NATIONAL TREATMENT PROTOCOL FOR RENAL DISEASES AND RENAL REPLACEMENT THERAPY

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Abbreviations

ABMR	antibody mediated rejection
ACEI	angiotensin converting enzyme inhibitor
ACR	albumin creatinine ratio
ADPKD	autosomal dominant polycystic kidney disease
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ANA	antinuclear antibody
ANCA	anti-neutrophilic cytoplasmic auto antibody
APD	automated peritoneal dialysis
ARB	angiotensin receptor blocker
ARF	acute renal failure
ATG	antithymocyte globulin
AZA	azathioprine
BMI	body mass index
BP	blood pressure
BPH	benign prostatic hypertrophy
CAPD	continuous ambulatory peritoneal dialysis
CCPD	continuous cycling peritoneal dialysis
CGN	chronic glomerulonephritis
CKD	chronic kidney disease
CKDEPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CRRT	continuous renal replacement therapy
C/S	culture and sensitivity
CXR	chest x ray
CYA	cyclophosphamide
CYP 450	cytochrome 450
DLC	differential leukocyte count

DNA	deoxyribonucleic acid
DPP-4i	4-dipeptidyl peptidase inhibitor
DSA	donor specific antibodies
DTPA	diethylenetriaminepentaacetic acid
EBV	epsteinbarr virus
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESA	erythropoiesis stimulating agent
ESKD	end stage kidney disease
FSGS	focal segmental glomerulosclerosis
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GN	glomerulonephritis
Hb	Hemoglobin
HCV	hepatitis C virus
HD	hemodialysis
HIV	human Immunodeficiency virus
HLA	human leukocyte antigen
HSP	Henoch Schlönlein Purpura
HSV	herpes simplex virus
ICU	intensive care unit
IPD	intermittent peritoneal dialysis
ISN	International Society of Nephrology
IgG	immunoglobin G
IgM	immunoglobin M
iMN	idiopathic membranous nephropathy
IP	Intraperitoneal
IPD	intermittent peritoneal dialysis
iPTH	intact parathyroid hormone
IVIG	intravenous immunoglobulin
KDIGO	Kidney Disease: Improving Global Outcomes

KDOQI	Kidney Disease Outcomes Quality Initiative
KFT	kidney function test
KUB	kidney, ureter and bladder
LFT	liver function test
LN	lupus nephritis
MAP	mean arterial pressure
MBD	mineral and bone disorder
MCD	minimal change disease
MDRD	modification of diet in renal disease
MMF	mycophenolate mofetil
MSU	mid stream Urine
MMF	mycophenolate mofetil
MSSA	methicillin sensitive *Staphylococcus aureus*
MRSA	methicillin resistant *Staphylococcus aureus*
NSAID	non-steroidal anti-inflammatory drugs
PCP	*Pneumocystis carinii* (*P. jiroveci*) pneumonia
PCR	protein creatinine ratio
PD	peritoneal dialysis
PET	peritoneal equilibrium test
PMN	polymorphonuclear neutrophils
PSA	prostate specific antigen
PSGN	post-streptococcal glomerulonephritis
RBC	red blood cells
RIFLE	Risk, Injury, Failure, loss of Kidney function, and End stage kidney disease
RME	routine and microscopic examination
RPGN	rapidly progressive glomerulonephritis
RRT	renal replacement therapy
SCr	serum creatinine
SLED	slow and low efficient dialysis
TORCH	toxoplasmosis, rubella cytomegalovirus, herpes

	simplex, and HIV
TLC	total leukocyte count
TSAT	transferrin saturation
tPA	tissue plasminogen activator
UF	Ultrafiltration
UPCR	urinary protein creatinine ratio
USG	ultrasonography
UTI	urinary tract infection
VZV	varicella zoster virus

CHAPTER 1. Glomerulonephritis

1.1. Background

Glomerulonephritis (GN) is the disease of glomerulus with variable clinical presentations ranging from asymptomatic urinary abnormalities to fulminant acute kidney injury (AKI) and chronic kidney disease (CKD). Due to lack of regular health check-ups, many of these asymptomatic patients in developing countries land up in the late stage with bilateral contracted kidneys needing urgent lifesaving renal replacement therapy. Early recognition and treatment of GN will not only increase the chance of cure of the disease but it will also retard the progression of CKD and delay the need for RRT.

1.2. Definition

Glomerulonephritis (GN) is a group of diseases of the glomerulus (from where blood gets filtered to form urine) due to abnormal immunological mechanisms from unknown etiology (primary) or known etiology (secondary) like infection, drug, malignancies, genetic or inherited disorder and multisystem disorder including collagen vascular diseases.

1.3. Clinical features

The common symptoms and signs of GN are:

- Frothy urine
- Puffy face and dependent edema
- Oliguria
- Frank hematuria and
- Hypertension

GN is invariably associated with abnormal urinary findings like proteinuria and/or hematuria (macroscopic or microscopic) that are usually persistent. Hematuria is usually accompanied by pyuria. Therefore, any patient with proteinuria, hematuria and pyuria needs to be evaluated for GN after excluding urinary tract infection and urological conditions like stone disease and uroepithelial malignancies.

Clinically the presentation of GN can be grouped broadly into:

Asymptomatic proteinuria with or without hematuria

This abnormal urinary finding isdetected on routine urine analysis during health check-up or evaluation of other health problems. These patients have normal kidney function with non-nephrotic range proteinuria with or without hypertension and it is the presentation of almost all GN. Frank hematuria that is recurrent and intermittent can also be due to a specific type of GN.

Acute nephritic presentation

Abrupt onset of edema (usually puffy face) with hematuria (microscopic or macroscopic), proteinuria, edema, azotemia and hypertension. This is the presentation of proliferative GN with active inflammation and might lead to a rapid deterioration of kidney function.

Nephrotic syndrome

Gradual onset of edema with nephrotic range proteinuria (>3.5 gm/1.73m^2/24 hours in an adult or >40 mg/m^2/h in children), hypoalbuminemia, hyperlipidemia with or without hypertension and renal impairment. It is the presentation of proliferative and non-proliferative GN.

Rapidly progressive GN

Here, GN manifests as a rapid rise of creatinine with active urinary sediments and features of acute kidney injury like oliguria, fluid overload, uremia, acidosis and hyperkalemia. It is mainly the presentation of active proliferative GN due to development of crescentic GN.

Chronic GN (CGN)

Irreversible damage of kidney due to GN with loss of kidney function that is persistent and is diagnosed by incidental findings on kidney health check-up, or during evaluation of hypertension or clinical features of CKD. They invariably will have proteinuria with or without hematuria and hypertension.

Hypertension

Evaluation of hypertension and its complications help to diagnose the presence of GN and these patients have abnormal urinary findings with or without renal impairment.

1.4. Investigations

The investigation in a patient with GN will confirm the diagnosis, find out the cause and detect the severity of proteinuria and renal impairment.

Following are the list of investigations:

- Urine routine examination - to confirm GN by the presence of persistent proteinuria, dysmorphic RBC, RBC cast and accompanied pyuria.
- Urine C/S - to diagnose infection and exclude GN.
- 24-hour urinary proteinuria or urinary protein creatinine ratio (UPCR). It will detect the severity of proteinuria.
- Kidney function test and serum electrolytes - urea, creatinine, sodium, potassium, chloride and bicarbonate.
- Blood sugar - to exclude diabetes mellitus as the cause of proteinuria.
- Total protein, serum albumin and fasting lipid profile - to diagnose nephrotic syndrome.
- Serological tests – HBsAg, Anti HCV, HIV, ANA, Anti-dsDNA, C3, C4, ANCA (cand p) and Anti GBM antibody.
- Ultrasound abdomen – it will describe the number of kidney, their location, size and echogenicity and exclude the urological disease and any abnormalities in the urinary tract.
- Kidney biopsy - except in children with nephrotic syndrome and clinically confirmed post-streptococcal GN (PSGN), kidney biopsy should be performed in all patients with glomerular proteinuria and hematuria for histopathological diagnosis of GN. It should be performed only by an experienced nephrologist. The kidney biopsy sample should be obtained for light microscopic,

immunofluorescence and electron microscopic examination for complete diagnosis.

1.5. Treatment

The objectives of treatment of GN with any presentation are to:

- Relieve symptoms
- Cure the disease with an improvement of renal function and remission of proteinuria
- Control blood pressure if hypertensive
- Retard the progression of CKD and delay ESKD if CGN is already established

***Treatment can be divided into two broad headings**:*

- General treatment
- Specific treatment

1.5.1. General Treatment

It depends upon the clinical presentation.

All patients with GN, except Minimal Change Disease (MCD),should be prescribed angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEI) unless contraindicated (low blood pressure, hyperkalemia or possibility of hyperkalemia in patients with severe renal impairment). They have renoprotective benefit beyond antihypertensive and antiproteinuric effect.

1.5.1.1. Asymptomatic proteinuria

The main target of treatment of this presentation is to reduce proteinuria and control of blood pressure. The prognosis of primary GN with this presentation is excellent and does not need immunosuppressive therapy.

The treatment include:

- ACEI or ARB
- Control of blood pressure (≤130/80 mmHg), if hypertensive.
- Regular follow up:
  - Three monthly (initially).
  - Six monthly (later, if stable)

- Anytime (if they develop swelling of the body, or decreased urine output or have frank hematuria).

1.5.1.2. Acute nephritic syndrome

All patients with this presentation should be admitted, as there is a possibility of uncontrolled hypertension and its complications (particularly in children with post-streptococcal GN) and rapidly progressive GN (RPGN).

The basic treatment include:

- Diuretics
- Antihypertensives (As these patients might be developing RPGN, ACEI/ARB are **NOT** the first choice unless renal function is stable and daily renal function is advisable).

1.5.1.3. Nephrotic syndrome

- Diet - low salt and low-fat diet (avoid egg yolk, meat fat and ghee) with fluid restriction of <1000 ml/24 hours and potassium restriction if renal impairment is present.
- Diuretics - high ceiling diuretic is the first choice. It is started with low dose and is gradually increased. If diuresis is not effective, metolazone is added followed by potassium-sparing diuretics in patients with normal renal function.
- Inj. 20% salt-poor human albumin – 50 to 100 ml IV infusion daily within 4 hours if severe hypoalbuminemia and anasarca is intractable and not responding to diuretic therapy.
- ACEI/ARB – as stated above (1.5.1).
- Lipid-lowering agent – add atorvastatin or rosuvastatin 10-20 mg daily at bedtime depending upon the severity of dyslipidemia and add fenofibrate if hypertriglyceridemia is present. Children with nephrotic syndrome and steroid-sensitive MCD in adults should not be prescribed lipid-lowering agent as they are expected to cure soon with specific (prednisolone) therapy.
- Treatment of complications – common complications of NS are infection and thromboembolism. Prophylactic therapy for these complications is not necessary and they should be treated if

present. However, Idiopathic Membranous Nephropathy (iMN) with markedly reduced serum albumin [<2.5 g/dl (<25 g/l)] should be treated with oral anticoagulation (warfarin) and/or heparin.

1.5.1.4. Rapidly progressive GN (RPGN)

Early recognition and treatment of this form of presentation is essential for both patient and renal survival.

All patients are admitted and evaluated daily for urine output, renal function test and other symptomatology. They should be treated timely with renal replacement therapy as in any other severe acute kidney injury for the survival of a patient.

All investigations including kidney biopsy to find out the cause should be performed in time and specific therapy including plasmapheresis (if necessary) should be started as early as possible without waiting for kidney biopsy report.

If the treatment is delayed, these patients may develop ESKD within weeks to months contradicting other presentation of GN where ESKD develops after years.

Treatment include:

- First line: Inj. Methylprednisolone 1 gm in 100 ml normal saline over one hour daily for three days followed by oral prednisolone 1 mg/kg body weight/day after morning meal is the first line universal treatment for RPGN due to any causes.
- Second line: Cyclophosphamide (oral or pulse) depending upon the cause and availability except in lupus nephritis where Mycophenolate mofetil can be used.

1.5.1.5. CGN

The treatment of CGN also includes ACEI/ARB to reduce proteinuria and adequate control of blood pressure. Once there is glomerular sclerosis, tubular atrophy and interstitial fibrosis in >50% of the biopsy sample or ultrasound shows increased echogenicity of grade 3 or 4 with loss of corticomedullary differentiation irrespective of the

kidney size, the patient should be treated in the line of CKD protocol (Chapter 3).

1.5.2. Specific treatment

Specific treatment is given in patients with glomerulonephritis with nephritic syndrome, nephrotic syndrome and RPGN in order to cure active inflammation and promote renal survival.

Specific treatment should be started only after confirmation of the cause and histopathological type of glomerulonephritis except in children with nephrotic syndrome and RPGN, that needs to be treated as early as possible as mentioned above. Moreover, etiology of RPGN as evidenced by serological test and other clinical manifestations can dictate the treatment of RPGN and its cause even without biopsy report.

Table 1. Definition of terms used in idiopathic nephrotic syndrome in adults and children

Term	Definition	
	Adults	**Pediatrics**
Relapse	Proteinuria ≥3.5 g/day occurring after complete remission obtained for >1 month	Albu-stix 3+ or proteinuria > 40 mg/m^2/hr occurring on 3 days within 1 week
Frequently relapsing	>2 relapses within 6 months	>2 relapses within 6 months
Complete remission	Reduction of proteinuria to ≤0.2 g/day and serum albumin >3.5 mg/dl	<4 mg/m^2/hr on at least 3 occasions within 7 days; serum albumin >3.5 mg/dl
Partial remission	Reduction of proteinuria to between 0.21 g/day and 3.4 g/day ± decrease in proteinuria of ≥50% from baseline	Disappearance of edema; increase in serum albumin >3.5 mg/dl and persisting proteinuria >4 mg/m^2/hr or 100 mg/m^2/day
Steroid resistant	Persistence of proteinuria despite prednisone therapy, 1 mg/kg/day for 4 months	Persistence of proteinuria despite prednisone therapy, 60 mg/m^2 for 4 weeks
Steroid dependent: nephrotic syndrome recurs when therapy stopped or decreased	Two consecutive relapses occurring during therapy or within 14 days of completing corticosteroid therapy	Two relapses of proteinuria within 14 days after stopping or during alternate day corticosteroid therapy

1.5.2.1. Treatment of children with Nephrotic Syndrome

As most of the children with nephrotic syndrome suffer from minimal change disease, the treatment should be initiated immediately as follows:

First episode of Nephrotic Syndrome

- Tab. Prednisolone 2 mg/kg/day after morning meal daily for 6 weeks followed by 1.5 mg/kg on alternate days for another 6 weeks.
- Then taper gradually by 5 mg per week.
- Steroid-sensitive nephrotic syndrome in children should respond by 4 weeks and complete remission by 8 weeks.
- If there is no complete remission of proteinuria even by 8 weeks, they should be labelled as steroid-resistant nephrotic syndrome.

Steroid-dependent nephrotic syndrome

- Steroid-sparing agents like levamisole 2.5 mg/kg on alternate days for 9-12 months, or
- Cyclophosphamide 2 mg/kg/day for 3 months (Maximum cumulative dose-168 mg/kg) and Cyclophosphamide should be started after remission with corticosteroids.
- If proteinuria relapses even after these treatments, third-line therapy with calcineurin inhibitor, preferably Cyclosporine should be considered.

