

Pathogenesis

- Autoantibodies form immune complexes which are deposited in glomerular capillary endothelium with resultant complement mediated inflammation.

Clinical presentation

- The majority of children with SLE are adolescent females. The most common presentation is as nephritic or nephrotic syndrome with hypertension and impaired renal function. Less than 2% of patients may have a picture of acute kidney injury with rapidly progressive glomerulonephritis.

WHO classification of Lupus Nephritis

- Kidney biopsy remains the gold standard for establishing the diagnosis of lupus nephritis. WHO classification based on histopathology, immunofluorescence, and electron microscopy is useful to determine the selection of specific immunosuppressive therapies and to guide the patient and parents about prognosis. INSERT TABLE HERE.

Diagnosis

- The diagnosis of SLE is confirmed by detecting antinuclear antibody(ANA), low C3 and C4, and raised anti double stranded DNA antibody. Renal biopsy is performed in all patients to classify the disease severity.

Treatment

- The treatment of lupus nephritis depends on its severity. For class I and II, no specific therapy is required. In moderate to severe nephritis (Class III and IV), therapy is initiated with prednisolone 1-2mg/kg/d for 4-6 weeks and then gradually tapered to a maintenance dose of 0.2 to 0.3 mg/kg daily for 2-3 years or more. These patients are also given 5-6 monthly intravenous cyclophosphamide pulses at a dose of 500 -1000mg/m². Subsequently, cyclophosphamide is replaced by azathioprine (1-2mg/kg/d OD) or mycophenolate mofetil (25-30mg/kg/d in 2 divided doses). For class V nephritis, a combination of prednisolone and a calcineurin inhibitor (cyclosporine or tacrolimus) or mycophenolate mofetil is given. For patients presenting with AKI (rapidly progressive GN), 3-6 daily or alternate day pulses of intravenous methylprednisolone (15-20mg/g/dose) are used followed by oral prednisolone.

NEPHROTIC SYNDROME**CASE**

A 4-year-old previously healthy boy presents with acute onset of **facial edema** and **generalized swelling**. Examination reveals an afebrile child with a BP of 90/50 mmHg. He is alert with significant bilateral periorbital edema and pitting pedal edema. He has ascites with no organomegaly. His scrotum and lower extremities have tense pitting edema. On laboratory investigations, electrolytes, urea, and creatinine are normal. Urine dipstick shows **protein 4+**. A 24 hours collection of urine reveals a protein excretion of **2.5 g/24 hour**. There is also **hypoalbuminemia** and **hypercholesterolemia**.

NEPHROTIC SYNDROME (NS)

- It is the most common renal disease in children
- It is characterized by
 - ✓ Progressive generalized edema
 - ✓ Heavy proteinuria > 1 g /m²/ 24hr
 - ✓ Hypoalbuminemia < 2.5 g/dl
 - ✓ Hypercholesterolemia>220mg/dl

Classification According to response to Steroids

1. **Steroid Sensitive Nephrotic Syndrome (SSNS)** 85-90% NS patients who enter remission with corticosteroid treatment.
2. **Steroid Resistant Nephrotic Syndrome (SRNS)** 10-15% NS patients who fail to enter remission after 8 weeks of treatment with corticosteroids.
3. **Steroid Dependent NS (SDNS)** SSNS who relapse while patient is still on steroids(usually tapering dose) or within 2 weeks of stopping steroids
4. **Frequent Relapsing NS (FRNS)** SSNS who relapse 4 or more times in any 12 months period or 2 relapses in 6 months.
5. **Infrequent Relapsing NS (IRNS)** SSNS who relapse 1-3 times in any 12-months period or 1 relapse in 6 months.

Remission:

Urine dipstick proteinuria 0 to trace for 3 consecutive days with resolution of edema and normalization of serum albumin to at least 3.5 G/dl.

Relapse:

- Urine dipstick > 2+ for 3 consecutive days usually with recurrence of edema.

Classification according to age.

