The Egyptian Society Of Nephrology & Transplantation

ESNT – Chapter 2

ESNT Guidelines

(GN, MGRS, PE, PD)

First Edition, December 2019

The Quality Care of Renal Patients Guidelines
Nephrology Initiatives of Care and Excellency

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Part (I) Glomerulonephritis

Glomerular diseases

Clinical syndromes of glomerular diseases

1-Isolated hematuria

2-Isolated non-nephrotic proteinuria

3-Nephrotic syndrome:

Proteinuria 3.5 gm per 24 hours
Hypoalbuminemia, usually less than 3.5 g/dL,
Edema (peripheral or periorbital, occasionally ascites or pleural effusions),
Hyperlipidemia

4-Acute nephritic syndrome:

Acute onset (days) of:
Hematuria—macroscopic or microscopic (dysmorphic or RBC casts), Hypertension
Oliguria
Edema—moderate Proteinuria—mild to moderate
Azotemia

5-Rapidly Progressive Glomerulonephritis(RPGN):

- Acute onset of rapidly progressive renal failure developed from weeks to months with diffuse glomerular crescents
- Hematuria
- Oliguria
- Proteinuria
- hypertension

6-Chronic kidney disease

Differential diagnosis of glomerular disease

1-Proteinuric syndromes:

- Minimal Change Disease(MCD).
- Focal Segmental Glomerulosclerosis.
- Membranous nephropathy.
- Class V lupus nephritis.
- Amyloidosis.
- Diabetic glomerulosclerosis.
- Light Chain Deposition Disease.

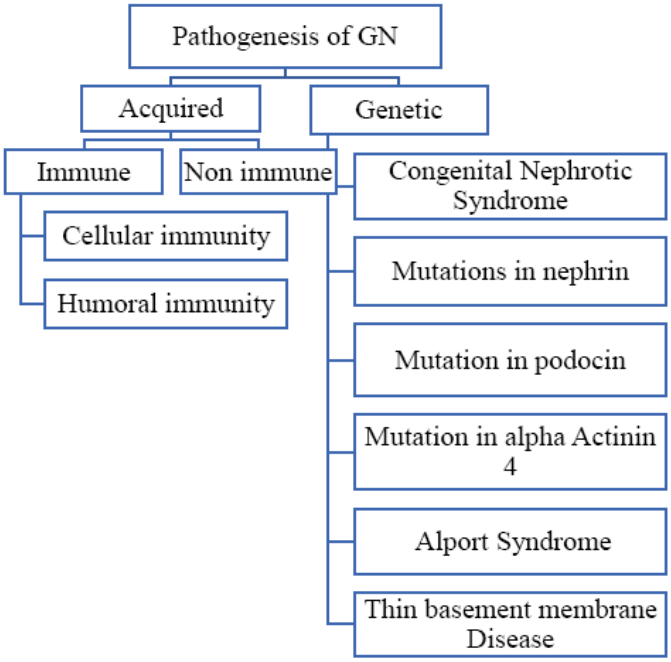
2-Hematuric syndromes

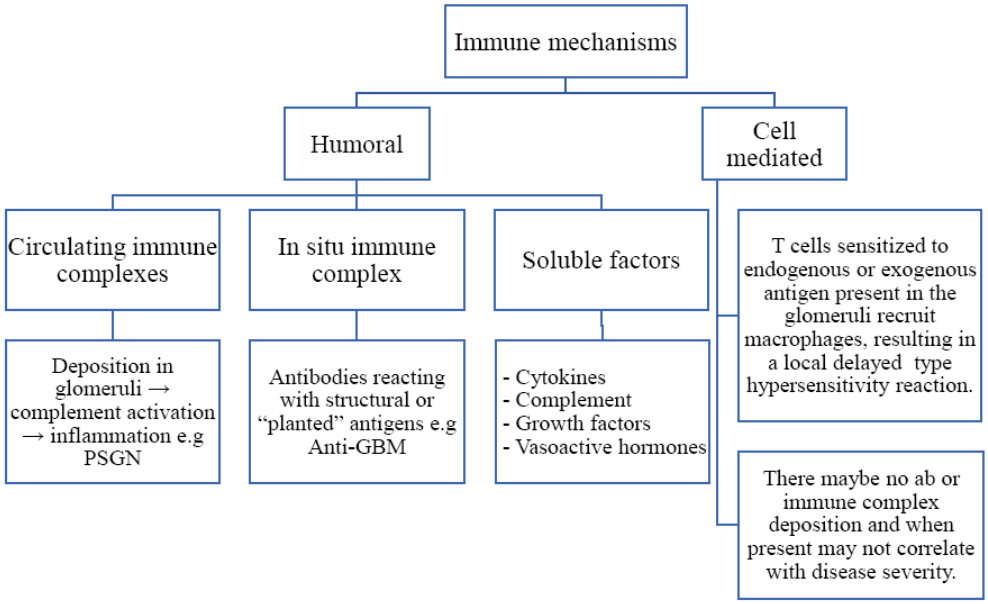
- IgA nephropathy.
- Class III&IV lupus nephritis.
- Post-streptococcal GN.
- Anti-GBM nephritis.
- Pauci-immune GN.

3-Both nephritic and nephrotic

- Membrano-proliferative GN
- Fibrillary GN
- Hereditery

Pathogenesis of GN



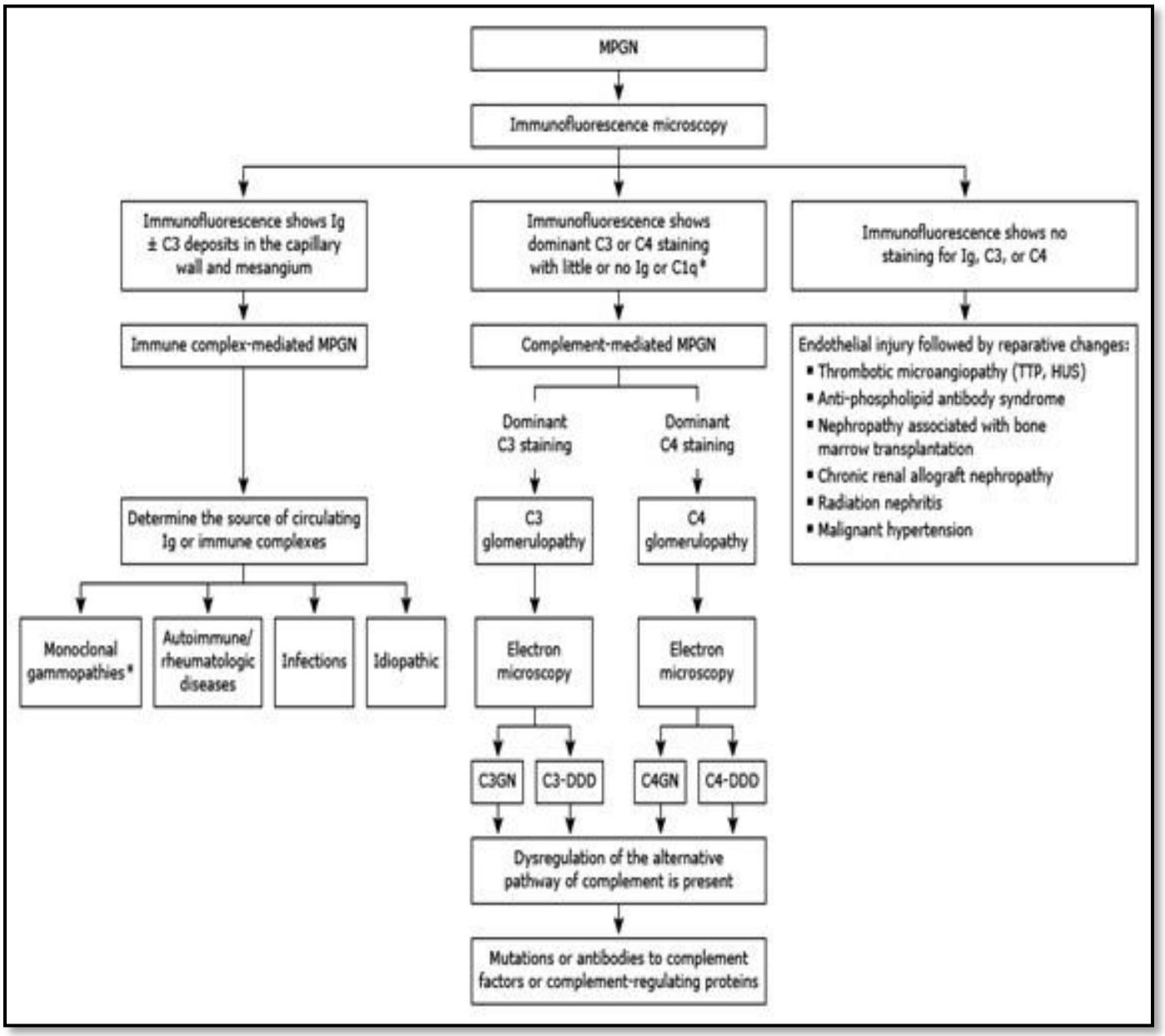


Pathogenic classification of GN

Pathogenetic type	Specific disease entity	Pattern of injury: Focal or diffuse	Score or class
Immune-complex GN	IgA nephropathy, IgA vasculitis, lupus nephritis, infection-related GN, fibrillary GN with polyclonal Ig deposits.	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing or multiple	Oxford/MEST scores for IgA nephropathy & ISN/RPS class for lupus nephritis
Pauci-immune GN	MPO-ANCA GN, proteinase 3-ANCA GN, ANCA-negative GN	Necrotizing, crescentic, sclerosing, or multiple	Focal, crescentic, mixed, or sclerosing class (Berden/EUVAS class)
Anti-GBM GN	Anti-GBM GN	Necrotizing, crescentic, sclerosing, or mixed.	

Pathogenetic type	Specific disease entity	Pattern of injury: Focal or diffuse
Monoclonal Ig GN	Monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, immunotactoid glomerulopathy, fibrillary GN with monoclonal Ig deposits.	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing or multiple.
C3 glomerulopathy	C3 GN, dense deposit disease.	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing or multiple.

New classification of MPGN



Major patterns of glomerular injury

Pattern of glomerular injury	
No abnormality by L.M	1. No glomerular disease. 2. Glomerular disease with no light microscopic changes (e.g. minimal change glomerulopathy, thin basement membrane nephropathy). 3. Mild or early glomerular disease (e.g. ISN/RPS Class I lupus nephritis, IgA nephropathy, C1q nephropathy, membranous glomerulopathy, amyloidosis, Alport syndrome, etc.).
Thick capillary walls without hypercellularity or mesangial expansion	1. Membranous glomerulopathy (primary or secondary) (>Stage I). 2. Thrombotic microangiopathy with expanded subendothelial zone. 3. Preeclampsia/eclampsia with endothelial swelling. 4. Fibrillary glomerulonephritis with predominance of capillary wall deposits.
Thick walls with mesangial expansion but little or no hypercellularity	1. Diabetic glomerulosclerosis with diffuse rather than nodular sclerosis. 2. Secondary membranous glomerulopathy with mesangial immune deposits. 3. Amyloidosis. 4. Monoclonal immunoglobulin deposition disease. 5. Fibrillary glomerulonephritis. 6. Dense deposit disease (type II membranoproliferative glomerulonephritis).
Focal segmental glomerular sclerosis without hypercellularity	1. Focal segmental glomerulosclerosis (primary or secondary). 2. Chronic sclerotic phase of a focal glomerulonephritis. 3. Hereditary nephritis (Alport syndrome).

Mesangial or endocapillary hypercellularity	1. Focal or diffuse mesangioproliferative glomerulonephritis. 2. Focal or diffuse (endocapillary) proliferative glomerulonephritis. 3. Acute (“exudative”) diffuse proliferative postinfectious glomerulonephritis. 4. Membranoproliferative glomerulonephritis (type I, II or III).
Extracapillary hypercellularity	1. ANCA crescentic glomerulonephritis (paucity of immunoglobulin by IFM). 2. Immune complex crescentic glomerulonephritis ((granular immunoglobulin by IFM). 3. Anti-GBM crescentic glomerulonephritis (linear immunoglobulin by IFM). 4. Collapsing variant of focal segmental glomerulosclerosis (including HIV nephropathy).
Membrano-proliferative, lobular or nodular pattern	1. Membranoproliferative glomerulonephritis (type I, II/DDD, or IIIB/IIIS). 2. Diabetic glomerulosclerosis with nodular mesangial expansion (KW nodules). 3. Monoclonal immunoglobulin deposition disease with nodular sclerosis. 4. Idiopathic (smoking associated) nodular glomerulosclerosis. 5. Thrombotic microangiopathy. 6. Fibrillary glomerulonephritis. 7. Immunotactoid glomerulopathy.
Advanced diffuse global glomerular sclerosis	1. End stage glomerular disease. 2. End stage vascular disease. 3. End stage tubulointerstitial disease.

Approach to a patient with glomerular disease

1-clinical presentation and lab investigations

- **History taking and examination**
- **Laboratory investigations**
  - Urinalysis: RBCs, RBCs cast, proteinuria.
  - Quantitative urinary protein. Nephrotic range proteinuria (>3.5 gm/24h), subnephrotic range.
  - Renal function tests: blood urea, creatinine, estimated GFR, creatinine clearance.
  - Renal imaging (to differentiate between acute and chronic and to exclude obstructive uropathy)

2-Renal biopsy for histopathological diagnosis

3-Recognize the underlying causes

- ANA (antinuclear antidoy) Anti-ds DNA positive in systemic lupus erythromatosis (SLE).
- C3, C4 (complement) may be comsumed.
- ASOT (anti-streptolysin O titre) positive in post streptococcal GN.
- ANCA (antineutrophilic antibody) positive in Wagner granulomatosis.
- Antiglomerular basement membrane (AGBM) positive in Goodpasuture syndrome.
- Viral marker (HCV antibodies, HBSAg, HIV antibodies).
- Newer marker (In primary MN, serologic tests for anti-PLA2R are positive in 75% to 80% of cases).

Indications for renal biopsy

1-Acute nephritic syndrome

Including RPGN **except for** patients with a presumptive diagnosis of poststreptococcal glomerulonephritis based upon the clinical history of recent pharyngitis or skin infection and a positive streptozyme test and/or throat or skin culture for group A beta-hemolytic streptococcal infection and patients with glomerulonephritis associated with endocarditis

2-Nephrotic syndrome

Except:

- Patients with **diabetes mellitus** for many years in whom the initial manifestation is moderately increased albuminuria (formerly called microalbuminuria) that slowly progresses to overt proteinuria over many years
- **Patients with nephrotic syndrome that seems, from the history and presence of extrarenal involvement, to be due to primary or secondary amyloidosis**, which can be diagnosed by less invasive tissue biopsy (such as abdominal fat pad or rectal biopsy). By contrast, a biopsy is usually performed in patients with active lupus nephritis to determine the type of disease that is present
- **Children under the age of six years with the acute onset of nephrotic syndrome,** since over 90 percent have minimal change disease. Other causes of nephrotic syndrome may occur in older children
- Patients with overt (already diagnosed) **malignancy**. The major associations are membranous nephropathy with solid tumors and less often a hematologic malignancy such was chronic lymphocytic leukemia; and minimal change disease with lymphoma or leukemia. In these settings, the nephrotic syndrome often resolves with effective treatment of the malignancy.
- Patients with **massive obesity who have slowly increasing proteinuria** over time that is often subnephrotic rather than the abrupt onset of nephrotic syndrome.
- Patients with nephrotic syndrome that **may be related to a drug** such as a nonsteroidal anti-inflammatory agent, pamidronate, penicillamine, gold, or lithium. The time to recovery after cessation of the offending

drug can be as long as several years

In diabetic nephropathy biopsy indicated if urinary active sediment, rapid decline in GFR, absence of retinopathy).

3- Unexplained acute renal failure

After exclusion of:

prerenal disease,acute tubular necrosis and urinary tract obstruction.

4-SLE

- Proteinuria greater than 500 mg/day
- An active urinary sediment with persistent dysmorphic hematuria
- A rising serum creatinine that is not clearly attributable to another cause

5-Isolated non-nephrotic proteinuria

Only if associated with:

- Glomerular hematuria
- Renal impairment
- Presence of clinical or serologic evidence of a systemic disease that can cause glomerulonephritis

6-Isolated glomerular hematuria

Biopsy is **not necessary** if serum creatinine is normal,blood pressure is normal and no proteinuria

Treatment

General Specific

- **Edema treatment:**

– Salt restriction (1.5-2gm sodium /day

– Diuretics: oral loop diuretics, if resistance twice daily, IV bolus or IV infusion, +/- albumin.

Combination of loop D and metolazone is effective combination.

- **Control BP** of goal 130/80 mmHg . No evidence support BP <125/75.

– The antihypertensive agents of choice should be (ACEi) or (ARB)

- **Proteinuria**

- The antiproteinuric agents of choice are ACE-I or ARB, which may reduce proteinuria by up to 40–50% in a dose dependent manner, particularly if the patient complies with dietary salt restriction.

– Adequate dietary protein (0.8–1.0 g/kg daily) with a high carbohydrate intake to maximize utilization of that protein.

- **Treatment of hypercholesterolemia:**

follow the guidelines that apply to those at high risk for the development of cardiovascular disease.

– statin, fibrate (not together).

– Statin not prove to reduce the CV risk, but it can decrease deterioration in GFR.

- Thrombosis: Full-dose anticoagulation with LMWH or warfarin is mandatory in pt with thrombosis.

– It should also be considered if serum albumin <2.0–2.5 g/dl

– with one or more of the following:

- proteinuria >10 g/

- body mass index (BMI) >35 kg/m2

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Specific treatment

⚠ Important definitions of nephrotic syndrome in children:

Classification	Definition
Nephrotic syndrome	Edema, uPCR ≥2000 mg/g (X200 mg/mmol), or ≥300 mg/dl, or 3+ protein on urine dipstick, hypoalbuminaemia ≤2.5 g/dl (≤25 g/l)
Complete remission	uPCR <200 mg/g (<20 mg/mmol) or <1+ of protein on urine dipstick for 3 consecutive days
Partial remission	Proteinuria reduction of 50% or greater from the presenting value and absolute uPCR between 200 and 2000 mg/g (20–200 mg/mmol)
No remission	Failure to reduce urine protein excretion by 50% from baseline or persistent excretion uPCR >2000 mg/g (>200 mg/mmol)
Infrequent relapse	One relapse within 6 months of initial response, or one to three relapses in any 12-month period
Frequent relapse	Two or more relapses within 6 months of initial response, or four or more relapses in any 12-month period
Steroid dependence	Two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy

⚠Important definitions of GN in adults:

•**Complete remission**	**24-h proteinuria of ≤0.3 g and serum albumin of ≥3.5 g/dL, persisting for at least 1 month. Renal survival 100% (Rate of decline of GFR 1.5ml/min/y)**
•**Partial remission**	24-h proteinuria of >0.3 g and <3 g, along with a rise of serum albumin of ≥3 g/dL and stable renal function, Or A 50% reduction from peak proteinuria.Renal survival 90% (Rate of decline of GFR 2ml/min/y)
•**Relapse**	24-h proteinuria of ≥3 g/day for more than 3 days with incipient decline in serum albumin levels.
•**Multiple relapses**	More than 3 relapses/year may be considered to meet the definition.
•**Steroid Dependency**	Two relapses occurring during steroid therapy or within 14 days of completing steroid therapy.
•**Treatment failure**	Renal survival 45% (Rate of decline of GFR 10 ml/min/y).

Steroid-sensitive nephrotic syndrome in children

Treatment of the initial episode of SSNS

Corticosteroid therapy **(prednisone or prednisolone) for at least** 12 weeks. **(1B)**

- **Oral prednisone be administered** as a single daily dose **(1B) starting at** 60 mg/m$_2$/d **or** 2 mg/kg/d **to a maximum 60 mg/d. (1D)**
- **Daily oral prednisone be given for 4–6 weeks (1C) followed** by alternate-day **medication as a single daily dose starting at** 40 mg/m$_2$ **or 1.5 mg/kg (maximum 40 mg on alternate days) (1D) and continued for** 2–5 months **with tapering of the dose. (1B)**

Rationale:

- There is moderate-quality evidence that administering prednisone for three months reduces the risk of relapse in children with the first episode of SSNS, with an increase in benefit seen with up to 6 months of treatment.
- There is moderate-quality evidence that corticosteroid therapy should be given as a single daily dose for at least4 weeks, followed by alternate-day therapy for 2–5 months. The initial dose regimen of corticosteroid therapy is based on recommendations from the ISKDC, and has not been defined in RCTs.

Treatment of relapsing SSNS with corticosteroids

- **Infrequent relapses of SSNS:**
  - **Single-daily dose of prednisone 60 mg/m$_2$ or 2 mg/kg (maximum of 60 mg/d)** until the child has been in complete remission for at least 3 days. **(2D). After achieving complete remission, children be given prednisone as a** single dose on alternate days **(40 mg/m$_2$ per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days)** for at least 4 weeks**. (2C)**

- **Frequently relapsing (FR) and steroid-dependent (SD)**
  - **Daily** prednisone until the child has been in remission for at least 3 days**, followed by alternate-day prednisone for at least 3 months**. (2C)
  - Prednisone to be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with FR and SD SSNS. (2D)
  - Prednisone to be given at the lowest dose to maintain remission without major adverse effects in children with SD SSNS where alternate-day prednisone therapy is not effective. (2D)
  - Prednisone to be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone. (2C)

Rationale:

- In children with infrequent relapses of SSNS, corticosteroid therapy regimens are based on empirical recommendations from the ISKDC and an RCT in children with FR SSNS.
- In children with FR and SD SSNS, there is low-quality evidence that increasing the duration of corticosteroid therapy increases the duration of remission.
- In children with SD SSNS, there is low-quality evidence that changing children from alternate-day to daily corticosteroids at onset of upper respiratory infections reduced the risk of relapse.
- In children with FR and SD SSNS, there is very low–quality evidence that low-dose alternate-day or daily

Corticosteroid-sparing agents

for children with FR SSNS and SD SSNS,
who develop steroid-related adverse effects.

1-Alkylating agents

- ### cyclophosphamide

-Dose: (2 mg/kg/d)
-Duration: 8–12 weeks (maximum cumulative dose
168 mg/kg). (2C)
-Not be started until the child has achieved remission with corticosteroids.

- ### Chlorambucil

Dose: (0.1–0.2 mg/kg/d)
Duration: 8 weeks (maximum cumulative dose
11.2 mg/kg)

2-Levamisole

Dose of 2.5 mg/kg on alternate days (2B) for at least 12 months

3-Calcinurin inhibitors

Duration : 12months

- ### Cyclosporin

  Dose: 4–5 mg/kg/d (starting dose) in two divided doses.

- ### Tacrolimus

  Dose: 0.1 mg/kg/d (starting dose) given in two divided doses be used instead of cyclosporine when the cosmetic side-effects of cyclosporine are unacceptable

4-MMF

Duration: 12month
(starting dose 1200 mg/m2/d) be given in two divided doses)

Rationale:

In children with FR and SD SSNS:

- There is moderate-quality evidence to support the use of alkylating agents (cyclophosphamide, chlorambucil), levamisole, and CNI (cyclosporine, tacrolimus)
- There is low-quality evidence to support the use of mycophenolate mofetil (MMF).
- There is very low–quality evidence to support the efficacy of rituximab.
- There is moderate-quality evidence to demonstrate that mizoribine and azathioprine are not effective.

Rituximab:

Only in children with SD SSNS who have FR despite optimal combinations of prednisone and corticosteroid sparing agents and/or who have serious adverse effects of therapy(2C)

Mizoribine:

Not to be used as corticosteroid sparing agent in FR and SD SSNS(2C)

Azathioprine:

Not to be used as corticosteroid sparing agent in FR and SD SSNS(1B)

Treatment of steroid resistant nephrotic syndrome in children:

Steroid resistance is defined as failure to response a minimum of 8 weeks treatment with corticosteroids. (2D)

- Evaluation of children with SRNS (Not Graded)
  - A diagnostic kidney biopsy;
  - Evaluation of kidney function by GFR or eGFR;
  - Quantitation of urine protein excretion.

Supportive therapy

We suggest that MCD patients who have AKI be treated with renal replacement therapy as indicated, but together with corticosteroids, as for a first episode of MCD. (2D)

We suggest that, for the initial episode of nephrotic syndrome associated with MCD, statins not be used to treat hyperlipidemia, and ACE-I or ARBs not be used in normotensive patients to lower proteinuria. (2D)

Minimal Change Disease in adults

Initial episode

Corticosteroid therapy (prednisone or prednisolone):

- Daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day single dose of 2 mg/kg (maximum 120 mg).
- If the initial high dose is tolerated and complete remission is achieved maintain for 4 weeks, if complete remission is not achieved maximum period is 16 weeks.
- In case of remission taper slowly over 6 month after achieving complete remission.
- Oral cyclophosphamide or CNIs are suggested for patients for patients with relative contraindications or intolerance to high-dose corticosteroids.

Rationale:

- There is only low-quality evidence to recommend corticosteroids in the treatment of adult MCD. This recommendation is based largely on extrapolation from RCTs in children, as well as small RCTs and observational studies in adults.
- There is only low-quality evidence to define the optimal dose and duration of corticosteroids in adults, but a high dose until remission is achieved followed by a slow taper to minimize relapse is usually prescribed.
- There is very low–quality evidence suggesting that alternate-day is equivalent to daily corticosteroids in adult MCD.
- MCD in adults may take a longer time to remit compared to MCD in children.

Infrequent relapses:

the same initial dose and duration of corticosteroids

Frequently relapsing/steroid dependent:

- Oral **cyclophosphamide** 2–2.5 mg/kg/d for 8 weeks.
- For patients who have relapsed despite cyclophosphamide, or for people who wish to preserve their fertility: **CNI** (cyclosporine 3–5 mg/kg/d or tacrolimus 0.05–0.1 mg/kg/d in divided doses) for 1–2 years.
- If the patient is intolerant to corticosteroids, cyclophosphamide, and CNIs: **MMF** 500–1000 mg twice daily for 1–2 years

Rationale:

- There is low-quality evidence to suggest the value of alkylating agents in adult FR/SD MCD. Support for this approach comes from RCTs in children, and observational studies in adults.
- There is low-quality evidence to suggest that CNIs can induce complete or partial remission in adult MCD, but relapse rates may be higher than with alkylating agents after cessation of CNIs.
- There is very low–quality evidence to suggest the use of MMF as a corticosteroid or CNI-sparing agent

Steroid resistant

Re-evaluate patients who are corticosteroid-resistant for other causes of nephrotic syndrome. (Not Graded)

- In case of **AKI**: renal replacement therapy as indicated, but together with corticosteroids, as for a first episode of MCD.