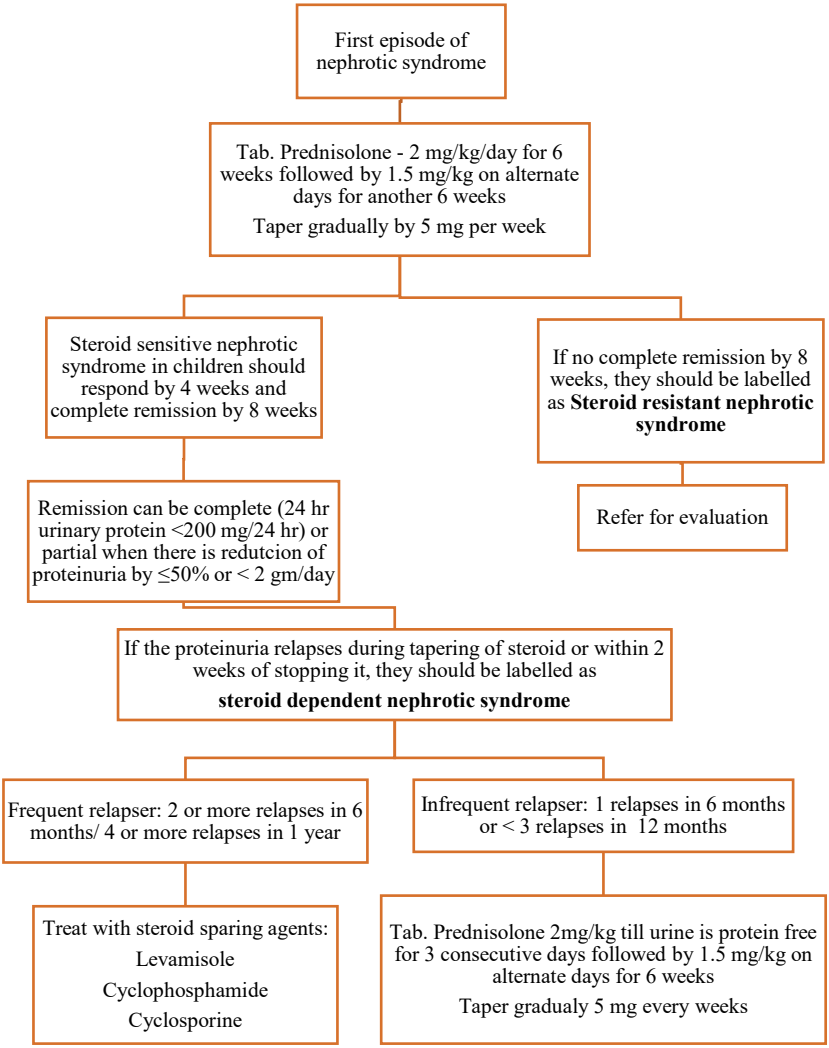

Figure 1. Treatment algorithm for Nephrotic Syndrome (Children)

1.5.2.2. Treatment of Minimal Change Disease in Adults

The first episode of nephrotic syndrome

- Tab. Prednisolone1mg/kg/day for 4 weeks (if complete remission) to 16 weeks (if complete remission is not achieved) and then tapered slowly over 6 months after achieving remission.

Infrequent relapse: same as above.

Frequent relapse and steroid-dependent minimal change disease:

- Tab. Cyclophosphamide 2 - 2.5 mg/kg/day for 12 weeks.
- For patients who relapse despite using cyclophosphamide or if contraindicated, a calcineurin inhibitor (CNI) should be started. Tab. Cyclosporine 3 - 5 mg/kg/day or Tab. Tacrolimus 0.05 - 0.1 mg/kg/day in 2 divided doses for 1-2 years. *(Please check blood level of cyclosporine and tacrolimus)*
- If CNIs or cyclophosphamide is contraindicated then MMF 500-1000 mg twice daily for 1-2 years should be considered.

Steroid-resistant MCD - Needs further evaluation for another causes of nephrotic syndrome.

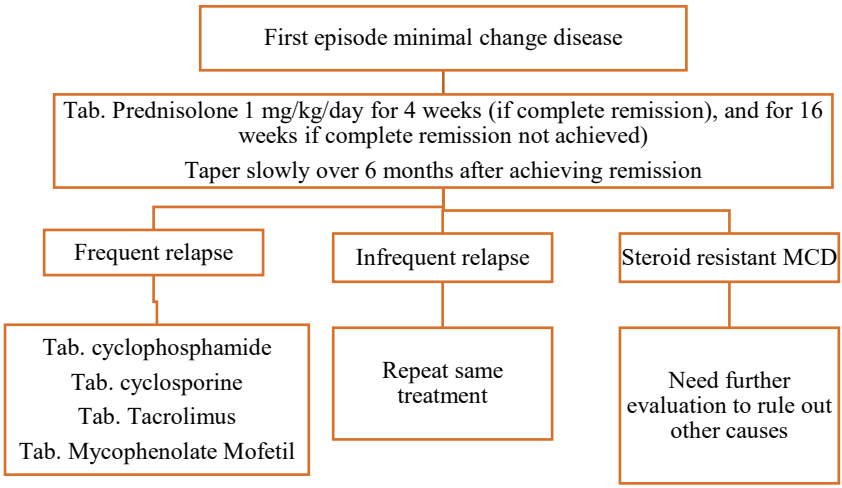

Figure 2. Treatment algorithm for Minimal Change Disease (Adults)

1.5.2.3. Treatment of Focal Segmental Glomerulosclerosis (FSGS)

Secondary causes of FSGS should be excluded in all patients.
Specific treatment should be initiated only in patients with FSGS with nephrotic syndrome.

First episode of Nephrotic syndrome

Tab. Prednisolone 1 mg/kg/day once daily after morning meal for 4-16 weeks or till remission (whichever is earlier) and then tapered over 6 months after remission.
If corticosteroid is contraindicated, CNI should be the initial treatment.

Treatment of relapse is same as per MCD relapse.

Treatment of steroid-resistant FSGS

- CNI with low dose prednisolone are the drugs of choice for these patients.
  - Tab. Cyclosporine 3-5 mg/kg/day (initial target trough levels 125 – 175 ng/ml [104–146 nmol/l]) for 4 - 6 weeks and in case of partial or complete remission treatment should be continued for 1 year and then slowly tapered by 25% in every 2 months and if no remission by 6 months, cyclosporine treatment should be discontinued.

    OR

  - Tacrolimus 0.1 – 0.2 mg/kg/d in two divided doses (initial target trough levels 5 – 10 ng/ml [6–12 nmol/l]) may also be used similarly as cyclosporine.
- Prednisone 0.15 mg/kg/d has to be added for 4 – 6 months, then tapered off over 4 – 8 weeks.
- In patients with steroid resistant FSGS and not tolerating CNI, MMF and dexamethasone can be used.

1.5.2.4. Treatment of IgA Nephropathy (IgAN)

- ARB/ACEI, at the maximum tolerated dose, is the initial first-line therapy in patients of IgAN with target blood pressure of <130/80 mmHg in order to achieve proteinuria of <1g/day.
- Patient with proteinuria >1 g/day, despite 3 – 6 months of optimized supportive care and GFR >50 ml/min per 1.73 m^2, is treated with a 6-month course of corticosteroid therapy.
- Second line immunosuppressive therapies are not advocated in IgA nephropathy.
- Omega-3 free fatty acid (fish oil) are also found to have a beneficial effect in IgA nephropathy.
- IgA nephropathy with crescentic GN should be treated with Inj. Methylprednisone 1 gm IV daily for 3 days followed by Tab. Prednisolone 1 mg/kg daily after morning meal for 2 months with gradual tapering and Tab. Cyclophosphamide 2 mg/kg daily for 3 months.

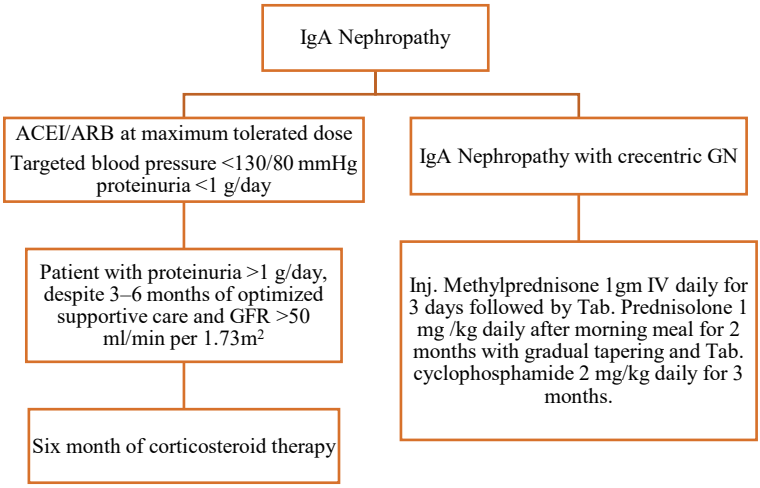

Figure 3. Treatment algorithm for IgA nephropathy

1.5.2.5. Treatment of Henoch – Schönlein Purpura (HSP) Nephritis

- Do not use corticosteroids to prevent HSP nephritis.
- Persistent proteinuria of >0.5 - 1 g/d/1.73 m^2: ACEIs/ARBs.
- Persistent proteinuria of >1 g/d/1.73 m^2 with eGFR >50 ml/min after initial ACEI/ARB therapy: 6-month course of corticosteroid therapy similar to IgA nephropathy.
- Crescentic HSP with nephrotic syndrome and/or deteriorating kidney function are treated the same as for crescentic IgAN.

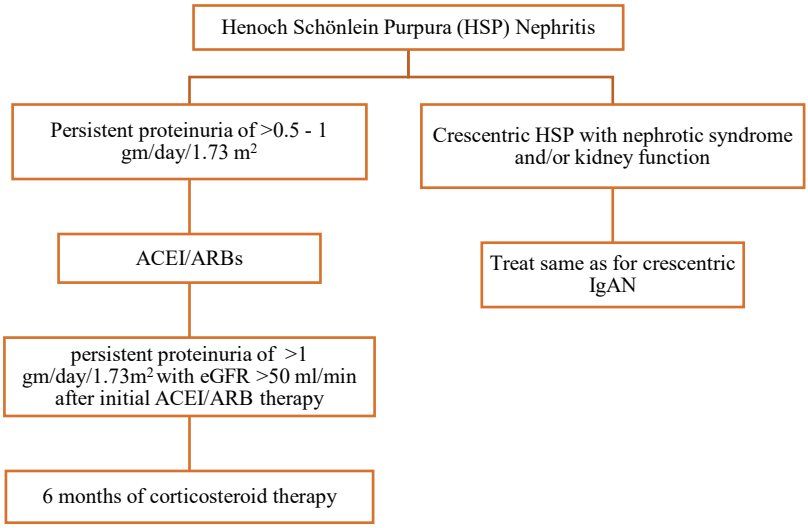

Figure 4. Treatment algorithm for Henoch Schönlein Purpura (HSP) nephritis

1.5.2.6. Treatment of Membranoproliferative GN

Membranoproliferative GN (MPGN) is now considered as the pattern of injury as it can be present in multiple diseases like lupus, plasma cell dyscrasia, complement disorder and infection associated GN.

The specific treatment of MPGN depends upon the cause irrespective of presentation.

After exclusion of secondary causes, idiopathic MPGN with nephrotic syndrome should be treated with prednisolone 1 mg/kg/day after morning meal for 1 - 2 months and tapered slowly over 6 months.

If there is no remission of proteinuria or progressive decline of kidney function, oral cyclophosphamide 2 mg/kg or MMF 1 - 2 gm/day in 2 divided dosage needs to be added.

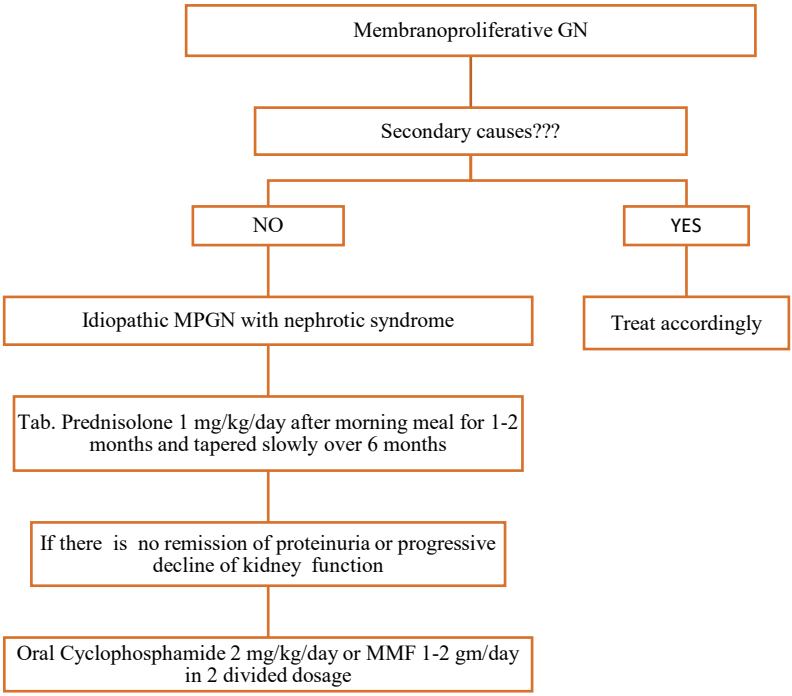

Figure 5. Treatment algorithm for MPGN

1.5.2.7. Treatment of Membranous Nephropathy

After exclusion of secondary causes, idiopathic membranous nephropathy with nephrotic syndrome should be treated as follows:

- 24 hours urine total protein upto 4 gm with normal kidney function.
  - Treat with ACEI/ARBs with adequate control of blood pressure.
- 24 hours urine total protein of 4 - 8 gm with normal kidney function.
  - Treat with ACEI/ARBs for 6 months.
- Any range of proteinuria with renal impairment, 24 hours urine total protein ≥ 8 gm at presentation or patients with persistent proteinuria of 4-8 gm after 6 months of ACEI/ARBs
  - Treat with Modified Ponticelli regimen consisting three pulses of immunosuppressives.

  Each pulse consists of Inj. Methylprednisolone 1 gm IV daily for 3 days followed by Tab. Prednisolone 0.5 mg/kg/day for 27 days followed by Tab. Cyclophosphamide 2 mg/kg/day for another 30 days.
- After complete remission, the patient should continue ACEI/ARB.
- After partial remission also, the patient should continue ACEI/ARB for another 6 months.
- If the patient doesn't respond to Modified Ponticelli regimen or achieves partial remission with the regimen and proteinuria persists even after 6 months of ACEI/ARB therapy then such patients should be treated with Calcineurin inhibitor (CNI). If CNI shows no improvement, then MMF should be the alternative therapy.
- The first relapse should be treated with the same initial regimen and in the treatment of the second relapse, another immunosuppressant should be considered.

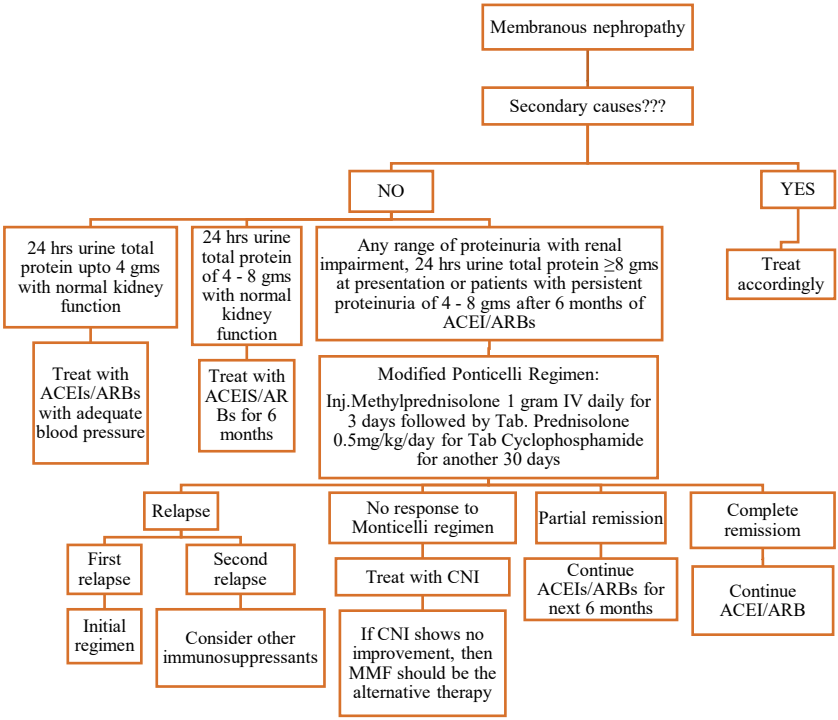

Figure 6. Treatment algorithm for Membranous Nephropathy

1.5.2.8. Treatment of Lupus Nephritis

Treatment of patients with lupus nephritis depends upon clinical presentation, histopathological class and activity/chronicity index in kidney biopsy.