1. **Congenital Nephrotic Syndrome (CNS)** With onset at birth or before age 3 months
2. **Infantile Onset Nephrotic Syndrome (INS)** With onset between age 3 month to 12 months
3. **Childhood Nephrotic Syndrome** With onset between age 1 year to 12 years
4. **Adolescent Nephrotic Syndrome** With onset after age 12 years

Classification according to Etiology

1. Primary /Idiopathic Nephrotic Syndrome
2. Etiology unknown

Secondary Nephrotic Syndrome

- Secondary to some underlying external cause. All these classifications have therapeutic as well as prognostic implications.

Atypical features in Nephrotic syndrome

These may include one or more of the following;

1. Persistent microscopic hematuria or gross hematuria
2. Persistent low C3 level
3. Persistent hypertension
4. Deranged RFTs
5. Age < 1yr or >12years
6. External manifestation of a systematic disease

IDIOPATHIC NEPHROTIC SYNDROME

- This is the most common type of nephrotic syndrome(NS) in children
- It accounts for about 90% of childhood NS.
- Overall incidence is between 2-6 cases per 100,000 children.
- It is more common in boys than girls (2:1) and typically occurs between 2-6 years of age.
- The disease is immune mediated and usually occurs after viral respiratory infections.
- **Primary histologic subtypes include:**
 - Minimal change Nephrotic Syndrome 75%
 - Focal Segmental Glomerulosclerosis (FSGS) 10% (MCNS)
 - Mesangioproliferative Glomerulonephritis (MesPGN)5%
 - Membranoproliferative Glomerulonephritis (MPGN) 4%
 - Membranous Nephropathy (MN) 1.5%
 - Immunoglobulin A Nephropathy(IgAN)
 - IgM Nephropathy.
 - C1q Nephropathy.

Pathogenesis (Mechanism of proteinuria)

- Glomerular capillary wall comprises 3 layers; an inner endothelial layer, a basement membrane and an outer epithelial layer composed of specialized cells called Podocytes. All 3 layers are negatively charged. Plasma albumin is also negatively charged. In nephrotic syndrome, due to loss of negative electrical charge on the basement membrane and epithelium, albumin is lost in urine.
- There is a generalized disorder of T-cell function which results in production of lymphokines which increase vascular permeability leading to proteinuria.
- In MCNS, proteinuria is selective; only albuminuria. In other lesions high molecular weight globulins are also lost in urine.

Pathophysiology:

- Edema is the cardinal feature of NS. There are 2 hypotheses of edema formation.

Underfill hypothesis:

- Heavy proteinuria is NS leads to hypoproteinemia and a fall in plasma oncotic pressure.
- Decrease in plasma oncotic pressure results in leakage of plasma water into the interstitium, producing edema.
- Resulting hypovolemia stimulates renin-angiotensin-aldosterone system (RAAS), release of antidiuretic hormone (ADH) and inhibition of atrial natriuretic peptide (ANP).
- All these lead to salt and water retention further aggravating edema formation. MCNS better approximates to the underfill hypothesis.

Overfill hypothesis:

- In NS due to lesions other than minimal change, there is primary alteration in renal function causing salt and water retention, circulating volume expansion and an increase in plasma hydrostatic pressure leading to leakage of excess water into the interstitium.

Pathology:**Minimal Change Disease: 75%**

- Glomeruli appear normal or show a minimal increase in mesangial cells and matrix.
- Immunofluorescence is normal.
- Electron microscopy shows fusion of epithelial foot processes.
- More than 95% children with MCNS respond to corticosteroids.

Focal Segmental Glomerulosclerosis (FSGS) 10%

- Glomeruli show sclerotic lesions that are both focal (present only in a proportion of glomeruli) and segmental (a portion of glomerulus).
- Immunofluorescence microscopy shows IgM and C₃ deposits.
- Electron microscopy shows segmental scarring of glomerular tuft with obliteration of capillary lumen.
- Only 20% patients with FSGS respond to prednisone.
- Disease is often progressive and leads to endstage kidney disease.