- **Statins** not be used to treat hyperlipidemia, and ACE-I or ARBs not be used in normotensive patients to lower proteinuria.

Rationale:

- AKI may accompany MCD in adults. This is usually reversible with continued steroid therapy. Supportive care, including renal replacement therapy, may be temporarily required. Proteinuria in adult MCD will typically remit with corticosteroids. As a consequence, the accompanying hyperlipidemia will remit with resolution of proteinuria, negating the need for statin therapy.
- Proteinuria in adult MCD will typically remit with corticosteroids, and statins and RAS blockade to help reduce proteinuria are not necessary if early remission is achieved.

Idiopathic focal segmental glomerulosclerosis

Initial evaluation

- Undertake thorough evaluation to exclude secondary forms of FSGS.
- Do not routinely perform genetic testing.

Rationale:

- FSGS should be classified as idiopathic (primary) FSGS or secondary FSGS. This is not merely semantic, but has therapeutic implications.
- Idiopathic FSGS is defined by exclusion of any other identifiable cause of secondary FSGS and should be evaluated by detailed examination of the patient, including medical history, physical examination, family history, kidney imaging, and kidney pathology, including electron micoscopy studies.
- There are no good data to support genetic testing in adults with FSGS, even in cases of steroid resistance.
- In the absence of a family history of FSGS, mutations of NPHS1 (nephrin), NPHS2 (podocin), alpha-actinin-4, CD2AP, and TRPC-6 are detected in only 0–3% of adults with FSGS.
- In addition, some patients with a genetic abnormality have responded to therapy, suggesting that the results of genetic analysis should not change treatment decisions.
- African-Americans with FSGS are likely to have mutations in the apolipoprotein L1 (APOL1) gene.
- Most patients will present with non-nephrotic proteinuria. The therapeutic implications of this mutation are currently unknown, so this guideline does not suggest routine testing for APOL1 mutations.

Initial treatment:

- Corticosteroid and immunosuppressive therapy to be considered **only** in idiopathic FSGS associated with clinical features of the nephrotic syndrome.
- Prednisone -at a daily single dose of 1 mg/kg (maximum 80 mg) or alternate-day dose of 2 mg/kg (maximum 120 mg).
- The initial high dose of corticosteroids be given for a **minimum of 4 weeks**; continue high-dose
- Corticosteroids to be given up to a **maximum of 16 weeks,** as tolerated, or until complete remission has been achieved, whichever is earlier.
- Corticosteroids to be tapered slowly over a period of **6 months** after achieving complete remission.
- **CNIs** be considered as first-line therapy for patients with relative contraindications or intolerance to high-dose corticosteroids

Rationale:

- Most patients that progress have persistent nephrotic range proteinuria; patients with non-nephrotic proteinuria are at low risk for progressive kidney failure and ESRD.
- Those with sustained non-nephrotic proteinuria are at increased risk of cardiovascular morbidity and mortality.
- Those risks should be managed, including treatment of proteinuria with RAS blockade and control of blood pressure.
- There is low-quality evidence to recommend corticosteroid or immunosuppressive therapy in primary FSGS when accompanied by nephrotic syndrome.
- There is no evidence to suggest corticosteroid or immunosuppressive therapy in secondary FSGS.

Treatment of steroid resistant FSGS

- Cyclosporine at 3–5 mg/kg/d in divided doses -for at least 4–6 months OR **Tacrolimus 0.1-0.2 mg/kg/d (intial target 5-10 ng/ml) in 2 divided doses)** and **Prednisone** 0.15 mg/kg/d for 4-6 m, then taper off over 4-8wks.
- If there is a partial or complete remission, continue cyclosporine treatment for at least 12 months, followed by a slow taper.
- If cyclosporine is not tolerated > a combination of MMF + high dose dexamethasone is recommended

Rationale

- Cyclosporine is effective in inducing remission of proteinuria in patients with steroid-resistant FSGS. Remissions can develop slowly, and may take 3–6 months after start of therapy.
- A partial remission provides a substantial outcome benefit.
- Relapses are very frequent after withdrawal of cyclosporine.
- More prolonged treatment may lead to more persistent remissions. Relapses occur frequently when using cyclosporine for a 6-month period.
- A longer duration of therapy and slow tapering strategy in cyclosporine-responsive patients can be used in FSGS similar to that advised in adults with MCD.
- There is limited evidence to support the efficacy of other regimens in patients with steroid-resistant proteinuria.

Idiopathic membranous nephropathy

Evaluation of MN

Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven MN.

Rationale

- MN is due to a clinically recognizable underlying disorder in a variable percentage of cases, depending on age and geography.
- The recognition of the underlying disorder responsible for MN has important implications for prognosis and therapy.
- MN is typically a disease of adults (fewer than 3% of cases are found in children). The frequency and etiology of secondary causes varies in different geographic areas.
- IMN is often a ‘‘diagnosis of exclusion’’. A recent study200 has shown that about 70–80% of patients exhibit circulating antibodies of IgG4 subtype against a conformation-dependent epitope in the M-type phospholipase A2 receptor. Such autoantibodies appear to be absent or very uncommon in patients with secondary MN.
- If the absence of autoantibodies to phospholipase A2 receptor in secondary MN is validated and a sensitive and specific assay for autoantibodies becomes available, it could become a valuable marker to positively identify (‘‘rule in’’) IMN.
- The IgG4 subclass dominates in the deposits of IMN, while IgG1, IgG2, and/or IgG3 dominate in secondary forms of MN.
- The most important secondary causes include systemic lupus (in younger women), chronic hepatitis B infection (especially in East Asia196), drugs (such as nonsteroidal anti-inflammatory agents, gold and mercury compounds) and malignancy (especially in patients presenting over the age of 65 years).
- Specific evaluations should exclude secondary causes of MN before specific immunosuppressive therapy is considered. Detailed morphological studies

show mesangial deposits by electron microscopy and prominent IgG1, 2, or 3 subclass deposits by immunofluorescence in secondary MN. These features can be helpful in suspecting a secondary form of MN.

Initial therapy is recommended to be started ONLY in patients with nephrotic syndrome AND when at least ONE of the following conditions is met:

- Urinary protein excretion persistently exceeds 4 g/d AND remains at over 50% of the baseline value, AND does not show progressive decline, during antihypertensive and antiproteinuric therapy during an observation period of at least 6 months.
- The presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome.
- SCr has risen by 30% or more within 6 to 12 months from the time of diagnosis but the eGFR is not less than 25–30 ml/min/1.73m2 AND this change is not explained by superimposed complications.

DO NOT use immunosuppressive therapy in patients with a SCr persistently >3.5 mg/dl (or an eGFR <30 ml/min per 1.73m2) AND reduction of kidney size on ultrasound (e.g., o8 cm in length) OR those with concomitant severe or potentially life-threatening infections.

Rationale:

- There is low- to moderate-quality evidence to support a recommendation that patients with time-averaged proteinuria o4.0 g/d or those who achieve a complete or partial remission have an excellent long-term prognosis.
- Observational studies of the natural history of IMN have shown that male gender, persistent heavy proteinuria, and elevated SCr at diagnosis predict the risk of later progressive decline in kidney function, although these factors may not all be independent risks.
- About 30–35% of patients with IMN eventually undergo spontaneous remission of nephrotic syndrome; therefore, it is reasonable to delay specific therapy for at least 6 months utilizing supportive therapy, including RAS blockade unless the patient has unexplained rapid deterioration in

kidney function or there are complications related to uncontrolled nephrotic syndrome. However, the frequency of spontaneous remissions is lower with higher grades of proteinuria at presentation.

- It may be difficult to define precisely the time of onset of a partial remission, since some patients experience a slow reduction in proteinuria, even in the absence of specific treatment, to non-nephrotic levels over several years.
- There is support for the use of predictive models for determining risk of progression in IMN (i.e., persistent proteinuria 44 g/d and/or decline in kidney function over a 6-month period of observation).
- There is low-quality evidence to support a recommendation that the period of observation may be extended in patients who exhibit a consistent progressive decline in proteinuria during observation, have stable kidney function, and no complications related to the nephrotic state

Initial treatment (ponticelli regimen)

Month 1	IV methylprednisolone 1gm daily for 3 days then oral prednisolone(0.5mg/kg/day) for 27 days
Month 2	Oral cyclophosphamide 2mg/kg/day for 30 days
Month 3	Repeat month 1
Month 4	Repeat month 2
Month 5	Repeat month 1
Month 6	Repeat month 2

- Manage **conservatively** for **at least 6 months** following the completion of this regimen before being considered a treatment failure if there is no remission, unless kidney function is deteriorating or severe, disabling, or potentially life-threatening symptoms related to the nephrotic syndrome are present.
- Perform a repeat kidney biopsy only if the patient has rapidly deteriorating kidney function (doubling of SCr over 1–2 month of observation), in the absence of massive proteinuria (>15 g/d).
- Daily (noncyclical) use of oral alkylating agents may also be effective, but can be associated with greater risk of toxicity, particularly when administered for 46 months.

Rationale:

- There is moderate-quality evidence to recommend a 6-month cyclical regimen of alternating alkylating agents (cyclophosphamide or chlorambucil) plus i.v. pulse and oral corticosteroids for initial therapy of IMN meeting the criteria This evidence indicates this treatment is superior to supportive therapy alone in inducing remissions and preventing long-term decline of kidney function, including the need for dialysis, in patients with IMN and persisting nephrotic syndrome.
- Other combined regimens of cyclophosphamide and corticosteroids have also been used. Some omit i.v methylprednisolone, others use alkylating agent and corticosteroids concurrently, rather than cyclically, for a longer duration. However, the long-term efficacy and safety of these regimens are less well-established than the cyclical regimen. The safety and efficacy of i.v. cyclophosphamide-based regimens for treatment of IMN have not been sufficiently evaluated to warrant any recommendations. One small (underpowered) controlled trial in progressive IMN was negative.The evidence is insufficient to make any recommendations regarding the use of

i.v. compared to oral cyclophosphamide.

- A complete or partial remission of nephrotic syndrome is associated with an excellent long-term prognosis; therefore, persisting remission of the nephrotic state is an acceptable surrogate end-point to assess overall efficacy of treatment.
- Treated patients may continue to enter complete or partial remission for as long as 12–18 months following completion of the regimen, so it is reasonable to wait this period of time before deciding whether the initial treatment has been unsuccessful providing that serum albumin levels or kidney function are not deteriorating, and that morbid events have not supervened. During the period of observation, patients should continue to receive ACE-I or ARBs, other antihypertensives, and other supportive therapies as clinically indicated. In comparative studies, cyclophosphamide has a superior safety profile compared to chlorambucil. There is low-quality evidence that cyclophosphamide can lead to more frequent and longer remissions than chlorambucil.
- Cumulative toxicities alkylating agents can be significant and require careful monitoring by the treating physician. A recent study of the use of cyclophosphamide- or chlorambucil-based regimens in IMN has raised concerns regarding safety, given a reported adverse-event rate that exceeded 80%. This is in contrast to the older long-term RCT of cyclical alkylating agents and steroids, where the regimens were well-tolerated with an acceptably low frequency of serious adverse events. Risks of this regimen are now known to be increased if alkylating agents are used in patients with reduced renal function, older age, and/or concomitant comorbidities as evidenced in this recent report.
- Since the decline in GFR in IMN is often very gradual, especially in the absence of massive proteinuria, any acceleration of the rate of decline indicates the possibility of a superimposed disease process (such as crescentic glomerulonephritis or acute interstitial nephritis, which is often drug-related) that might dictate a change in treatment approach. A repeat kidney biopsy is necessary to identify these conditions.
- Relapses of nephrotic syndrome occur in about 25% of patients treated with the ‘‘Ponticelli’’ regimen. A similar fraction of patients with spontaneous remissions also will relapse

- Consider **CNI** for at least 6 months as an alternative if the previously mentioned regimen is **contraindicated.**
- If **there's no partial or complete remission after 6 months** of treatment> discontinue CNI.
- Reduce the dose of CNI at intervals of 4–8 weeks to a level of about 50% of the starting dosage, provided that remission is maintained and no treatment-limiting CNI-related nephrotoxicity occurs, and continued for at least 12 months.
- Monitor CNI blood levels regularly during the initial treatment period, and whenever there is an unexplained rise in SCr (>20%) during therapy.

Cyclical corticosteroid/alkylating-agent regimen in IMN risks *versus* benefits

Risks	Benefits
○ Enhanced risk of opportunistic infection ○ Reactivation of viral hepatitis ○ Alopecia ○ Gonadal damage (aspermatogenesis, ovulation failure) ○ Hemorrhagic cystitis (cyclophosphamide only) ○ Neoplasia (myelodysplastic syndrome, acute myelogenous leukemia ○ Transitional cell carcinoma of the bladder, ureter or pelvis ○ Toxic hepatitis	○ Prevention of CKD and ESRD ○ Avoidance of complications of nephrotic syndrome (thrombosis, accelerated atherogenesis) ○ Prevention of CKD and ESRD ○ Avoidance of complications of nephrotic syndrome (thrombosis, accelerated atherogenesis) ○ Prolongation of life; improved quality of life.

Treatment of relapse:

- Reinstitute the same therapy that resulted in the initial remission.
- If a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy, the regimen be repeated only once for treatment of a relapse.
- **No more than one course** of the cyclical corticosteroid/alkylating-agent regimen be given **in children.**

Treatment of resistant IMN:

We suggest that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI. (2C)
We suggest that patients with IMN resistant to CNI-based initial therapy be treated with an alkylating agent/steroid-based therapy. (2C)

Idiopathic membranoproliferative glomerulonephritis(MPGN)

For idiopathic MPGN accompanied by nephrotic syndrome AND progressive decline of kidney function

Oral cyclophosphamide or MMF plus low-dose alternate day or daily corticosteroids with initial therapy limited to **less than 6 months** is recommended.

Rationale:

There is very low–quality evidence to suggest the benefit of an immunosuppressive agent plus corticosteroids in the treatment of idiopathic (type I) MPGN with nephrotic syndrome and/or deteriorating kidney function.

IgA nephropathy

- Proteinuria 0.5-1gm/1.7m2 adult (0.5-1gm/day children): We suggest ACE-I or ARB treatment (2D) blood pressure treatment goals of 130/80mmHg (Not Graded)

- Proteinuria >1gm: We recommend long-term ACE-I or ARB with up-titration of the drug depending on blood pressure. (1B) BP goal <125/75mmHg (Not Graded)

- Patients with persistent proteinuria >1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR>50 ml/min per 1.73m2, receive a 6-month course of corticosteroid therapy.
  IV bolus injections of 1 g methylprednisolone for 3 days each at months 1, 3, and 5, followed by oral steroid 0.5 mg/kg prednisone on alternate days for 6 months OR 6-month regime of oral prednisone A starting with 0.8–1 mg/kg/d for 2 months and then reduced by 0.2 mg/kg/d per month for the next 4 months

- Corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients is not recommended (unless there is crescentic IgAN with rapidly deteriorating kidney function.

- If GFR is <30 ml/min per 1.73m2 immunosuppressive agents are not recommended, unless there is crescentic IgAN with rapidly deteriorating kidney function.

- MMF is not recommended in IgA nephropathy.

Rationale:

- Many of the trials using ACE-I/ARBs in IgAN recruited patients with proteinuria >1 g/d while some recruited patients with proteinuria >0.5 g/d.
- In registry data, 477 the rate of decline of function increased with the amount of proteinuria; those with sustained proteinuria>3 g/d lost kidney function 25-fold faster than those with proteinuria >1 g/d. Patients who presented with >3 g/d who achieved proteinuria >1 g/d had a similar course to patients who had >1 g/d throughout, and fared far better than patients who never achieved this level. There is, as yet, no evidence in IgAN that reducing proteinuria below 1 g/d in adults gives additional benefit.
- Several RCTs have shown that ACE-I and ARBs can reduce proteinuria and improve kidney function (assessed by reduction of the slope of GFR deterioration;. However, there is, as yet, no definitive study of sufficient duration to show the benefit of either ACE-I or ARBs in reducing the incidence of ESRD. There are no data to suggest preference of ACE-I over ARBs, or vice versa, except in terms of a lesser side-effect profile with ARBs compared to ACE-I.
- One study suggested the combination of ACE-I and ARBs induced a 73% greater reduction of proteinuria than monotherapy (ACE-I 38% and ARB 30%, respectively). A small study of seven pediatric IgAN patients also showed some benefits with a combination of ACE-I and ARB. However, more studies are needed to determine whether the definite benefit of combination therapy is effective, leading to a better kidney outcome.

- Using **fish oil** in the treatment of IgAN is recommended in case of persistent proteinuria >1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control).
- Anti-platelet agents and tonsillectomy are not recommended as a treatment for IgAN

Atypical forms of IgAN

MCD with mesangial IgA deposits	Treatment as for MCD in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy.
AKI associated with macroscopic hematuria	General supportive care for AKI in IgAN, with a kidney biopsy performed during an episode of macroscopic hematuria showing only ATN and intratubular erythrocyte casts
Crescentic IgAN	steroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic IgAN,

Immunosuppressant treatment in IgA (if crescentic IgAN with rapidly deteriorating kidney function)

Initial treatment:

Cyclophosphamide Given with pulse and oral steroids or Rituximab+ IV or oral steroids

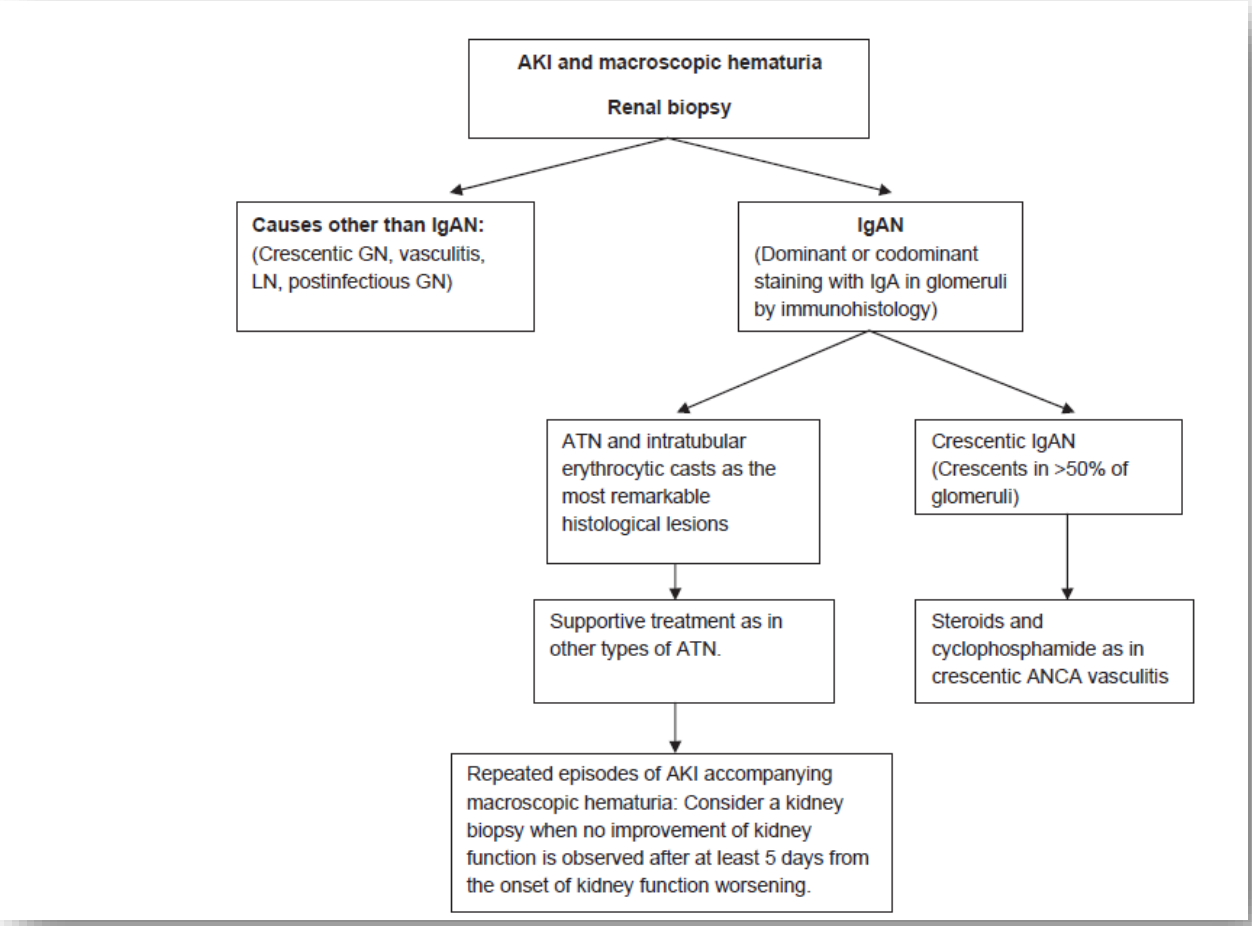
- **Dose of steroids:** (0ral 1 mg/kg/d (max 60 mg daily) for 4 weeks
  Taper down over 3–4 months or IV
- **Dose for cyclophosphamide**
  - IV Pulse : 0.75 g/m2q 3–4 weeks (Decrease initial dose to 0.5 g/m2 if age>60 years or GFR<20 ml/min per 1.73 m2). Adjust subsequent doses to achieve a 2-week nadir leukocyte count >3000/mm3
  - An alternative IV cyclophosphamide dosing schema is 15 mg/kg given every 2 weeks for three pulses, followed by 15 mg/kg given every 3 weeks for 3 months beyond remission, with reductions for age and estimated GFR.
  - Oral Cyclophosphamide: 1.5–2 mg/kg/d, reduce if age>60 years or GFR<20 ml/min per 1.73 m2
- **Dose of Rituximab**
  IV 375 mg/m2 Weekly for 4 weeks.

Continuing maintenance therapy for at least 18 months in patients who remain in complete remission.

Azathioprine 1–2 mg/kg/d orally, MMF, up to 1 g twice daily, be used for maintenance therapy in patients who are allergic to, or intolerant of, azathioprine.

Trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease.

Methotrexate (initially 0.3 mg/kg/wk, maximum 25 mg/wk) for maintenance therapy in patients intolerant of azathioprine and MMF, but not if GFR is<60 ml/min per 1.73 m2



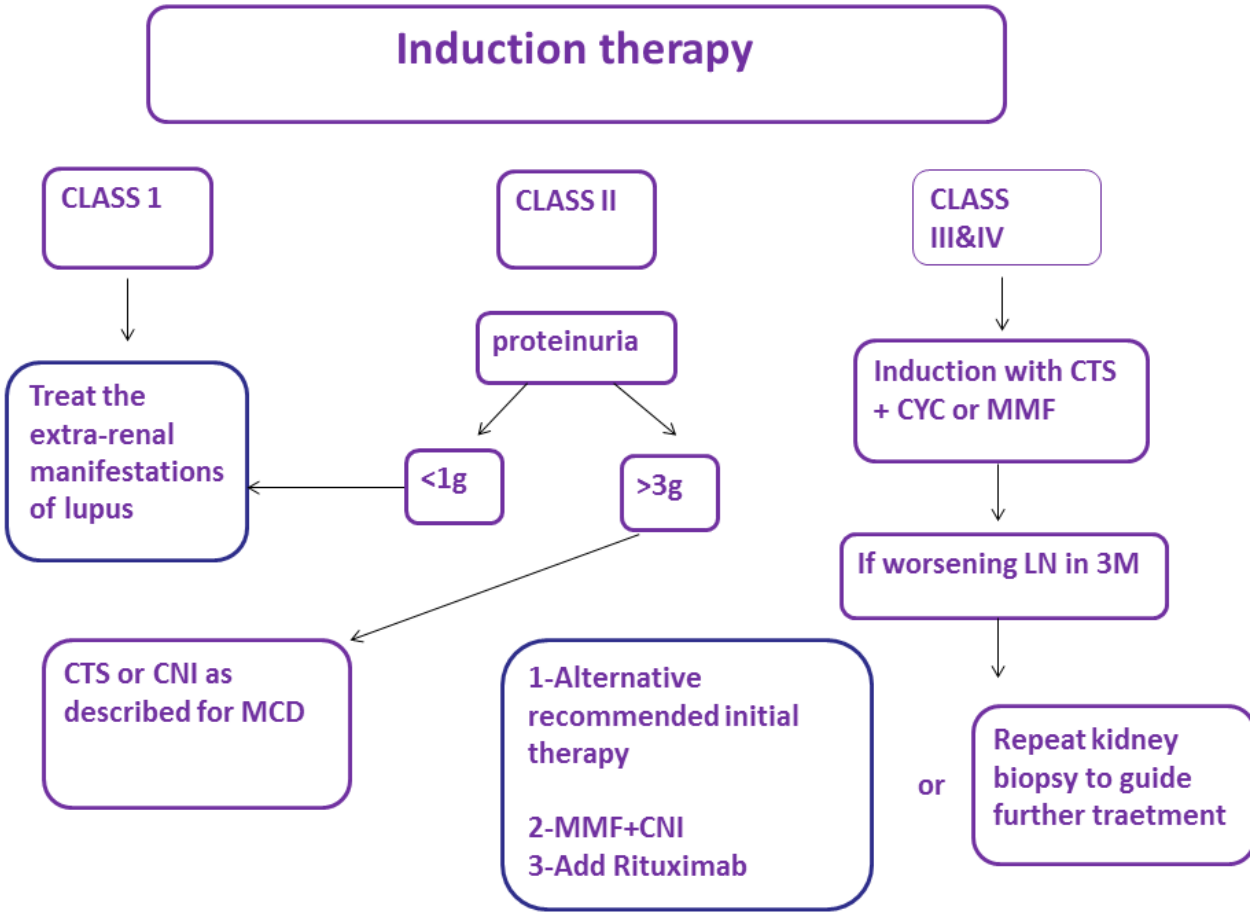
Henoch-Schonlein purpura nephritis

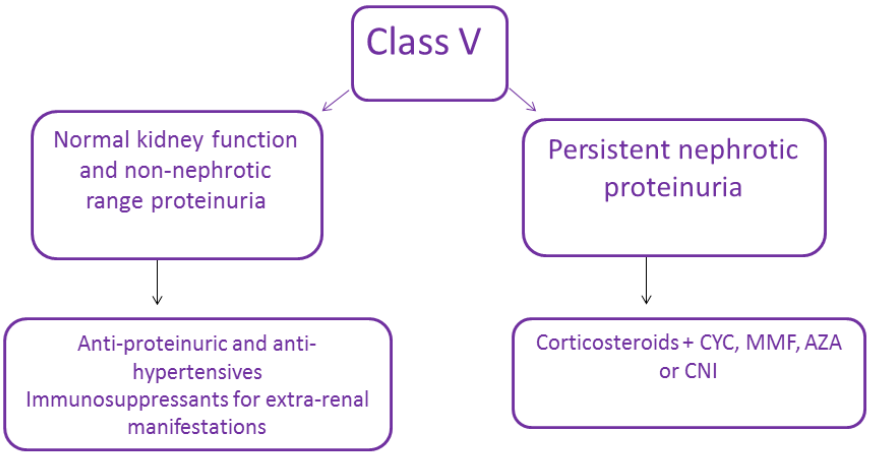
- Children with HSP nephritis and persistent proteinuria,> 0.5–1 g/d per 1.73m2, are treated with ACE-I or ARBs.
- Children with persistent proteinuria, >1 g/d per 1.73m2, after a trial of ACE-I or ARBs, and GFR 450 ml/min per 1.73m2, be treated the same as for IgAN with a 6-month course of corticosteroid therapy.
- Corticosteroids are not recommended to prevent HSP nephritis.
- Adults to be treated the same as in children.

