosuppressive drugs are guided by risk evaluation based on a combination of change in serum creatinine, serum albumin, and proteinuria. (Figure 3) When available, serum PLA2Rab levels, urine protein selectivity index, and excretion of low molecular weight proteins provide added value.

8

Immunological monitoring

Whilst clinical remission is the goal of therapy, immunological response precedes clinical response by several months. In patients with PLA2Rab positive MN, regular assessment of PLA2Rab after start of therapy enables early evaluation of treatment response and provides guidance for treatment change.

9

Treatment resistance

Lack of clinical response after several lines of therapies defines resistance, and patients should be referred to an expert center to discuss additional therapy. Residual proteinuria per se is not a sign of active MN, and especially in patients with immunological remission or normalized serum albumin levels, secondary FSGS must be excluded.

10

Kidney transplantation

Evaluation of PLA2Rab and if necessary PLA2R-antigen aids in predicting post-transplant recurrence. In patients with recurrent MN and proteinuria >1 g/day, rituximab is effective therapy. (Figure 4)

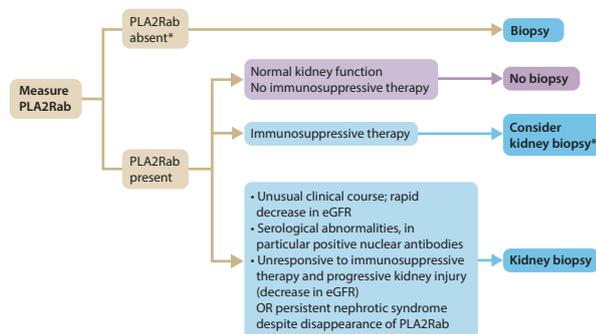


Figure 1

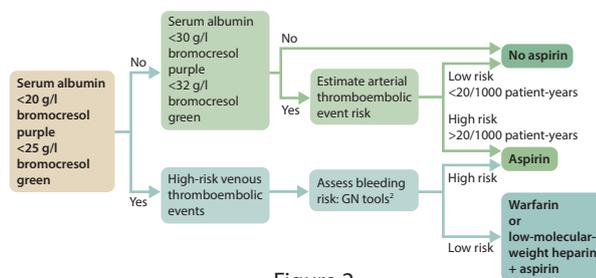


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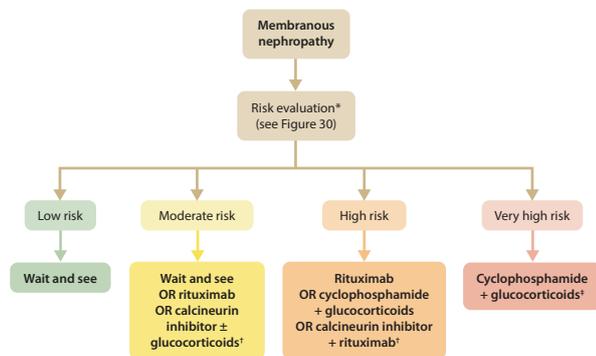


Figure 3

Pretransplant evaluation: maximal efforts to ascertain if MN is associated with PLA2Rab*

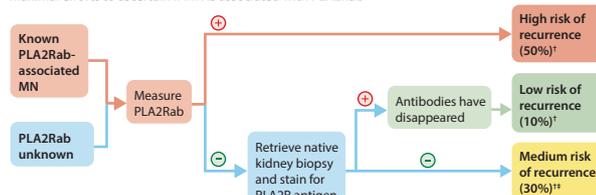


Figure 4

1

Diagnosis of minimal change disease (MCD)

MCD is diagnosed by kidney biopsy. There are no non-invasive biomarkers available.

2

Initial treatment of MCD

For initial treatment of MCD, high dose glucocorticoids are recommended.

3

Duration of glucocorticoids for initial treatment

High doses of glucocorticoids should be given for no longer than 16 weeks.