Mesangioproliferative GN:

- There is diffuse increase in mesangial cells and matrix
- Immunofluorescence might reveal IgM and/ or IgA deposits.
- Electron microscopy reveals increased mesangial cells and matrix as well as fusion of epithelial foot processes.
- About 50% respond to corticosteroids.

Clinical Findings:

- NS in children is most common between ages 2-6 years.
- MCNS is present in 85-90% in patients < 6 years of age. In contrast, in adolescents only 20-30% have MCNS. FSGS is more common in this older age group.
- Typically, the child develops periorbital swelling and oliguria follow flu like symptoms.
- Within few days edema becomes generalized when patient develops ascites, pleural effusion and scrotal

swelling in boys. There is often oliguria and mild abdominal pain.

- With marked generalized anasarca, there may be dyspnea.
- Blood pressure is often low normal.
- Occasionally, a patient may present with complications listed below.

Diagnosis:

- Dipstick proteinuria 3+ or 4 +
- Timed Urine collection: proteinuria $> 40\text{mg}/\text{m}^2/\text{hour}$ or $>1\text{g}/\text{m}^2/24$ hours
- Spot Urinary Protein: creatinine = $> 2(\text{mg}/\text{mg})$
- Hypoalbuminemia < 2.5 g/dl
- Hypercholesterolemia $> 220\text{mg}/\text{dl}$

Pre requisites before starting steroid Therapy:

- Rule out TB by tuberculin test and chest X-ray
- HBsAG, anti HCV and serum ALT levels.

Management:

General Management:

- Most patient can be managed as outpatients.
- Parental counseling is very important for best outcome. Tell them about the disease nature, its long duration, natural relapsing course, side effects of treatment and regular follow up.

Diet:

- Increase protein intake to 130% to 140% of the RDA for age.
- Avoid saturated fats that can worsen hyperlipidemia.
- Restrict salt intake to $< 2\text{g}/\text{day}$, No added salt is to be advised.

Diuretics:

- Not normally required. Injudicious use in all patients with NS may lead to grave complications such as shock, acute kidney injury (AKI) and thromboembolism .
- Very cautions use may be needed when:
 - Severe generalized anasarca causing respiratory distress.
 - Imminent scrotal skin rupture.
- It is best to infuse salt free albumin 20% or 25% at a dose of 1 g/ kg along with furosemide in such situations.

Specific Management:

Treatment of initial episode of NS:

- In suspected MCNS, start with prednisolone $60\text{mg}/\text{m}^2/\text{day}$ or $2\text{ mg}/\text{kg}/\text{day}$ (maximum $60\text{ mg}/\text{day}$) for 4-6 weeks as a single morning dose after breakfast.
- If remission is achieved, prednisone $40\text{ mg}/\text{m}^2\text{qod}$ or $1.5\text{ mg}/\text{kg}\text{ qod}$ is given for another 2-5 months, with tapering. A minimum total duration of treatment is 12 weeks.

Treatment of IRNS:

- Prednisone $60\text{mg}/\text{m}^2/\text{day}$ or $2\text{ mg}/\text{ kg}/\text{day}$ until dipstick protein is -ve for 3 days.
- Then $40\text{ mg}/\text{m}^2/\text{day}$ or $1.5\text{mg}/\text{kg}/\text{day}$ on alternate days for 4 weeks, then stop.

Treatment of FRNS:

Continue infrequent relapse treatment for 3 months at lowest dose to maintain remission or use corticosteroid sparing agents like cyclophosphamide, levamisole, calcineurin inhibitors (cyclosporine A, Tacrolimus) or mycophenolate mofetil.

Treatment of SDNS:

Treatment duration is prolonged with lowest effective dose of prednisolone ($0.25\text{ mg}/\text{kg}/\text{day}$ or $< 0.5\text{ mg}/\text{kg}/\text{qod}$) avoiding steroid toxicity. Steroid sparing agents as for FRNS are often utilized.