Rationale:

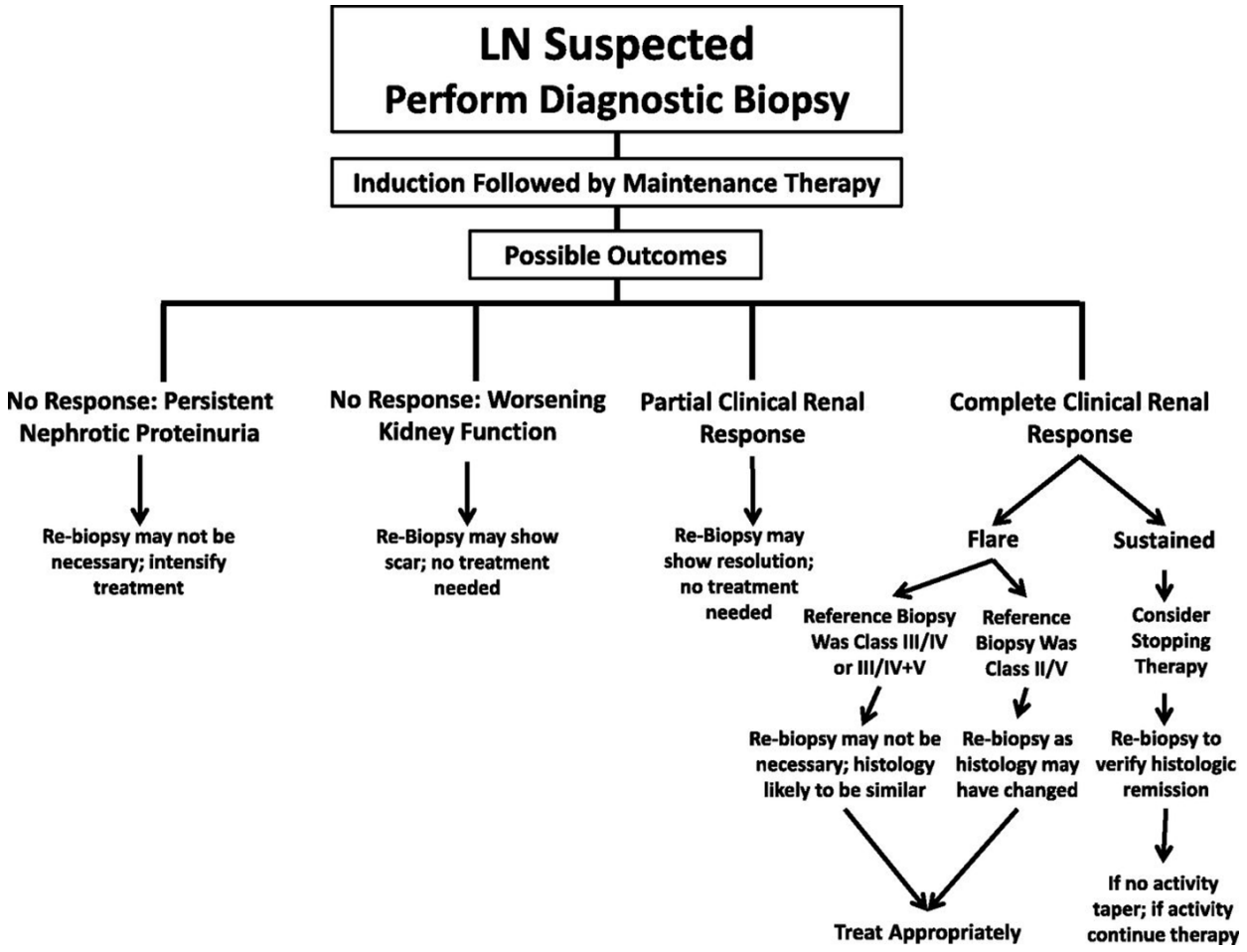
- There is no evidence for the use of RAS blockade in HSP nephritis in children, but an RCT in children and young adults with IgAN demonstrated the benefit of this therapy in reducing proteinuria and maintaining GFR.
- There is no evidence for the use of oral corticosteroids in HSP nephritis, but data from RCTs in adults with IgAN have demonstrated a benefit in reducing proteinuria and maintaining GFR.
- There is very low–quality evidence for the benefit of high dose corticosteroids and immunosuppressive agents in HSP nephritis with deteriorating kidney function.

Lupus nephritis





Regimen	A. NIH	B. Euro-Lupus	C. Oral cyclophosphamide	D. MMF
Cyclophosphamide	i.v. cyclophosphamide 0.5–1 g/m^2; monthly for 6 months	i.v. cyclophosphamide 500 mg; every 2 weeks for 3 months	Oral cyclophosphamide 1.0–1.5 mg/kg/d (maximum dose 150 mg/d) for 2–4 months	—
MMF	—	—	—	MMF up to 3 g/d for 6 months
Benefit shown by RCT in proliferative LN	Yes	Yes	Yes	Yes
Benefit shown by RCT in severe proliferative LN	Yes	Untested	Untested	Untested
Comments	Effective in whites, blacks, Hispanics, Chinese	Effective in whites. Untested in blacks, Hispanics, Chinese	Effective in whites, blacks, Chinese; easy to administer and lower cost than i.v. cyclophosphamide	Effective in whites, blacks, Hispanics, Chinese; high cost



Rationale:

- **Class I** LN has no clinical kidney manifestations.
- Class I LN is not associated with long-term impairment of kidney function.
- Kidney tissue obtained for research purposes in patients with systemic lupus but without clinical signs of kidney disease showed LN was present in about 90% of patients, far more than the 40% or so who manifest clinical kidney disease. In some patients with clinically silent class I LN, there is transformation to more aggressive and clinically relevant forms of LN. However, at present, there are no data to suggest that every patient with

lupus requires a kidney biopsy, or that treatment of class I LN is clinically necessary.

- There are no evidence-based data on the treatment of **class II** LN
  Proliferative LN (class III or IV) is an aggressive disease.
  - Before 1970, kidney survival and overall patient survival in diffuse proliferative LN were very poor, in the range of 20–25%.
  - Patient and kidney survival in class III and IV LN have dramatically improved through the use of intensive immunosuppression.
  - The International Society of Nephrology/Renal Pathology Society classification of LN assigns activity (A) or chronicity (C) in class III and IV LN. Our treatment recommendations are for active or active plus chronic lesions. Thorough review with the nephropathologist is required to ensure accurate classification prior to starting therapy.
  - Therapy for class III and IV LN has initial and maintenance phases. The objective is to rapidly decrease kidney inflammation by initial intensive treatment, and then consolidate treatment over a longer time. The initial phase is often called induction, which implies remission is achieved at its completion. This, however, is often not the case, and remissions continue to occur well into the maintenance phase. The term ‘‘initial’’ treatment is therefore preferred.
  - The benefit of the addition of cyclophosphamide to corticosteroids for initial treatment was shown in controlled trials demonstrating that, during long term follow-up, this combination decreased the frequency of kidney relapse, CKD, and ESRD compared to corticosteroids alone.
  - The evolution of initial therapy in proliferative LN has been to reduce toxicity while maintaining efficacy. This has resulted in several modifications of cyclophosphamide dosing, and the introduction of MMF as an alternative to cyclophosphamide.
  - The efficacy of newer initial treatment regimens should be assessed not only by initial responses, but also by longterm effects on kidney relapse, and development of CKD.

Maintenance therapy

- **Azathioprine** (1.5-2.5mg/kg/day) or **MMF** (1-2g/day) in two divided doses, and low dose corticosteroids
  -Duration> at least 12 months
  - If no complete remission after 12 months > repeat kidney biopsy.
- In patients who are intolerant to MMF and azathioprine> CNI with low dose corticosteroids.
- While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, treatment to be increased to the previous level of immunosuppression that controlled the LN.

Rationale:

- There is moderate-quality evidence from RCTs in patients with class III/IV LN that prolonged maintenance therapy after initial treatment is required.
- There is moderate-quality evidence that maintenance therapy with azathioprine or MMF is superior to maintenance with cyclophosphamide as judged by risk of death, and risk of development of CKD.
- There is moderate-quality evidence that azathioprine and cyclosporine A have comparable efficacy as maintenance therapies for class III/IV LN.
- There is very low–quality evidence to guide the duration of maintenance therapy after complete remission, but most randomized studies of class III/IV LN have given therapy for several years.

Systemic lupus and TMA	○ The antiphospholipid antibody syndrome (APS) involving the kidney in systemic lupus patients, with or without LN, be treated by anticoagulation (target [INR] 2–3). ○ systemic lupus and thrombotic thrombocytopenic purpura (TTP) receive plasma exchange
Systemic lupus and pregnancy	○ Delay pregnancy until **a complete remission** of LN has been achieved. ○ Discontinue **CYC**, **MMF**, **ACE** or **ARBs** ○ **Hydroquine** to be continued during pregnancy ○ If the patient is on **MMF** and became pregnant> shift to **AZA** ○ **Low dose Aspirin** to be used during pregnancy to decrease the risk of fetal loss. ○ Corticosteroids and AZA not to be tapered during pregnancy and at least for 3 months after delivery.

According to 2019 update of the EULAR recommendations of SLE

Hydroxychloriquine is recommended for **ALL** lupus patients,(unless contraindicated).

- **Maximum dose :** 5mg/kg/day (real body weight)
- Baseline fundus examination must be done before start of therapy
- Follow up fundus examination after **5 years** then **annually.**

Criteria of diagnosis of relapse of lupus nephritis

Mild kidney relapse	Moderate kidney relapse	Severe kidney relapse
Increase in glomerular hematuria from <5 to >15 RBC/hpf, with ≥2 acanthocytes/hpf *and/or* recurrence of ≥1 RBC cast, WBC cast (no infection), or both	If baseline creatinine is: <2.0 mg/dl [<177 μmol/l], an increase of 0.20–1.0 mg/dl [17.7–88.4 μmol/l] ≥2.0 mg/dl [≥177 μmol/l], an increase of 0.40–1.5 mg/dl [35.4–132.6 μmol/l] *and/or* If baseline uPCR is: <500 mg/g [<50 mg/mmol], an increase to ≥1000 mg/g [≥100 mg/mmol] 500–1000 mg/g [50–100 mg/mmol], an increase to ≥2000 mg/g [≥200 mg/mmol], but less than absolute increase of <5000 mg/g [<500 mg/mmol] >1000 mg/g [>100 mg/mmol], an increase of ≥2-fold with absolute uPCR <5000 mg/g [<500 mg/mmol]	If baseline creatinine is: <2 mg/dl [<177 μmol/l], an increase of >1.0 mg/dl [>88.4 μmol/l] ≥2 mg/dl [≥177 μmol/l], an increase of >1.5 mg/dl [>132.6 μmol/l] *and/or* an absolute increase of uPCR >5000 mg/g [>500 mg/mmol]

Treatment of relapse of LN

- Treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. (2B)
- The patient at risk for excessive lifetime cyclophosphamide exposure, then we suggest a non–cyclophosphamide- based initial regimen be used (Regimen D). (2B)
- Consider a repeat kidney biopsy during relapse if there is suspicion that the histologic class of LN has changed (not graded).

Treatment of resistant disease

- In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a repeat kidney biopsy to distinguish active LN from scarring. (Not Graded)
- Treat patients with worsening SCr and/or proteinuria who continue to have active LN on biopsy with one of the alternative initial treatment regimens. (Not Graded
- KDIGO suggest that non responders who have failed more than one of the recommended initial regimens may be considered for treatment with rituximab, i.v. immunoglobulin, or CNIs. (2D)

Pauci-immune focal and segmental necrotizing glomerulonephritis

Initial treatment:

- **Cyclophosphamide** and **corticosteroids**.
- **Rituximab** and **corticosteroids** are recommended as an **alternative** initial treatment if cyclophosphamide is contraindicated (in patients without severe disease).
- Addition of **plasmapheresis** is recommended for:
  - Patients who require dialysis.
  - Patients with rapidly rising serum creatinine.
  - Patients with diffuse pulmonary hemorrhage.
  - Patients with overlap syndrome of ANCA vasculitis and anti-GBM GN
- Discontinue cyclophosphamide after 3 months in patients who remain dialysis dependent and in patients without extra-renal manifestations of the disease.

Rationale:

- Without therapy, ANCA vasculitis with GN is associated with very poor outcomes.
- There is high-quality evidence for treatment with corticosteroids and cyclophosphamide that has dramatically improved the short- and long-term outcomes of ANCA vasculitis associated with systemic disease.
- Immunosuppressive therapy may not be appropriate in patients with severe NCGN already requiring dialysis.
- All patients with extrarenal manifestations of disease should receive immunosuppressive therapy regardless of the degree of kidney dysfunction.
- There is high-quality evidence that plasmapheresis provides additional benefit in those with severe NCGN.
- There is low-quality evidence that plasmapheresis provides additional benefit for diffuse pulmonary hemorrhage.
- There is evidence that rituximab is not inferior to Cyclophosphamide in induction therapy.

Agent	Route	Initial dose
cyclophosphamide	**iv**	0.75 g/m2 q 3–4 weeks. Decrease initial dose to 0.5 g/m2 if age 460 years or GFR o20 ml/min per 1.73m2. Adjust subsequent doses to achieve a 2-week nadir leukocyte count 43000/mm3.
cyclophosphamide	**po**	1.5–2 mg/kg/d, reduce if age 460 years or GFR o20 ml/min per 1.73m2. Adjust the daily dose to keep leucocyte count 43000/mm3.
corticosteroids	**iv**	Pulse methylprednisolone: 500mg i.v. daily3 days.
corticosteroids	**po**	Prednisone 1 mg/kg/d for 4 weeks, not exceeding 60mg daily. Taper down over 3–4 months.
Rituximab	**iv**	375 mg/m2 weekly4.
plasmapheresis		60 ml/kg volume replacement. Vasculitis: Seven treatments over 14 days If diffuse pulmonary hemorrhage, daily until the bleeding stops, then every other day, total 7–10 treatments. Vasculitis in association with anti-GBM antibodies: Daily for 14 days or until anti-GBM antibodies are undetectable.

Maintenance therapy:

- Recommended for patients who achieved complete remission.
- Duration: 18 months (for patients who remain in complete remission).
- Not recommended for patients who remain dialysis dependent and patients who have no extra-renal manifestations.
  - Choice of agent:
    - Oral **azathioprine** 1mg/kg/d
    - **MMF** for patients who are allergic to or intolerant to azathioprine.
    - Addition of **trimethoprim-sulfamethoxazole** in patients with upper respiratory tract disease.
    - **Methotrexate** (initially 0.3mg/kg/wk, maximum 25mg/wk) in patients who are intolerant to MMF and azathioprinebut but not if GFR is <60 ml/min per 1.73m2.

Rationale:

There is moderate-quality evidence that maintenance therapy is required in those at high risk of relapse or who have received less than 6 months induction treatment with cyclophosphamide.

- There is low-quality evidence that the duration of maintenance therapy should be at least 18 months.
- There is moderate-quality evidence that azathioprine is the preferred maintenance immunosuppressive agent, being equivalent in efficacy to cyclophosphamide in an RCT with a more favorable adverse-effect profile.
- There is moderate-quality evidence that trimethoprimsulfamethoxazole as an adjunct to maintenance therapy reduces the risk of relapse, but only in those with upper respiratory tract disease due to vasculitis.

Treatment of relapse:

- Severe relapse of ANCA vasculitis is treated with the same as mentioned in initial therapy.
- Other relapses are treated with reinstitution of the same immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide.

Rationale:

- Relapse is associated with increased risk of ESRD.
- Relapse is associated with severe or life-threatening extrarenal damage.
- There is low-quality evidence that relapses are responsive to reintroduction or increased dosing of immunosuppression, but the preferred treatment regimen has not been defined

Resistant disease:

In ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids, the addition of rituximab
(1C), and suggest i.v. immunoglobulin (2C) or plasmapheresis (2D) as alternatives is recommended.

Transplantation:

- Delay transplantation until patients are in complete extra-renal remission for 12 months**.**
- Do not delay transplantation for patients who are in complete remission but are still ANCA-positive.

Anti-glomerular basement membrane antibody glomerulonephritis

Treatment of anti GBM GN

- Start immunosuppression with **cyclophosphamide and corticosteroids plus plasmapheresis** in all patients with anti-GBM GN **except** those who are dialysis-dependent at presentation and have 100% crescents in an adequate biopsy sample, and do not have pulmonary hemorrhage.
- Start treatment for anti-GBM GN **without delay** once the diagnosis is confirmed. If the diagnosis is highly suspected, it would be appropriate to begin high-dose corticosteroids and plasmapheresis while waiting for confirmation.
- No maintenance immunosuppressive therapy for anti-GBM GN is recommended.
- Defer kidney transplantation after anti-GBM GN until anti-GBM antibodies have been undetectable for a minimum of 6 months.

Rationale:

- Patient and kidney survival in untreated anti-GBM GN is poor**.**
- There is moderate-quality evidence that intense immunosuppression plus plasmapheresis improves patient and kidney survival; this evidence comes from one small RCT, one large, and several smaller retrospective series. All of these studies demonstrate good patient survival and moderate kidney survival, providing a compelling rationale to use immunosuppression and plasmapheresis.
- Many patients at presentation have severe kidney failure, and require dialysis. This is usually correlated with the number of glomeruli that show crescents on kidney biopsy. Despite intense immunosuppression, patients who are dialysis-dependent at the start of treatment and have 85–100% glomerular crescents do not recover kidney function, and generally will

require long-term RRT.

- Because the progression of anti-GBM GN can be very rapid, and outcome is related to the severity at presentation, it is appropriate to start treatment immediately with high-dose corticosteroids. After the diagnosis is confirmed, cyclophosphamide and plasmapheresis must be started. Patients should be free of infection or receiving appropriate antimicrobial therapy.
- Patients with pulmonary hemorrhage as well as anti- GBM GN (Goodpasture's disease) should receive treatment with corticosteroids, cyclophosphamide, and plasmapheresis, even in the setting of severe kidney failure and extensive glomerular crescent formation. Without such therapy, Goodpasture's disease has a very high mortality. There is, however, no definite evidence that plasmapheresis is beneficial when there are only minor clinical signs of pulmonary hemorrhage.
- Because anti-GBM antibodies are pathogenic, it is prudent to wait until they are undetectable before considering a kidney transplant for those with ESRD.

Corticosteroids	
Week	Prednisone dose
0–2	Methylprednisolone 500–1000 mg/d i.v. for 3 days, followed by prednisone, 1 mg/kg/d IBW (maximum 80 mg/d)
2–4	0.6 mg/kg/d
4–8	0.4 mg/kg/d
8–10	30 mg/d
10–11	25 mg/d
11–12	20 mg/d
12–13	17.5 mg/d
13–14	15 mg/d
14–15	12.5 mg/d
15–16	10 mg/d
16–	IBW <70 kg: 7.5 mg/d IBW ≥ 70 kg: 10 mg/d
Discontinue after 6 months	

Infection-related glomerulonephritis

Bacterial
Mycobacterium leprae, M. tuberculosis
Treponema pallidum
Salmonella typhi, S. paratyphi, S. typhimurium
Streptococcus pneumoniae, S. virdans, S. pyogenes
Staphylococcus aureus, S. epidermidis, S. albus
Leptospira species[a]
Yersinia enterocolitica[a]
Neisseria meningitidis, Neisseria gonorrhoeae[a]
Corynebacterium diphtheriae[a]
Coxiella burnettii[a]
Brucella abortus[a]
Listeria monocytogenes[a]

Fungal
Histoplasma capsulatum[a]
Candida[a]
Coccidiodes immitis[a]

Protozoal
Plasmodium malariae, P. falciparum
Leishmania donovani
Toxoplasma gondii
Trypanosoma cruzi, T. bruci
Toxocara canis[a]
Strongyloides stercoralis[a]

Viral
Hepatitis B and C
Human immunodeficiency virus
Epstein-Barr virus
Coxsackie B
ECHO virus
Cytomegalovirus
Varicella zoster
Mumps
Rubella
Influenza

Helminthic
Schistosoma mansoni, S. japonicum, S. haematobium
Wuchereria bancrofti
Brugia malayi
Loa loa
Onchocerca volvulus
Trichinella spiralis[a]

ECHO, enteric cytopathic human orphan; GN, glomerulonephritis.
[a]Only case reports documented.

Bacterial infection

(Post streptococcal GN-infective endocarditis-related GN-Shunt nephropathy)

For the following infection-related GN, we suggest appropriate treatment of the infectious disease and standard approaches to management of the kidney manifestations: (2D)

Human Immunodeficiency virus (HIV) infection– related glomerular disorders

KDIGO recommends that antiretroviral therapy be initiated in all patients with biopsy-proven HIV-associated nephropathy, regardless of CD4 count. (1B)

Hepatitis B virus (HBV) infection–related GN

We recommend that patients with HBV infection and GN receive treatment with interferon-a or with nucleoside analogues as recommended for the general population by standard clinical practice guidelines for HBV infection (1C)

Dosage adjustment of drugs for HBV infection according to kidney function (endogenous CrCl)

Drug	CrCl >50 (ml/min)	CrCl 30<50 (ml/min)	CrCl 10-30 (ml/min) CrCl	<10 (ml/min)
Lamivudine	300mg p.o. q.d or 150mg p.o. b.i.d.	150mg p.o. q.d.	150mg first dose then 100mg p.o. q.d.a	150mg first dose then 50mg p.o. q.d.
Adefovir	10mg p.o. q.d.	10mg p.o. every 48 hours	10mg po every 72 hours	No dosing recommended
Entecavir	0.5mg p.o. q.d.	0.25mg p.o. q.d.	0.15mg p.o. q.d.	0.05mg p.o. q.d.
Entecavir (in lamivudine refractory patients)	1mg p.o. q.d.	0.5mg p.o. q.d.	0.3mg p.o. q.d.	0.1mg p.o. q.d.
Telbivudine	600mg p.o. q.d.	600mg p.o. every 48 hours	600mg p.o. every 72 hours	600mg p.o. every 96 hours
Tenofovir	300mg p.o. q.d.	300mg p.o. q.d every 48 hours	300mg p.o. q.d every 72–96 hours	300mg p.o. q.w.

b.i.d., twice daily; CrCl, creatinine clearance; HBV, hepatitis B virus; p.o., orally; q.d., every day; q.w., once a week.

Adapted by permission from Macmillan Publishers Ltd: Kidney International. Olsen SK, Brown RS, Jr. Hepatitis B treatment: Lessons for the nephrologist. Kidney Int 2006; 70: 1897–1904;387 accessed http://www.nature.com/ki/journal/v70/n11/pdf/5001908a.pdf. Supplemented with data from ref 389.