4

Taper of glucocorticoids for initial treatment

A gradual glucocorticoid taper should start 2 weeks after remission and for up to a total of 24 weeks of glucocorticoid exposure.

5

Contraindications for glucocorticoids

Initial treatment regimens for patients with contraindications to glucocorticoids include cyclophosphamide, calcineurin inhibitors, and mycophenolate mofetil/sodium mycophenolate (with reduced-dose glucocorticoids). (Figure 1)

6

Prognosis

Long-term kidney survival is excellent in treatment-responsive patients.

7

Glucocorticoid-refractory patients

Glucocorticoid-refractory patients are treated similar to glucocorticoid-refractory focal segmental glomerulosclerosis.

8

Infrequent relapses

Infrequent relapses of minimal change disease are treated similarly to the initial presentation, with lower and less prolonged doses of glucocorticoids.

9

Frequently relapsing/steroid-dependent (FR/SD) MCD

After remission is induced with glucocorticoids, for frequently relapsing or steroid-dependent patients, cyclophosphamide, rituximab, calcineurin inhibitors, and mycophenolate mofetil/sodium mycophenolate may be used to prolong remission and reduce relapse rates. (Figure 2)

10

Choice of therapy for FR/SD MCD

In general, there are no known differences between the medications used of FR/SD MCD. Patient choice, local availability, and costs need to be considered.

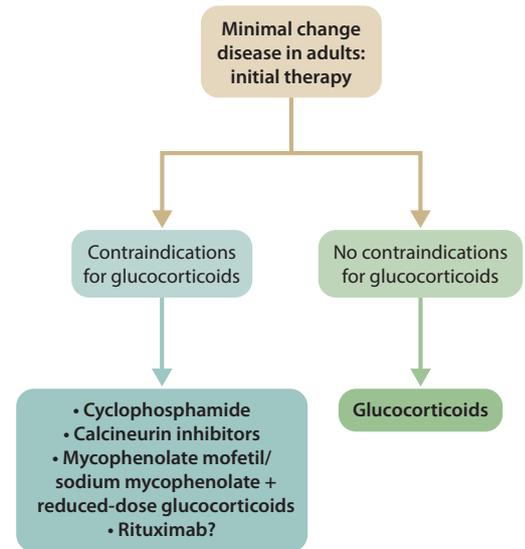


Figure 1

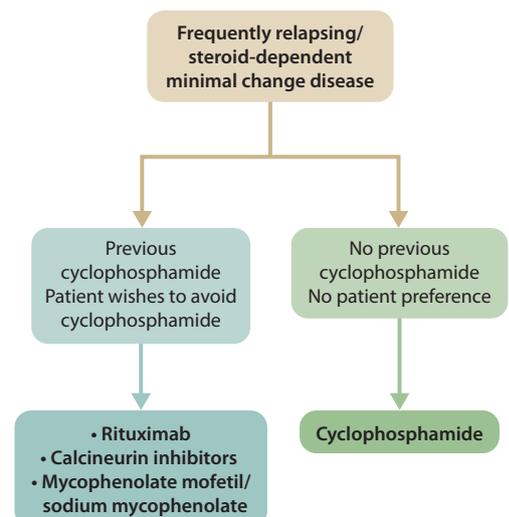


Figure 2

1

Initial management

Below the age of 1 year, all children fulfilling the definition of nephrotic syndrome should be referred to a specialist in pediatric nephrology. This also applies to all forms of nephrotic syndrome that are steroid-resistant, atypical (including onset >12 years of age), or steroid-sensitive requiring a glucocorticoid-sparing agent.

2

Kidney biopsy

The prognosis for childhood nephrotic syndrome is best predicted by the patient's response to initial treatment and frequency of relapse during the first year after treatment. Therefore, a kidney biopsy is not usually needed at initial presentation unless the patient displays steroid resistance, has an atypical clinical course, or is > 12 years of age at presentation.