Adverse Effects of steroids:

- Cushingoid features and obesity
- Hypertension
- Growth retardation (Short stature)
- Behaviour changes like aggression, hyperactivity, sleep disturbances
- Increased susceptibility to infections
- Gastritis
- Osteoporosis and Osteopenia
- Posterior subcapsular cataracts
- Diabetes mellitus
- Benign intracranial hypertension
- Delayed wound healing
- Proximal myopathy
- Adrenal Suppression
- These side effects are to be kept in mind and countered whenever possible.

Complications of NS and their Management

Infections:

- NS patients are prone to significant infections due to defective humoral and cellular immunity as well as due to use of steroids.
- Always keep a high index of suspicion for infections as the child may be afebrile despite harboring severe infection.
- Common infections in NS include cellulitis, peritonitis, pneumonia, UTIs, and bacteremia.
- Chickenpox and shingles are medical emergency in children receiving immunosuppressive drugs.
- If an infection is suspected , a blood culture should be taken first and then empiric broad spectrum antibiotic therapy started.
- For spontaneous bacterial peritonitis, peritoneal fluid analysis, gram staining and culture should be done and broad spectrum antibiotics covering pneumococcus and gram negative bacteria started.

Thromboembolism:

- NS patients are prone to both arterial and venous thrombosis.
- Predisposing factors include:
 - Thrombocytosis and increased platelet aggregability
 - Increased clotting factors 5,7,8,10,1
 - Decreased antithrombin III.
 - Hypovolemia and increased blood viscosity.
 - Corticosteroid therapy.

- Injudicious use of diuretics.
- Treatment will include low molecular weight heparin, regular heparin warfarin, antiplatelet agents like clopidogrel, low dose aspirin.

Relapse with upper respiratory Infection:

Most relapses are associated with viral respiratory infections.

If the child is already receiving alternate day treatment with steroids and develops URI with relapse of proteinuria, the same dose is given daily for one week and if remission is achieved, bring back to same alternate day dosage. If the child is off medications, prednisolone 0.5 mg/kg/day for one week is recommended to prevent relapse.

Home Monitoring of Proteinuria:

This is quite simple and cheap with urinary dipstick. The first morning specimen of urine is tested daily for proteinuria and a diary is maintained. This is very helpful to detect early relapse of proteinuria and thus to prevent relapse of the disease by giving daily prednisolone (0.5 mg/kg/d) for one week.

Calcineurin Inhibitors (CNIs)

Cyclosporin A:

- Dose is 4-5mg/kg/day (1000-150mg/m² /d) in 2 divided dose
- Side effects: Nephrotoxicity (Monitor trough levels 8-150ng/ml)
Cosmetic side effects e.g. Hirsutism, gum hypertrophy
Others: Hypertension, hypercholesterolemia , tremors

Tacrolimus:

- Action is similar to cyclosporine
- Dose is 0.1-0.15mg/kg/d in 2 divided dose taken before meals.
- No cosmetic side effects and no lipid abnormalities but nephrotoxicity and hypertension are seen
- Other side effects include diarrhea , headache , high blood glucose level.

Mycophenolate Mofetil:

- Dose is 30mg/kg/d (600-750 mg/m²/d) in 2 divided dose taken before meals
- No nephrotoxicity or cosmetic side effects
- May cause leucopenia , raised transaminases.

Levamisole:

- Dose is 2-2.5mg/kg/day
- Effective in only FRNS and SDNS
- Side effects: G1 upset , flu-like symptoms, transient leucopenia skin rash

Inj. Rituximab:

- Anti CD 20 monoclonal antibody
- Two to four weekly doses (IV infusion 375mg/m²)
- Rescue therapy in FRNS, SDNS and SRNS
- Long term safety is still to be established

Note:

Low dose alternate day prednisolone is combined with all these second line drugs.

Immunizations in children with nephrotic syndrome

- Vaccination reduces the risk of serious infections in nephrotic syndrome.

- Pneumococcal vaccination and influenza vaccination are indicated. Influenza vaccination is recommended annually to the children and their household contacts.
- Live virus vaccines should be deferred until the prednisolone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days.
- Live virus vaccines are contraindicated in children receiving cyclophosphamide or cyclosporine.
- Following close contact of child with varicella infection, varicella-zoster immune globulin is given. Healthy household contacts are immunized with live vaccines to protect the child with nephrotic syndrome from infection. Protect the child with nephrotic syndrome from direct exposure of gastrointestinal or respiratory secretions of vaccinated contacts for 3-6 weeks after vaccination.