Clinico-pathological classification for schistosomal glomerulopathy

Class	Light-microscopic pattern	IF	Asymptomatic proteinuria	Nephrotic syndrome	Hypertension	Progression to ESRD	Response to treatment
I	Minimal lesion Focal proliferative Diffuse proliferative	Mesangial IgM, C3, schistosomal gut antigens	+++	+	+/_	?	+/_
II	Exudative Endocapillary C3	schistosomal antigens	-	_	+++	?	+++
III	A. Mesangio-capillary type I	Mesangial IgG, C3, schistosomal gut antigen (early), IgA (late)	+	++	++	++	-
	B. Mesangio-capillary type II	Mesangial and subepithelial IgG, C3, schistosomal gut antigen (early), IgA (late)	+	+++	+	++	-
IV	Focal and segmental glomerulo-sclerosis	Mesangial IgG, IgM, IgA	+	+++	+++	+++	-
V	Amyloidosis	Mesangial IgG	+	+++	+/-	+++	-

- KDIGO suggest that blood culture for Salmonella be considered in all patients with hepatosplenic schistosomiasis who show urinary abnormalities and/or reduced GFR. (2C)
- KDIGO suggest that all patients who show a positive blood culture for Salmonella receive anti-Salmonella therapy. (2C)

Diagnosis and management of Kidney diseases associated with HCV infection

- KDIGO recommend that a kidney biopsy be performed in HCV-infected patients with clinical evidence of glomerular disease. (*1B*)
- KDIGO recommend that patients with HCV-associated glomerular disease be treated for HCV. (*1A*)
- KDIGO recommend that patients with HCV-related glomerular disease showing stable kidney function and/or non-nephrotic proteinuria be treated initially with DAA. (*1B*)
- KDIGO recommend that patients with cryoglobulinemic flare, nephrotic syndrome, or progressive kidney failure be treated with both DAA and immunosuppressive agents and/or plasma-exchange. (*1B*)
- KDIGO 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. (*1A*)
- KDIGO recommends rituximab as the first-line immunosuppressive treatment. (*1B*)

Treatment of HCV infection in patients with CKD

KDIGO recommend that all CKD patients infected with HCV be evaluated for antiviral therapy. (*1A*)

- KDIGO recommend an interferon-free regimen. (*1A*)
- KDIGO recommend choice of specific regimen be based on HCV genotype (and subtype), viral load, drug-drug interactions, eGFR category, stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities. (*1A*)
- Treat kidney transplant candidates in collaboration with the transplant center to optimize timing of therapy. (*Not Graded*)
- KDIGO recommend that patients with eGFR > 30 ml/min/1.73 m2 be treated with any licensed DAA-based regimen. (*1A*)
- KDIGO recommend that patients with eGFR < 30 ml/min/1.73 m2 be treated with DAA based regimens, preferentially ribavirin-free (*1B*), as follows:
  - HCV genotype 1 subtype A the use of grazoprevir/elbasvir (*1A*) and for HCV genotype 1 subtype B, grazoprevir/elbasvir (*1A*) or the "PROD" regimen (the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir) (*1B*) for 12 weeks.
  - **HCV genotype 4 the use of grazoprevir/elbasvir or the "2D" regimen (the combination of ritonavir-boosted paritaprevir, ombitasvir regimen) for 12 weeks. (*2D*)**
  - Treat patients with HCV genotypes 2, 3, 5, and 6 on a case-by-case basis. (*Not Graded*)

- **KDIGO recommends that all kidney transplant recipients infected with HCV be evaluated for treatment. (1B)**
    - Treatment is recommended with a DAA-based regimen. (*1A*)
    - The choice of regimen be based on HCV genotype (and subtype), viral load, drug-drug interactions, eGFR category, stage of hepatic fibrosis, liver transplant candidacy, and comorbidities. (*1A*)
    - Treatment with interferon be avoided. (*1A*)
    - Pre-treatment assessment for drug-drug interactions between the DAA-based regimen and other concomitant medications including immunosuppressive drugs in kidney transplant recipients. (*1A*)
    - The calcineurin inhibitor levels be monitored during and after DAA treatment. (*1B*)

PREVENTING HCV TRANSMISSION IN HEMODIALYSIS UNITS

- KDIGO recommend that hemodialysis facilities adhere to standard infection-control procedures including hygienic precautions that effectively prevent transfer of blood and blood-contaminated fluids between patients to prevent transmission of blood-borne pathogens. (*1A*)
    - Regular observational audits of infection control procedures in hemodialysis units. (*1C*)
    - Not using dedicated dialysis machines for HCV-infected patients. (*1D*)
    - Not isolating HCV-infected hemodialysis patients. (*2C*)

- The dialyzers of HCV-infected patients can be reused if there is adherence to standard infection-control procedures. (*2D*)
- KDIGO recommend aggressive measures be taken to improve hand hygiene (and proper glove use), injection safety, and environmental cleaning and disinfection when a new case of HCV is identified that is likely to be dialysis-related. (*1A*)
- Strategies to prevent HCV transmission within hemodialysis units should prioritize adherence to standard infection control practices and should not primarily rely upon the treatment of HCV-infected patients. (*Not Graded)*

Follow-up HCV screening of in-center hemodialysis patients

- Screening in-center hemodialysis patients for HCV every 6 months. (1B)
  - Report any new HCV infection identified in a hemodialysis patient to the appropriate public health authority. (Not Graded)
  - If a new HCV infection is identified in a hemodialysis facility, all patients within the facility who were NAT negative recommended to be tested for HCV infection and the frequency of subsequent HCV testing for these patients be increased. (1A)
- Hemodialysis patients with resolved HCV infection undergo repeat testing every 6 months using NAT. (1B)
- Patients have serum alanine aminotransferase (ALT) level checked upon initiation of in-center hemodialysis or upon transfer to another facility or modality.
- NAT-negative hemodialysis patients have serum alanine aminotransferase (ALT) level checked monthly. (2B)

Supreme Council and NCCVH Hepatitis C Updated Treatment Protocol (December2016)

Inclusion Criteria:

1. HCV RNA positivity.

2. Age: >18years.

-Patients ≥ 65years old should undergo cardiologic assessment prior to therapy by ECG , echocardiography and cardiologic consultation

Exclusion criteria: any of the following,

1.Child's C cirrhotic patients.

2.Plateletcount<50000/mm3

3.HCC,except 6 months after intervention aiming at cure with no evidence Of activity by dynamic imaging(CTorMRI).

4.Extra-hepatic malignancy except after two years of disease-free interval.

-In cases of lymphomas and chronic lymphocytic leukemia, treatment Can be initiated immediately after remission based on the treating oncologist report.

5.Pregnancy or inability to use effective contraception

6.Inadequately controlled diabetes mellitus (HbA1c>9%).

Treatment of patients with chronic kidney disease (CKD):

•In patients having a serum creatinine > the upper normal level, eGFR is calculated, and, accordingly,

-Patients with CKD e GFR >30ml/ min are treated by the usual treatment regimens.

–Patients with CKD e GFR ≤ 30ml/min are treated by

–Paritaprevir-r/Ombitasvir + ribavirin, provided the followings are fulfilled:

• Patients have compensated liver (Child A cirrhosis or no cirrhosis)

•Hb level is at least 10 g/dL.

•The patient has no associated uncontrolled co-morbidity (Cardiac, neuro-psychic,..)

• A nephrologist consultation is done. A report determining the treatment eligibility and necessity, and the exact ribavirin recommended dose (and time of administration in relation to dialysis).

•In case of dialysis, the patient should be aware of the high risk of re-infection by signing a consent form.

Recommended ribavirin dosing in chronically HCV-infected patients with CKD

Renal impairment and CL_{CR}, ml/min	Renal severity	RBV dose (mg/day)
Normal (>80 ml/min)	None	1,000/1,200
CKD stage 3 (30–50 ml/min)	Moderate	200 alternating with 400
CKD stage 4 (<30 ml/min)	Severe	200
CKD stage 5 (dialysis)	ESRD	200

Modified from *Viekira Pak* Prescribing Information, AbbVie Inc.

Drugs Contraindicated for Use with Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir	
Drug Class	**Drug(s) within Class that are Contraindicated**
Alpha1-adrenoreceptor antagonist	Alfuzosin HCL
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital
Antihyperlipidemic agent	Gemfibrozil
Antimycobacterial	Rifampin
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine
Ethinyl estradiol-containing products	Ethinyl estradiol-containing medications such as combined oral contraceptives
Herbal Product	St. John's Wort *(Hypericum perforatum)*
HMG-CoA Reductase	Lovastatin, simvastatin
Neuroleptics	Pimozide
Non-nucleoside reverse transcriptase inhibitor	Efavirenz
Phosphodiesterase-5 (PDE5) inhibitor	Sildenafil when dosed as *Revatio* for the treatment of pulmonary arterial hypertension (PAH)
Sedatives/hypnotics	Triazolam; Orally administered midazolam

The Egyptian Society Of Nephrology & Transplantation

ESNT Guidelines – Chapter 2

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Part (II) MGRS

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE (MGRS)

INTRODUCTION:

The term monoclonal gammopathy of renal significance (MGRS) has been introduced in 2012 by the International Kidney and Monoclonal Gammopathy Research Group (IKMG). A newer concept to denote hematologic conditions distinct from monoclonal gammopathy of undetermined significance (MGUS), which by definition does not have evidence of end-organ damage. It signifies the presence of nephron-toxic monoclonal immunoglobulins or their components -produced by a B-cell or plasma cell clone that cause a wide range of kidney lesions.

1. DEFINITION

Box 1| Updated definition (IKMG)

Any B cell or plasma cell clonal lymphoproliferation with both of the following characteristics:

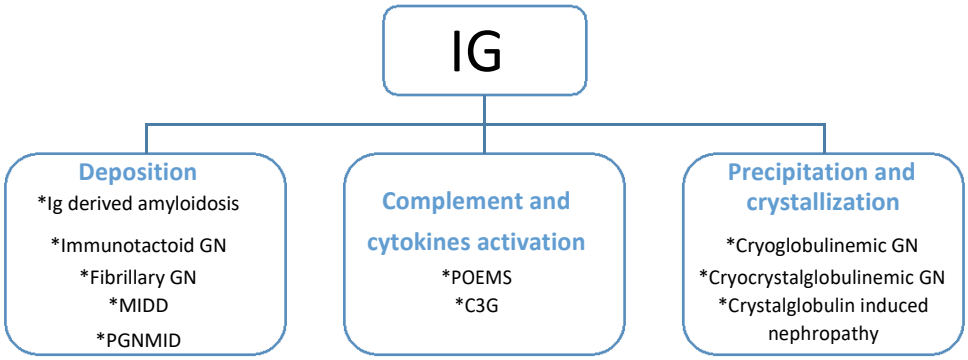
- One or more kidney lesions that are related to the produced monoclonal immunoglobulin.
- The underlying B cell or plasma cell clone does not cause tumor complications or meet any current hematological criteria for specific therapy.

Rationale

The original definition of MGRS included all small B cell clones that produced a toxic monoclonal protein. Although this definition was based on the dangerous small B cell clones concept, the nature of the clonal disease was not well defined. The new IKMG consensus definition of MGRS (BOX 1) includes all B cell or plasma cell proliferative disorders (such as SMM, SWM and monoclonal B cell lymphocytosis (MBL; a diagnosis that is the equivalent of MGUS for clones of the CLL lineage)) that produce a nephrotoxic monoclonal immunoglobulin. Low- grade CLL and low- grade B cell non- Hodgkin lymphomas, such as marginal zone lymphoma, mantle- cell lymphoma or mucosa- associated lymphoid tissue (MALT) lymphoma are also considered to be MGRS when they are associated with renal lesions. These low- grade proliferative disorders would be classified as MGUS, and affected patients would be monitored for progression but not offered treatment if not for the renal injury.

At the end of the spectrum when the condition progresses to over malignancy such as; multiple myeloma, Waldenstrom macroglobulinemia, advanced CLL or malignant lymphoma, the disease is no longer a MGRS.

2. PATHOGENESIS



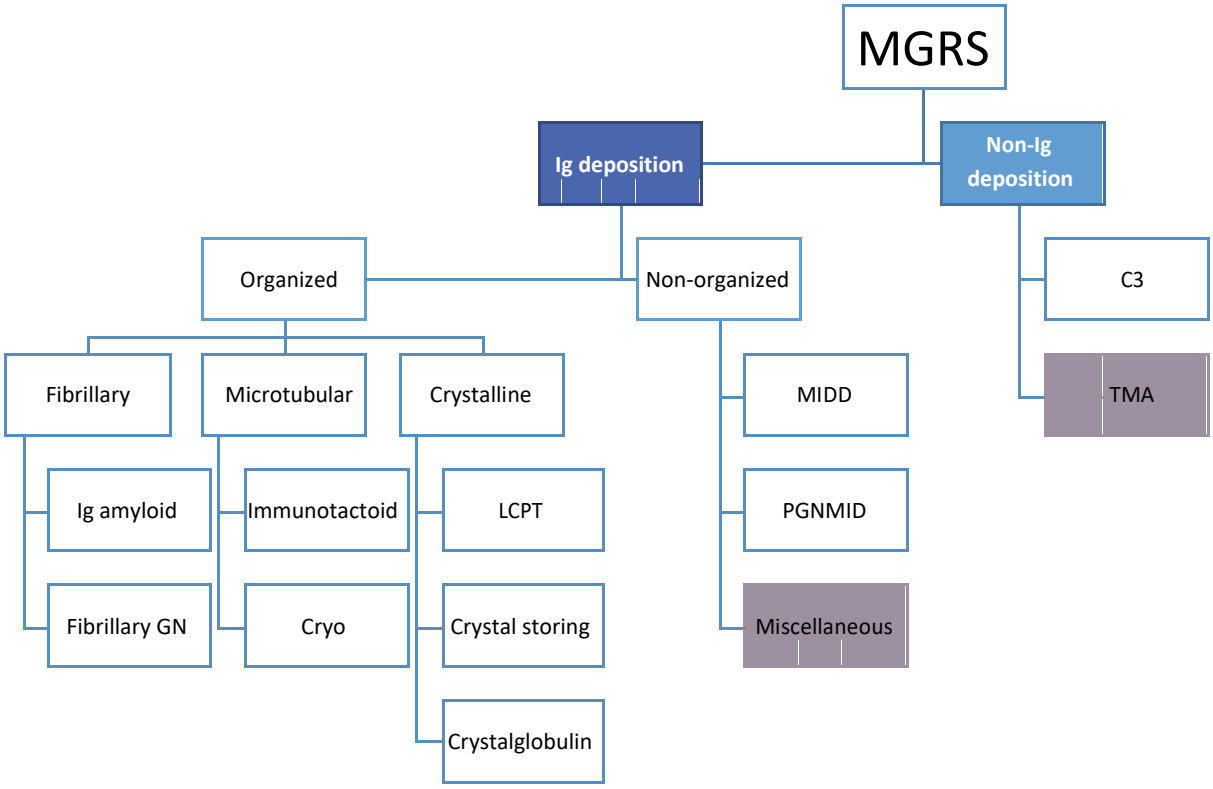
Several mechanisms of nephrotoxicity have been involved in the pathogenesis of MGRS lesions, which include deposition, complement activation, cytokine activation, and precipitation.

Deposition being the most common is seen in Ig-related (AIg) amyloidosis, monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, immunotactoid GN, and monoclonal fibrillary GN. Deposition in extrarenal sites can occur especially in AIg amyloidosis and monoclonal Ig deposition disease, while being rare with immunotactoid GN and fibrillary GN and has not been described in proliferative GN with monoclonal Ig deposits.

Precipitation is the mechanism of injury in cryoglobulinemia and (cryo)crystalglobulinemia. In contrast to precipitation in cast nephropathy which occur in distal tubules it occurs intravascularly in cryoglobulinemic GN. Cryoglobulins are most characteristically found in the glomerular capillaries, often resulting in pseudo-thrombi formation described as cryoplugs.

Complement activation and cytokine activation are also associated with M proteins. The incidence of monoclonal gammopathy in patients with C3 glomerulopathy has been found to far exceed that of the normal population, especially in people 50 years of age. Although C3 nephritic factor and autoantibody against factor H have been reported in some patients and while others have complement gene polymorphisms, the mechanism of complement activation remains undetermined in the majority of patients. Complement is also activated in monoclonal gammopathy–associated membranous nephropathy, proliferative GN with monoclonal Ig deposits, immunotactoid GN, fibrillary GN, and cryoglobulinemic GN. Cytokine activation is involved in the renal lesion of patients with polyneuropathy, endocrinopathy, organomegaly, monoclonal gammopathy, and skin changes (POEMS) syndrome. The cytokines activation results in a glomerulopathy that resembles thrombotic microangiopathy but without the microangiopathic hemolytic anemia. Interestingly, the M protein is not identifiable in the kidney in either of these entities, and a direct link to either mechanism has not been identified.

3. CLASSIFICATION



Monoclonal gammopathy of renal significance (MGRS)-associated renal lesions are initially separated by the presence or absence of monoclonal immunoglobulin deposits in kidney biopsy samples. They are further subcategorized by the ultrastructural characteristics of the deposits into organized and non-organized. Organized deposits are further subdivided into fibrillar, microtubular and inclusions or crystalline categories. The miscellaneous category represents polyclonal glomerulopathies that sometimes present with monoclonal immunoglobulin deposits, such as monotypic membranous nephropathy and monotypic anti-glomerular basement membrane disease. Thrombotic microangiopathy currently has a provisional status as an MGRS-associated lesion pending further evidence. Because this lesion has no immunoglobulin deposits and is best identified by electron microscopy. LCPT, light- chain proximal tubulopathy; MIDD, monoclonal immunoglobulin deposition disease; PGNMID, proliferative glomerulonephritis and monoclonal immunoglobulin deposits.

4. CLINICAL PRESENTATION

LESION	CLINICAL FEATURES	EXTRA RENAL
Ig-related amyloidosis (AL, AHL, AH)	Proteinuria, NS, CKD HTN and hematuria uncommon	Frequent: heart, liver, peripheral nerve
Fibrillary GN	Proteinuria, HTN, hematuria, CKD, NS	_____
Immunotactoid GN	Proteinuria, NS, CKD, hematuria Hypocomplementemia	Uncommon: peripheral nerve, skin
Type 1 cryoglobulinemic GN	Proteinuria, hematuria Nephritic/nephrotic syndrome, AKI, CKD, HTN purpura, arthralgias, hypocomplementemia	Frequent: skin, peripheral nerve, joints
Light chain Fanconi syndrome	Proximal tubule dysfunctiona Slowly progressive CKD	Bone (osteomalacia)
Proximal tubulopathy without crystals	Tubular proteinuria± progressive CKD	_____
Crystal-storing histiocytosis	Proximal tubule dysfunction CKD	Bone marrow, liver, spleen, LN, lung, skin, cornea
Monoclonal Ig deposition disease (LCDD, LHCDD, HCDD)	Proteinuria, NS, CKD, AKI HTN and hematuria uncommon	Common, often asymptomatic: heart, liver, lung
Proliferative GN with monoclonal Ig deposits	Proteinuria, hematuria, NS, CKD, AKI	_____
C3 GN	Hematuria, proteinuria, CKD Low C3 level and normal C4 level common	_____
Thrombotic microangiopathy	Proteinuria, hematuria, Anemia, thrombocytopenia, schistocytes	_____

5. SCREENING

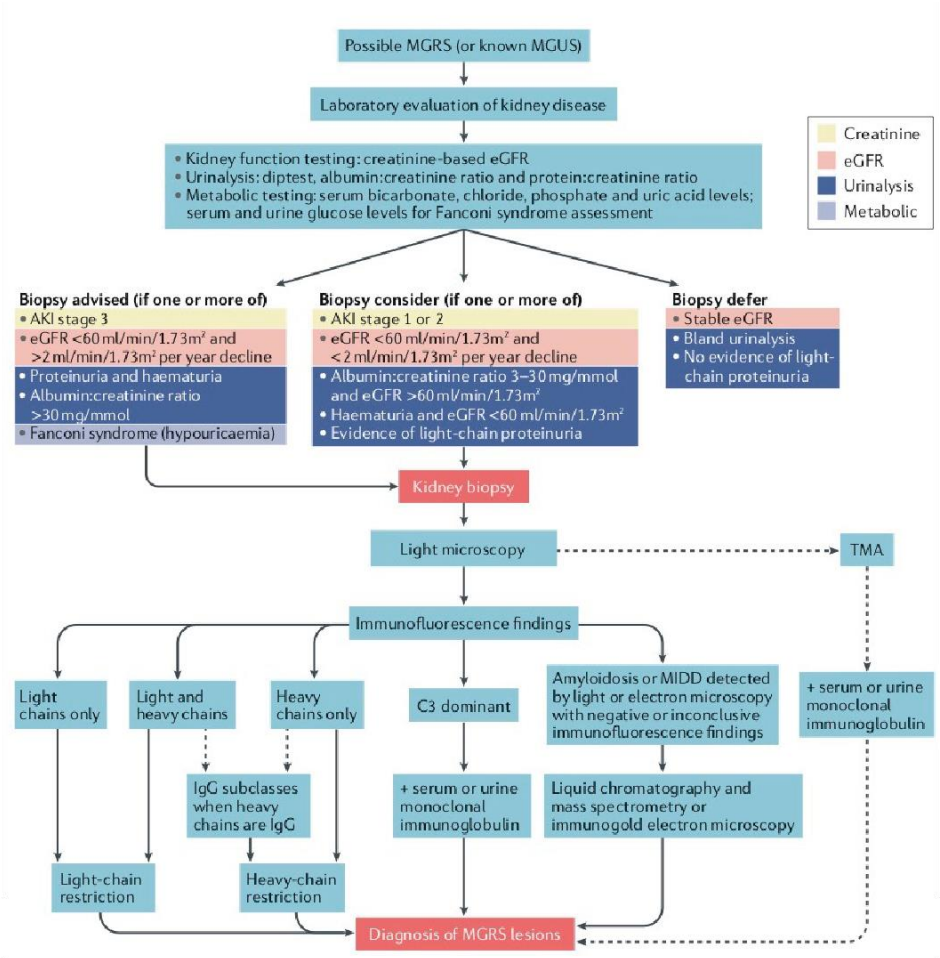
We recommend performing Serum protein electrophoresis (SPEP), immunofixation (IF) and serum free light chain (FLC) tests when considering the possibility of monoclonal gammopathy in patients with various renal manifestations.

Rational:

	MM	SMM	AL amyloidosis
SPEP	87.6%	94.2%	65.9%
Serum IFE	94.4%	98.4%	73.8%
Serum FLC	96.8%	81.2%	88.3%
SPEP and Serum FLC	100%	99.5%	94.2%
SPEP, Serum IFE, and serum FLC assay	100%	100%	97.1%

Sensitivity of Serum Paraprotein Testing for Multiple Myeloma, Smoldering Myeloma, and AL Amyloidosis

6. DIAGNOSIS



RENAL BIOPSY: INDICATIONS

- We recommend that renal biopsy is mandatory to assess type and severity of MGRS-associated kidney disease.
- We recommend that biopsy is still important in patients with advanced kidney disease planning for transplantation due to high recurrence rate.
- Older patients (>70 years) shouldn't discourage kidney biopsy as most of MGRS-associated diseases occur >50 years.
- We recommend renal biopsy for patients with kidney disease and monoclonal gammopathy aged <50 years
- We recommend renal biopsy for patients with unexplained progressive proteinuria
- We recommend renal biopsy for diabetic patients with rapid progression of kidney disease.
- We recommend renal biopsy for those with known risk factors for chronic kidney disease but an atypical clinical course.
- We recommend renal biopsy for those with monoclonal gammopathy and unexplained kidney disease

- In AL amyloidosis; minimally invasive biopsy from abdominal fat or minor salivary glands maybe performed initially.

RENAL BIOPSY: EVALUATION

- We recommend that diagnosis of MGRS requires integration of morphological features seen on light microscopy, immunohistochemistry (IF or immunoperoxidase) and ultrastructure by electron microscopy.

RENAL BIOPSY: INTERPRETATION

GLOMERULAR LESIONS

Glomerular disease	Light microscopic findings	IF findings (Ig type)	Ultrastructural findings
AL amyloidosis *AH amyloidosis* *AHL amyloidosis*	Congo-red-positive mesangial and CW deposits (dichroism + birefringence under polarized light) Vascular and tubulo interstitial involvement common	AL: LC deposits, mostly lambda AH: HC deposits (γ1, or γ4, or α), with first constant domain (CH1) deletion AHL: LC and HC deposits, mostly $\gamma + \lambda$ or $\alpha + \kappa$	Randomly arranged unbranched fibrils 7–14 nm in diameter
ITGN/GOMMID	Mesangial GN with membranous features MPGN Interstitial tumoral infiltrate common (CLL)	Granular/smudgy deposits in mesangium and CW (pred. subepithelial) Monotypic IgG deposits (IgG1 > IgG2 > IgG3) ($\kappa > \lambda$) C3, C4, C1q deposits	Parallely arranged microtubules 10–60 nm, with hollow core
Type I cryoglobulinemic GN	MPGN Endocapillary GN Glomerular thrombi common Intrarenal vasculitis occasional	Granular deposits in mesangium, CW (pred. subendothelial), vascular walls Glomerular thrombi Monotypic IgG, IgM, or IgA ($\kappa > \lambda$) - C3, C4, C1q deposits	Microtubules 10 to 90 nm Extra + intracellular crystals (crystal-cryoglobulinemia)
MIDD	Nodular glomerulosclerosis (constant in HCDD) Thickened TBM and vascular walls	Linear deposits along TBM, GBM and around arteriolar/arterial myocytes LCDD: mostly kappa (Vκ4) HCDD: truncated HC (γ1, or γ3, or γ4, or α), with CH1 deletion. C3 deposits in γ1 and γ3 HCDD LHCDD: LC + truncated HC deposits	Amorphous deposits in TBM, GBM, mesangium and arteriolar/arterial walls
PGNMID	MPGN Endocapillary GN Membranous GN Mesangial GN	Granular deposits in mesangium, CW Monotypic IgG deposits: IgG3 most common, or IgG1, or IgG2 ($\kappa > \lambda$) Rarley, monotypic IgM, IgA, or LC deposits C3 + C1q deposits	Non-organized granular deposits in mesangium, subendothelial and/or subepithelial zone
C3 glomerulopathy with monoclonal gammopathy	MPGN Mesangial GN Endocapillary proliferative GN	Granular C3 deposits in mesangium and CW No or paucity of Ig deposits	'Sausage shaped' intramembranous and large rounded mesangial electron dense deposits in DDD Ill-defined mesangial, intramembranous and subendothelial electron dense deposits in C3GN Humps common in DDD and C3GN

TUBULAR LESIONS

Tubular disorder	Light microscopic findings	IF findings (Ig type)	Ultrastructural findings
Light chain Fanconi syndrome	PTC atrophy and dedifferentiation Intra-cytoplasmic inclusions	PTC LC inclusions Almost always kappa: Vκ1, or Vκ3 (rare)	Crystals (rhomboid) within PTC lysosomes or free in the cytoplasm
Proximal tubulopathy without crystals	PTC atrophy and dedifferentiation PTC cytoplasmic swelling	PTC LC staining Lambda or kappa	Amorphous granular accumulations of LCs Increased lysosomes with a mottled appearance
Crystal-storing histiocytosis	Histiocytes with crystalline inclusions (pseudo-pseudo Gaucher cells) in the interstitium and perirenal fat PTC atrophy and dedifferentiation	PTC LC inclusions Mostly kappa :Vκ1 or Vκ3	Crystals (needle-shaped) within histiocytes and occasionally in PTC and glomerular cells

CLONAL IDENTIFICATION

We recommend that bone marrow aspiration and biopsy should be performed to evaluate the types of clone (of plasmacytic or lymphocytic nature) in most cases with MGRS.