1.5.2.8.1. Class I and II LN:

- With proteinuria <1 g/d - ACEI/ARB and immunosuppressive as dictated by the extra-renal clinical manifestations of lupus.
- With proteinuria >3 g/d-Corticosteroids or CNIs as described for MCD.

1.5.2.8.2. Class III LN (focal LN) and class IV LN (diffuse LN):

- **Induction therapy:** The induction therapy consists of corticosteroids combined with either cyclophosphamide or mycophenolate mofetil for initial 6 months.
  - ***Corticosteroid therapy*** – All patients with rapid rising creatinine with or without oliguria/anuria (RPGN), crescentic GN or high activity index on kidney biopsy should be treated with IV Methylprednisolone 500 – 1000 mg in 100 ml normal saline over half an hour daily for three days followed by oral prednisolone 1 mg/kg/day for at least one month and tapered gradually. Remaining patients with non-nephrotic proteinuria, nephrotic syndrome and the nephritic syndrome with low activity index can be treated with oral prednisolone 1 mg/kg/day as an induction agent and tapered gradually after 1 month.
  - ***Immunosuppressive therapy*** – All patients with Lupus Class III and IV should also be treated with either pulse intravenous cyclophosphamide (CYA) (0.5 – 1 g/m^2) monthly for six months or MMF (1 – 2 gm) daily in two divided dosages for six months as an induction therapy and if patients show worsening LN (rising serum creatinine or worsening proteinuria) during the first 3 months of treatment, change of immunosuppressive to an alternative agent (CYA

to MMF and MMF to CYA) has to be done and repeat kidney biopsy to be performed to guide further treatment.

- **Maintenance therapy**– After induction therapy, all patients should continue maintenance therapy for at least two years after complete remission with gradual tapering after 1 year of complete remission. If complete remission has not been achieved after 12 months of maintenance therapy repeat kidney biopsy has to be performed and if proteinuria or kidney function deteriorates during maintenance therapy, treatment has to be increased to the previous level of immunosuppression that controls the activity of LN.
  - The maintenance therapy includes low dose steroid and immunosuppressive drugs.
  - Steroid – low dose oral prednisolone (<10 mg) daily after the morning meal.
  - Immunosuppressives – following are the drugs for maintenance therapy.
    - Inj. Cyclophosphamide (500 – 1000 mg/m^2) every 3 months for total 6-8 dosage.
    - Mycophenolate mofetil (1 – 2 g/d in 2 divided doses)
    - Tab. Azathioprine (1.5 – 2.5 mg/kg/d)
    - CNIs with low-dose corticosteroids is used for maintenance therapy in patients who are intolerant of MMF and azathioprine.

1.5.2.8.3. Class V LN (membranous LN):

- Non-nephrotic proteinuria with normal kidney function – ACEI/ARB with adequate control of blood pressure.
- Nephrotic range proteinuria with or without renal impairment – specific therapy as described for class IV lupus.
- Patients with class V LN, normal kidney function, and non–nephrotic range proteinuria are treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extra-renal manifestations of systemic lupus.

1.5.2.8.4. Class VI LN (advanced sclerosis LN):

No immunosuppressive therapy and should be treated as CKD in general.

1.5.2.8.5. Relapse of LN

Relapse of LN after complete or partial remission should be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. If resuming the original therapy wouldput the patient at risk for excessive lifetime cyclophosphamide exposure, then a non–cyclophosphamide-based initial regimen needs to be used. A repeat kidney biopsy needs to be considered during relapse if there is a suspicion that the histologic class of LN could have changed, or there is uncertainty whether the rising SCr and/or worsening proteinuria represents disease activity or chronicity.

1.5.2.8.6. Treatment of resistant disease

In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, a repeat kidney biopsy should be considered to distinguish active LN from scarring. Patient with worsening SCr and/or proteinuria who continue to have active LN on biopsy should be treated with one of the alternative initial treatment regimens. Non-responders who have failed more than one of the recommended initial regimens may be considered for treatment with rituximab, IV immunoglobulin or CNIs.

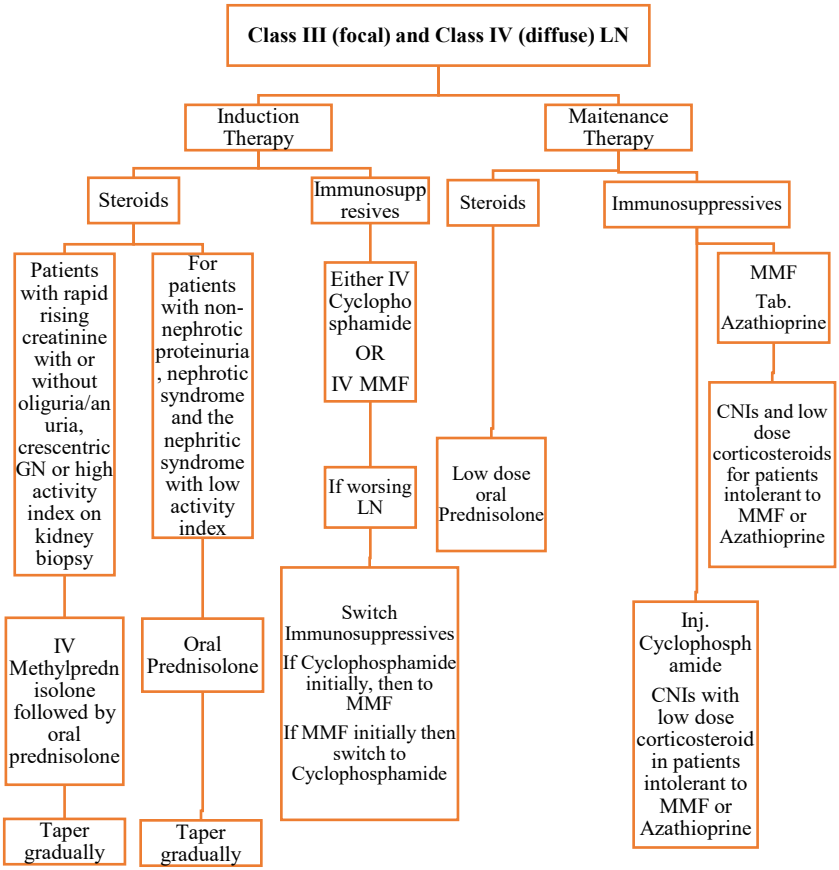

Figure 7. Treatment algorithm for Class III and Class IV LN

1.5.2.9. Treatment of ANCA Associated Pauci Immune Focal and Segmental Necrotizing GN

Induction Therapy

Steroid and immunosuppressive therapy

- ***Corticosteroids***– Inj. Methylprednisolone 500 – 1000 mg IV daily for 3 days followed by oral prednisolone 1 mg/kg /day after morning meal for a minimum of 1 month with gradual tapering over 6 months.
- ***Immunosuppressives*** – Oral Cyclophosphamide 2 mg/kg /day for 12 weeks. Rituximab can be used for patients without severe disease or in whom cyclophosphamide is contraindicated.
- Plasmapheresis – Addition of plasmapheresis in following special patient populations has shown benefit in renal and patient survival.
- Patients requiring dialysis or with rapidly increasing SCr.
- Patients with diffuse pulmonary haemorrhage.
- Patients with overlap syndrome of ANCA vasculitis and anti-GBM GN.

Maintenance therapy

It is initiated once patient achieves at least partial remission and continued for at least 18 months in patients who remain in complete remission. It should not be continued in patients who are dialysis dependent even after 12 weeks of cyclophosphamide therapy and without extra-renal manifestation of the disease.

Agents for maintenance therapy are:

- Azathioprine 1 – 2 mg/kg/d.
- MMF - 1 – 2 gm/day in two divided doses, if patients are intolerant or allergic to azathioprine.
- Trimethoprim-sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease.
- Methotrexate (initially 0.3 mg/kg/week, maximum 25 mg/week) for maintenance therapy in patients intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m^2.

1.5.2.9.1. Treatment of relapse

- Patients with severe relapse of ANCA vasculitis (life- or organ-threatening) – Treatment is the same as initial therapy.
- Other relapses of ANCA vasculitis – Reinstitution of immunosuppressive therapy or increase in its intensity with agents other than cyclophosphamide, including instituting or increasing dose of corticosteroids, with or without azathioprine or MMF.

1.5.2.9.2. Treatment of resistant disease

- Addition of rituximab if resistant to induction therapy with cyclophosphamide and corticosteroids.
- IV immunoglobulin or plasmapheresis may be used as alternatives.

1.5.2.9.3. Monitoring

Immunosuppressive should not be changed based on ANCA titer alone.

1.5.2.9.4. Transplantation

Transplantation has to be deferred until patients are in complete extra-renal remission for 12 months and it should not be deferred if patients are in complete extra-renal remission but are still ANCA-positive.

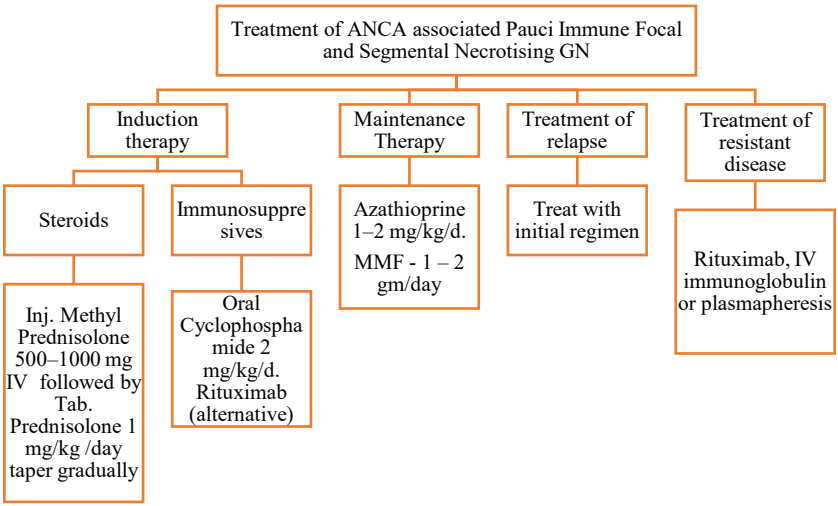

Figure 8. Treatment algorithm for ANCA associated Pauci Immune Focal and Segmental Necrotising GN

1.5.2.10. Treatment of Anti Glomerular Basement Membrane Antibody GN

- ***Corticosteroids***– Inj. Methyl Prednisolone 0.5 - 1 gm daily IV for three days followed by oral prednisolone 1 mg/kg daily with gradual tapering after 1–2 months and to be continued up to six months.
- ***Immunosuppressives***- Oral cyclophosphamide 2 mg/kg daily for 12 weeks
- ***Plasmapheresis*** - To all patients except
  - Those who are dialysis-dependent at presentation
  - Those who have 100% crescents in an adequate kidney biopsy sample
  - Those who do not have a pulmonary hemorrhage.

Special precautions

- ***Start*** treatment 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.
- Defer kidney transplantation after anti-GBM GN until anti-GBM antibodies have been undetectable for a minimum of 6 months.

1.5.2.11. Infection-related Glomerulonephritis

No immunosuppressive treatment for post-infectious or infection related GN. Treatment of infection itself cures the GN except for patients with HCV and mixed cryoglobulinemia (IgG/IgM) with nephrotic proteinuria or evidence of progressive kidney disease or an acute flare of cryoglobulinemia are to be treated with plasmapheresis, rituximab, or cyclophosphamide, in conjunction with IV Methylprednisolone, and concomitant antiviral therapy.

CHAPTER 2. Acute Kidney Injury

2.1. Background

Acute kidney injury (AKI), previously known as acute renal failure (ARF), is an abrupt but usually reversible decline in glomerular filtration with retention of metabolic waste products and derangement of electrolytes and acid-base balance in hours to days. A patient with AKI has increased morbidity and mortality. It is a common, harmful but is a preventable condition in most instances. It complicates ~5% of hospital admissions and 30% of ICU admissions. Mortality rate is about 25 - 80% (In-hospital mortality rate: 40 - 50%; ICU mortality rate: 70 - 80%).

Even mild, reversible AKI has important clinical consequences so early detection and treatment may improve the outcome of AKI. Treatment of AKI depends on underlying etiology and it may need temporary renal replacement therapy like dialysis. Following flowchart describes how AKI especially community-acquired can be managed in resource-poor countries like ours.

Table 2. Flowchart showing management of community acquired AKI

Risk Assessment	Recognition	Response	Renal Support	Rehabilitation
Susceptibilities **Risk factors**	KDIGO Definition Staging	Fluids Inotropes Medication review referral	Hemodialysis	Follow up Recovery Quality of life

There are two types of AKI namely Community-acquired and Hospital-acquired. There is a movement by International Society of Nephrology (ISN) to decrease mortality of AKI (community acquired) to zero by 2025, in short also known as '0 by 25'.

This protocol will cover staging, etiology, recognition of risk factors, diagnosis, treatment and prevention of AKI.

2.2. Definition

AKI is now defined as any of the following based on the serum creatinine and/or urine output.

- Increase in SCr by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hrs;

OR

- Increase in SCr to ≥1.5 times baseline, within prior 7 days;

OR

- Urine volume is <0.5 ml/kg/h for 6 hours.

2.3. Staging of AKI

There are many ways of staging of AKI, like RIFLE and AKIN, but nowadays to make uniformity a different staging has been proposed by KDIGO in 2012.

Table 3. KDIGO staging of AKI

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline ***OR*** ≥0.3mg/dl (≥26.5 µmol/l) increase	< 0.5 ml/kg/hr for 6-12 hrs
2	2.0-2.9 times baseline	<0.5 ml/kg/hr for ≥ 12 hrs
3	3.0 times baseline ***OR*** Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 µmol/l) ***OR*** Initiation of renal replacement therapy **OR** In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/hr for ≥24 hrs ***OR*** Anuria for ≥12 hrs

- Be aware, even a patient with normal creatinine may have AKI by definition.
- Creatinine depends on age, sex, muscle mass.
- Creatinine clearance is usually calculated in a steady state condition.

2.4. Etiologies of AKI

It can be divided into pre-renal, intrinsic renal and post-renal as shown in the figure below. In managing the case of AKI, knowing an etiology is very important, as the treatment is different depending upon the etiology.

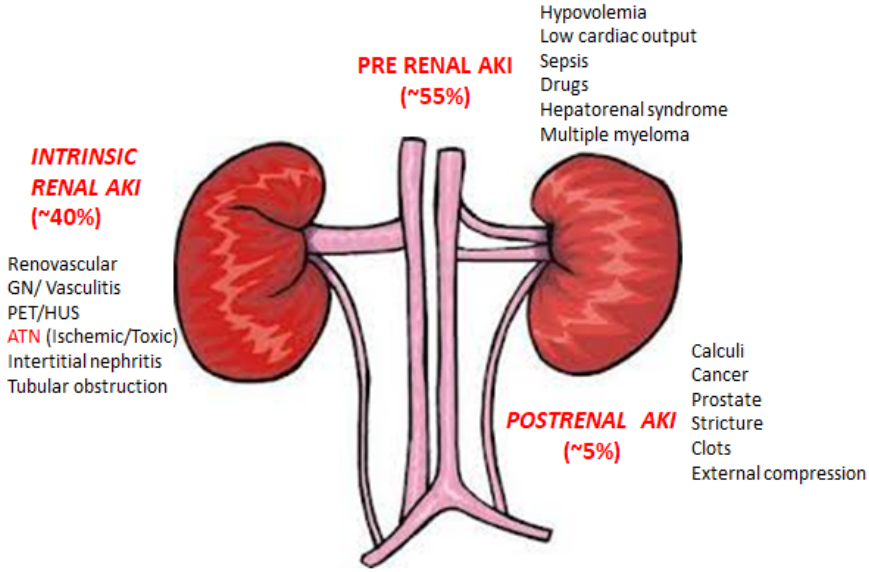

Figure 9. Etiologies of AKI

Special questions to be asked to find out the etiology in history

- Ingestion of nephrotoxic drug including herbals.
- History of trauma or unaccustomed exertion.
- Evidence of connective tissue disorders.
- Exposure to toxic substances/ heavy metals.