Prognosis

- Many children with steroid-responsive nephrotic syndrome have repeated relapses.
- These repeated relapses usually decrease in frequency as the child grows older.
- Children who respond rapidly to steroids and children who have no relapses during the first 6 months after diagnosis usually follow an infrequently relapsing course.
- Child with steroid-responsive nephrotic syndrome is unlikely to develop chronic kidney disease.
- Children with steroid-resistant nephrotic syndrome (especially caused by FSGS) have a much poorer prognosis. They develop progressive renal insufficiency leading to end stage renal disease.

SECONDARY NS

Nephrotic Syndrome secondary to some underlying systemic disease, malignancy or drugs usually presents with atypical features like hematuria, hypertension, deranged RFT , hypocomplementemia and age > 8 years

Systemic Diseases:

- SLE
- HSP
- Hepatitis B virus
- Hepatitis C virus
- HIV
- Malaria

Malignancy:

- Hodgkin lymphoma
- Carcinoma lung
- Carcinoma GIT

Drugs + Chemicals:

- Penicillamine , captopril ,NSAID (cause membranous nephropathy)
- Ethosuximide, lithium , probenid (cause MCNS)
- Procainamide ,Chlorpropamide, Phenytoin (Cause MPGN)

Note: We have to find and treat the underlying cause only in secondary nephrotic syndrome. Omitting the suspected causative drug is necessary.

Congenital NS (NS)**CASE**

A 2 months old male baby presents with decreased urine output and generalized body swelling. Urine examination shows 4+ protein.

- Nephrotic syndrome manifesting at birth or within first 3 months of life is called congenital nephrotic syndrome.
- Congenital nephrotic syndrome has a poorer prognosis.
- Congenital nephrotic syndrome may be classified as primary or as secondary.
- Primary congenital nephrotic syndrome is due to some syndromes inherited as autosomal recessive disorders.
- Secondary congenital nephrotic syndrome may be caused by:
 - In utero infections (cytomegalovirus, toxoplasmosis, syphilis, hepatitis B and C, HIV)
 - Infantile systemic lupus erythematosus
 - Mercury exposure
- Affected infants with congenital nephrotic syndrome present at birth with:
 - Edema caused by massive proteinuria
 - An enlarged placenta (>25% of the infant's weight)
- There is severe hypoalbuminemia, hyperlipidemia, and hypogammaglobulinemia.
- Prenatal diagnosis of congenital nephrotic syndrome can be made by the presence of elevated α -fetoprotein levels (maternal and amniotic).
- **Denys-Drash syndrome:**
 - There is abnormal podocyte function.
 - Patients present with early-onset nephrotic syndrome, progressive renal insufficiency, ambiguous genitalia, and Wilms tumors.
- **Pierson syndrome:**
 - Patients present with congenital nephrotic syndrome and bilateral microcoria (fixed narrowing of the pupil).
- **Diagnosis of congenital nephrotic syndrome is made clinically by:**
 - Severe generalized edema.
 - Poor growth and nutrition with hypoalbuminemia
 - Increased susceptibility to infections
 - Hypothyroidism (from urinary loss of thyroxin-binding globulin)
 - Increased risk of thrombotic events
- Most infants have progressive renal insufficiency.
- Secondary congenital nephrotic syndrome can be treated by treating the underlying cause, such as syphilis.
- Management of primary congenital nephrotic syndrome includes:

- Intensive supportive care with intravenous albumin and diuretics
- Regular administration of intravenous γ -globulin
- Aggressive nutritional support
- Make effort to decrease urinary protein loss with angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, and prostaglandin synthesis inhibitors.
- If above measures fail then unilateral nephrectomy is indicated.
- Bilateral nephrectomies and chronic dialysis is indicated if conservative management fails and patients suffer from persistent anasarca or repeated severe infections.
- Renal transplantation is the definitive treatment of congenital nephrotic syndrome.
- Congenital NS patients are universally hypothyroid due to loss of thyroxin globulin (TBG) in urine. Therefore, all CNS patients are given thyroxin replacement therapy.
- Vaccination: No vaccination is advised in CNS as all formed globulins are lost in urine.