Morphological assessment include quantification of plasma cell clone and evaluation for presence of atypical lymphocytes as well as amyloid deposition.

In patients with CLL clones, diagnosis could be made with peripheral blood flow cytometry.

If bone marrow evaluation does not reveal a clonal hematological disorder, we recommend that next step could be to perform imaging studies (such as CT with or without PET, or whole-body MRI) to look for a localized plasmacytoma or for lymphadenopathy in low-stage, low-grade lymphoma.

***The involved lymph nodes should undergo biopsy**

7. TREATMENT

Clone-directed therapy is the key. Thus, clonal identification is extremely important in choosing the right treatment. The renal histology, however, remains useful for predicting the natural history, clinical features, and recurrence after kidney transplantation.

For Ig related amyloidosis we recommend:
Cyclophosphamide and dexamethasone, bortezomib. The triple regimen produces response rates as high as 94%, with 66%–71% having a very good partial response (VGPR).

A difference of the involved minus the uninvolved sFLC of <40 mg/L or >90% reduction of difference of the involved minus the uninvolved sFLC,

For immunotactoid glomerulopathy we recommend;
CLL-type regimens incorporating bendamustine/corticosteroids/cyclophosphamide with rituximab
For cases not associated with CLL, bortezomib-based regimens

For cryoglobulinemic GN we recommend:
treatment only for symptomatic/progressive systemic disease (renal), depending on underlying:
clone Plasma cell: antimyeloma drugs (ASCT may be considered)
LPL clone: treat along lines of WM (rituximab backbone)
B-cell clone: rituximab-based therapy

HCV^+ Minimally symptomatic: antiviral therapy

Symptomatic vasculitis: rituximab/high-dose dexamethasone (+ antiviral therapy)

Rapidly progressive renal disease: TPE + definitive therapy as for symptomatic vasculitis

For LCPT with FS we recommend:

CKD stage I-III: chemotherapy based on

bortezomib/cyclophosphamide/thalidomide/bendamustine, ASCT may be considered for

nonresponding patients CKD stage IV-V: eligible for renal transplant, bortezomib-based therapy

followed by ASCT; not eligible for renal transplant, symptomatic management

For MIDD we recommend:

CKD stage I-III: bortezomib-based therapy, followed by ASCT (in the absence of extrarenal manifestations and good performance status) CKD stage IV-V: eligible for renal transplant, bortezomib-based therapy followed by ASCT; not eligible for renal transplant, bortezomib-based therapy only (to protect extrarenal organs, heart)

For PGNMID we recommend:

CKD stage I-II with proteinuria < 1 g/d and nonprogressive disease: symptomatic treatment

CKD stage I-II with proteinuria > 1 g/d or progressive disease and CKD stage III-IV: chemotherapy* with or without ASCT

CKD stage V: eligible for renal transplant, chemotherapy followed by ASCT; not eligible for renal transplant, symptomatic management; no identifiable MG: no consensus, may benefit from chemotherapy prior to renal transplant

TRANSPLANTATION

Kidney transplantation could be successfully performed without recurrence only after complete hematological response

A complete response is defined by negative serum and urine immunofixation and normal sFLC ratio

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Part (III) Plasma Exchange

Therapeutic Plasma Exchange in Clinical Practice

Definitions

Apharesis:

A procedure in which blood of the patient or donor is passed through a medical device which separates one or more components of blood and returns the remainder with or without extracorporeal treatment or replacement of the separated component.

Therapeutic apharesis:

A therapeutic procedure in which blood of the patient is passed through an extracorporeal medical device which separates components of blood to treat a disease. This is a general term which includes all apheresis-based procedures used therapeutically.

Therapeutic plasma exchange:

A therapeutic procedure in which blood of the patient is passed through a medical device which separates plasma from other components of blood. The plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution.

Plasmapharesis:

A procedure in which blood of the patient or the donor is passed through a medical device which separates plasma from other components of blood and the plasma is removed (i.e., less than 15% of total plasma volume) without the use of colloid replacement solution. This procedure is used to collect plasma for blood components or plasma derivatives.

1) Indications:

1.1.Use plasma exchange to remove molecules only having the following characteristics:

- Must be toxic.
- Have a molecular weight > 15000 D.
- Have low turnover.
- Have a slow rate of formation.
- Have a low volume of distribution.

1.2.Use plasma exchange for the following indications:

Disease	*Indication*	*Category*	*Grade*
Acute disseminated encephalomyelitis	Steroid Refractory	II	2C
Acute inflammatory demyelinating polyradiculoneuropathy/ Guillain-Barre syndrome	**Primary Treatment** After IVIG	I III	1A 2C
Acute liver failure		III	2B
Amyloidosis, systemic		IV	2C

Disease	*Indication*	*Category*	*Grade*
ANCA-associated rapidly progressive glomerulonephritis (Granulomatosis with polyangiitis; and Microscopic Polyangiitis)	**Dialysis dependence** **DAH** Dialysis independence	I I III	1A 1C 2C
Anti-glomerular basement membrane disease (Goodpasture's syndrome)	Dialysis dependence **DAH** **Dialysis independence**	III I I	2B 1C 1B
Aplastic anemia, pure red cell aplasia	Aplastic anemia Pure red cell aplasia	III III	2C 2C
Atopic (neuro-) dermatitis (atopic eczema), recalcitrant		III	2C
Autoimmune hemolytic anemia; WAIHA; cold agglutinin disease	Severe WAIHA Severe cold agglutinin disease	III II	2C 2C
Catastrophic antiphospholipid syndrome		II	2C
Chronic focal encephalitis (Rasmussen Encephalitis)		III	2C
Chronic inflammatory demyelinating polyradiculoneuropathy		I	1B
Coagulation factor inhibitors	Alloantibody Autoantibody	IV III	2C 2C
Cryoglobulinemia	Symptomatic/severe	II	2A

Disease	*Indication*	*Category*	*Grade*
Dermatomyositis/polymyositis		IV	2B
Dilated cardiomyopathy, idiopathic	NYHA II-IV	III	2C
Erythropoietic porphyria, liver disease		III	2C
Familial hypercholesterolemia	Homozygotes with small blood volume	II	1C
Focal segmental glomerulosclerosis	**Recurrent in transplanted kidney**	I	1B
Hashimoto's encephalopathy: Steroid responsive encephalopathy associated with autoimmune thyroiditis		II	2C
HELLP syndrome	Postpartum Antepartum	III IV	2C 2C
Hematopoietic stem cell transplantation, ABO Incompatible	Major HPC, Marrow Major HPC, Apheresis	II II	1B 2B
Hematopoietic stem cell transplantation, HLA desensitization		III	2C
Henoch-Schonlein purpura	Crescentic Severe extrarenal disease	III III	2C 2C
Heparin induced thrombocytopenia & thrombosis	Pre-cardiopulmonary bypass Thrombosis	III III	2C 2C
Hypertriglyceridemic pancreatitis		III	2C

Disease	*Indication*	*Category*	*Grade*
Hyperviscosity in monoclonal gammopathies	**Symptomatic** **Prophylaxis for rituximab**	I I	1B 1C
Immune thrombocytopenia	Refractory	III	2C
Immunoglobulin A nephropathy	Crescentic Chronic progressive	III III	2B 2C
Lambert-Eaton myasthenic syndrome		II	2C
Liver transplantation	**Desensitization, ABOi LD** Desensitization, ABOi DD Antibody mediated rejection (ABOi & HLA)	I III III	1C 2C 2C
Multiple sclerosis	Acute CNS inflammatory demyelinating Chronic progressive	II III	1B 2B
Myasthenia gravis	**Moderate-severe** **Pre-thymectomy**	I I	1B 1C
Myeloma cast nephropathy		II	2B
Nephrogenic systemic fibrosis		III	2C
Neuromyelitis optica spectrum disorders	Acute Maintenance	II III	1B 2C

Disease	*Indication*	*Category*	*Grade*
Overdose, envenomation and poisoning	Mushroom poisoning	II	2C
	Envenomation	III	2C
	Drug overdose/poisoning	III	2C
Paraneoplastic neurological syndromes		III	2C
Paraproteinemic demyelinating neuropathies/chronic acquired demyelinating polyneuropathies	Anti-MAG neuropathy	III	1C
	Multifocal Motor Neuropathy	IV	1C
	IgG/IgA	I	1B
	IgM	I	1C
	Multiple myeloma	III	2C
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; Sydenham's chorea	PANDAS exacerbation	II	1B
	Sydenham's chorea, severe	III	2B
Pemphigus vulgaris	Severe	III	2B
Phytanic acid storage disease (Refsum's disease)		II	2C
Post transfusion purpura		III	2C
Progressive multifocal leukoenchephalopathy associated with natalizumab		I	1C

Disease	*Indication*	*Category*	*Grade*
Pruritus due to hepatobiliary diseases	Treatment resistant	III	1C
Psoriasis	Disseminated pustular	IV	2C
Renal transplantation, ABO compatible	**Antibody mediated rejection** **Desensitization, LD** Desensitization, DD	I I III	1B 1B 2C
Renal transplantation, ABO incompatible	**Desensitization, LD** Antibody medicated rejection A2/A2B into B, DD	I II IV	1B 1B 1B
Scleroderma (systemic sclerosis)		III	2C
Sepsis with multi-organ failure		III	2B
Sudden sensorineural hearing loss		III	2C
Systemic lupus erythematosus	Severe Nephritis	II IV	2C 1B
Thrombotic microangiopathy, coagulation mediated	THBD mutation	III	2C

Disease	*Indication*	*Category*	*Grade*
Thrombotic microangiopathy, complement mediated	Complement factor gene mutations	III	2C
	Factor H autoantibodies	I	2C
	MCP mutations	III	1C
Thrombotic microangiopathy, drug associated	**Ticlopidine**	I	2B
	Clopidogrel	III	2B
	Calcineurin inhibitors	III	2C
	Gemcitabine	IV	2C
	Quinine	IV	2C
Thrombotic microangiopathy, hematopoietic stem cell transplantation associated		III	2C
Thrombotic microangiopathy, Shiga toxin mediated	Severe neurological symptoms	III	2C
	Streptococcus pneumoniae	III	2C
	Absence of severe neurological symptoms	IV	1C
Thrombotic thrombocytopenic purpura		I	1A
Thyroid storm		III	2C
Toxic epidermal necrolysis	Refractory	III	2B

Disease	*Indication*	*Category*	*Grade*
Vasculitis	HBV-PAN Idiopathic PAN EGPA Behcet's disease	II IV III III	2C 1B 1B 2C
Voltage-gated potassium channel antibodies		II	2C
Wilson's disease, fulminant	**Fulminant**	I	1C

* DAH: diffuse alveolar hemorrhage; DD: deceased donor; EGPA:eosinophilic granulomatosis with polyangiitis; LD:living donor;PAN: polyarteritis nodasa; WAIHA: warm autoimmune hemolytic anemia.

* Category I recommendations are bold highlighted.

Recommendation	*Description*	*Implications*
Grade 1A	Strong recommendation High quality evidence	Can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendations Moderate quality evidence	Can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendations low quality or very low quality evidence	May change when higher quality evidences are available

Recommendation	***Description***	***Implications***
Grade 2A	Weak recommendations High quality evidence	Best actions may depend on the circumstances
Grade 2B	Weak recommendations Moderate quality evidence	Best actions may depend on the circumstances
Grade 2C	Weak recommendations low quality or very low quality evidence	Other alternatives may be equally reasonable

Category	***Description***
I	*Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.*
II	*Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.*
III	*Optimum role of apheresis therapy is not established. Decision making should be individualized.*
IV	*Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. Institutional Review Board (IRB) approval is desirable if apheresis treatment is undertaken in these circumstances.*

1.3. Initiate plasma exchange urgently in the following situations:

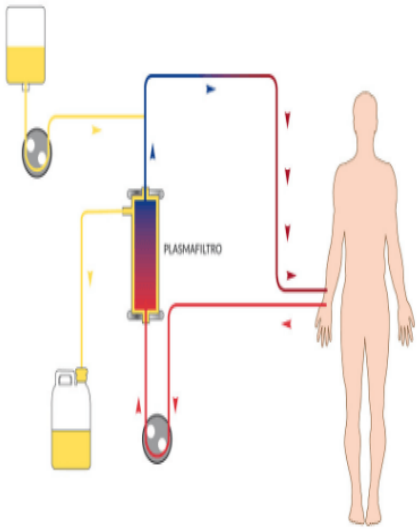
- Thrombotic thrombocytopenic purpura.
- Catastrophic antiphospholipid syndrome .
- Acute pancreatitis due to hypertriglyceridaemia.

- Intoxication by drugs or poisoning.
- Hyperviscosity syndromes.
- Acute fulminating hepatitis.
- Acute inflammatory demyelinating polyneuropathy (Gullian Barre syndrome)
- Myasthenia gravis

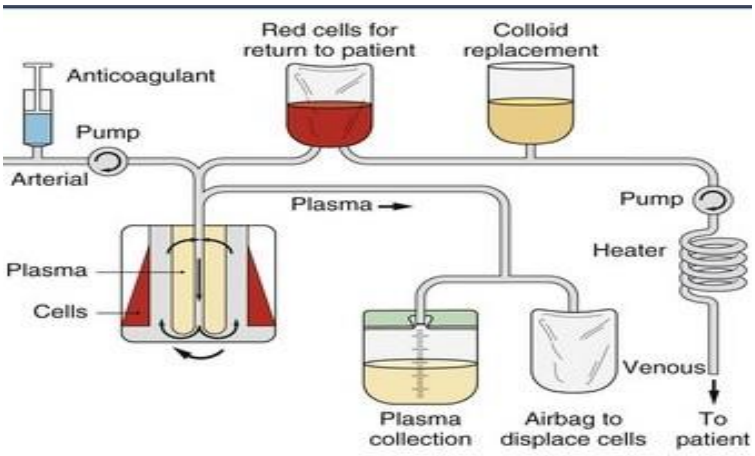
2) Technique:

2.1.Perform TPE using one of two methods:

i) Membrane TPE:



ii) Centrifuge TPE:



Comparison between cTPE and m TPE:

Procedure	***Centrifugal TPE***	***Membrane TPE***
Apparatus	Centrifuge	Dialysis machine or CRRT Machine+ Plasma separation membrane
Blood Flow (ml/min)	10-150	150
Priming and setting time(min)	10-15	20-40
Procedure time	90-120 m	130-160 m
Plasma removal efficiency (PRE) %	80-93	27-53
Efficiency related factors	*Dimensions of the centrifuge *Revolution speed	*Membrane related factors *Filtration fraction: Ultrafiltration rate/plasma flow rate
Blood in the Circuit (ml)	~180	~125
Molecular Weight Cutoff	No	Sieving coefficients ranging from that of albumin (67,000) to B-lipoprotein (2,400,000), and potentially up to that of cryoglobulins (900,000)

Procedure	***Centrifugal TPE***	***Membrane TPE***
Specific adverse events	Cell count t affection Citrate side effects	*Hemolysis. *Membrane rupture *Membrane clotting if filtration fraction is exceeded. *Heparin side effects. *Biocompatibility issues.

2.2. Except is certain situations, each exchange should be performed one or two days apart.

- Causes of spaced sessions:
    - Coagulation factors replenishment,
    - Giving time for rebound of removed substance (e.g: IgG).

2.3. Each exchange should consist of 1 to 1.5 plasma volumes depending on the condition and the severity.

Calculation of plasma volume:

- To be individualized,
- Estimated plasma volume (L)=0.07 (set) × weight (kg) × (1−hematocrit).
- E.g., for a 70 kg patient with a hematocrit of 35% the calculation would be as follows (0.07 kg × 70 kg × 1 - 0.35)=3.185 L

2.4. Avoid sudden withdrawal in certain situations (e.g:TTP). Gradual decrease of session frequency and session spacing are advised.

- Cessation of TPE after several procedures can result in pretreatment or even higher levels of IgG, especially if the patient is not on immunosuppressive therapy. (Gradual withdrawal, TTP)

2.5.In membrane TPE*; t*o avoid filter clotting within the separator, the filtration fraction should be limited to 30%–35% of the plasma

As a result, 3–4 times the calculated blood volume will need to be processed to achieve the desired plasma clearance.

2.6. Monitoring of the following laboratory parameters is advised before each session of TPE.

- CBC,
- Molecular target level levels,
- Coagulation profile.
- Electrolyte studies should be performed.
- For a patient undergoing therapeutic cytapheresis, the appropriate cell count determines the adequacy of response.

2.7. Adequate and timely fluid replacement is mandatory to prevent hypotension during the session.

2.8. To prevent anaphylaxis during the session; Stop ACE inhibitors 24-48 h before treatment; pretreatment with intravenous/antihistamine, use biocompatible membranes and adequate priming of the filter to clear ethylene oxide are advised

3) Anticoagulation:

3.1. Consider bleeding risk/benefit before initiating plasma exchange.

TPE is a risk of bleeding state:

- Regardless of the anticoagulant used, attention must be paid to clinical signs or symptoms of active bleeding and laboratory values that could suggest that the patient is at risk of hemorrhage.
- TPE lowers the coagulation factors significantly by 2–3 fold with relatively smaller decrease in Factors VII and IX.
- A single plasma volume exchange with albumin as the only replacement fluid has been shown to reduce fibrinogen by 85%, increase the prothrombin time (PT) by 30%, and double the partial thromboplastin time (PTT).
- Most coagulation factor activity is close to pre-TPE levels within 24 to 48 h of the procedure, with the exception of fibrinogen, which is at 65% of pre-TPE levels at 48 h.
- If a patient is starting out with a high INR, the danger of a bleeding diathesis is likely to be reduced when TPE is performed with FFP in the replacement.

3.2.Use Citrate as an anticoagulant in centrifuge plasma exchange.

- Ensure maximum infusion rate that does not exceed 0.9 ml/min/L TBV. The inlet: AC/WB 13:1 for all TPE procedures
- Can lead to a metabolic alkalosis, careful attention must be given to acid-base balance.
- Citrate is preferred over heparin because it is effective, has a shorter half-life (30–60 min), has a more favorable safety profile, and its effects can be reversed more rapidly (with calcium).
- Because plasma also contains citrate, increased symptoms due to citrate typically are seen in procedures that use plasma in replacement fluids.

- Human 5% albumin is made relatively calcium poor during processing, and thus albumin replacement fluid readily binds ionized calcium and may augment some of the effects of citrate.

- Prophylaxis of citrate toxicity: 10 ml of 10% calcium gluconate for every liter of plasma volume filtered

3.3. Perform TPE first followed by dialysis to correct citrate induced alkalemia if HD and TPE are required on the same day

3.4. Use Heparin or citrate in membrane plasma exchange.

- Heparin Bolus: 1000 units and maintenance: 500 units/h.
- Treatment of heparin overdose: IV protamine sulphate:1 mg for each 100 units of UFH.
- Risk of heparin induced thrombocytopenia (HIT). Citrate is the best option in this case.

3.5. Consider bleeding risk before the procedure in cases maintained on warfarin.

- If the patient is to be restarted on warfarin therapy after the procedure is completed, the lowest effective dose of vitamin K should be used; an oral dose of 2-2.5 mg may suffice for non-urgent situations, but 5–10 mg IV is recommended for urgent reversal.
- Alternatively, plasma can be used as a part of the replacement fluid during the TPE or the patient could be switched to UFH or LMWH before the procedure

4) Replacement Solutions:

4.1.Use the following replacement solutions:

- Human Serum Albumin (HSA)
- Fresh frozen plasma (FP)

4.2.Use the following percent of replacement solutions in the following situations:

- ***75% FFP -25% HSA :*** HUS,TTP, following renal biopsy andrenal transplant.
- ***20% FFP- 80%HSA:*** For patients requiring frequent TPE or with depleting coagulation factors. Better to use FFP at the end of the procedure.
- ***100% HSA:*** Patients requiring infrequent exchanges and satisfactory coagulation parameters.

4.3. FFP administration is advisable with multiple consecutive treatments.
Depletion of coagulation factors XIII and fibrinogen; INR increases by 30% and activated partial thromboplastin time doubles after a single therapy; reversing in 24 h.

4.4. A single dose of intravenous IgG is advisable as multiple TPE can decrease IgG for several weeks
Single TPE serum immunoglobulin will reduce by 60%.

4.5. Use fresh frozen plasma in the following situation:

- Replace deficient plasma factors in TTP.
- Pre-existing defect in haemostatic system.
- After 2nd -3rd session (depletion of clotting factors).

- INR values of >1.5 to 2.0 or a fibrinogen value of <100 mg/dL prior to apheresis ordinarily indicate the need for use of at least some plasma during TPE.
- Catastrophic antiphospholipid syndrome (CAPS).
- Pulmonary–renal syndrome with active lung hemorrhage.
- Membranoproliferative GN (MPGN) type II with factor H deficiency.

5) Plasma exchange in renal disorders:

5.1.Intensive regimen involving several TPE procedures and the institution of immunosuppressive therapy is required to significantly reduce IgG levels.

5.2.In ANCA-negative rapidly progressive GN; no DAH;

- 7 exchanges in 14 days; 5% albumin.

5.3.Anti-GBM disease with DAH, Anti-GBM disease with no DAH, renal failure, not requiring dialysis (potential for renal recovery);

- 14 daily exchanges.
- Use 5% albumin and likely to require plasma as 50% replacement fluid by 2nd plasma exchange.
- 100% plasma replacement fluid in the presence of DAH.

5.4. Anti-GBM disease No DAH; renal failure requiring dialysis;

- Exchanges until the time of renal biopsy. Use 5% albumin unless DAH or need to prevent coagulopathy.

5.5.Anti-GBM disease partially responding with elevated ant-GBM titers;

- 14 daily exchanges, then cease if renal function stabilized for final 72 h.
- Consider a further 7 exchanges over 14 days if renal function continues to progressively improve after initial 14 daily exchanges

5.6.Catastrophic antiphospholipid antibody syndrome;

- Daily; 1-3 weeks then re-evaluate .
- Use Albumin unless plasma is required to prevent coagulopathy

5.7. Cryoglobulinemia;

- Consider daily for 7 exchanges;
- May require weekly-monthly maintenance.
- Albumin unless plasma is required to prevent coagulopathy
- Warmed lines and replacement solution to prevent precipitation

5.8.Acquired TTP;

- Daily exchanges.
- Plasma or cryoplasma.
- Gradual withdrawal.

5.9.Secondary TMA autoimmune related, e.g., SLE;

- Total of 7 sessions
- Day after day exchanges.
- Replace with albumin unless plasma is required to prevent coagulopathy.

5.10.Secondary TMA - drug related;

- Consider TPE (7 sessions)
- Albumin unless plasma is required to prevent coagulopathy

5.11.Antibody-mediated rejection;

- TPE is used in combination with Intravenous immunoglobulin.
- Alternate days for 10 days; 5%.
- Albumin unless plasma is required to prevent coagulopathy.
- +IVIG post-TPE.

5.12.Recurrent post-transplantation FSGS;

- 3 daily exchanges followed by ≥6 more exchanges in subsequent 2 weeks.
- May require ongoing therapy.
- Use albumin unless plasma is required to prevent coagulopathy

5.13.Plasma exchange is to be considered in intoxication of the following drugs;

- Natalizumab (to facilitate immune reconstitution)
- Rituximab (severe infusion reaction)
- Cisplatin
- Vincristine
- L-thyroxine (33%)

ESNT Guidelines – Chapter 2

First Edition, December 2019

Part (IV) Peritoneal Dialysis

Peritoneal Dialysis guidelines

Introduction:

- Peritoneal dialysis (PD) has been long established as an important part of renal replacement therapy that is frequently selected by patients as their preferred initial mode of therapy and is a therapeutic option for patients wishing or needing to swap from HD and after renal transplant failure.
- PD is regarded as the best option for infants and small children. NICE Clinical Guidelines (2011) recommends PD as the initial dialysis treatment of choice of chronic kidney disease stage 5 for children aged 2 years or older, people with residual renal function and adults without significant associated comorbidities.

➢ PD Guideline 1 : Initiation / Transition to Peritoneal Dialysis

1.1: Patient selection

Suitable candidates for PD are those in need for dialysis, and have been simultaneously qualified for PD as home therapy, being unable to perform regular hemodialysis or who showed a specific interest in having PD as a feasible home option.

1.2: Contraindications to PD

Upon demonstration of patient's interest for PD, a dedicated team has to conduct an initial assessment to evaluate patient's eligibility.
Contraindications for PD referral are traditionally classified as medical or social. If there are no absolute contraindications, the PD team is made aware of the patient's choice and the patient is referred to the PD program.

1.2.1: Absolute Contraindications

- Documented loss of peritoneal membrane function or extensive abdominal adhesions that limit dialysate flow.
- Uncorrectable mechanical defects that prevent effective PD or increase the risk of infection (e.g. surgically irreparable hernia, stomas/conduits, suprapubic G tubes, omphalocele, gastroschisis, diaphragmatic hernia, bladder extrophy, active diverticulitis)

1.2.2: Relative Contraindications

- New intra-abdominal foreign bodies (abdominal vascular prosthesis, recent ventricular peritoneal shunt)
- Intolerance to PD volumes necessary to achieve adequate PD dose
- Inflammatory or ischemic bowel disease
- Severe malnutrition
- Frequent episodes of diverticulitis

1.2.3: Social Contraindications

- Unmanaged active psychiatric disorders and social problems
- Patient living in a residence that does not permit PD
- Patient's spouse or family is not supportive of PD at home
- Patient's residence has insufficient storage space for PD supplies and equipment

1.3: Assessment of PD program convenience

Several aspects have to be addressed by our team to evaluate appropriateness of PD to selected patients such as:

- Potential barriers for successful PD and appropriate solutions : CAPD, APD, PD Assist
- Setting for PD: home, assisted living, long term care.
- PD catheter placement: Referral for catheter insertion
- Patient’s ability and readiness to learn
- Individualized training plan inclusive of learning objectives, content, teaching methods and aids, and evaluation phases

The following potential barriers require an in depth assessment by the PD team.