2.5. Identification and managing risk factors and stressors

2.5.1. Risk factors and stressors for acquiring AKI

Table 4. Risk factors and stressors for acquiring AKI

Comorbidity	Kidney stressor
Age >65 years Diabetes mellitus Cirrhosis/hepatic failure Heart failure CKD eGFR <60 ml/min/1.73m^2 Albuminuria: Glomerular disease, renal transplant recipient Protein/calorie malnutrition Oliguria	Sepsis/shock/hypoxemia Volume depletion Cardiopulmonary bypass Exposure of nephrotoxic drugs (vancomycin, gentamycin, NSAIDs, ARB ACEI, cisplatin/carboplatin, methotrexate) Iodinated contrast Invasive mechanical ventilation Multiorgan failure

All patients with above risk factors as shown in table particularly those who are acutely ill, undergoing surgery or getting intravascular iodinated contrast agents should be evaluated for development or worsening of AKI.

2.5.2. Assessment of CKD patients with risk factors

- Monitor urine output strictly; if possible hourly.
- Monitor serum creatinine regularly (daily or alternate days) and compare with previous report.
- Calculate eGFR.
- Correct hypotension based upon the etiology of it; maintain MAP of 65 - 70 mmHg.
- Identify the cause of AKI.
- Avoid nephrotoxic drugs.

Methods to calculate eGFR:

* Cockcroft-Gault equation

CrCl, mL/min ={((l40–age) x weight)/(72xSCr, mg/dL)}x 0.85 (if female)

* Modification of diet in renal disease study (MDRD)

GFR = 186 × Serum Cr$^{-1.154}$ × age$^{-0.203}$ × 1.212 (if patient is black) × 0.742 (if female)

* CKD-EPI

CKD-EPI creatinine = A X $(Scr/B)_C$ X 0.993^{age} X (1.159 if black), where A, B and C are the following:

Female		**Male**	
Scr ≤ 0.7	A = 144 B = 0.7 C = -0.329	Scr ≤ 0.9	A = 141 B = 0.9 C = -0.411
Scr> 0.7	A = 144 B = 0.7 C = -1.209	Scr> 0.9	A = 141 B = 0.9 C = -1.209

In adults having iodinated contrast agents

Before offering iodinated contrast agents to adults for emergency or non-emergency imaging, assess their risk of AKI by calculating eGFR. Increased risk is associated with:

- CKD (eGFR ≤60 ml/min/1.73 m^2)
- Diabetes but only with CKD (eGFR <60 ml/min/1.73 m^2)
- Heart failure
- Renal transplant
- Age ≥65 years
- Hypovolaemia
- Contrast agents (increasing volume of contrast agent or intra-arterial administration of contrast agent)

- Drugs (NSAIDs, metformin, ACE inhibitors, ARBs, diuretics)

Ensure that risk assessment does not delay emergency imaging and surgery!

2.5.3. Risk scores for prediction of AKI

Positive and negative predictive values in the validation cohort were 32 and 95, respectively. Thus, using this model, 32% of patients with score ≥5 points are likely to develop AKI within 48 hours; 95% of patients with score <5 points are unlikely to develop AKI.

Table 5. Risk scores prediction of AKI

	Risk factor	Points
Chronic	Chronic kidney disease	2
	Chronic liver disease	2
	Congestive heart failure	2
	Hypertension	2
	Atherosclerotic coronary vascular disease	2
Acute	pH ≤7.30	3
	Nephrotoxic exposure	3
	Severe infection/sepsis	2
	Mechanical ventilaltion	2
	Anemia	1

2.6. Investigations to be done in AKI

- Kidney function test (KFT: urea, creatinine, sodium, potassium ± chloride and bicarbonate)
- Urine RME
  - Muddy brown cast
  - RBC cast
  - WBC cast
- ProteinuriaUSG of KUB
- ABG

- Other supporting investigations:
  - CBC, panculture and other specific tests to identify the source of infection
  - Serum calcium, phosphorus, albumin, uric acid
  - CPK-total, LDH,
  - HBsAg, Anti HCV and HIV I/II
  - BT/CT/PT-INR
  - ANA, dsDNA, complement levels and ANCA if vasculitis is suspected
  - Urine for Bence Jones protein and serum protein electrophoresis
  - ECG, echocardiogram

2.7. Complications of AKI

- Fluid overload, pulmonary edema
- Uremic conditions
  - Uremic encephalopathy
  - Uremic pericarditis
  - Uremic gastropathy
- Metabolic acidosis
- Hyperkalemia

Do not wait for complications to develop!

2.8. When should a patient be referred to a nephrologist?

Discuss the management of AKI with a nephrologist as soon as possible and within 24 hours of diagnosis when one or more of the following is present:

- A possible diagnosis that may need specialist treatment (for example, vasculitis, glomerulonephritis, tubulointerstitial nephritis, myeloma)
- AKI with no clear cause
- Inadequate response to treatment

- Complications associated with AKI
- Stage 3 AKI
- Renal transplant patient
- CKD stage 4 or 5

Early recognition and early referral may avoid RRT

2.9. Treatment of AKI

Once AKI is established, every effort should be applied to reverse it by removing the precipitating factors and to stop the progression. We should look for the complications of AKI. Sometimes we may have to perform renal replacement therapy.

Treatment of AKI depends upon the etiology. Fore and foremost thing to do is to treat the etiology.

Evaluate carefully for the reversible causes.

2.10. Management of AKI

- General Management
- Treatment of specific causes
- Treatment of complications

2.10.1. General management

- Strict intake and output charting
- Daily weighing
- Stop nephrotoxic drugs
- Maintain fluid and nutrition

2.10.2. Treatment of specific causes

2.10.2.1. In hypovolemic shock

- Patient may present with:
  - History suggestive of fluid loss, bleeding or third space loss like in acute pancreatitis may be present
  - Thirst
  - History of decreased urine output

- Signs of dehydration
- Tachycardia, hypotension and postural drop of blood pressure

- CVP can be used to assess but is not reliable. If available USG can be used to look at the inferior venacava for fluid status. Besides test like elevating a leg-end of the bed to observe whether BP rises can be handy sometimes.
- Maintain fluid status by giving normal saline boluses and assess for the reversal of dehydration. Use inotropic agents if necessary to increase the blood pressure.
- Transfuse blood if hypovolemia is due to bleeding.
- Maintain MAP 65 - 70 mmHg.

2.10.3. In sepsis

- Follow sepsis bundle and remove the source of the sepsis.
- Be cautious with the antibiotics and its dosing. The dose should be adjusted as per the creatinine clearance. However, the loading dose can be given at its usual dose.

2.10.4. In obstructive uropathy

- Patient may complain of abdominal or flank pain, hesitancy and dribbling of urine. There may be palpable bladder and may have hematuria if stone is present. Painless hematuria may signify malignancy.
- Once confirmed with the help of USG KUB; catheterization should be done and urgent urological consultation should be done.

2.10.5. Other causes

- Thorough evaluation and treatment of the underlying conditions have to be addressed. Treatment will direct towards the underlying causes e.g. hepatorenal syndrome, rhabdomyolysis, cardiorenal syndrome, vasculitis.

2.11. Treatment of complications

Management of intravascular volume overload

- Salt (1 - 2 g/d) and water (usually <0.5 - 1 L/d) restriction
- Diuretics
- Ultrafiltration or dialysis

2.11.1. Conservative treatment of hyperkalemia

- In all patients with AKI, potassium in infusion and medications and potassium sparing diuretics should be avoided as much as possible.
- Dietary potassium intake should be restricted to approximately 2 gm daily.
- Patients who have severe hyperkalemia (defined as K^+ >6.5 mEq/L) or rapidly rising serum potassium should not receive any dietary potassium until hyperkalemia is addressed (either by diaysis or by medical therapy).
    - Immediate therapy is warranted if electrocardiographic changes or peripheral neuromuscular abnormalities are present, regardless of the degree of hyperkalemia.
    - Send ABG and ECG and rule out pseudohyperkalemia.
    - Restriction of dietary K^+ intake (usually <40 mmol/d).
    - Eliminate K^+ supplements and K^+-sparing diuretics.
    - Calcium gluconate (10 mL of 10% solution over 5 - 10 min): especially if patient has cardiac features of hyperkalemia; can be repeated till the rhythm is stabilized.
    - Bolus doses of glucose (50 mL of 50% dextrose) and regular insulin (10 units).
    - β_2-agonist (Salbutamol) nebulization.
    - Sodium bicarbonate (usually 50-100 mmol) if patient has metabolic acidosis.
    - Potassium-binding ion exchange resins.
    - Loop diuretics like furosemide and torsemide can decrease the K^+ if patient has good urine output.
    - Hemodialysis (with low K^+ dialysate).

- All patients with AKI and hyperkalemia that is refractory to medical therapy should be dialyzed unless hyperkalemia is mild (i.e. ≤5.5 mEq/L) and the cause of AKI is known to be easily reversed (such as prerenal AKI due to volume depletion or ACE inhibitors or ARBs).
- Among patients who require dialysis, medical therapy of hyperkalemia is often required while dialysis is being arranged.
- Oral potassium-binding resins can be considered in mild hyperkalemia. But make sure that patient is passing stool. DO NOT COMBINE RESIN WITH LACTULOSE.

2.11.2. Management of metabolic acidosis

- Dialyze patients with severe oligo-anuric AKI who are volume overloaded and have severe metabolic acidosis (pH <7.1) regardless of the cause of acidosis.
- Do not dialyze patients with mild organic acidosis (i.e. pH ≥7.1), unless they have another indication. Treatment of such patients is primarily directed at:
  - Reversing underlying causes of excessive acid production (e.g. treatment of sepsis, optimization of ventilation, tissue perfusion and insulin therapy).
  - Administer bicarbonate in the following settings:
    - Non-anion gap acidosis related to diarrhea or other etiologies.
    - Severe organic acidosis (pH <7.1 mEq/L) while awaiting dialysis.
    - When cause of AKI is readily reversible (e.g. prerenal AKI due to volume depletion or obstruction).
    - AKI due to rhabdomyolysis in order to prevent further renal injury (i.e. ATN), provided other indications for dialysis are not present and the patient is not volume overloaded.

Method to calculate HCO_3 deficit

HCO_3 deficit = 0.6 x weight {kg} x (desired HCO_3{mmol/L} - measured HCO_3{mmol/L})
(50% of the amount is corrected immediately and rest slowly over 24 hrs; however, this is only a rough guide so should always check HCO_3 serially)

2.12. Renal replacement therapy (RRT)

In AKI, modes of RRT are either continuous or intermittent. Decision of the initiation of RRT should be done after consultation with the nephrologist.

- Continuous:
  - Peritoneal dialysis (PD)
  - Continuous renal replacement therapy (CRRT)
- Intermittent:
  - Intermittent hemodialysis
  - Slow and low efficient dialysis (SLED)

    Patients of AKI can have unstable cardiovascular status especially those who are admitted in ICU with sepsis. In these group of patients either CRRT, SLED or PD can be considered depending upon the availability of manpower and logistics.

2.12.1. Indications of RRT

RRT can be started as per the discretion of the nephrologist. It does not have any magic numbers at what time it should be started.

- If the patient develops uremic complications or the complications of AKI that could not be managed conservatively.
- RRT can also be used supportively in the context of multiple organ failure.
- Renal supportive therapy:
  - Optimization of fluid balance
  - Nutritional balance
  - Removal of inflammatory markers (CRRT)

- Control of resistant hyperpyrexia

2.12.2. Measures to consider before initiating RRT

- Explain the patient and party about the procedure and it being only supportive treatment.
- High risk consent mentioning the possibilities of complications (especially if the patient's vitals are unstable) and sign the document.
- Send the investigations:
  - Viral markers: HBsAg, Anti HCV and HIV I & II
    - Repeat the viral markers if the center is changed
  - Bleeding profile: Platelet, BT, CT, PT-INR
    - Preferably platelet should be >100,000/cumm
    - INR <2 and BT,CT in a reasonable range
  - Access:
    Preferably right internal jugular vein and use uncuffed double or triple lumen dialysis catheter
    - If expertise is not available or it is difficult to place the catheter in internal jugular choose femoral vein and then as a last resort use subclavian vein.
    - Preferably, to be kept under USG guidance if facility is available.
    - If bleeding profile is deranged; defer the procedure till it can be performed safely.
    - Fresh frozen plasma and/or platelet rich products can be used to reverse the bleeding profile abnormality.
    - Choose femoral vein if bleeding profile is deranged.
    - Check both the lumen for free flow of blood after insertion of catheter.
    - Once catheter is placed in internal jugular or subclavian vein, check CXR should be done prior to initiation of dialysis to rule out the complications like pneumothorax.
    - Arrange fresh packed red cell (preferably) if the patient is anemic (Hb<8 gm%) and transfuse during RRT.

- If the patient is severely anemic then prime with blood to start HD.

2.12.3. Prescription of hemodialysis

Refer to Annex 1.

2.12.4. Prescription for SLED

Refer to Annex 2.

2.12.4.1. Prescription for PD

When there is no provision of hemodialysis, peritoneal dialysis can be used as a modality for treatment of AKI. There are many studies showing that high volume PD and CRRT is equivalent.

- Inspect abdomen for any contraindications for placement of catheter. Make sure urinary bladder is empty.
- Insert PD catheter preferably soft catheter rather than rigid catheter under local anesthesia.
- Prescription: Refer to Annex 3.

When to stop dialysis:

- If patient is clinically improving.
- When urine output is increasing and is ≥1L/24hrs.
- Urea and creatinine is improving without dialysis.
- If the patient is deteriorating other than because of renal cause and is irreversible.
- Decide regarding the removal of catheter, if
  - Patient is passing urine ≥1 Ltr/24hrs.
  - There is stabilization of KFT, either it has come down to normal or close to previous KFT report without RRT.
  - Patient has no complications of uremia.
  - There is a complication related to catheter.

2.13. Nutrition in AKI

Table 6. Nutrition requirement in AK.

Total energy	**20 - 30 Kcal/kg body weight (BW)**		
Carbohydrates	3 - 5 g/kg BW		
Fats	0.8 - 1 g/kg BW		
Proteins	Not on RRT	On RRT	On CRRT
	0.8 – 1 g/kg BW	1 - 1.5 g/kg BW	1.7 g/kg BW

2.14. What should not be done in AKI?

- Do not give diuretics unless patient is volume overloaded.
- Do not use dopamine for renal perfusion purpose.
- Do not delay renal replacement therapy.
- Do not give $NaHCO_3$ in managing metabolic acidosis if patient is fluid overloaded.

2.15. When to do renal biopsy in AKI?

- Unexplained AKI lasting more than 2 weeks.
- If features of other diseases like acute nephritis, connective tissue disorders are present.

2.16. Follow up of AKI

- Renal recovery usually occurs within 2 weeks but may take longer time in some cases.
- In some cases, the recovery may not be complete and in others, the patient may land up in ESKD.
- Once discharged from the hospital, it is advisable to keep the patient in regular follow up depending upon the condition and feasibility of the patient.
- They should be advised to avoid nephrotoxic drugs.

CHAPTER 3. Chronic Kidney Disease

3.1. Background

Chronic kidney disease (CKD) is a worldwide public health problem and there is a rising incidence of kidney disease with poor outcomes and a high cost of treatment. The prevalence of earlier stages of CKD has also increased and there are evidence to show that treatment in earlier stages is effective in slowing the progression toward kidney failure.