3

Treatment of first episode

Initial treatment of nephrotic syndrome with oral prednisone/prednisolone in children should not be prolonged beyond 12 weeks: evidence is insufficient to choose between giving 4 weeks at full dose followed by 4 weeks on alternate-day glucocorticoid dosing (total 8 weeks) or giving 6 weeks at full dose followed by 6 weeks of alternate-day dosing (total 12 weeks). (Figure 1)

4

Treatment of relapse

Treatment of relapse should include prednisone as a single daily dose of 60 mg/m² or 2 mg/kg (maximum 60 mg/d) until the child remits completely for at least 3 days. After achieving complete remission, reduce prednisone to 40 mg/m² or 1.5 mg/kg (maximum 50 mg/d) on alternate days for at least 4 weeks.

5

Introduction of glucocorticoid-sparing agent

For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse events, and for all children with steroid-dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents be prescribed. (Figure 1)

6

Choice of glucocorticoid-sparing agent: the patient

Choosing the most appropriate steroid-sparing agent between oral cyclophosphamide, levamisole, mycophenolate mofetil, rituximab, and calcineurin inhibitors depends on specific patient-related issues such as resources, compliance, potential for adverse effects, and patient preferences.

7

Choice of glucocorticoid-sparing agent: the disease

Among glucocorticoid-sparing agents for steroid-sensitive nephrotic syndrome, oral cyclophosphamide and levamisole may be preferable in frequently relapsing forms. Mycophenolate mofetil, rituximab, and calcineurin inhibitors may be preferable in steroid-dependent forms of disease.

8

Genetic testing

For steroid-resistant nephrotic syndrome, consider the possibility of a genetic cause where immunosuppression may not be useful. Genetic testing performed by experts should be rapidly implemented, particularly in infantile forms, if there is a positive family history of kidney disease and/or the patient has syndromic features.

9

RAAS blockade for SRNS

In children with steroid-resistant nephrotic syndrome, a renin-angiotensin-aldosterone system inhibitor should be started, with careful evaluation of volume depletion to minimize the risk of AKI.

10

Calcineurin inhibitor for SRNS

We recommend using cyclosporine or tacrolimus as initial second-line therapy for children with steroid-resistant nephrotic syndrome.

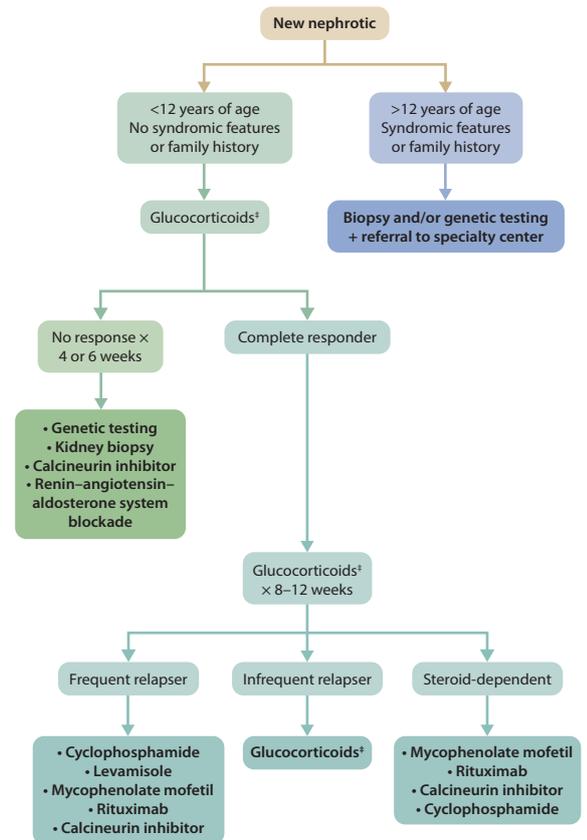


Figure 1