- Limited mobility or manual dexterity, limited use of hands
- Poor vision
- Obesity (may be candidate for pre-sternal catheter)
- Multiple previous abdominal surgeries
- Colostomy (may be candidate for pre-sternal catheter)
- Psycho-emotional capacity (e.g., lack of judgment, cognitive decline, issues with caregiver)

➢ PD Guideline 2 : Equipment and Resources

2.1: Requirements for an efficient PD program

- ✓ A robust and effective CKD education program that offers and encourages PD as a therapy option.
- ✓ A standardized assessment process to identify and triage appropriate patients to PD.
- ✓ Transition guidelines designed to support the care and preparation of patients to PD.
- ✓ Multidisciplinary patient centered support systems inclusive of but not limited to: patients and families, physicians, nursing, social work, dietitians, pharmacists, occupational therapy, surgery, radiology, comorbidity clinics (diabetic, cardiology, hypertension), community support services.
- ✓ Access to timely PD catheter procedures.
- ✓ Standardized patient training program incorporating adult learning principles.
- ✓ Clinical practice based on current international standards.
- ✓ Continuous quality improvement work to monitor a variety of domains at a program, health authority and provincial level.
- ✓ Structured training and continuing education for members of the multidisciplinary PD clinical team.

2.2: Equipment and Resources

2.2.1 :

We recommend that Peritoneal Dialysis should be part of a comprehensive and integrated service for renal replacement therapies, including haemodialysis, transplantation and conservative care. Both continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD), in all its forms should be available (1C).

2.2.2 :

We recommend that a dedicated PD nursing team should be part of the multidisciplinary team (1C). We also recommend that , each unit should have a designated lead clinician for PD (1C). Assisted PD should be available to patients wishing to have home dialysis treatment but unable to perform self-care PD (1C).

Rationale:

- Evidence from observational studies or registry data, with all its limitations, indicate that PD used in the context of an integrated dialysis programme is associated with good clinical outcomes, certainly comparable to haemodialysis and potentially better in the first 2 years of dialysis. NICE recommends PD as the initial dialysis treatment of choice of CKD stage 5 for children aged 2 years or older, people with residual renal function and adults without significant associated comorbidities (NICE Clinical Woodrow et al. BMC Nephrology (2017) 18:333 Page 5 of 23 Guideline 125, 2011).

- PD has a significant technique failure rate however, so patients need to be able to switch treatment modality (to either temporary or permanent HD) in a timely manner, which has implications for HD capacity and the timing for HD access creation. PD modalities (CAPD v. APD) have a different impact on life-style; one randomised study found that APD creates more time for the patient to spend with family or continue employment but is associated with reduced quality of sleep. APD is usually the preferred modality for children. There are medical indications for APD, but generally initial modality choice is a lifestyle issue. Studies suggest no difference in outcomes resulting from selection of CAPD or APD as initial PD modality.

- The success of a PD program is dependent upon specialised nurses with appropriate skills in assessing and training patients for PD, monitoring of treatment and with sufficient resources to provide continued care in the community. A randomised trial of more intensive training has shown that this reduces peritonitis risk and there is some evidence to support the benefit of regular home reviews of PD technique. Several studies have documented the benefits of home visits in identifying new problems, reducing peritonitis and non-compliance. The requirement for specialist nurses with the skills to deal with complex patient educational issues is highlighted by the ISPD Guideline (2016) for teaching PD to patients and caregivers.

- Having a designated lead clinician for PD in each unit may help to promote PD as a therapy option and to develop clinical management policies. Assisted PD, with provision of nursing support in the community to help with part of the workload and procedures associated with PD, is a useful option to overcome an important barrier to home dialysis therapy . Assisted APD should be available for patients, who are often but not always elderly, wishing to have dialysis at home, but are unable to perform self-care PD and may also be used as a temporary measure for established patients temporarily unable to perform PD independently or for those unable to start PD alone but may later become independent.

2.2.3 :

We recommend that all equipment and fluid used in the delivery and monitoring of PD therapies should comply with the relevant standards for medical fluids and devices (1C).
We recommend that the use of disconnect systems should be standard unless clinically contraindicated (1A).

2.2.4 :

We suggest that biocompatible PD solutions (solutions that have normal pH and/or low concentrations of glucose degradation products) should be used in patients experiencing infusion pain (2B).
We also suggest that biocompatible PD solutions may be considered for better preservation of residual renal function with long term (>12 month) use (2B).

Rationale:

- Disconnect systems have been shown through randomised trials to be associated with a lower peritonitis risk, especially in infections due to touch contamination.

- A minority of patients commencing PD will experience infusion pain, often severe enough to consider discontinuing the therapy. A double blind randomised study demonstrated that pain could be prevented by using a normal pH, bicarbonate-lactate buffered dialysis fluid (Physioneal). Standard solutions are clearly bio-incompatible, with low pH (~ 5.2), lactate rather than bicarbonate buffer, high osmolality and high concentrations of glucose which also result in high concentrations of glucose degradation products (GDPs). Many in vitro and ex vivo studies have demonstrated the relative toxicity of these solutions, with all of the bioincompatible features playing their part. There is also strong observational evidence that firstly detrimental functional changes to the peritoneal membrane occur with time on treatment, which are more exaggerated in patients using solutions with high glucose concentration early in their time on therapy and secondly, that morphological changesoccur that are related to time on treatment which include membrane thickening and vascular scarring. Time on treatment is also the greatest risk factor for encapsulating peritoneal sclerosis (EPS). Systemic benefits possibly include reduced circulating advanced glycation end-products and better glycaemic control in diabetics . The area with the strongest evidence for clinical benefit of biocompatible solutions is in the preservation of residual renal function.

➢ PD Guideline 3 : Preparation for Peritoneal Dialysis

3.1: Patient preparation and optimisation of PD modality

We recommend that all patients (and parents of paediatric patients) should be adequately prepared for renal replacement therapy and this should include receiving information and education about PD treatment, delivered by an experienced team. Patients commencing RRT in an unplanned fashion for whatever reason should receive this information once appropriate (1C). Fast track education and urgent PD catheter insertion with acute start of PD should be available, and be offered to suitable patients urgently starting on RRT who wish to avoid temporary HD, with the associated negative aspects of temporary vascular access and disruption to their lives (1C).

3.1.1 : Patient education / training and setting treatment plan

- The patient should be receive a comprehensive training that covers all basic information on PD and exchange process along with importance of implying a strict aseptic technique, emergency measures for contamination, exit site care and possible complications i.e. peritonitis, exit site infections, pain, fluid balance, inflow and outflow problems, leaks,…etc

- A training strategy with various audio-visual teaching mateial should be incorporated in the PD education program. Printed hand-outs, videos, role play and demonstration of the whole procedure if possible with a hands-on approach and/or practice mannequins would be of great value to the patient.

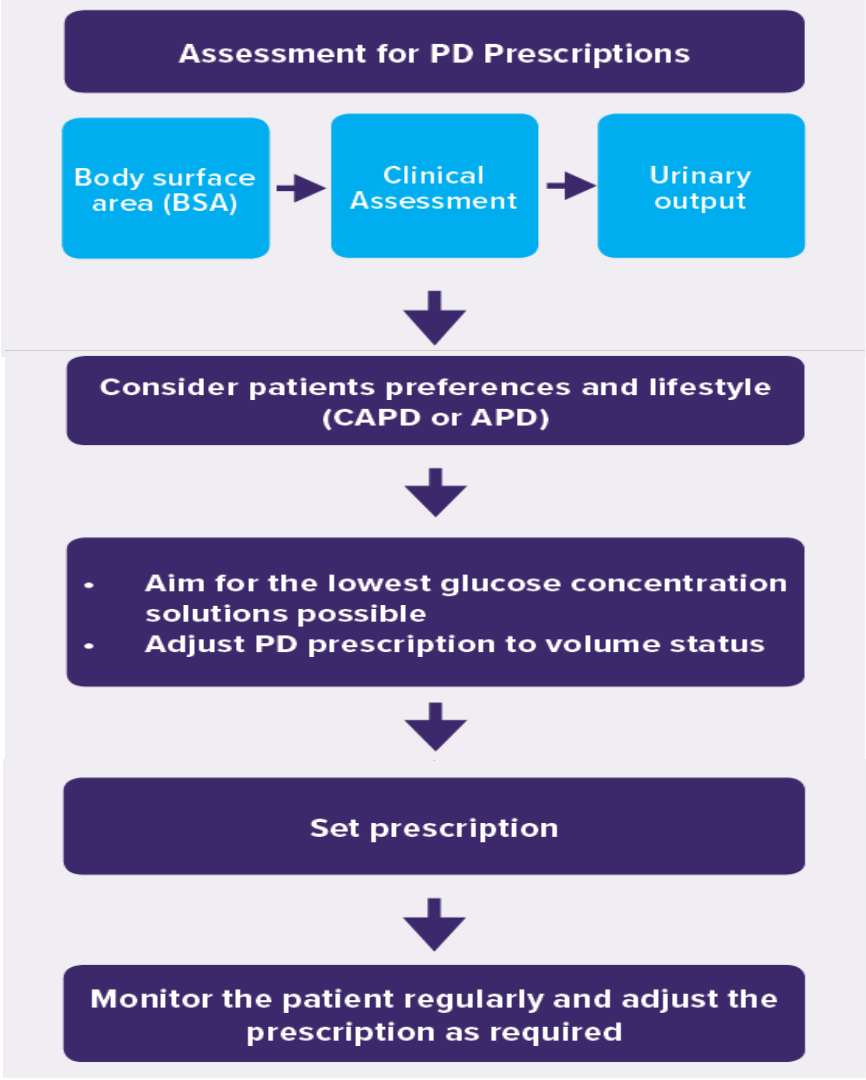
- A suitable teaching environment is always preferred; one that is physically and psychologically comfortable for the learner. The dedicated space should be well lit, free from minimal external distractions, large enough for supplies, teaching aids, patient, family and PD nurse. Suggested locations are a specialised PD clinic, or a conventient space in the patient's house or a hospital room.

- The length of training is based on several factors; patient's attention span, current uremic symptoms and ability to process information. On average, training for CAPD is usually completed in 4-5 days with an additional 1-2 days for APD training. Training sessions should be held on consecutive days with frequent breaks scheduled according to the patients learning style and pace. Minimizing new concepts to no more than 4 new concepts/hour is recommended.

- Preferably a 1:1 nurse to patient approach is utilized for initial training. The same PD nurse should be involved for the duration of training for consistency. Training should continue until the PD nurse determines that the patient can meet the following training objectives:
    a) Able to safely perform all required procedures.
    b) Recognizes contamination and infection.
    c) Able to identify appropriate responses to specific complications/situations.
    d) Understands when and how to communicate with the PD dialysis clinic.

3.1.2 : Peritoneal dialysis prescription adjustment

The primary goal of PD prescription, regardless of modality, is to optimize patients' preference, outcomes and quality of life.



3.1.2.1 : Intermittent Peritoneal Dialysis

Intermittent peritoneal dialysis (IPD) offered daily or every other day is available in some programs as:

- A bridge therapy between catheter insertion and commencement of CAPD or APD if training is delayed.
- A break in procedure for 1 week prior to PD training
- An urgent starting therapy for ESRD patients who do not have an access in place for dialysis. IPD is done for the pediatric in-patient requiring acute PD for volume control.
- A temporary option for PD related complications (i.e. leaks)

3.1.2.2 : Acute / Urgent Peritoneal Dialysis

Urgent start PD is defined as initiation of PD in the unplanned incident ESRD before the traditional waiting period of 2 or more weeks after PD catheter placement. Research indicates that PD is a viable option for the late presenting patient with advanced kidney disease requiring urgent dialysis.

Indications for Urgent PD

- Advanced CKD patients without a plan for dialysis.
- Patients who choose home dialysis as a long term modality option but do not have an access in place.
- Volume overload with cardiovascular compromise.
- Acute kidney injury.
- Problematic vascular access.
- Hemodynamically unstable.
- Elderly with complex comorbidities.

Special considerations for Urgent PD

- Patients requiring hernia repair.
- Active intra-abdominal infection (i.e. acute diverticulitis)
- Recent abdominal surgery (within the past 6 weeks)
- Recent cardiovascular thrombotic event requiring ongoing anti-platelet therapy or anti-coagulation (that cannot be safely interrupted for PD catheter insertion).

Advantages of Urgent PD:

1. Avoidance of temporary vascular catheters.
2. Requires a single procedure for both urgent and long term access.
3. Provides the patient with the lifestyle opportunities of home dialysis.
4. Allows for a gentle, incremental dialysis initiation.
5. Technically simpler than HD or Continuous Renal Replacement Therapy (CRRT).
6. Can be initiated quickly.
7. More cost effective.
8. Less complex equipment.
9. Avoids vascular problems: infection, hemorrhage, thrombosis, embolism, stenosis.
10. Provides time to achieve fluid electrolyte balance and toxin removal before training.
11. Opportunity to meet and develop relationships with the PD team before self managing.
12. Facilitates patient/family learning by observing staff performing PD therapy.
13. Does not require anticoagulation.
14. Reduced risk of acquiring Hepatitis B and C.
15. Less hypotensive episodes.
16. Helps preserve residual kidney function longer than conventional HD.
17. Facilitates discharge from hospital.

3.2: Peritoneal Dialysis Catheter Insertion

3.2.1 :

We recommend that, where possible, timing of PD catheter insertion should be planned to accommodate patient convenience, commencement of training between 10 days and 6 weeks and before RRT is essential to enable correction of early catheter-related problems without the need for temporary haemodialysis (1C).

3.2.2 :

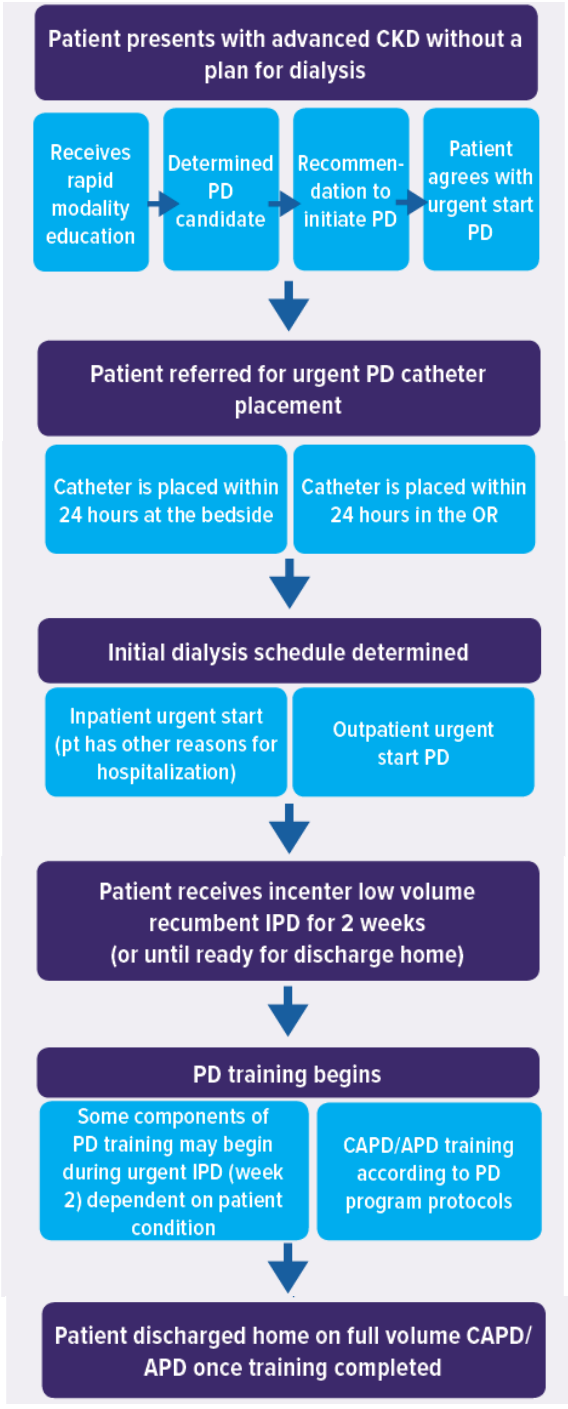
We recommend that PD catheter insertion practice should be managed according to the Guidelines. Paediatric PD access procedures will routinely be performed under general anaesthetia. We also recommend that peri-operative catheter care and catheter complications (leaks, hernias, obstruction) should be managed according to the International Society of Peritoneal Dialysis guidelines 2005, and for children, the European Elective Chronic Peritoneal Dialysis Guideline 2001.

Rationale:

- For management of the catheter in the peri-operative period, and for catheter related problems including leak (internal and external), poor flow, obstruction and hernias, the guidelines developed by the International Society of Peritoneal Dialysis and the European Elective Chronic Peritoneal Guideline should be used.
- Catheter problems due to increased intra-peritoneal pressure, especially leaks, hernias and prolapse are an important medical indication for the use of APD either temporarily or permanently; poor flow or catheter related flow pain should be treated with tidal APD. In the majority of cases where surgical repair for mechanical complications is required (e.g. catheter replacement, hernia repair) it is possible to avoid the need for temporary haemodialysis. In many PD patients, remaining residual renal function may permit an adequate period post-surgery before dialysis needs to be recommenced. Where PD does need to start soon after surgery, in many cases this may be safely achieved by initial use of APD with small volume exchanges and avoiding a day dwell in ambulant patients.

- Referrals for PD catheter should be considered when the GFR is approximately 15 ml/min/1.73m^2 whilst optimising local PD program catheter placement options, timeline and patient needs. Surgical catheter insertion should be performed at least 2 weeks before starting peritoneal dialysis. The access should be placed early enough to ensure the patient can train for peritoneal dialysis while residual renal function is adequate to avoid the need for urgent hemodialysis and a central venous catheter insertion.
- The ISPD Clinical Practice Guidelines for Peritoneal Access recommend that local expertise at individual centres should govern the choice of method of PD catheter insertion.
- Chronic PD catheters are inserted in three ways:
    a) As a surgical procedure in the operating room performed by a vascular / general surgeon. It may be done using an open incision and surgical dissection (laparotomy) or a laparoscopic technique. Both are done as a same day or short stay (1 – 2 day post-operative stay) procedures and under a general anaesthetic. The need for a surgical method involving direct vision with open insertion is determined by patient characteristics, such as history of significant abdominal surgeries, the need for hernia repairs, vascular access failure or severe liver disease.
    b) As a “bedside” (non-surgical) procedure performed by a nephrologist who has had specialized training in this technique. This is done as an outpatient procedure and may involve an overnight stay. Procedures are done using a local anaesthetic +/- an anti-anxiety medication, narcotics or conscious sedation.
    c) As a radiological procedure in a fluoroscopic radiology setting performed by an interventional radiologist.

- Regardless of the method of insertion, the exit site should be allowed to heal for approximately 2-3 weeks before commencing PD exchanges. Special considerations of using small volumes with the patient in the supine position should be implemented if the catheter is required immediately following insertion.


Patient presents with advanced CKD without a plan for dialysis
Receives rapid modality education
Determined PD candidate
Recommen-dation to initiate PD
Patient agrees with urgent start PD
Patient referred for urgent PD catheter placement
Catheter is placed within 24 hours at the bedside
Catheter is placed within 24 hours in the OR
Initial dialysis schedule determined
Inpatient urgent start (pt has other reasons for hospitalization)
Outpatient urgent start PD
Patient receives incenter low volume recumbent IPD for 2 weeks (or until ready for discharge home)
PD training begins
Some components of PD training may begin during urgent IPD (week 2) dependent on patient condition
CAPD/APD training according to PD program protocols
Patient discharged home on full volume CAPD/ APD once training completed

3.3: PD patient follow-up and re-training

We recommend that a multidisciplinary follow-up protocol is a key requirement of PD care. It could be delivered in the form of regular clinic visits and/or telephone contacts, home visits, community support and patient record keeping which is crucial in the reassessment of patient learning needs and potential prevention or reduction of PD associated complications.

3.3.1 : PD patient follow-up schedule

- Stable adult PD patients are followed at multidisciplinary clinic appointments at a minimum rate of at least once every 3-4 months. Pediatric patients should be seen every 4-6 weeks. Frequency of clinic appointments are determined by the multidisciplinary team based on patient's needs and preferences, patient's ability to self-manage and geographic distance to the clinic.

- It is recommended that home visits should be scheduled as a part of patient care when deemed necessary. Home visits provide visualization and insight into the adaptation of PD into the patient's daily life permitting the ability to alter or modify treatment parameters in order to achieve positive clinical outcomes. Considerations for home visits should basically cover periods after lengthy hospitalizations, peritonitis episodes, identified changes in patients' or family's ability to self manage, and/or cope with aspects of care, and evidence of care giver burn out.

3.3.2 : PD multidisciplinary health care team objectives

3.3.2.1 :

All members of PD multidisciplinary team should work in collaboration with patients and their families to develop patient-centered management plans, goal setting and advanced care planning. Basically, the PD multidisciplinary health care team should include: a nephrologist, a registered nurse, a registered dietitian, a clinical pharmacist, a registered social worker and the unit clerk. Additional team members should be considered for pediatric programs such as a psychologist and a child life specialist.

Rationale:

- A successful PD program is dependent on the expertise of all members of the multidisciplinary team, thereby maximizing the utilization as well as quality of PD. To ensure effective and cohesive teamwork among PD team members, definition and understanding of individuals' roles is important.

- Nephrologists are usually involved in patients' transition to Peritoneal dialysis from pre- dialysis care or any alternative modality of renal replacement therapy. Often, the nephrologist specializing in PD care can differ from the patient's primary nephrologist, and transition of care between physicians should occur once the patient has undergone PD catheter insertion. Nephrologists work in partnership with the multidisciplinary team to establish therapeutic relationships which focus on delivering patient-centred care. They play important roles in pre-dialysis counselling, catheter insertions, patient treatment, and quality management.

- A registered PD nurse has many important roles, including that of a patient caregiver, educator, and care-coordinator. The PD nurse provides ongoing education and support for patients throughout their PD journey and ensures continuity of care between the patient and healthcare team incorporating a case management approach. The RN is integral at maintaining and managing relationships and communication between PD product vendors and the PD program and patients. Patients often rely on their PD nurse as the principal source of advice on many aspects of treatment.

- The significant role of nutrition in the care of dialysis patients is well documented. The registered dietitian provides education and clinical guidance to assess patients' nutritional needs, develop and implement individual nutrition programs and monitor and evaluate the patients' response.

- Peritoneal dialysis patients often require multiple pharmacotherapies and complicated drug regimens to manage their condition. The pharmacist works in collaboration with the team to provide medication compliance counseling, drug interaction screening, medication reconciliation, evaluation and interpretation of drug level assays, education for staff and patients and enhanced overall medication management.

- The registered social worker is also essential to the well-being of patients throughout their transition and their adjustment to all phases of renal care. They work together with the healthcare team to develop a plan of care inclusive of assessment, support, consultative and direct services to address patient needs related to high social determinants of health and risk factors in adaptation to chronic illness, self-care and self-management.

- The PD unit clerk/co-ordinator provides administrative support to ensure efficient day to day operations of PD programs. Description of specific roles and responsibilities can be obtained by contacting the lead chairperson for each discipline.

3.3.2.2 :

Initial and ongoing training and education is a key component of an efficient PD program. A variety of educational support facilities should be available at a local, provincial, national and international level in order to provide a comprehensive evaluation that covers all aspects regarding PD technique and patient evaluation and management.

- The patient's continuous assessment should always include (but is not limited to) :
    1. A comprehensive physical assessment, any associated comorbidity and systematic symptom review (e.g. dyspnea, Chest pain, muscle cramps, constipation, diarrhea, pruritus, appetite changes, nausea/vomiting, insomnia, restless legs, pain, falls,..)
    2. PD regimen and current prescription, PD technique preview
    3. Exit site assessment
    4. Catheter function
    5. Volume status
    6. Peritoneal ultrafiltration, solute transport (Adequacy/PET/ 24 hour urine)
    7. Peritonitis/exit site and tunnel infections
    8. Review of recent hospitalizations
    9. Chemistry and hematology review, laboratory follow up, culture results
    10. Nutritional assessment and management
    11. Medication review
    12. Psycho social review (patient and family support)
    13. Patient goal setting, learning needs and continuing education when indicated
    14. Transplant status

ADULT PD PATIENT	INITIATION OF PD	MONTHLY	EVERY 3 MONTHS	EVERY 6 MONTHS	ANNUALLY
CBC, Na, K+, Cl-, Ca2+, PO4, HCO3-, BUN, Albumin, RBS, Creatinine	■	■			
HbA1C (diabetics), Ferritin, Fe, TIBC, %Sat., PTH			■		
AST, Alk Phos				■	
TSH, HbsAg, AntiHBs,AntiHBc, HCV					■
Lipid profile				■	
Transplant antibodies (if applicable)		■			
Peritoneal equilibration test (PET): performed 4-6 wks. post training and then PRN	■				PRN
24 hour adequacy collection: (dialysate and urine) performed 4-6 wks. post training and PRN following	■				PRN
24 hour urine collection (if applicable)	■			■	
ARO testing	■				■
Viral Hepatitis B, C, HIV	■				■
TB screening (questionnaire, chest x ray, interferon gamma release assay)	■				

PEDIATRIC PD PATIENT	INITIATION OF PD	MONTHLY	EVERY 3 MONTHS	EVERY 6 MONTHS	ANNUALLY
BUN, Cr, Na, K, Cl, HCO3, Mg, glucose, Ca, iCa PO4, alk phos, albumin, CRP, PTH, CBC, diff, platelets, retic count, Fe, ferritin, transferrin sat	■	■			
Uric acid, Vit B12, TSH, total protein, 1,25 dihydroxy, 0,25 hydroxy			■		
Hep C, Hep A, HSV, CMV, EBV, VZV, MMR, cholesterol (HDL/LDL), triglycerides, selenium, zinc, AST, ALT, GGT, billirubin (conj/unconj)				■	
Anti-HBs, HBsAg, Total Anti-HBc, HIV					■
Transplant antibodies (if applicable)		■			
Peritoneal equilibration test (PET): performed when patient reaches optimal fill volume (4-8 weeks post PD initiation)	■			■	
24-hour adequacy collection: (dialysate and urine) with PET and every 6 months following	■			■	
24-hour urine collection (if applicable) performed with PET and every 3 months following	■		■		

➢ PD Guideline 4 : Solute clearance and Fluid management

4.1: Solute clearance

4.1.1 :

We recommend that both residual urine and peritoneal dialysis components of small solute clearance should be measured at least every six months or more frequently depending on residual renal function to achieve clearance targets or if clinically or biochemically indicated in adults and in children. Both urea and/or creatinine clearances can be used to monitor dialysis adequacy and should be interpreted within the limits of the methods (1C).