3.2. Definition

CKD is defined as "Kidney damage seen as structural or functional abnormalities, and persisting for three months or more irrespective of the cause OR an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2 with or without kidney damage."

Markers of kidney damage are (one or more)

- Albuminuria (ACR ≥30 mg/d)
- Urinary sediment abnormality
- Electrolyte abnormality due to tubular disorder
- Abnormalities on histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

Table 7. Staging of chronic kidney disease (2012 KDIGO guidelines)

Stage	Terms	GFR (ml/min/1.73m^2)
G1	Normal or high	> 90
G2	Mildly decreased	60 – 89
G3a	Mild to moderately decreased	45 – 59
G3b	Moderate to severely decreased	30 – 44
G4	Severely decreased	15 – 29
G5	Kidney failure	< 15

3.3. Causes of chronic kidney disease

- Diabetic kidney disease
- Hypertensive nephrosclerosis

- Chronic glomerulonephritis
- Autosomal dominant polycystic kidney disease (ADPKD).
- Tubulointerstitial nephropathy
- Obstructive uropathy including benign hyperplasia of prostate (BPH)
- Previous history of AKI
- Ischemic kidney disease
- Chronic pyelonephritis
- Alport's syndrome and other congenital kidney diseases
- Congenital defects of bladder and ureters

3.4. Evaluation of chronic kidney disease

When an eGFR of <60 ml/min/1.73m^2 or markers of kidney damage are found in a patient, a detailed history of medical conditions, family history of kidney disease, past history of kidney problems such as hypertension, proteinuria, hematuria, symptoms of prostatic disease and use of specific medications should be obtained. Moreover, the duration of kidney disease and chronicity can be obtained by:

- Review of past measurements of eGFR.
- Review of past measurements of albuminuria or proteinuria and urine examinations.
- Imaging findings such as reduced kidney size and reduction in cortical thickness.
- Pathological findings such as fibrosis and atrophy in renal biosy.

The physical examination findings like skin pigmentation, scratch marks, left ventricular hypertrophy and hypertensive fundal changes also favor CKD.

Chronicity should not be assumed, as AKI can present with similar abnormalities.

3.5. Investigations

3.5.1. Objectives of investigation in CKD

- Confirmation of CKD
- Staging of CKD

- To find out the etiology
- To find out the complications

ALL INVESTIGATIONS ARE NOT REQUIRED IN EVERY PATIENT, BUT IS DIRECTED BY CLINICAL CONTEXT AND AVAILABILITY OF RESOURCES

3.5.2. Examination of urine

- Routine and microscopic examination of urine for urinary sediments and albuminuria (both are markers of kidney damage):
  - Persistent albuminuria (proteinuria) and isolated non-visible hematuria with abnormal RBC morphology (dysmorphic) in glomerular disorders.
  - RBC casts in proliferative glomerulonephritis.
  - WBC cast in pyelonephritis or interstitial nephritis.
  - Granular casts and renal tubular epithelial cells in many parenchymal diseases.
- Quantitative urinary protein estimation
  - Untimed "Spot" urine samples- albumin creatinine ratio (ACR), protein creatinine ratio (PCR).
  - 24 hour urinary protein estimation: a gold standard.
- Midstream urine (MSU) for culture and sensitivity test.

Table 8. Albuminuria categories in CKD

Category	Albumin Creatinine Ratio (ACR) (mg/g)	Terms
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased (microalbuminuria)
A3	>300	Severely increased*

*Urine ACR > 2200 mg/g may be accompanied by signs and symptoms of nephrotic syndrome e.g. low serum albumin, edema and high serum cholesterol.

3.5.3. Blood investigation

- Complete blood count and peripheral blood smear
- Biochemical tests
  - Blood sugar
  - Renal function test (urea, creatinine, sodium, potassium, chloride, bicarbonate)
  - Serum calcium and phosphorus
  - Serum uric acid
  - Serum total protein and albumin
  - Thyroid function test in diabetic kidney disease
  - Blood for HBsAg, anti-HCV and anti-HIV
  - Serum protein electrophoresis in a suspected case of multiple myeloma
  - Coagulation profile: bleeding time, clotting time and prothrombin time
  - Serum PTH level (CKD stage 3 onwards)
  - Serum Vitamin D level (CKD stage 3 onwards)
  - Serum iron profile (serum ferritin level and transferrin saturation)
  - Serum Vitamin B12 level
  - Serum folic acid
  - Connective tissue disorder markers (ANA, Complements, p-ANCA, c-ANCA, Anti-GBM etc.) if indicated.

3.5.4. Ultrasound of KUB

To assess kidney structure i.e. kidney shape, size, symmetry, cortico-medullary differentiation, cortical thickness, evidence of obstruction.

3.6. Treatment of chronic kidney disease

According to different stages of CKD, treatment plan can be:

3.6.1. Conservative treatment

- *The aims of conservative treatment are to:*
  - Treat the etiology
  - Slow the disease progression and thereby postpone the onset of renal replacement therapy (dialysis, transplantation)

- Avoid the development of complications and treatment (mineral bone disease, cardiovascular diseases)

- *Conservative treatment includes a broad spectrum of measures:*
  - Treatment/ control of underlying diseases, e.g. diabetes mellitus, hypertension.
  - Control of hypertension, which often develops as the disease progresses.
  - Dietary protein restriction (supplemented with medication containing essential ketoacids/amino acids)
  - Correction of salt and water imbalances
  - Treatment of anemia
  - Treatment of hyperphosphatemia and prophylactic treatment of bone disease
  - Correction of high levels of lipids
  - Avoiding medications that could damage the kidneys
  - Smoking cessation
  - Weight control (diet, lifestyle changes)
  - Vaccination

3.6.1.1. Treatment

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) has issued several clinical practice guidelines for managing all stages of CKD and related complications.

3.6.1.1.1. Lifestyle modification and diet

- Physical activity compatible with cardiovascular health and tolerance (at least 30 mins five times a week)
- Keep BMI between 20 to 25
- Stop smoking
- Avoid alcohol intake
- Avoid nephrotoxic drugs/herbals and ayurvedics
- Fluid restriction (depending on urine output and volume status)
- Calorie: 30 - 35 kcal/kg
- Protein intake:
  - GFR <30 ml/min/ 1.73 m^2: 0.8 g/kg/day

- Under dialysis: 1.0 to 1.5 g/kg/day
- Salt intake: <90 mmol (<2 g/day of sodium, corresponding to 5 g of NaCl)
- Potassium: restriction depending upon the stage of CKD and serum potassium level
- Phosphorus: 800 mg/day

3.6.1.1.2. Treatment of causes of CKD

- ***Control of proteinuria***
  - ACE inhibitors or ARBs are the drug of choice for reducing proteinuria in diabetic and non-diabetic CKD patients.
  - In Modification of Diet in Renal Disease (MDRD) study, dietary protein restriction (0.6 gm/kg/day versus a usual protein diet of 1.3 gm/kg/day) did not significantly affect the mean change in glomerular filtration rate over three years.
  - In selected patients, aldosterone-receptor antagonists may decrease proteinuria, but should always monitor K^+ for hyperkalemia.
- ***Control of blood sugar***
  - Glycemic control should be a part of a multifactorial intervention strategy that addresses blood pressure control and cardiovascular risk, and promotes the use of ACE inhibitors, angiotensin-receptor blockers, statins and acetylsalicylic acid.
  - Metformin is recommended for most patients with type 2 diabetes with stage 1 or 2 CKD who have a stable renal function that has been unchanged over the past 3 months and metformin may be continued in patients with stable stage 3 CKD. Metformin should be stopped if there are acute changes in renal function or during periods of illnesses that could precipitate changes such as gastrointestinal upset, dehydration, cardiac or respiratory failure or after intravenous contrast administration.
  - Risk of hypoglycaemia should be assessed regularly for patients taking insulin or insulin secretagogues and patients

should be taught how to recognize, detect and treat hypoglycemia.

- Short-acting sulfonylureas (gliclazide and glipizide) are preferred over long-acting agents. Repaglinide - a non-sulphonylurea insulin secretagogue can be prescribed safely in CKD patients and DPP-4 inhibitors (sitagliptin and saxagliptin) need a dose adjustment. Linagliptin can be used without dose modification.

Insulin:

CKD is associated with insulin resistance and decreased insulin degradation which leads to a marked decrease in insulin requirement. Several different insulin regimens can be used to achieve glycemic control (HbA1c <7.0). Some suggest that long-acting insulin preparation should be avoided.

Table 9. Dose recommendations can be followed while treating with insulin

eGFR	
>50 ml/min/1.73m^2	No dose adjustment
10 – 50 ml/min/1.73m^2	Reduced to ~75% of baseline
<10 ml/min/1.73m^2	Reduced by 50%

- ***Control of hypertension***
  - Aggressive blood pressure control can help delay the decline in renal function in patients with CKD. Target blood pressure in CKD is less than 130/80 mmHg. Systolic blood pressure control is considered more important than diastolic blood pressure control.
  - For patients with proteinuric CKD, antihypertensive therapy should include an ACE inhibitor or an angiotensin-receptor blocker as tolerated with close monitoring for renal deterioration (serum creatinine level increases >30% from baseline) and for hyperkalemia. Avoid these agents in patients

with advanced renal failure, bilateral renal artery stenosis or renal artery stenosis in a solitary kidney.

- For patients with non-proteinuric CKD, antihypertensive therapy should include an ACE inhibitor, an angiotensin-receptor blocker, a thiazide diuretic, a β-blocker or a long-acting calcium-channel blocker. For renovascular hypertension, caution should be taken with the use of an ACE inhibitor because of the risk of development of acute renal failure.

- ***Treatment of other causes***

Every effort should be made to treat the known causes of CKD including renal stone diseases and urinary tract obstruction.

3.6.1.1.3. Treatment of complications of CKD

- ***Treatment of anemia***
  - Anemia with CKD is defined when hemoglobin concentration is < 13.0 g/dl in males and < 12.0 g/dl in females.
  - Anemia in CKD usually presents as normocytic normochromic anemia due to insufficient production of erythropoietin along with other additional factors like iron deficiency, anemia of chronic disease, severe hyperparathyroidism with consequent bone marrow fibrosis, shortened red cell survival and platelets dysfunction.
  - All patients of CKD with anemia should be evaluated for other causes of anemia like GI bleeding, malignancy, Vit B12 and folate deficiency.
  - For patients who have hemoglobin level of <11.0 g/dl, iron should be administered to maintain a level of ferritin >500 ng/ml and transferrin saturation >30% before starting Erythropoiesis stimulating agent (ESA).
  - The oral form of iron is the preferred first-line therapy for patients with CKD. Patients who do not achieve serum ferritin or transferrin saturation targets while taking the oral form of iron or who do not tolerate the oral form should receive the intravenous form of iron.

Iron therapy

HD dependent CKD:

5 ml (100mg elemental iron), undiluted slowly IV over 2-5 minutes or 5 ml diluted in a maximum of 100ml of 0.9% sodium chloride IV over at least 15 minutes to one hour per dialysis session not to exceed a total cumulative dose of 1000 mg divided in 3 doses/week.

Non-dialysis dependent CKD:

10 ml (200 mg elemental iron), undiluted IV over 2-5 minutes for 5 doses in over 14 days or alternatively 25 ml (500 mg elemental iron) diluted in a maximum of 250 ml of 0.9% sodium chloride IV over 210 to 240 minutes administered on day 1 and day 14.

Peritoneal dialysis dependent CKD:

2 infusion of 15 ml (300 mg of elemental iron) each diluted in a maximum of 250 ml of 0.9% sodium chloride administered over 90 minutes 14 days apart, then 20 ml (400 mg of elemental iron) diluted in 0.9% of sodium chloride over 150 minutes on 28^{th} day (after 14 days), cumulative 1000 mg divided in 3 doses. IV compatibilities: 0.9% sodium chloride solution. IV preparation: Do not dilute to concentrations below 1 mg/ml. Visually inspect or particulate matter and discoloration prior to infusion. Stable for 7 days at controlled room temperature 25^0C. Do not freeze.

Note: Iron sucrose administration requires monitoring of hematologic and hematinic parameters such as hemoglobin, hematocrit, serum ferritin and transferrin saturation. Iron sucrose should be withheld in patients with evidence of iron overload.

For patients with anemia and adequate iron stores, ESA should be initiated if their hemoglobin level falls below 10g/dl. (ESA should be prescribed in conjunction with a specialist).

ESA (Erythropoiesis stimulating agents):

- **Erythropoietin alfa:**

The approximate dose of Erythropoietin is 50-100 U/kg of body weight/week.

- **Darbepoietin alfa:**
  - *CKD patients on dialysis:*

  0.45 mcg/kg of body weight as S.C. or IV injection weekly

  OR

  0.75 mcg/kg of body weight as SC or IV injection once in every 2 weeks.
  - *CKD patients not on dialysis:*

0.45 mcg/kg of body weight as SC or IV injection once at 4 week intervals.

Dosage equivalent: Ranges from 200-600: 1.

Table 10. Recommended Conversion rate of erythropoietin and darbepoietin

Erythropoietin alfa (Units/week)	Darbepoietin (mcg/week)
5000 – 10,999	25
11,000 – 17,999	40
18,000 – 33,999	60

Key points for practitioners to remember while treating anemia in CKD
Work-up for anemia in CKD should include assessment of secondary causes including iron deficiency (Iron profile: Ferritin and TSAT). Iron replacement is often effective in anemia of CKD as initial therapy and clinician and patient preference, and availability of local resources should determine the routes of administration (intravenous or oral). ESA therapy is not recommended in those with active malignancy or recent history of malignancy. In most people with CKD, ESA should not be used to increase Hb concentration >11.5 g/dl.

- **Treatment of hyperphosphatemia and MBD**
  - Serum calcium, phosphate and parathyroid hormone and serum vitamin 25(OH)D levels should be measured and maintained within normal range but the target level of serum intact parathyroid hormone (i-PTH) is unknown.
  - Treatment options are:
    - Dietary phosphate restriction should be used continuously.
    - Therapy with calcium-containing phosphate binders (calcium carbonate or calcium acetate) should be initiated if dietary restriction fails to control.
    - If hypercalcaemia develops, the dose of calcium-containing phosphate binders or Vitamin D analogues should be stopped and consider for replacing with non calcium-based phosphate binders (lanthanum carbonate or sevelamer carbonate).
    - Hypocalcaemia should be corrected if the patient has symptoms or if it is associated with increased parathyroid hormone levels.
    - Consider prescribing Vitamin D analogues if serum levels of intact parathyroid hormone are >53 pmol/L.
    - If hyperphosphataemiais not corrected with calcium-containing phosphate binders, other phosphate binders can be used.

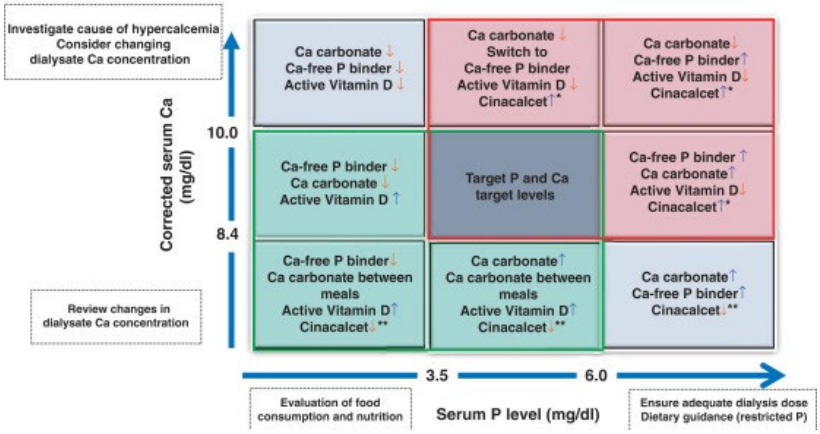

Figure 10. Example of how to treat hypercalcemia and hyperphosphatemia by adjusting relevant medication

- **Treatment of dyslipidemia**
  - Statin therapy should be initiated for patients with stage 1 to 3 CKD according to existing lipid guidelines for the general population.
  - Gemfibrozil may be considered as an alternative to statin
- **Treatment of hyperkalemia:** (Refer section 2.11.1)
- **Treatment of metabolic acidosis**: (Refer section 2.11.2)
- **Vaccination for CKD patients**:
  - Influenza Vaccine: usual dose annually
  - Pneumococcal vaccine: Inj. Prevenar- intramuscularly once in a lifetime
  - Hepatitis B vaccine: CKD patients with >stage 3 onward, double dose (1 ml in each deltoid muscle) for 4 doses at 0, 1, 2 and 6 months time. Protective antibody levels against hepatitis B should be checked annually

3.7. Follow up of CKD patients

The following graph shows how a CKD patient is to be followed up according to albuminuria level and eGFR.

Table 11. Guide to Frequency monitoring (number of times per year) by GFR and Albumin Category

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

3.8. Referral to nephrologist

Early identification and referral of patients with CKD have potential to reverse, delay or prevent progression of the disease and is a key focus of international initiatives in the area of kidney disease.

3.8.1. Goals of referral

- Provision of specific therapy based on diagnosis
- Slowing or arresting CKD progression
- Evaluation and management of co-morbid conditions
- Prevention and management of cardiovascular diseases
- Identification, prevention and management of CKD specific complications, e.g., malnutrition, anemia, bone disease and acidosis.
- Planning and preparation for renal replacement therapy, e.g., choice of modality, vascular access placement and care, pre-emptive transplantation

- Psychosocial support and provision of conservative care and palliative care options.

3.8.2. Conditions when a CKD patient should refer to nephrologist

- AKI or abrupt sustained fall in GFR
- GFR <30 ml/min/1.73m^2
- A consistent finding of significant proteinuria >500 mg/day
- Progression of CKD
- Urinary red cell casts
- CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
- Persistent abnormalities of serum potassium.

CHAPTER 4. Dialysis

4.1. Background

Nephrology Service was started in Nepal in 1973 with all sorts of medical management for kidney diseases along with the initiation of intermittent peritoneal dialysis (IPD) and Renal Biopsy. Later, in the year 1987, Hemodialysis service was started. Renal transplantation service is available in Nepal since 2008.

Renal Replacement Therapy (RRT) replaces non-endocrine functions of the kidney. It is the essential requirement for relieving patients' suffering due to end stage kidney disease (ESKD) and works as a bridge to renal transplantation or when transplantation is not available. Similarly, it can be used to support the patient with AKI for a temporary period (ref.chapter 2).

RRT for ESKD are of various types:

- Blood-based: Hemodialysis (HD), hemofiltration, hemodiafiltration
- Peritoneal dialysis (PD)
- Renal Transplantation

Each type of dialysis has advantages and disadvantages. People often can choose the type of long-term dialysis that best matches their needs. Hemodialysis and peritoneal dialysis, both of which are life support treatments; but dialysis does not treat kidney diseases. A nephrologist prescribes dialysis after detailed analysis and examination of the patient.

This section of the protocol will discuss on RRT in CKD (HD and PD) and next section (Chapter 5) will deal with renal transplantation.

4.2. Hemodialysis

4.2.1. Definition

- A medical procedure to remove fluid and waste products from the blood and to correct acid-base and electrolyte imbalances using a machine and a dialyzer also referred to as an “artificial kidney”.

- Hemodialysis utilizes an artificial kidney machine with a special filter to remove waste products and fluid from the blood.
- The machine is connected to the patient through a fistula, usually in the forearm, or a permanent catheter in the arm or chest.
- The blood is pumped from the patient's access site through the dialyzer that is washed with dialysate and then returned to the patient through a second needle placed near the first one in the forearm.
- The process usually lasts 4 hours and is repeated two to three times a week.
- Hemodialysis can be done at a hospital or clinic or as a stand-alone center.

4.2.2. Indications of Hemodialysis (HD)

- Fluid overload with pulmonary edema deteriorating despite fluid and salt restriction and resistant to use of a maximal dose of diuretics.
- Hyperkalemia refractory to dietary restriction and medical management.
- Metabolic acidosis refractory to bicarbonate treatment.
- Uremic neuropathy (e.g., uremic encephalopathy, uremic asterixis).
- Uremic pericarditis.
- Uremic bleeding diathesis.
- Recent weight loss or deterioration of nutritional status in a patient with renal impairment known for 3 months, especially if accompanied by nausea, vomiting.
- Hyperphosphatemia refractory to dietary counselling and to treatment with phosphorus binders.
- Other uremic symptoms, with eGFR between 5 and 10 mL/min/1.73 m^2.

4.2.3. Contraindication for hemodialysis

- Patient in shock with severely low blood pressure (systolic pressure <80 mmHg); however, other modes of RRT like SLED and CRRT can be considered especially in AKI.
- Patient with heart failure due to severe myocardial lesions.
- Patient of end-stage malignant tumor with life expectancy less than a week.
- Patient with extreme other organ failures including hepatorenal syndrome type I or patient is dying.
- Patient without vascular access due to thrombosis of jugular, femoral veins and arteriovenous fistula/graft uncreatable.
- Patient with catheter-related bloodstream infection unless the catheter is changed.
- Patients having mental illness or refusing hemodialysis treatment.

4.2.4. Hemodialysis prescription

Hemodialysis prescription is an integral area in nephrology. Many parameters should be considered in prescribing hemodialysis, and all hemodialysis prescriptions must be modified as per the condition of a patient. In particular, each hemodialysis patient's electrolytes should be screened, and the dialysis protocol for each patient should correct any underlying or associated conditions.

The parameters commonly used during chronic hemodialysis prescription are:

- Ultrafiltration
- Dialysis duration
- Frequency of dialysis (thrice or twice)
- Appropriate anticoagulation measures
- Dialysate sodium, potassium, calcium, bicarbonate, magnesium, temperature, and glucose
- Type of dialyzer
- Blood flow rate
- Dialysate flow rate

Prescriptions in hemodialysis may require a comprehensive approach based on medications, laboratory test findings, and patient conditions. As many management goals are already discussed in chapter 3. As fixed dialysate composition is available in Nepal, only major parameters related to hemodialysis prescription will be discussed in this protocol.

Consent

Screening

All patient should be screened for HIV I & II, HBsAg and Anti HCV at the time of start of HD and every three months especially in those we receive blood transfusion and should be screened on those patients who change the center.

Access

Patient should be dialysed through AV fistula. However, if the patient does not have fistula then temporary access should be opened preferable in the right internal jugular vein.

Double lumened uncuffed non tunnelled soft catheters.

Cuffed tunnelled biluminal soft catheters.

Prescription of Hemodialysis Refer Annex 2.

Frequency of HD

- Generally twice a week schedule
- Consider thrice a week in following conditions:
    - If the patient is symptomatic with twice a week HD
        - Volume overloaded
        - Uremic symptoms
        - Issues with hyperkalemia

Investigations to be sent in patients on maintenance HD

- Hb%: Twice a month
- Pre and post KFT: Twice a month
- Calcium/Phosphorus: Every three months
- Viral screening: Every three months
- iPTH: If indicated

4.2.5. Complications during hemodialysis

The most common complications during hemodialysis are hypotension, cramps, nausea and vomiting, headache, chest pain, back pain, and itching. Besides these, hypertension, dialysis disequilibrium syndrome, air embolism, seizures, dialyzer reactions, fever and chills may occur during dialysis.

4.2.5.1. Hypotension

Definition: The systolic BP less than 90 mm Hg during hemodialysis.

Management

- Trendelenburg position
- Ultrafiltration rate should be reduced to as near zero as possible.
- A bolus of 0.9% saline (100 mL or more, as necessary) should be rapidly administered through the venous blood line. As an alternative to 0.9% saline, hypertonic saline, glucose, or albumin solutions can be used to treat the hypotensive episode.

Strategy to help prevent hypotension during dialysis

- Avoid excessive ultrafiltration below the patient's “dry weight”.
- Avoid large interdialytic weight gain (ideally <1 kg/day)
- Using a dialysis solution with a sodium level that is equal to or greater than the plasma value.
- Avoid intradialytic food ingestion in hypotension-prone patients.
- Give daily dose of antihypertensive medications after dialysis in hypotension-prone patients.
- Use bicarbonate containing dialysis solution.
- Correct anemia for cardiac stability.

4.2.5.2. Muscle cramps

The most important predisposing factors are:

- Hypotension (removal of a large volume of fluid)
- Patient's being below the dry weight
- Use of low sodium dialysis solution
- Electrolyte imbalance (e.g. hyponatremia, hypocalcaemia)

Management

- Stretching, massage, and heat application.
- When hypotension and muscle cramps occur concomitantly administration of hypertonic saline or glucose is very effective.
- Calcium gluconate injection for hypocalcemia.
- Sodium 60odelling/ sodium gradient dialysis for hyponatremia.

4.2.5.3. Nausea and vomiting

Management

- Treat any associated hypotension.
- Antiemetics can be administered for other causes of vomiting as needed.
    - Inj. Ondansetron or Metoclopramide.

4.2.5.4. Headache

The cause is largely unknown but may be due to:

- Disequilibrium syndrome
- A manifestation of caffeine withdrawal (in coffee drinkers)
- Dialysis may precipitate migraine headaches in those with a history of migraine disorder.
- With an atypical or particularly severe headache, a neurologic cause (particularly a bleeding event precipitated by anticoagulation) should be considered.

Management

- Acetaminophen can be given during dialysis.

4.2.5.5. Chest pain and back pain

The cause is unknown. Chest pain may be due to angina during dialysis, so, always rule out ischemic heart disease. Other potential causes are:

- Hemolysis
- Air embolism
- Pericarditis

4.2.5.6. Hypertension

Prevention

- Careful attention to dry weight and fluid removal.
- Avoidance of dialyzable antihypertensive medications.
- Limiting the use of high calcium dialysate.
- Achieving adequate sodium solute removal during hemodialysis.
- Using medications which inhibit the renin-angiotensin-aldosterone system or which lower endothelin.

Management

- Education by dietitians every 3 months
- Low salt intake (2 g/day sodium intake)
- Increased ultrafiltration (lowering of dry weight)
- Intradialytic sodium modeling
- More than three dialysis treatments per week (lowering of dry weight)
- Antihypertensives: consider if medications are cleared on dialysis.
- Medicines such as nifedipine, clonidine or a short-acting ACE inhibitor such as captopril can be used.

4.2.5.7. Dialysis disequilibrium syndrome

Management

- Mild disequilibrium.
  - Treatment is symptomatic.
  - If mild symptoms of disequilibrium develop in an acutely uremic patient during dialysis, the blood flow rate should be reduced to decrease the efficiency of solute removal and pH change, and consideration should be given to terminating the dialysis session earlier than planned.
- Severe disequilibrium.
  - If seizures, obtundation, or coma occur in the course of a dialysis session, dialysis should be stopped.

- The airway should be maintained and the patient ventilated if necessary.
- Treatment of seizures is discussed later (Section 4.2.5.9).
- The management of coma is supportive.
- If coma is due to disequilibrium, then the patient should improve within 24 hours.

4.2.5.8. Air embolism

Management

- The first step is to clamp the venous blood line and stop the blood pump.
- The patient is immediately placed in a recumbent position on the left side with the chest and head tilted downward.
- Further treatment includes cardiorespiratory support, including administration of 100% oxygen by mask or endotracheal tube.
- If air has gone into the heart, aspiration of air from the ventricle with a percutaneously inserted needle can be attempted.

4.2.5.9. Seizures

Management

- Stop dialysis
- Maintain patency of the airway.
- Blood should be sampled immediately and serum glucose, calcium, and other electrolyte values determined.
- IV glucose should be administered if hypoglycemia is suspected.
- If seizures persist, then 5 to 10 mg of diazepam can be infused slowly IV. Infusion can be repeated at 5-minute intervals to a maximum total dosage of 30 mg.
- Diazepam therapy can be followed by a loading dosage of phenytoin in a dose of 10 to 15 mg/kg given by slow IV infusion, at a rate no greater than 50 mg/min, during constant electrocardiographic monitoring to guard against phenytoin-induced bradycardia, atrioventricular conduction block, or other arrhythmias.

4.3. Peritoneal Dialysis

4.3.1. Definition

In PD, the patient's peritoneal membrane is used as an semipermeable membrane and fluid is kept inside the peritoneal cavity for some time (6-8 hrs or more in some cases) which is called dwell time. It is then drained out and fresh PD fluid is kept inside and the cycle repeats.

4.3.2. Types

Basically, there are two main types of PD.

- Continuous ambulatory peritoneal dialysis (CAPD).
- Continuous cycling peritoneal dialysis (CCPD).

CCPD uses a machine called cycler to do the exchange.

4.3.3. Indications

Strong indications of PD include the following:

- Vascular access failure
- Intolerance to hemodialysis
- Congestive heart failure
- Prosthetic valvular disease
- Children
- Patient preference
- Distance from a hemodialysis center
- Poor cardiac function
- Peripheral vascular disease

4.3.4. Contraindications

Contraindications to PD include the following:

- Documented type II ultrafiltration failure
- Severe inflammatory bowel disease
- Acute active diverticulitis
- Abdominal abscess
- Active ischemic bowel disease
- Severe active psychotic disorder
- Marked intellectual disability

- Third trimester of pregnancy

PD is not preferred but is possible in selected circumstances:

- Obesity
- Multiple hernias
- Severe backache
- Multiple abdominal surgeries
- Impaired manual dexterity
- Blindness
- Poor home situation
- Depression

4.3.5. Pre-operative care for tenckhoff catheter insertion

Procedure

- PD Staff to be contacted by medical staff when patients scheduled for theatre for tenckhoff insertion.
- Swab the nose and umbilicus for culture and sensitivity.
- Coagulation profile, viral marker, CBC, KFT and urine c/s result required preoperatively.
- Administer bowel preparation with a laxative (bisacodyl 2 tab) at night and ezivac enema at the morning of the procedure.
- Patient must fast from 12-midnight pre-op
- Ensure that the patient has taken shower in the morning of the procedure.
- Prophylactic IV antibiotics (Inj. Ceftriaxone 1 gm) to be administered in the morning of theatre as prescribed.
- Pass foleys catheter and ensure bladder is empty on the morning pre-theatre.
- Prepare patient for theatre as per surgical checklist.

4.3.6. Performing a manual exchange

Equipment

- Hard surface wipes
- Two connection shields.

- Two Minicaps/disconnect caps
- Two Blue clamps.
- Hand gel
- Warm Bag of dialysate fluid.

Procedure

- Wash hands as per protocol
- Wash down worktop with a Teepol solution, patients can use soap and water
- Clean with a hard surface wipe, cleaning in one direction only, covering the entire surface.
- Open bag – lay on a table
- Check for Clarity, Volume, Concentration, Expiry date, Leakage.
- Pull bag lines free.
- Lay table with all of the above requirements (7 in total)
- Open connection shield
- Apply hand gel
- Apply connection shield to the end of tubing on the bag
- Remove cap from your tube and connect yourself to the bag
- Open roller clamp and drain.
- When drained out, close roller clamp.
- Break the green seal on full bag line count to 15 to allow flush from full bag to drainage bag.
- Clamp drainage bag line.
- Open roller clamp to fill.
- When filled, clamp bag line.
- Close roller clamp and apply a clamp to the fill line.
- Open disconnect cap
- Apply hand gel
- Disconnect yourself and put a new cap on

4.3.6.1. Guidelines for commencing a peritoneal dialysis Prescription

- Commencing Fluid: Commence with PD fluid with dextrose concentration of 1.5 or 2.5% (Dianeal).
- Managing fluid overload: Use either 4.5% PD fluid for 4 hrs or use Icodextrin.
- Commencing Fill volume: Fill volume commences at 500mls and increase fill volume to two liters gradually as per patients' medical condition and tolerability
- PET test is done after 6 – 8 weeks of stable therapy and annually thereafter (Wait for four weeks for PET test after an episode of peritonitis).
- KT/V is recorded 4 monthly and change the prescription of dialysis as necessary or KT/V < 1.7.
- Commencing a Last Bag Option: All new patients to complete a 24-hour urine collection when training commences.
    - Urine output >1000 ml, No last bag necessary.
    - Urine output <1000 ml, the last bag option is necessary and Icodextrin is used.
- Guideline for using Icodextrin (7.5%)
    - Use Icodextrin in patients who have fluid overload

While using Icodextrin, it must be dwelled for atleast 10 - 12 hrs.