Rationale:

- Small solute clearance is one of the measurements of adequate dialysis treatment. There are two issues in measuring small solute clearance that need to be taken into consideration. First, the relationship to clinical outcomes of residual renal versus peritoneal small solute clearance is quantitatively different. Observational studies have shown that preserved renal clearance is associated with improved survival, independent of other known factors such as age and comorbidity. Randomised controlled trials designed to replace this residual renal function with peritoneal clearance did not show a proportional survival benefit. RRF can fall rapidly in some patients, certainly within a few weeks. If there are clinical concerns (e.g. if there is a change in symptoms, blood biochemistry, reported fall in urine output or after potential insults to residual renal function), or if achievement of solute clearance target is dependent on residual renal function, this should be undertaken more frequently.

- Second, there are two potential surrogate solutes, urea and creatinine, that can be used to measure solute clearance in PD patients. There is no clear evidence as to which is the more useful clinically, and both have their problems. Current advice, therefore, is that either one or both can be used, ensuring that minimal clearances are achieved for at least one, but clinicians should be aware of their differing limitations. Urea clearances are limited by the difficulty in PD patients of estimating V accurately, whilst peritoneal creatinine clearances are affected by membrane transport characteristics.

4.1.2:

We recommend that a combined urinary and peritoneal Kt/V_{urea} of 1.7/week or a creatinine clearance of 50 L/week/1.73m^2 should be considered as minimal treatment doses for adults (1A). We recommend/suggest that clearance targets for children should be a minimum of those for adults (1C). The dose of dialysis should be increased in patients experiencing uremic symptoms, or inadequate growth in children, even if meeting minimum clearance targets (1B). We recommend that a continuous 24 h PD regime is preferred to an intermittent regime for anuric patients.

Rationale:

- Two randomised controlled trials (ADEMEX and Hong Kong) have evaluated the impact of peritoneal solute clearances on clinical endpoints. Neither found that an increase of peritoneal $Kt/V_{urea} > 1.7$ was associated with an improvement in survival. One observational longitudinal study demonstrated that patients develop malnutrition once the Kt/V falls below 1.7 with a three-fold increase in the death rate. The NECOSAD study found that a creatinine clearance of <40 L/week or a Kt/V urea <1.5 was associated with increased mortality in anuric patients. The vast majority of PD patients will be able to reach these clearance targets, especially if APD is employed.
- These guidelines must however be viewed as recommendations for minimal overall clearance. In patients with residual renal function this renal clearance can be subtracted from the peritoneal clearance with confidence that the value of equivalent renal clearances is greater. Equally, in a patient achieving these clearances but experiencing uraemic symptoms, including reduced appetite or nutritional decline, or failing to achieve adequate acid base balance then the dialysis dose should be increased. In patients with borderline clearances, who fail to achieve these clearance targets, other aspects of patient wellbeing, long-term prognosis from other comorbidity and patient perspective should be considered in deciding whether switch of modality to haemodialysis is appropriate. It is important to note that spuriously low Kt/V urea may arise due to overestimation of V in patients with significant obesity. The large ANZDATA observational study suggested a lower survival with low peritoneal Kt/V .
- There is a discrepancy between clearance of small solutes and larger molecules, which are more dependent on time of contact of dialysate with the peritoneal membrane than dialysate volume. Thus continuous regimes are preferred to those with “dry” periods (e.g.NIPD), particularly in anuric patients, even if small solute clearance targets can be achieved without continuous therapy. An exception to this is the situation where a patient still has a large residual renal function.
- In paediatrics there is a lack of high quality evidence to determine clearance targets for children on PD. It is suggested by British Association of Paediatric Nephrology that the adult targets should be considered as minimum desirable, with an increase in PD prescription in the presence of features of uraemia, including inadequate growth. Evidence in small numbers of subjects has suggested that in children increasing dialysis prescription may reach a point of no further benefit or adverse effects on nutrition due to increased dialysate protein removal.

4.2: Ultrafilteration and Fluid management

4.2.1 :

We recommend that peritoneal membrane function should be monitored regularly (6 weeks after commencing treatment and at least annually or when clinically indicated) using a peritoneal equilibration test (PET) or equivalent. Daily urine and peritoneal ultrafiltration volumes, with appropriate correction for overfill, should be monitored at least every six-months (1C).

Rationale:

- Assessment of membrane function, specifically solute transport rate and ultrafiltration capacity is fundamental to PD prescription. This is for the following reasons:
    a) There is considerable variability between patients in both solute transport and ultrafiltration capacity that translates into real differences in achieved solute clearance and ultrafiltration unless they are accounted for in prescription practice
    b) Membrane function is an independent predictor of patient survival; specifically high solute transport and low ultrafiltration capacity are associated with worse outcomes
    c) Membrane function changes with time on therapy. There are early changes – usually during the first few weeks of treatment that can be avoided by performing tests 6 weeks after commencing PD. Later changes vary between patients but tend to be increasing solute transport and reduced ultrafiltration capacity; the rate of membrane change is accelerated in patients with earlier loss of residual renal function and greater requirement for hypertonic glucose solutions.

- Residual renal function, as discussed above, is one of the most important factors, along with age, comorbidity, nutritional status, plasma albumin and membrane function that predict survival in PD patients. Its rate of loss is variable and clinically significant changes can occur within 6 months. Total fluid removal is associated with patient survival, especially once anuric.

4.2.2 :

We recommend that dialysis regimens resulting in fluid reabsorption should be avoided. Patients with high or high average solute transport, at greatest risk of this problem, should be considered for APD and icodextrin (1A).

Rationale:

- Increased solute transport has been repeatedly shown to be associated with worse survival, especially in CAPD patients. The explanation for this association is most likely due to its effect on ultrafiltration when this is achieved with an osmotic gradient (using glucose or amino-acid dialysis fluids). The reason is twofold: first, due to more rapid absorption of glucose, the osmotic gradient is lost earlier in the cycle resulting in reduced ultrafiltration capacity. Second, once the osmotic gradient is dissipated the rate of fluid reabsorption in high transport patients is more rapid. This will result in significant fluid absorption, contributing to a positive fluid balance, during the long exchange. These problems associated with high transport can be avoided by using APD to shorten dwell length and by using icodextrin for the long exchange to prevent fluid reabsorption. Several randomised controlled trials have shown that icodextrin can achieve sustained ultrafiltration in the long dwell and that this translates into a reduction in extracellular fluid volume. A difference in practice for pediatrics is that patients with an underlying diagnosis of renal dysplasia are often polyuric, and so not so dependent on peritoneal ultrafiltration for maintenance of euvolaemia.

4.2.3 :

We recommend that dialysis regimens resulting in routine utilization of hypertonic (3.86%) glucose exchanges should be minimized. Where appropriate this should be achieved by using icodextrin or diuretics (1B).

Rationale:

- There is growing evidence that regular use of hypertonic glucose dialysis fluid (3.86%), and where possible glucose 2.27%, is to be avoided as far as possible. It is associated with acceleration in the detrimental changes in membrane function that occur with time on treatment, as well as several undesirable systemic effects including weight gain, poor diabetic control, delayed gastric emptying, hyperinsulinemia and adverse hemodynamic effects . In addition to patient education to avoid excessive salt and fluid intake, where possible the use of hypertonic glucose should be minimized by enhancing residual diuresis with the use of diuretics (e.g. furosemide 250 mg daily). Substituting icodextrin for glucose solutions during the long exchange will result in equivalent ultrafiltration whilst avoiding the systemic effects of the glucose load. Observational evidence would suggest that icodextrin is associated with less functional deterioration in the membrane in APD patients.

4.2.4 :

We recommend that treatment strategies that favor preservation of renal function or volume should be adopted whenever possible. These include the use of ACEi, ARBs (in adults only) and diuretics, and the avoidance of episodes of dehydration (1B). We recommend that anuric patients who are overhydrated and consistently achieve a daily ultrafiltration of less than 750 ml in adults (or equivalent volume for body size in pediatrics) should be closely monitored. These patients may benefit from prescription changes and/or modality switch (1B).

Rationale:

- This is the single most important parameter in PD patients, and also the one most likely to change with time. Clinically significant changes can occur within three months. Because secretion of creatinine by the kidney at low levels of function overestimates residual creatinine clearance, it is recommended to express this as the mean of the urea and creatinine clearances. Observational and randomised studies have shown that episodes of volume depletion, whether unintentional or in response to active fluid removal with the intent of changing blood pressure or fluid status, are associated with increased risk of loss in residual renal function. Care should be taken not to volume deplete a PD patient too rapidly or excessively. The need to determine an appropriate target weight to avoid the cardiac complications of occult fluid overload, whilst avoiding loss of residual renal function due to excessive fluid removal is a major challenge in the management of the PD patient who has still has a significant residual urine output.
- The use of diuretics to maintain urine volume is not associated with a risk to renal clearances. ACE inhibitors and ARBs have been shown in randomized studies in adults to maintain residual diuresis. Evidence in children is lacking, and a recent report from the International Pediatric Peritoneal Dialysis Network registry suggested that renin-angiotensin blockade could be associated with an increased risk of loss of residual renal function in children, and so these drugs are not recommended in pediatric PD patients.
- Observational studies have consistently shown that reduced peritoneal ultrafiltration is associated with worse survival rates; whilst this is seen in studies with or without residual urine, this effect is most marked in anuric patients. In the only prospective study to have pre-set an ultrafiltration target (750 ml/day), patients who remained below this had higher mortality after correcting for age, time on dialysis, comorbidity and nutritional status. It is likely this association is multifactorial, but failure to prescribe sufficient glucose or icodextrin and a lower ultrafiltration capacity of the membrane were factors in this study and should be considered. The European guidelines have suggested a 1 L minimal daily ultrafiltration target but there is insufficient evidence to say that such a target must be met at this stage. It is possible that in some patients with low ultrafiltration, this is appropriate to their low fluid intake, and that in these cases decreased survival possibly results from poor nutrition rather than fluid excess, and that increasing ultrafiltration would simply result in dehydration with its adverse effects. Blood pressure, salt (and fluid) intake, nutritional and fluid status, and presence of any features of uraemia should be taken into account. Nevertheless patients with less than 750 ml ultrafiltration once anuric should be very closely monitored and the potential benefits of modality switch considered.

➢ PD Guideline 5 : Infectious Complications of PD

5.1: Peritonitis rate

- **We recommend that PD units should undertake regular audit of their peritonitis and exit-site infection rates, including causative organism, treatment and outcomes. They should enter into active dialogue with their microbiology department and infection control team to develop optimal local treatment and prevention protocols (1B).**
- **We suggest that peritonitis rate should be standardly reported as number of episodes per patient-year (not graded).**
- **We suggest that organism-specific peritonitis rates should be reported as absolute rates, i.e. as number of episodes per year (not graded).**

TABLE 1
Methods for Reporting Peritonitis

- As rates (calculated for all infections and each organism): Number of infections by organism for a time period, divided by dialysis-years' time at risk, and expressed as episodes per year.
- As percentage of patients per period of time who are peritonitis free.
- As median peritonitis rate for the program (calculate peritonitis rate for each patient, and then obtain the median of these rates).

N.B. Relapsing peritonitis (see Table 6 for the definition) should be counted as a single episode.

5.2: Prevention of peritonitis

- **5.2.1:** **We recommend that patients (and/or care givers or parents) should undergo regular revision of their technique (at least annually or more frequently if indicated, such as after an episode of PD-related infection or a significant interruption to the patient performing PD) and receive intensified training if this is below standard (1C).**

- **5.2.2: Catheter placement**
  We recommend that systemic prophylactic antibiotics should be administered immediately prior to catheter insertion (1A).

- **5.2.3: Connection methods**
  We recommend that disconnect systems with a "flush before fill" design be used for continuous ambulatory PD (CAPD) (1A).

- **5.2.4: Exit-Site Care**
  We recommend that topical antibiotic administration should be used to reduce the frequency of exit-site infection and peritonitis (1A).
  We recommend prompt treatment of exit-site or catheter tunnel infection to reduce subsequent peritonitis risk (1C).

- **5.2.5: Bowel and Gynecological Source of Infection**
  We recommend that invasive procedures should be accompanied by antibiotic prophylaxis and emptying the abdomen of dialysis fluid for a period commensurate with the procedure (1C).

- **5.2.6: Continuous Quality Improvement**
  We recommend each PD center have a continuous quality improvement (CQI) program in place to reduce peritonitis rates (1C).
  We suggest that multidisciplinary teams running CQI programs in PD centers meet and review their units' performance metrics regularly (2C).

- **5.2.7: Secondary Prevention**
  We recommend anti-fungal prophylaxis when PD patients receive antibiotic courses to prevent fungal peritonitis (1B).

Rationale:

- The ISPD 2016 PD-related infections guideline, the ISPD 2011 position statement on reducing the incidence of PD-related infections, 2017 ISPD catheter-related infection recommendations and the 2012 ISPD guideline for prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving PD place increasing emphasis on prevention strategies. The following standards should be considered as minimal:
    1. Peritonitis rates of less than 0.5 episode per patient year in adults and children
    2. A primary cure rate of >80%
    3. A culture negative rate of <20%

- Patient training to perform PD technique by experienced PD nurses trained to do this as part of a formalized training program is essential in patients commencing PD. Greater experience of nurses providing training is associated with greater time to initial episode of peritonitis. It is recommended that review of patient PD technique is performed on a regular basis, at least annually, or more frequently if there is evidence of inadequate technique or development of PD –related infection, or a significant interruption in the performing PD e.g. after a significant period of hospitalization).

- Approaches that have been shown to reduce infection rates in randomized studies include increased intensity of training, use of flush before fill systems, antibiotic prophylaxis to cover catheter insertion and prevention of exit-site infections. Several studies have addressed the latter issue; following demonstration that the risk of Staph aureus exit site infection (the organism most frequently responsible) is associated with pre-existing skin carriage, several randomized studies demonstrated that clinical exit-site infection and associated peritonitis could be reduced by either nasal or exit-site application of mupirocin. This has led to the practice of applying mupirocin to all patients [122, 123] and this approach should be discussed with the local microbiology and infection control team. A systematic review. A more recent study, comparing mupirocin with gentamicin cream, found that the latter prevented both Staph aureus and Pseudomonas exit-site infections and peritonitis episodes. This approach should be considered in patients with a known history of Pseudomonas infections; again the policy should be discussed and agreed with the local microbiology team.

5.3: Initial presentation and management of peritonitis

5.3.1: Clinical presentation and Diagnosis of peritonitis

- **We recommend that peritonitis always be diagnosed when at least 2 of the following are present:**
  1. **Clinical features consistent with peritonitis, i.e. abdominal pain and/or cloudy dialysis effluent**
  2. **Dialysis effluent white cell count > 100/µL or > 0.1 × 109/L (after a dwell time of at least 2 hours), with > 50% polymorphonuclear leukocytes**
  3. **Positive dialysis effluent culture (1C).**
- **We recommend that PD patients presenting with cloudy effluent be presumed to have peritonitis and treated as such until the diagnosis can be confirmed or excluded (1C).**
- **We recommend that PD effluent be tested for cell count, differential, Gram stain, and culture whenever peritonitis is suspected (1C).**
- **We recommend that exit site infection is suggested by pain, swelling, crusting, erythema and serous discharge; purulent discharge always indicates infection. Swabs should be taken for culture and initial empiric therapy should be with oral antibiotics that will cover S.aureus and P. aeruginosa (1B).**

5.3.2: Identification of causative organism

- **We recommend that the blood-culture bottle be the preferred technique for bacterial culture of PD effluent (1C).**
- **We suggest that sampling and culture methods be reviewed and improved if more than 15% of peritonitis episodes are culture-negative (2C).**

5.3.3: Empiric Antibiotic Selection

- **We recommend that empirical antibiotic therapy be initiated as soon as possible after appropriate microbiological specimens have been obtained (1C).**
- **We recommend that empirical antibiotic regimens be center-specific and cover both gram-positive and gram-negative organisms (1C).**
- **We recommend that gram +ve organisms be covered by vancomycin or a 1st generation cephalosporin and gram -ve organisms by a 3rd generation cephalosporin or aminoglycoside (1B).**

5.3.4: Dosage of Antibiotics

- **We recommend that IP antibiotics be the preferred route of administration unless the patient has features of systemic sepsis (1B).**
- **We suggest that IP aminoglycoside be administered as daily intermittent dosing (2B).**
- **We recommend that prolonged courses of IP aminoglycoside be avoided (1C).**
- **We suggest that IP vancomycin be administered intermittently and the serum vancomycin level be kept above 15 µg/mL (2C).**
- **We suggest that IP cephalosporin be administered either continuously (in each exchange) or on a daily intermittent basis (2C).**

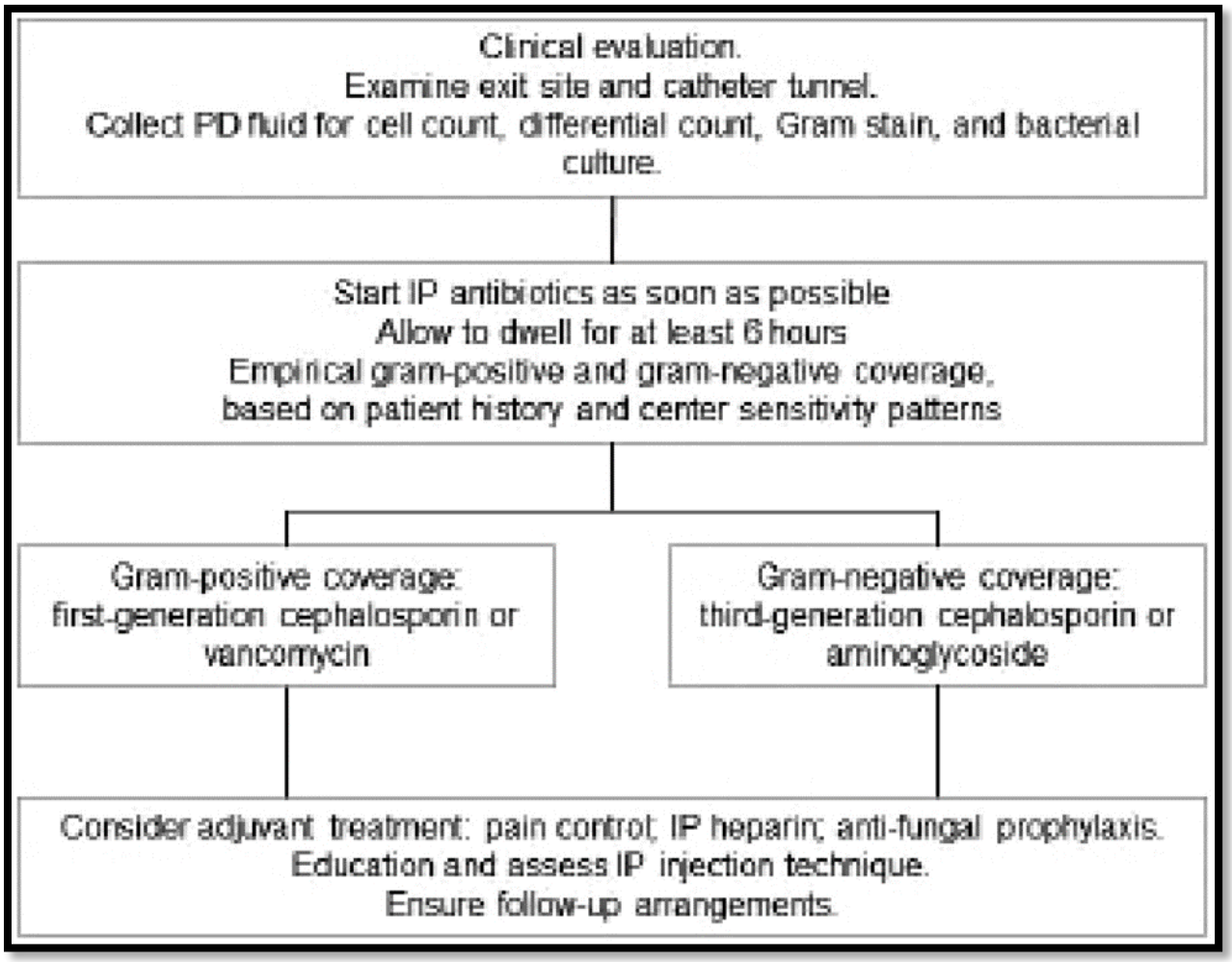


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TABLE 4
Differential Diagnosis of Cloudy Effluent

- Culture-positive infectious peritonitis
- Infectious peritonitis with sterile cultures
- Chemical peritonitis
- Calcium channel blockers
- Eosinophilia of the effluent
- Hemoperitoneum
- Malignancy (rare)
- Chylous effluent (rare)
- Specimen taken from “dry” abdomen

TABLE 5
Intraperitoneal Antibiotic Dosing Recommendations for Treatment of Peritonitis

	Intermittent (1 exchange daily)	Continuous (all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg daily (252)	LD 25 mg/L, MD 12 mg/L (253)
Gentamicin	0.6 mg/kg daily (254)	LD 8 mg/L, MD 4 mg/L (255,256)
Netilmicin	0.6 mg/kg daily (233)	MD 10 mg/L (257)
Tobramycin	0.6 mg/kg daily (253)	LD 3 mg/kg, MD 0.3 mg/kg (258,259)
Cephalosporins		
Cefazolin	15–20 mg/kg daily (260,261)	LD 500 mg/L, MD 125 mg/L (254)
Cefepime	1,000 mg daily (262,263)	LD 250–500 mg/L, MD 100–125 mg/L (262,263)
Cefoperazone	no data	LD 500 mg/L, MD 62.5–125 mg/L (264,265)
Cefotaxime	500–1,000 mg daily (266)	no data
Ceftazidime	1,000–1,500 mg daily (267,268)	LD 500 mg/L, MD 125 mg/L (236)
Ceftriaxone	1,000 mg daily (269)	no data
Penicillins		
Penicillin G	no data	LD 50,000 unit/L, MD 25,000 unit/L (270)
Amoxicillin	no data	MD 150 mg/L (271)
Ampicillin	no data	MD 125 mg/L (272,273)
Ampicillin/Sulbactam	2 gm/1 gm every 12 hours (274)	LD 750–100 mg/L, MD 100 mg/L (253)
Piperacillin/Tazobactam	no data	LD 4 gm/0.5 gm, MD 1 gm/0.125 gm (275)
Others		
Aztreonam	2 gm daily (242)	LD 1,000 mg/L, MD 250 mg/L (243,244)
Ciprofloxacin	no data	MD 50 mg/L (276)
Clindamycin	no data	MD 600 mg/bag (277)
Daptomycin	no data	LD 100 mg/L, MD 20 mg/L (278)
Imipenem/Cilastatin	500 mg in alternate exchange (244)	LD 250 mg/L, MD 50 mg/L (236)
Ofloxacin	no data	LD 200 mg, MD 25 mg/L (279)
Polymyxin B	no data	MD 300,000 unit (30 mg)/bag (280)
Quinupristin/Dalfopristin	25 mg/L in alternate exchange[a] (281)	no data
Meropenem	1 gm daily (282)	no data
Teicoplanin	15 mg/kg every 5 days (283)	LD 400 mg/bag, MD 20 mg/bag (229)
Vancomycin	15–30 mg/kg every 5–7 days[b] (284)	LD 30 mg/kg, MD 1.5 mg/kg/bag (285)
Antifungals		
Fluconazole	IP 200 mg every 24 to 48 hours (286)	no data
Voriconazole	IP 2.5 mg/kg daily (287)	no data

LD = loading dose in mg; MD = maintenance dose in mg; IP = intraperitoneal; APD = automated peritoneal dialysis.
[a] Given in conjunction with 500 mg intravenous twice daily (281).
[b] Supplemental doses may be needed for APD patients.

TABLE 6
Systemic Antibiotic Dosing Recommendations for Treatment of Peritonitis

Drug	Dosing
Anti-bacterials	
Ciprofloxacin (237)	oral 250 mg BD[a]
Colistin (288)	IV 300 mg loading, then 150–200 mg daily[b]
Ertapenem (289)	IV 500 mg daily
Levofloxacin (239)	oral 250 mg daily
Linezolid (290–292)	IV or oral 600 mg BD
Moxifloxacin (293)	oral 400 mg daily
Rifampicin (294,295)	450 mg daily for BW <50 kg; 600 mg daily for BW ≥50 kg
Trimethoprim/ Sulfamethoxazole (252)	oral 160 mg / 800 mg BD
Anti-fungals	
Amphotericin (296)	IV test dose 1 mg; starting dose 0.1 mg/kg/day over 6 hours; increased to target dose 0.75–1.0 mg/kg/day over 4 days
Caspofungin (297,298)	IV 70 mg loading, then 50 mg daily
Fluconazole (299)	oral 200 mg loading, then 50–100 mg daily
Flucytosine (296)	oral 1 gm/day
Posaconazole (300)	IV 400 mg every 12 hours
Voriconazole (301–303)	oral 200 mg every 12 hours

BD = twice a day; IV = intravenous; BW = body weight.