- Diabetic patients must have their capillary blood glucose machines checked by the diabetic nurse service to assess the compatibility of test strips with the use of Icodextrin.

4.3.7. Care of a patient with peritonitis

4.3.7.1. Procedure

- Monitor vital signs 4 hourly or as required and treat appropriately
- Assess patients level of pain and administer analgesia as prescribed
- Using a 2-litre manual drain bag, drain out the peritoneal effluent observing for cloudiness.

- An effluent sample to be obtained using 1 CBC Bottle & 1 blood culture bottle.
- Aerobic if the patient is not on antibiotics
- Anaerobic bottle if patient is on antibiotic treatment.
- Sample to be taken at the bedside using aseptic technique with sterile field and equipment.
- Order patient sample labels for fluid microscopy, culture & sensitivity.
- Flush peritoneal cavity with 500 ml of dialysate 1.5%, to be repeated 4 times.
- A 2-litre bag of dialysate 1.5% with the antibiotic added is used for final exchange.
- Commence patient on 4 hourly exchanges x 1.5% unless otherwise specified.
- Observe exit site and obtain swab if red/inflamed/oozing and send for C&S.
- Try to identify the underlying cause of infection.
- Re-educate patient and family on aseptic technique after each peritonitis episode.
- Record peritonitis episode on clinical vision and on the manual record.

4.3.7.2. Definitions of infections

- **Exit site colonisation:** A positive culture in the absence of an abnormal appearance is indicative of colonization rather than infection. Intensifying exit-site cleaning with antiseptics is advised.
- **Exit site infection:** Purulent drainage with or without erythema of the skin at the catheter-epidermal interface.
- **Tunnel infection:** Usually occurs in the presence of an exit site infection and may present as erythema, oedema or tenderness over the subcutaneous pathway.

- **Recurrent peritonitis:** An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism.
- **Relapsing peritonitis:** An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile episode.
- **Repeat peritonitis:** An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism.
- **Refractory peritonitis:** 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.

4.3.7.3. Guideline for the treatment of infection in PD patients

- Exit-site care and *S. aureus* colonisation
- Exit-site and tunnel infections
- Antibiotic prophylaxis prior to lower GI endoscopy
- Peritonitis
- Antibiotic advice

4.3.7.3.1. Exit-site care and *S. aureus* colonisation

- *Staphylococcus aureus* nasal carriage is associated with an increased risk of S. aureus exit-site infections, tunnel infections, peritonitis, and catheter loss.
- A single culture may yield a false negative result since many patients have an intermittent nasal carriage.
- Positive exit-site culture for *S. aureus* with no evidence of infection (i.e., denoting carriage). Intranasal mupirocin three times per day for 5–7 days.
- Screen subsequently (nasal swab) every 2 months.

4.3.7.3.2. Exit-site and tunnel infections

General points

- Exit site swabs must be taken prior to the commencement of antibiotic therapy
- Antibiotic therapy for exit-site / tunnel infections should always be complemented by intensified exit-site cleaning with povidone iodine or chlorhexidine 2.0%
- *S. aureus* and *P. aeruginosa* exit-site infections are often associated with concomitant tunnel infections and are the organisms that most often result in catheter-infection-related peritonitis; aggressive management is always indicated for these organisms.

Table 12. Antibiotic Therapy of Exit-Site and Tunnel Infections

Empiric therapy	Treatment	Duration of therapy
No previous MSSA/ MRSA/ *P. Aeruginosa*	Flucloxacillin 500 mg QID, PO	10-14 days
History of *P. aeruginosa* exit-site	Flucloxacillin 500 mg QID PO plus IP Gentamicin*	Continue treatment until the colonisation exit site appears entirely normal. Maybe >2wks
No improvement by day 3	Admit for IV antibiotics	
No improvement by day 5	Consider catheter removal	

4.3.7.3.3. Antibiotic prophylaxis prior to lower GI endoscopy

- Endoscopic imaging of the large bowel can result in peritonitis.
- Single dose Co-amoxiclav 1.2 g should be given at induction prior to the procedure (if penicillin allergic contact microbiology).

- It is important that phosphate-containing enemas and phosphate-containing bowel preparations are avoided in these patients.

4.3.7.3.4. Peritonitis

Antibiotic management

- Empiric therapy (Fig 12).
- Culture-negative peritonitis (Fig 13).
- Guided antibiotic treatment (Tables 13 - 15).

General points

- Effluent should be visually inspected daily, to determine if the clearing is occurring. If there is no improvement after 48 hours, cell counts and repeat cultures should be done.
- Dwell time must be a minimum of 6 hours in patients intermittently dosed with intraperitoneal antibiotics.
- Once culture results and sensitivities are known, antibiotic therapy should be adjusted as appropriate (Tables 13 - 15).

Indications for catheter removal

- Relapsing peritonitis
- Refractory peritonitis
- Fungal peritonitis
- Catheter-related peritonitis: Patients with an exit-site infection that progresses to peritonitis, or who present with an exit-site infection in conjunction with peritonitis with the same organism, will usually require catheter removal. The general exception is peritonitis due to coagulase-negative Staphylococcus, which is generally readily treated.

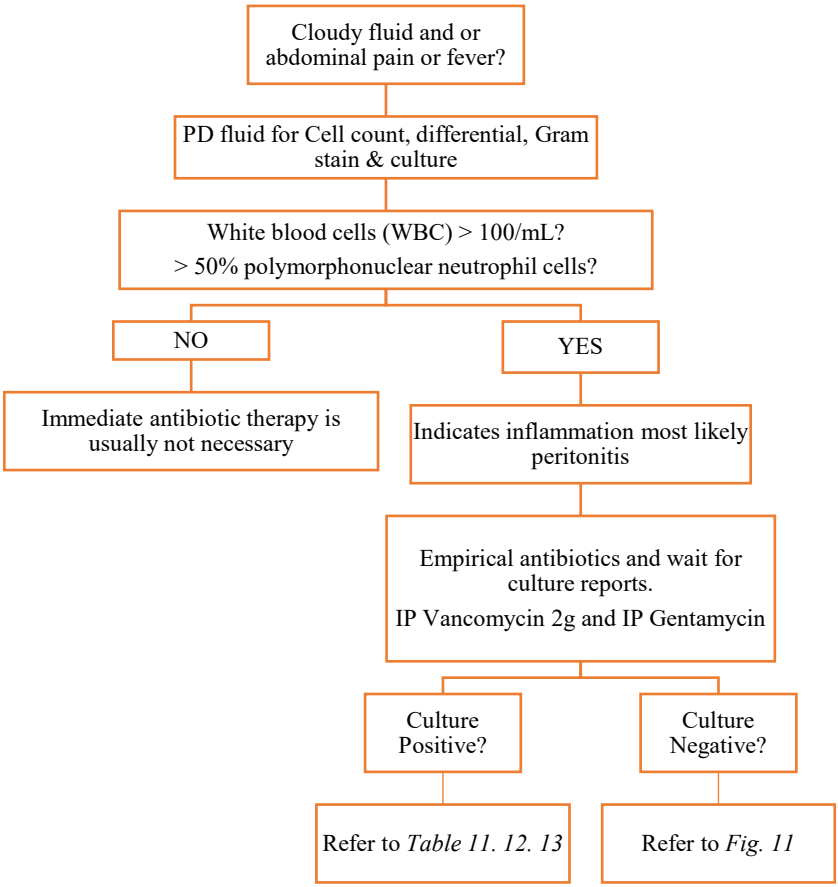

Figure 11: Empiric therapy of peritonitis

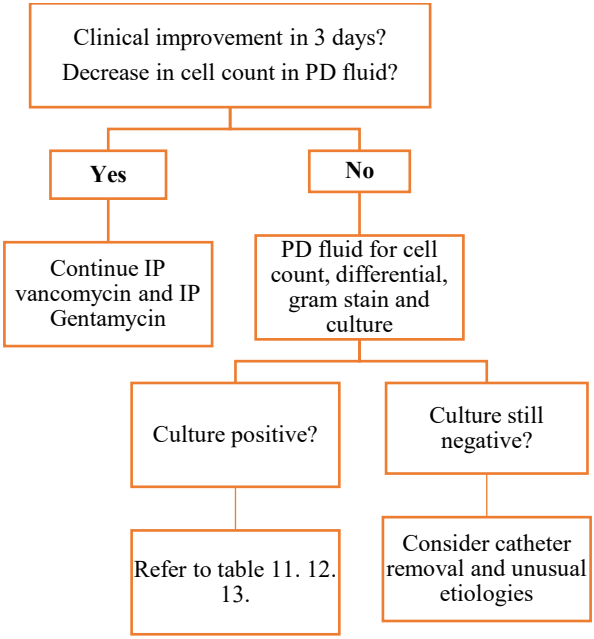

Figure 12: Culture-Negative Peritonitis

Guided antibiotic therapy

Table 13: Gram-positive organisms

Culture	Treatment	Comment	Duration
Streptococci	Sensitive to amoxicillin: Loading dose Amoxicillin 250-500 mg/L, maintenance dose 50mg/L in each exchange Resistant to Amoxicillin: IP Vancomycin	Evaluate for exit site or tunnel infection	2 weeks
Enterococci vancomycin resistant (VRE)	Sensitive to Amoxicillin: Loading dose Amoxicillin 250-500 mg/L, maintenance dose 50mg/L in each exchange plus Gentamicin in a separate bag if clinically unstable or not settling by day 3. Resistant to Amoxicillin: Discuss with microbiology	Rule out intra-abdominal pathology. Evaluate for exit site or tunnel infection.	3 weeks
S. aureus	IP Vancomycin If no improvement by day 3 - add second agent (check with microbiology) If no improvement by day 5 - remove the catheter	Causes severe peritonitis Very careful attention must be paid to the exit site and tunnel of the catheter. If the episode occurs in conjunction with an exit	3 weeks – IV therapy for 48-72hrs post resolution of pyrexia

		site infection - the infection will frequently prove refractory in which case the catheter must be removed.	
MRSA	IP vancomycin If no improvement by day 3 - add second agent (check with microbiology) If no improvement by day 5 remove catheter		3 weeks – IV therapy for 48 - 72 hrs post resolution of pyrexia
Coagulase-negative staphylococcus	IP Vancomycin	Evaluate for exit site or tunnel infection	2 weeks
Corynebacterium	IP Vancomycin	Evaluate for exit site or tunnel infection	3 weeks

Table 14:Gram-negative organisms

Culture	Treatment	Comments	Duration
P. aeruginosa	Check with microbiology re sensitivities before commencing therapy Two antibiotics should always be used	Consider surgical opinion if unstable If no clinical improvement after 3 days: 1. Often related to catheter infection, in such cases a. Catheter removal will be required b. Continue antibiotic therapy for 14 days post removal 2. Consider abdominal CT (?abscess)	3 weeks
Other gram negatives eg: *E. coli*, *Proteus*spp	Check with microbiology re sensitivities before commencing therapy	Consider surgical opinion if unstable If no clinical improvement after 3 days: 1. Repeat cell count, gram stain & culture 2. Consider catheter removal	2 - 3 weeks

Table 15: Other organisms

Culture	Treatment	Comments	Duration
Polymicrobial (multiple gram-negative organisms and/or anaerobes)	Check with microbiology re sensitivities before commencing therapy	Surgical opinion for all polymicrobial infections If no clinical improvement after 3 days: 1. Often related to catheter infection … in such cases a. Catheter removal will be required b. Continue antibiotic therapy for 14 days post removal 2. Consider abdominal CT (?abscess)	3 weeks
Fungal	Stop antibiotics Remove catheter Discuss with microbiology		2-4 weeks
TB	Discuss with microbiology and respiratory medicine	Consider when the patient not responding to antibiotic therapy Remove catheter if no clinical improvement	12 months

4.3.7.3.5. Antibiotic advice

- **Antibiotic dosing**
  - ***Vancomycin***
    - First dose 2 g, the subsequent dose should be 1g unless high clearance predicates 2 g intermittent dosing. Target range for vancomycin: 15-20 mg/l, repeat dosing when serum level <20 mg/l.
  - ***Gentamicin***
    - APD - 0.6 mg/kg daily if UO <400 ml, 1.0 mg/kg daily if UO >400 ml (in one >6 hr dwell/day)
    - CAPD – 8 mg/L loading dose, 4 mg/L maintenance dose each dwell.
- **Antibiotic incompatibility**
  - ***Amoxicillin / Gentamicin incompatibility***
    - These agents are incompatible in PD fluid necessitating sequential dosing. Gentamicin should be added to dialysate as indicated by serum levels. The interruption to amoxicillin dosing should be compensated for by increasing the amoxicillin maintenance dose to 100mg/L in the dwell immediately preceding gentamicin dwell.
  - **Quinolones**
    - When given concomitantly with sevelamer or calcium may chelate, resulting in reduced quinolone absorption. Administration of the quinolone should, therefore, be separated from these drugs by at least 2 hours (with the quinolone administered first). If the resolution of infection is slow, consideration should be given to IV quinolone therapy.
- **Alternative antibiotics in event of an allergy**
  - ***Flucloxacillin/amoxicillin → vancomycin***
    Vancomycin → contact microbiology

4.3.8. Mechanical issues in patients under PD

4.3.8.1. Unblocking a tenckhoff catheter with medication (Heparin, urokinase, TPA).

4.3.8.1.1. Procedure:

- Clamp tenckhoff catheter above titanium.
- Remove the transfer set.
- Apply medication syringe to the end of titanium, remove clamp using sterile gauze and gently attempt to flush medication into a tube.
- Re-clamp catheter prior to removing syringe using sterile gauze.
- Apply a new transfer set to the tenckhoff tube.
- Perform flush with 300 ml dialysate solution and monitor inflow/outflow and effluent.
- If flushing unsuccessful inform medical team for further instructions.

4.3.8.2. Change of transfer set

- Patients transfer set to be changed routinely every six months.
- When the transfer set is damaged/contaminated it must be changed immediately.

N.B An exchange must be performed if the transfer set is changed due to contamination. Prophylactic antibiotic treatment is required vancomycin 1g IP (check allergies).

4.3.8.3. Change of titanium adaptor

NB. If Patient notices tenckhoffis damaged at home inform them to clamp above damaged area and attend hospital straight away.

An exchange must be performed if the titanium adaptor is changed due to contamination or damage. Prophylactic antibiotic treatment is required vancomycin 1g IP (check allergies).

4.3.9. Procedure for intra-peritoneal administration of medications

4.3.9.1. Indications

- This procedure is carried out when IP medication is required.
- IP medications are normally given into a manual bag.

4.3.9.2. Procedure

- Set up a trolley with the above equipment.
- Wash hands and apply sterile gloves.
- Draw up medication as charted.
- Soak dialysate bag port for 5 minutes with aqueous povidone iodine solution.
- Soak medication port for 5 minutes with aqueous povidone iodine solution.
- Draw up medication as prescribed.
- Change needles.
- Inject medication into port on dialysate bag and shake bag.
- Continue as per manual exchange.
- Document on drug cardex and dialysis flow sheet.

4.3.9.3. Recommended Intra-peritoneal medication dosages

4.3.9.3.1. Antibiotics IP

- ***Vancomycin***
  - 2grams IP stat and 1gram IP as per levels re-dosing with level 20 or below
- ***Gentamycin***
  - 40mgs IP stat and repeat as per levels (level< 2)
- ***Teicoplanin***
  - 15mg per kg IP stat with levels and repeat day 5 or 400mg BD IP.

4.3.9.3.2. Potassium IP

- KCL vials 2 - 4 mEq per litre of dialysate fluid IP

4.3.9.3.3. Insulin IP

- Total daily insulin divided between exchanges, with additional insulin dose as per glucose concentration of the dialysate bag. Extra 2 IU per 1.5% glucose bag 4 IU per 2.5% glucose bag 8 IU per 4.25% glucose bag
- Check blood sugar level one hour after each exchange.

4.3.9.3.4. Anticoagulants

Heparin IP

- 500 IU of heparin per litre of dialysate fluid or 1000 IU of heparin per litre of dialysate fluid during peritonitis episode.

Urokinase IP

- 10,000 IU in 5 ml of sterile water.

TPA IP

- Tissue Plasminogen Activator no guideline approved to date CT contrast dose to detect PD leak PD nurse must inject the contrast dose 100 ml of contrast to 2 litres of PD fluid. The patient should be ambulatory for approx. 30 mins combining walking and sitting pre CT scan.

CHAPTER 5. Renal transplantation

5.1. Background

- Organ transplantation is a medical procedure in which an organ is removed from one body to be placed in the body of a recipient to replace a damaged or missing organ.
- Organ transplantation is often the only treatment for end-stage organ failure.

5.2. Definition

- Renal transplantation is the treatment of choice for patients with end-stage kidney disease (ESKD).
- As it provides a superior long-term outcome, the quality of life is better after transplantation when compared to dialysis.
- Although all patients with ESKD are fit to undergo renal transplantation, not all individuals with ESKD will have renal transplantations. There are two major limiting factors the first is the unavailability of organs and second is the presence of co-morbid conditions in an individual that will get worse after the transplantation.

5.3. Sources of kidneys for transplantation

Kidneys for the transplantation can come from two sources:

5.3.1. Cadaveric donor

- These donors have been previously healthy people who have died suddenly for example in a car accident and who had already decided to donate their organs after brain death. These organs are donated with the family's consent, once brain death has been confirmed.

5.3.2. Live donors

- These donors can be either related or unrelated. But in Nepal only related donors can donate, the law prohibits unrelated donations. All donors are thoroughly assessed to determine their potential suitability as a live donor.

5.3.2.1. Who can be live donors?

Mother, father, son, daughter, brother, sister, cousin, niece, nephew, husband, wife, grandmother, grandfather, aunt, uncle, brother in law, sister in law.

5.3.3. Acceptance for donation

A number of factors are considered before being accepted as a living donor. The donor must offer voluntarily to donate and must be under no family pressure to do so. They must be educated about the donation.

5.4. Donor assessment and compatibility

Initial compatibility is a matching of the blood group

Table 16. Blood group matching and compatibility

Blood type	Can receive from blood type	Can donate fromblood type
O	O	O, A, B, AB
A	O, A	A, AB
B	O, B	B, AB
AB	O, A, B, AB	AB

Although blood group compatibility is important, nowadays, ABO incompatible transplantations are being performed successfully. However, they must have negative tissue cross match with the recipient.

5.4.1. Donor evaluation

- Detail history and examination
- Laboratory and radiologic evaluation
  - Blood group, tissue typing and crossmatch
  - CBC (including Hb, TLC, DLC, platelets)
  - ESR
  - Coagulation
  - Urea, creatinine, Na^{+}, K^{+}, Ca^{2+}, PO_4^{3-}, LFT

- Urine RME
- Urine culture (x2)
- Urinary albumin/creatinine ratio
- 24-hour urine protein estimation and Creatinine clearance (x2)
- Serum uric acid
- Fasting lipids
- HBsAg, HIV, HSV, Hep. C, EBV
- CMV, TORCH
- CXR and ECG
- PSA (males > 50 years old)
- Mammogram (females > 45 years old) or breast U/S if indicated.
- PAP smear (most females)
- Renal ultrasound
- Renal DTPA / split function
- Spiral CT angiogram ± formal DSA if required

- Tissue Type Work-up:(T & B Cell Cross Match) x 2.
- Tissue type – crossmatch.
- Recipient HLA antibody testing as required (ELISA, Luminexetc).

5.5. Evaluation by surgeons

5.5.1. Recipient evaluation

- The standard evaluation consists of medical fitness, cardiac status, vascular status, status of the immune system, presence of chronic infection, urological evaluation especially in children and adolescent with the history of recurrent UTI or history of obstructive uropathy.
- Immunological evaluation consists of HLA typing (HLA-A, B and DR) and screening for the cytotoxic antibodies against the donor lymphocytes and tissue crossmatch.

5.5.2. Laboratory and radiologic evaluation

- CBC

- Viral serology
- Liver function test
- PTH, calcium, phosphate
- Chest X-ray
- PSA (men >50)
- Mammogram (female >50)
- PAP smear

5.5.3. Absolute contraindications

- Presence of active infections
- Active systemic neoplastic disease
- Active immunological disease
- Uncontrolled psychosis
- Any medical condition with a severely shortened life expectancy.
- Positive cytotoxic T cell cross match.

Once the donor and recipient are evaluated and accepted, the surgical date is fixed.

Recipients are admitted two to three before the planned transplantation surgery

Donors are admitted one day before the date of surgery.

Renal transplant surgery- the kidney is placed in the iliac fossa in the extraperitoneal space. The donor renal artery is often anastomosed either to the internal iliac artery or to the external iliac artery. The renal vein is anastomosed to the external iliac vein.

5.6. Drugs used after renal transplantation

5.6.1. Immunosuppressive drugs

Immunosuppression will usually follow a basic regimen of triple therapy with:

- Steroids
- Mycophenolate mofetil (MMF) or azathioprine (AZA) as an alternative.
- Calcineurin inhibitor (CNI): Tacrolimus/FK 506 or Cyclosporine.

Corticosteroids

Corticosteroids are the cornerstone of transplant immunosuppression. They act as an agonist of glucocorticoids. They regulate immune response by regulation of the transcription factors activator protein.

Main sided effects - Osteoporosis, cataracts, avascular necrosis of femoral head, hypertension, hyperglycemia, hyperlipidemia, cushingoid features etc.

Mycophenolate mofetil

Mycophenolate mofetil is an important component of the immunosuppression regimen. Mycophenolate reversibly inhibits inosine monophosphate dehydrogenase (IMPDH) which blocks the de novo synthesis of purine biosynthesis that selectively interferes with the proliferation of T and B cells and decreased antibody production.

Side effects – Gastrointestinal toxicities like oesophagitis, gastritis, diarrhoea, oral ulcerations, bone marrow suppression etc

Azathioprine

Azathioprine suppresses the proliferation of activated T and B cells and also block the purine synthesis. It is metabolized in the liver and converted to hypoxanthine guanine phosphoribosyl transferase, so allopurinol (xanthine oxidase inhibitor) will increase its level so the use of azathioprine should be avoided with allopurinol.

Side effects - Major side effect is bone marrow suppression leading to leucopenia, anemia, thrombocytopenia.

Calcineurin inhibitors

Calcineurin inhibitors (cyclosporine and tacrolimus) are the mainstay of immunosuppression. Both act by binding with immunophilins and subsequently inhibiting calcineurin which downregulates the activation of T cells. Tacrolimus inhibits calcineurin with greater potency than cyclosporine.

Side effects –both causes nephrotoxicity, hyperkalemia, hypertension, diabetes. Gingival hyperplasia and hirsutism are more common with cyclosporine whereas tremor and glucose intolerance is more common with tacrolimus.

As both the drugs are metabolised through CYP3A4 it interacts with the drugs that affect the level of CYP3A4. Many interactions involve the cytochrome P450 3A enzyme (enzyme induction or inhibition).
Drug interactions for the CNIs are numerous. The potential for interaction should be assessed carefully whenever there are changes in medications.
Commonly used drugs that increase CNI concentrations include calcium antagonists (especially diltiazem, verapamil), corticosteroids, antifungals (ketoconazole, fluconazole), macrolide antibiotics (erythromycin, roxithromycin) and the mTOR inhibitors (sirolimus and everolimus). Grapefruit juice also increases CNI concentrations.
Commonly used drugs that decrease CNI concentrations include anti-epileptics (eg. barbiturates, phenytoin, carbamazepine) and rifampicin.

5.6.2. Induction agents

Induction with basiliximab or ATG may be added for recipients at high risk of rejection because of immunological or functional reason.

Basiliximab

It is a chimeric monoclonal anti-CD25 antibody. It induces relatively mild immunosuppression and is used as an induction agent to prevent rejection.

Anti-thymocyte globulin

Polyclonal anti-lymphocyte agents are produced by immunizing animals with human thymus-derived lymphoid cells. rabbit anti-thymocyte globulin is currently the preferred preparation. It is used as an induction agent or for the treatment of corticosteroid rejection.

5.6.3. Other medications

Mouth care

- Nystatin (1 month) 1ml orally QID
- Candid oral drop QID (for 1 month) – lozenges

Ulcer prophylaxis

- Pantoprazole 20 mg daily or Ranitidine 150 mg BID – first 3 months at least.

PCP prophylaxis

- Cotrimoxazole
  If Sulfa allergy: Dapsone 100 mg three times a week.

CMV prophylaxis

- Valgancyclovir

5.7. Post-transplantation infection

Infection is the second most common cause of death in renal transplant patients.

Predisposing factors are *immunosuppression, vascular or urinary catheters, stents*etc

Causes *of infection*-

- Infection source and sites are:– urinary tract, respiratory, wound, intraabdominal.
- Bacterial – Nocardia, Listeria, mycobacterium species
- Viral –HSV, CMV, VZV, influenza, BK virus infection
- Fungal-candida, aspergillus , Cryptococcus
- Parasites-*Pneumocystis carinii*, strongyloides species, leshmaniasis.

5.8. Rejection

- Rejection is an immunological response involving the recognition of foreign antigens on donor tissues by recipient lymphocytes or antibodies and destruction of the antigen-bearing graft.
- Rejection both acute and chronic is defined by histologic findings after transplant biopsy.
- It is divided into:
  - T cell-mediated rejection
  - Antibody-mediated rejection.

5.8.1. Diagnosis and treatment of acute rejection

Rejection may occur at any time. Signs suggestive of rejection include:

- Rise in serum creatinine
- Hypertension
- Oliguria; Oedema

- Rarely pyrexia, graft tenderness and swelling
- Proteinuria /hematuria

Unless there are major impediments or contraindications all episodes of rejection should be biopsy proven. If there is a degree of urgency and biopsy cannot be done then a pulse of IV methylprednisolone can be given.

5.8.2. Acute cellular rejection

Treatment of acute cellular rejection continues to be pulse steroid.

- Methylprednisolone 250 mg IV pulse daily for three days.
- If the levels of CNI are low then it should be increased.
- In case of severe cellular rejection or steroid-resistant cellular rejection, ATG should be given.

5.8.3. Acute antibody-mediated rejection

It may be possible to anticipate patients with a high risk of this rejection

- Previous graft
- High PRA
- Previous crossmatch positive
- Antibody specificities

5.8.3.1. Diagnosis

- Presence of donor-specific antibodies at the time of rejection.
- Widespread C4d positivity including PTC.
- PMN, Macrophages or thrombi in peritubular capillaries.

5.8.3.2. Treatment

Depending on which of the features are present, treatment can be chosen:

- Steroid
- Optimization of CNI and MMF
- Plasmapheresis + IVIG
- Rituximab

Plasma exchange

- Plasma exchange can be given: Five exchanges over seven days
- If the rejection is severe first two exchanges can be done in the first 2 subsequent days

Follow up

Review after 7-10 days this will include:

- Re-biopsy
- DSA level

In the case of ongoing ABMR, further course of plasma exchange + IVIG can be considered.

In case of refractory ABMR consider rituximab 375mg/m^2.

Annexes

Annex 1. Prescription for starting hemodialysis (Acute and maintenance)

- Duration: One to one and half an hour on the 1st day, gradually increase the duration to 4 hours depending on patient's condition. Dialysis can be done up to 2-3 days continuously increasing the duration of the dialysis. There after decide regarding the dialysis depending on the condition of the patient.
- Anticoagulation:
  - Unfractionated Heparin (UFH) is to be used as an anticoagulation
    - Administration differs from center to center and ideally it should be monitored with bedside activated coagulation time (ACT) of 140–180 sec (80% above baseline), or in the laboratory by targeting an activated partial thromboplastin time ratio (aPTTr) of 1.5–2.5.
    - Use UFH 2000U in circulation before starting the dialysis which is drained out completely.
      - Rate: Bolus at the initiation (1000U; 25-50U/Kg) and infusion @ 1000U/hr (500-1500U/hr)
      - It is not necessary to give infusion of heparin when patient is being dialysed for less than 3 hrs.
      - Stop heparin infusion 30-60 mins before stopping the dialysis when dialysing through fistula or graft. Do not use heparin on the first day if catheter has been placed on the same day
      - Do not use heparin if there is bleeding abnormality, recent surgery, pericarditis and has thrombocytopenia (<100,000/cumm) or heparin induced thrombocytopenia (HIT).
      - In patients who are dialysed through catheters heparin lock is prepared and pushed into the ports at the end of the dialysis.

- Normal saline flush: If heparin is contraindicated then use saline bolus flushes in between (25–150 mL injected into the arterial line every 15–30 min).

Signs of clotting in the circuit
Extremely dark blood in circuit
Black streaks in dialysers: clotted fibers
Clots in arterial side header
Foaming and clot in drio chamber and venous trap
Rapid filling of transducer monitors with blood
Increase in venous pressure

- Blood pump rate: Start with low pump rate of 180 to 200ml/min then gradually increase to 250-300 as tolerated.
- Dialysate flow rate: ~700ml/min
- Target reduction of urea: ~60% in each session
- Ultrafiltration: as per the patient's condition
- If patient has severe metabolic acidosis: Inj. 7.5% Sodium bicarbonate (50-100ml) boluses can be considered while patient is under dialysis.
- Check for complications: especially hypotension and hypoglycaemia.
  - It is advisable to give Inj. 25% dextrose (25ml) to patient of sepsis or diabetes at the start of the dialysis and in between with regular checking of blood glucose with glucometer.
  - If patient becomes hypotensive: Stop ultrafiltration, give bolus of normal saline or Inj. 25% dextrose and raise the leg end. If still hypotensive then stop dialysis and return the blood to the patient.
    - Consider changing to SLED
- Patient with pulmonary edema:
  - Procedure can be started with isolated ultrafiltration and remove the fluid then continue with regular HD, or

Do a sequential HD and Iso UF.**Annex 2. Prescription for SLED**

- Duration: 1st day 4 to 6 hrs then can be increased up to 8 to 12 hrs. SLED can be done daily or on alternate day basis. Night is preferable time for SLED because the HD machines are free at this hour of the day and patient is not taken for any investigational procedures.
- Anticoagulation: Refer Annex 1
- Blood pump rate: ~100ml/min
- Dialysate flow rate: ~300-500ml/min
- Target reduction of urea: ~60% in each session
- Ultrafiltration: as per the patient's condition
- If patient has severe metabolic acidosis: Refer Annex 1Check for complications: Refer Annex 1.

Annex 3. Prescription for peritoneal dialysis in AKI

- Fluid containing Bicarbonate buffer is recommended
- Once, K^+ falls below 4mEq, K^+ should be added for dialysate
- Check K^+ once daily or twice daily at least
- For initial 24 hrs, duration of cycle time is dictated by clinical circumstances like presence of acidosis, hyperkalaemia and fluid overload.
- Short cycle time (every 1-2 hrs) may be needed in first 24 hrs.
- Once clinical circumstances is improved, cycle time maybe increased to 4-6 hrs.
- Cycle time fill: 1-10 min, drain 2 min, dwell- 60-90 mins.
- Fill volume : Start with 10-20 ml/kg, then increase upto 30-40 ml/kg (800-1000ml/m^2).
- Addition:
    - Heparin 500 U/l diasylate
    - ± Antibiotics
- Fluid choice:
    - Fluid overload/pulmonary edema- 4.25% Dextrose
    - Mild fluid overload: alternate 1.5% and 4.25% or use 2.5% Dextrose
    - Euvolaemic/hypovolaemic: 1.5% Dextrose

Further readings

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