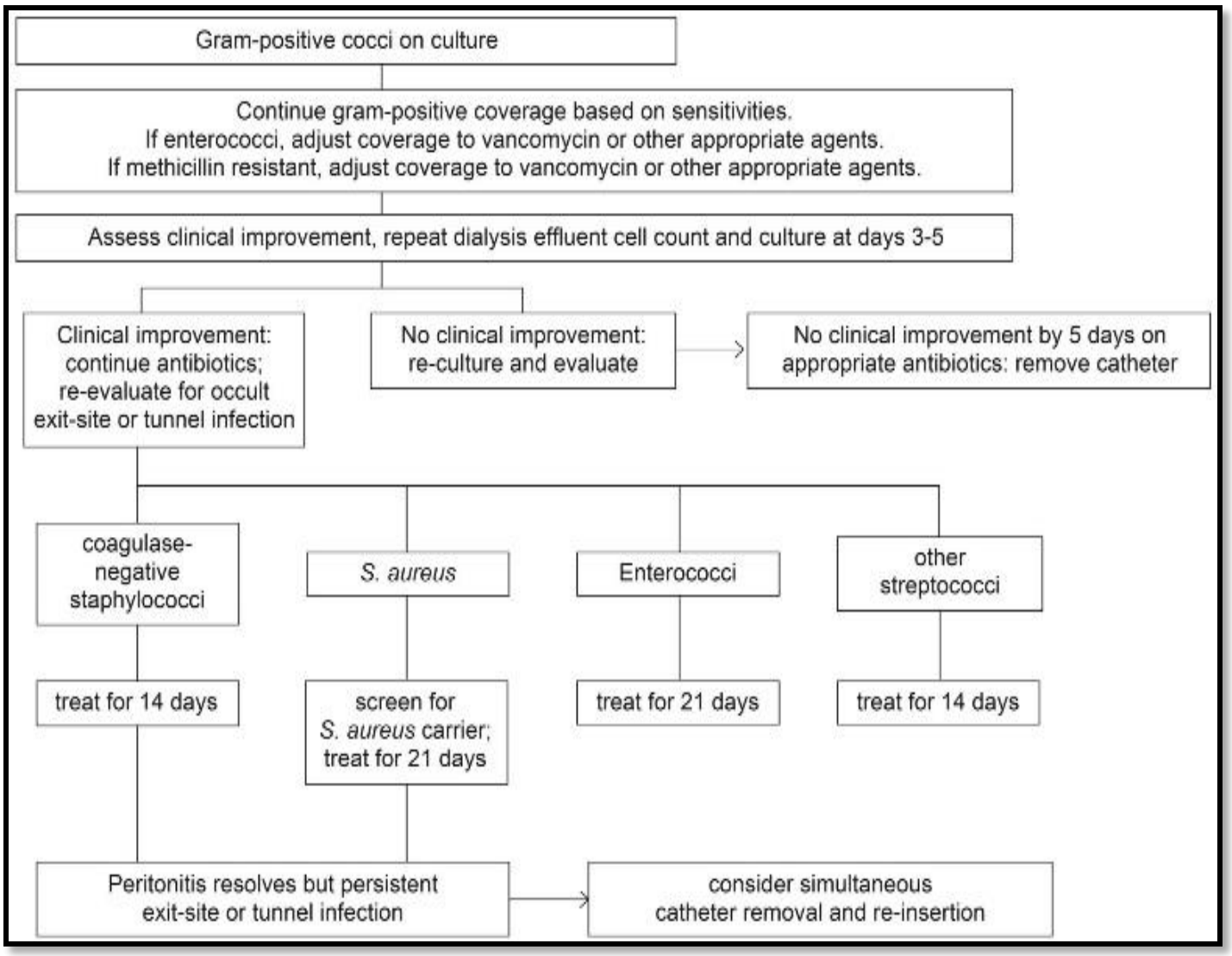
[a] Ciprofloxacin 500 mg BD may be needed if residual glomerular filtration rate is above 5 mL/min.

[b] Expressed as colistin base activity (CBA).

5.4: Subsequent management of peritonitis

5.4.1:

We recommend that antibiotic therapy be adjusted to narrow-spectrum agents, as appropriate, once culture results and sensitivities are known. (1C).



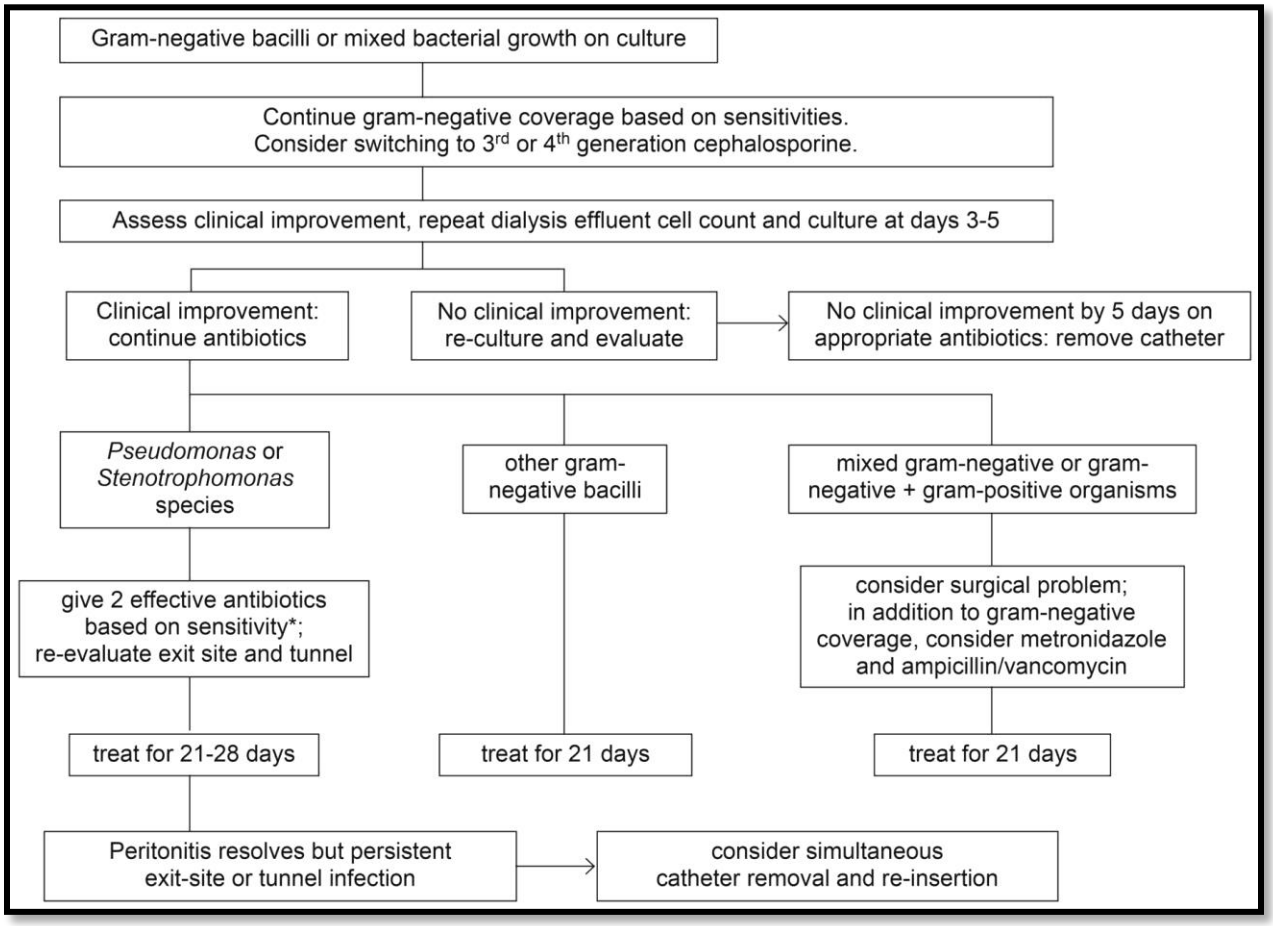


TABLE 7
Terminology for Peritonitis

- Recurrent: An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism
- Relapsing: An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile episode
- Repeat: An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism
- Refractory: Failure of the effluent to clear after 5 days of appropriate antibiotics
- Catheter-related peritonitis: Peritonitis in conjunction with an exit-site or tunnel infection with the same organism or one site sterile

N.B. Relapsing episodes should not be counted as another episode during the calculation of peritonitis rates; recurrent and repeat episodes should be counted.

5.4.2: Refractory Peritonitis

- **We recommend that the PD catheter be removed promptly in refractory peritonitis episodes, defined as failure of the PD effluent to clear up after 5 days of appropriate antibiotics (1C).**

5.4.3: Relapsing, Recurrent, and Repeat Peritonitis

- **We recommend that timely catheter removal be considered for relapsing, recurrent, or repeat peritonitis episodes (1C).**

Coagulase-negative staphylococcus

- **We suggest that coagulase-negative staphylococci generally be treated with IP cephalosporins or vancomycin, according to antimicrobial susceptibility, for a period of 2 weeks. (2C).**

Enterococcus species

- **We suggest that enterococcal peritonitis be treated for 3 weeks with IP vancomycin (2C).**
- **We suggest adding IP aminoglycoside for severe enterococcal peritonitis (2D).**
- **For peritonitis due to vancomycin-resistant Enterococcus (VRE), we suggest treatment for 3 weeks with IP ampicillin if the organism is susceptible or with alternative antibiotics (linezolid, quinupristin / dalfopristin, daptomycin or teicoplanin, based on antimicrobial susceptibilities) if the organism is ampicillin-resistant (2D).**

Streptococcal species

- **We suggest that streptococcal peritonitis be treated with appropriate antibiotics, such as IP ampicillin, for 2 weeks (2C).**

Staphylococcus aureus

- **We suggest that Staphylococcus aureus peritonitis be treated with effective antibiotics for 3 weeks (2C).**

Cornyebacterium peritonitis

- **We suggest that corynebacterial peritonitis be treated with effective antibiotics for 3 weeks (2C).**

Pseudomonas Peritonitis

- **We suggest that Pseudomonas peritonitis be treated with 2 antibiotics with different mechanisms of action and to which the organism is sensitive (e.g. IP gentamicin or oral ciprofloxacin with IP ceftazidime or cefepime) for 3 weeks (2C).**
- **We suggest that Pseudomonas peritonitis with concomitant exit-site and tunnel infection be treated with catheter removal (2D).**

Other Gram-Negative Bacteria

- **We suggest that non-Pseudomonas gram-negative peritonitis be treated with effective antibiotics for at least 3 weeks (2C).**

5.4.4: Polymicrobial Peritonitis

- **We recommend that If multiple enteric organisms (multiple gram-negative or mixed gram-negative/gram-positive organisms) are grown from PD effluent, we suggest that surgical evaluation be obtained immediately when there is no prompt clinical response (1C) and that the patient be treated with metronidazole in conjunction with IP vancomycin and either IP aminoglycoside or IP ceftazidime for a minimum period of 3 weeks (2C).**
- **If multiple gram-positive organisms are grown from PD effluent, we suggest that patients be treated with effective antibiotics for 3 weeks (2C).**

5.4.5: Culture negative Peritonitis

- **We suggest that negative effluent cultures on day 3 warrant a repeat dialysis effluent WBC count with differential (2D).**
- **If the culture-negative peritonitis is resolving at day 3, we suggest discontinuing aminoglycoside therapy and continuing treatment with gram-positive coverage (e.g. first-generation cephalosporin or vancomycin) for 2 weeks (2C).**
- **If the culture-negative peritonitis is not resolving at day 3, we suggest special culture techniques be considered for isolation of unusual organisms (2C).**

5.4.6: Fungal Peritonitis

- **We recommend immediate catheter removal when fungi are identified in PD effluent (1C).**
- **We suggest that treatment with an appropriate anti-fungal agent be continued for at least 2 weeks after catheter removal (2C).**

5.4.7: Tuberculous Peritonitis

- **Although classical symptoms of fever, abdominal pain, and cloudy effluent may occur with TB peritonitis, the diagnosis should be considered in any patient with refractory or relapsing peritonitis with negative bacterial cultures. Similar to bacterial peritonitis, most cases have PMN in the dialysis effluent at initial presentation, but lymphocytosis in the dialysis effluent usually becomes obvious later. Overall diagnostic yield could be improved by centrifuging a large volume of effluent (50 to 100 mL), followed by culturing the sediment in both solid and fluid media. Alternatively, mycobacterial DNA PCR can be performed. Laparoscopy with biopsy of the peritoneum or omentum has also been advocated for rapid diagnosis if the index of suspicion is high.**
- **The treatment protocol should be based on general protocols for treatment of TB. In general, pyrazinamide and ofloxacin could be stopped after 2 months, while rifampicin and isoniazid should be continued for a total of 12 to 18 months. Pyridoxine (50 to 100 mg/day) should be given to avoid isoniazid-induced neurotoxicity. However, long-term use of pyridoxine at a higher dose (e.g. 200 mg daily) is in itself associated with neuropathy and should be avoided.**
- **Many patients respond to anti-TB therapy without catheter removal. However, it is important to differentiate miliary TB, where peritonitis is part of the disseminated disease, from isolated TB peritonitis without extraperitoneal infection, because the duration of anti-tuberculous therapy is different.**

5.4.8: Catheter removal and Re-insertion

- **We recommend that PD catheters be removed for refractory, relapsing, or fungal peritonitis unless there are clinical contraindications (1C).**
- **We suggest that it is appropriate to consider return to PD for many patients who have had their catheter removed for refractory, relapsing, or fungal peritonitis (2C).**
- **We suggest that if re-insertion of a new catheter is attempted after a PD catheter is removed for refractory, relapsing, or fungal peritonitis, it be performed at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms (2D).**
- **For refractory peritonitis and fungal peritonitis, simultaneous re-insertion of a new PD catheter is not recommended, and patients should be put on temporary hemodialysis. Observational studies suggest that effective antibiotics should be continued for at least 2 weeks after catheter removal for refractory peritonitis. Re-insertion of a new catheter should be done by laparoscopic or mini-laparotomy approach so that adhesion can be directly visualized.**

TABLE 8

Indications for Catheter Removal

- Refractory peritonitis
- Relapsing peritonitis
- Refractory exit-site and tunnel infection
- Fungal peritonitis
- Catheter removal may also be considered for
  - repeat peritonitis
  - mycobacterial peritonitis
  - multiple enteric organisms

Rationale:

- The International Society of Peritoneal Dialysis (ISPD) has developed a simple scoring system for exit site signs and symptoms which is easy to use and gives guidance on when to treat immediately rather than waiting for a swab result. Purulent discharge is an absolute indicator for antibiotic treatment.

- The ISPD has become less dogmatic about the initial choice of antibiotic treatment for peritonitis, provided that gram positive and negative infections are covered. It is recognized that patterns of resistance vary considerably and thus a local policy must be developed. Studies do not currently demonstrate a favored regime. For exit site infections the presence of a tunnel infection should be recognized as it may require more aggressive management. We also noted that infections from Gram negative organisms are more likely to lead to refractory or recurrent peritonitis. A single study suggested that treating Gram negative peritonitis with 2 appropriate antibiotics might be associated with better outcomes. It is also important to be aware of the potential for impaired absorption of oral antibiotics in some situations, e.g. co-prescription of ciprofloxacin with some phosphate binders.

- We would emphasize according to ISPD guidelines that it is important that timely PD catheter removal is undertaken in refractory PD peritonitis. PD catheter removal or swap is also required in refractory exit site infections, and may be required earlier where there is a Pseudomonas infection or associated tunnel infection, which can be confirmed by ultrasound imaging.

- There will be a lower threshold in pediatrics for admission for IV antibiotics (at least for first 48 h), especially in infants and small children where oral antibiotics commonly cause diarrhea/feed intolerance.

➢ PD Guideline 6 : Encapsulating Peritoneal Sclerosis (EPS)

6.1: Diagnosis of EPS

- **We recommend that the diagnosis of encapsulating peritoneal sclerosis (EPS) requires the presence of a combination of clinical and radiological features of intestinal obstruction and encapsulation(1B). We recommend that the radiological technique of choice for the diagnosis of EPS is CT scanning (1B).**
- **We recommend that radiological and biochemical screening methods are NOT of sufficient sensitivity and specificity to be used clinically to identify early or imminent development of EPS in asymptomatic PD patients (1C).**

Rationale:

- Encapsulating peritoneal sclerosis (EPS) is rare, but serious complication of long-term PD. It involves formation of an inflammatory, and later fibrotic, “cocoon” surrounding the gastrointestinal tract. This results in features of abdominal inflammation and intestinal obstruction. Symptoms may include abdominal pain, nausea, vomiting and haemoperitoneum and may predate definitive diagnosis by significant time periods in some instances. Typical appearances will be noted at laparotomy or laparoscopy. EPS should be distinguished from the thickening of the peritoneal membrane that typically occurs with time on PD, but which is not associated with obstructive features. Changes in peritoneal membrane small solute transport and ultrafiltration capacity often occur, but are also common in long-term PD and not always present in EPS, so are not of diagnostic value for EPS. There is no gold standard for the diagnosis of EPS, and it is recommended that the condition is diagnosed by the presence of the combination of characteristic clinical and radiological features.

- Radiology plays a key role in the diagnosis of EPS. Plain abdominal X-rays may show features of bowel obstruction, but are non-diagnostic, except in cases where peritoneal calcification is present as a feature suggestive of EPS. CT scanning is recommended as the definitive radiological investigation for the diagnosis of EPS. It has high reproducibility and evaluation has provided the basis of a standardised approach to CT diagnosis of EPS. The presence of peritoneal calcification, bowel wall thickening, bowel tethering, and bowel dilatation are the features with greatest agreement between reporting radiologists. Abdominal ultrasound may detect characteristic features in EPS. However, there is a limitation to depth of penetration of sound waves which may limit ability for thorough evaluation of the abdomen, and it is operator-dependent. Small bowel contrast studies may also have a role in defining the presence of strictures prior to surgery. At present, there are no investigations that can be recommended to monitor or screen patients on long-term PD to identify those who will develop EPS. One study has demonstrated that in patients developing EPS, who had abdominal CT scans for other reasons within a period of a year or less prior to diagnosis of EPS, there were no radiological abnormalities to suggest imminent development of EPS.

6.2: Management of EPS

- **We recommend that patients with suspected EPS should be referred or discussed early with units who have expertise in EPS surgery. Surgery should be performed by teams experienced in EPS surgery (1B).**
- **We recommend that patients with EPS should have early dietetic referral and monitoring of nutritional status, with nutritional support by oral enteral, or often parenteral supplementation usually required (1C).**
- **We suggest that there is no clear evidence to support a recommendation for the use of any medical therapy for treating EPS. Corticosteroids, immunosuppressants and tamoxifen have been used, and may be tried at the physician's discretion (2C).**
- **We suggest that PD should usually be discontinued after diagnosis of EPS with transfer to haemodialysis. However, this should be an individual patient decision considering, patient wishes, life expectancy and quality of life (2C).**

Rationale:

- Optimal management of EPS requires integrated care from an expert team experienced in managing this condition. Multiple disciplinary input includes PD physicians, nurses, surgeons, dieticians, radiologists and intensive care physicians. There is increasingly strong evidence for a central role for surgery in the management of EPS. Whilst earlier experience of EPS reported a high mortality for patients with this condition, and complications following surgery, in experienced hands, surgery results in high rates of resolution of symptoms and survival, and possibly superior relief of obstruction compared with conservative treatment with nutrition and/or drug treatment. Surgery should be performed by a surgical team which has a high level of expertise and experience with EPS, and the appropriate multidisciplinary input and peri-operative renal and intensive care support. Indications for surgery include non-responsiveness to medical treatment, bowel obstruction (acute and recurrent subacute), intraperitoneal bleeds, and peritonitis. A proportion of patients with EPS may have a good outcome without surgery so further work to define those most likely to benefit from surgery is needed. Where possible, surgery should be timed to take place electively before the patient is too ill or nutritionally depleted. Surgery involves careful dissection of thickened peritoneum from bowel loops to achieve maximal removal of sclerotic membrane from the bowel wall, whilst avoiding inadvertent perforation.

- Reduced nutritional intake resulting from intestinal dysfunction, plus an ongoing inflammatory state in EPS, can lead to severe protein energy wasting. Nutritional state is associated with survival in EPS. Patients with EPS should be referred early to a renal dietician to allow nutritional assessment, monitoring and institution of nutritional support where needed. In more severe cases, parenteral nutrition may be required, and in patients where intestinal function does not recover, this may be required on a permanent basis. In milder cases, nutrition support may be managed with an energy dense diet or prescription of oral nutritional supplements and antiemetics. Where patients are unable to tolerate adequate oral intake, nasogastric or nasojejunal feeding may be utilised.

- Whilst there has been much interest in drug treatments for EPS, there is no robust evidence to support the use of anti-inflammatory or antifibrotic drugs in this condition. Corticosteroids have been most commonly used, particularly in the Japanese literature. Any benefit is most likely with use in the early inflammatory stage of EPS. However there is not strong objective evidence for their effectiveness, and in EPS side effects of immunosuppression and protein catabolism are a particular concern. There are reports of use of immunosuppressants including azathioprine and cyclosporine in EPS. However evidence is largely as case reports, and as a common setting for development of EPS is following transplantation, in patients taking these drugs, their therapeutic effectiveness is doubtful. There is increasing interest in the role of tamoxifen, which is effective in other fibrotic conditions, in EPS. There is a suggestion from retrospective data of a beneficial effect of tamoxifen on survival or that it could even have a preventative role, but robust evidence is currently lacking.

- PD is usually discontinued and the PD catheter removed after diagnosis of EPS, with transfer to haemodialysis. However, as some cases are mild, the individual patient's wishes and clinical state should be considered, as stopping PD may not be appropriate in a patient with mild symptoms and a poor long term prognosis, where continuation of PD and/or later conservative management may be appropriate. Also, there is experience in Japan of leaving the PD catheter in and performing peritoneal lavage after diagnosis of EPS, with observational non-randomised studies suggesting some benefit, though this approach is not widespread in other countries.

6.3: Duration of PD therapy

We recommend that there is no optimal duration of peritoneal dialysis or indication for routine elective modality switching. Decisions regarding the duration of therapy should be tailored to the individual patient, taking into account clinical and social factors and patient wishes, and should follow the principles outlined in the ISPD Length of Time on Peritoneal Dialysis and Encapsulating Peritoneal Sclerosis Position Paper (1C).

➢ PD Guideline 7 : Metabolic factors

We recommend that standard strategies to optimise diabetic control should be used; these should be complemented by dialysis prescription regimens that minimise glucose, including glucose-free solutions (icodextrin and amino-acids), where possible (1B).

Rationale:

Optimal Glycaemic control can be made worse by glucose absorption across the peritoneal membrane. Dialysis regimens that incorporate less glucose and more glucose free (amino acid, icodextrin) solutions have been shown to improve glycaemic control. Diabetes is a rare cause of end-stage renal failure in paediatrics, but these principles would also apply to children on PD who have diabetes. The IMPENDIA-EDEN randomised controlled study compared all-glucose regimes with regimes including both icodextrin and amino acid PD dialysis fluids in diabetic patients on PD demonstrated a 0.5% reduction in glycated haemoglobin. Serum triglyceride, very-low-density lipoprotein, and apolipoprotein B also improved. However it is important to note that the intervention group suffered an increase in adverse events and deaths, including events related to extracellular fluid expansion. It is therefore critical that this approach with use of low-glucose solutions is accompanied by careful monitoring of hydration and is not at the expense of a decline in fluid management. It also should not be an alternative to appropriate use of hypoglycaemic drugs, and monitoring for hypoglycaemia is important in patients where dialysate glucose load is reduced.

We recommend that plasma bicarbonate should be maintained within the normal range. This can be achieved inthe vast majority of patients by adjusting the dialysis dose and/or dialysate buffer concentration (1B).

Rationale:

Two randomised controlled trials have suggested that clinical outcomes, including gaining lean body mass and reduced hospital admissions are achieved if the plasma bicarbonate is kept within the upper half of the normal range. Generally this can be achieved by using dialysis fluids with a 40 mmol buffer capacity (lactate or bicarbonate results in similar plasma bicarbonate levels) and ensuring that the dialysis dose is adequate. Whilst bicarbonate solutions may have a role in biocompatibility, they are generally not required to achieve satisfactory acid-base balance in adults. The main reason for using a 35 mmol buffer capacity solution (25:10 bicarbonate:lactate mix) is to avoid excessive alkalinisation. Plasma bicarbonate will also be affected by some phosphate binders that either increase, or occasionally decrease concentrations. Control of acidosis is especially important in malnourished patients who may benefit from the glucose available in dialysis solutions as a calories source. Amino acid solutions were developed in an attempt to address protein calorie malnutrition. In using amino acid solutions it is essential to ensure that acidosis does not develop and to use the solution at the same time as there is a significant intake of carbohydrate.

We suggest that central obesity can worsen or develop in some PD patients. The risk of this problem, and associated metabolic complications, notably increased atherogenicity of lipid profiles and insulin resistance, can be reduced by avoiding excessive glucose prescription and using icodextrin (2C).

Rationale:

Optimal Weight gain, or regain, is common after starting peritoneal dialysis and this is associated with a worsening in the lipid profile, though there may not be a significant difference from haemodialysis. Randomised studies comparing glucose 2.27% with icodextrin in the long exchange have shown that the latter prevents weight gain, which in body composition studies is at least in part fat weight. Substituting icodextrin for 2.27% glucose in the long dwell also improves insulin resistance. There is limited available trial data on the benefit of statins in PD patients with a hard clinical endpoint. There is no data on the effects of lipid-lowering in children on PD as well. There are good reasons for believing that the lipid abnormalities in the PD patient population may be different to patients on HD, and potentially more atherogenic. The KDIGO guideline for lipid management in CKD suggests that statins and/or ezetimibe are not commenced in dialysis patients, but that they are continued if a patient is receiving them before stating dialysis, though it is important to note that the majority of evidence this is based on is derived in haemodialysis patients.

We recommend that awareness of the effects of Icodextrin on assays for estimation of amylase and glucose (using glucose dehydrogenase) should be disseminated to patients, relatives, laboratory and clinical staff (1C).

Rationale:

Use of icodextrin is associated with circulating levels of metabolites that can interfere with laboratory assays for amylase (or actually suppress amylase activity) and for glucose when finger-prick tests that utilise glucose dehydrogenase as their substrate are employed (manufactured by Boehringer Mannheim). In the case of amylase, the measured level will be reduced by 90%, leading to the potential failure in the diagnosis of pancreatitis. No adverse events have been reported, but clinicians should be aware of this possibility. If clinical concern remains then plasma lipase can be used. In the case of glucose measurements, the methods using glucose dehydrogenase will overestimate blood glucose levels, leading to a failure to diagnose hypoglycaemia. This has been reported on several occasions in the literature and has contributed to at least one death. Typically these errors occur in places and circumstances in which staff not familiar with peritoneal dialysis work, for example emergency rooms and non-renal wards. A number of solutions to this problem are under active review (e.g. use of alarm bracelets) but it is also the responsibility of health-care professionals to ensure that clinical environments in which their patients using icodextrin may find themselves are notified of this issue on a routine basis.