INFANTILE NS (INS)

- When NS onset is between 3 months to 12 months of age, it is labeled as infantile NS. Rare syndromic forms and autosomal recessive FSGS and autosomal dominant FSGS may have infantile onset. They are all steroid resistant forms. Few INS patients may have MCNS and MesPGN and may respond to prednisolone
- Initial renal biopsy is recommended in all INS patients.

Adolescent NS

- First episode of NS after 12 years of age is labeled as adolescent NS. Initial renal biopsy is recommended. Membranous nephropathy and MPGN are more common at this age. The mainstay of treatment is ACEI or ARB for initial 6 months. If high grade proteinuria persists, CNIs, MMF or rituximab may be considered. If however biopsy shows childhood lesions like MCNS, MesPGN or FSGS, the same protocol of treatment as of children of younger age group.

Steroid Resistant Nephrotic Syndrome (SRNS)

- Renal biopsy is recommended before starting specific therapy.
- Most patients have FSGS (80%) followed by MesPGN, MCNS and MPGN.
- There is 50% risk of progression to ESKD within 5 years of disease onset.
- Calcineurin Inhibitors (CNIs) (cyclosporine and tacrolimus) are recommended as initial therapy
- Mycophenolate Mofetil has been shown to be effective in some patient.
- Strict control of hypertension is very important to prevent progression to CKD
- ACE inhibitors like enalapril and ARBs like losartan potassium may be given as an adjunct to reduce proteinuria in SRNS

Alternative Therapies in the treatment of NS

Alternative therapies are given in FRNS, SDNS and SRNS patients.

Cyclophosphamide:

- Effective in FRNS and SDNS to prolong remission and reduce the number of relapses.
- Dose is 2-2.5mg/ kg/day, single daily dose for 8-12 weeks (Total cumulative dose should not exceed 150-170mg/kg.)
- Main side effects include neutropenia, hemorrhagic cystitis , alopecia ,sterility, increased risk of future malignancy
- During treatment with cyclophosphamide white cells count should be monitored weekly, if the counts falls below 5000/mm3, drug should be stopped.
- Encourage increased fluid intake to prevent hemorrhagic cystitis.

Acute kidney Injury : (AKI)

CASE

A 4-year-old girl presents with history of **anuria**, dysuria and abdominal pain of 24 hours duration. There is now frank **hematuria**. On examination she is pale. Blood pressure is 120/80 mmHg (**hypertension**). Plasma sodium is 139 mmol/L (**hypernatremia**), potassium 6 mmol/L (**hyperkalemia**), chloride 100 mmol/L, bicarbonate 18 mmol/L (**metabolic acidosis**), **urea** and **creatinine raised**. Abdominal radiograph reveals **calcification** in both kidneys. Abdominal ultrasound shows left-sided hydronephrosis and hydroureter and multiple stones in both kidneys causing **obstruction**.

- Prerenal AKI due to hypovolemia and superimposed sepsis may occur . Underlying lesion is usually acute tubular necrosis (ATN) .
- Complete recovery is the rule with prompt treatment

Shock:

- An occasional patient may land with hypovolemic shock due to inappropriate high dose of diuretics. Urgent volume replacement is needed in such patient.

Hyperlipidemia:

- Dietary fat restricted to <30% of calories and saturated fats to <10% of calories
- Hyperlipidemia resolves as the patient goes into remission

Malnutrition:

- This is common SRNS and frequent relapsers due to heavy protein losses
- Muscle wasting is masked by edema
- High protein diet is recommended throughout the treatment course.

Osteoporosis:

Vitamin D supplementation (e.g. cholecalciferol) and calcium supplements are often needed to minimize osteoporosis

Gastritis: Give H2 blockers, proton pump inhibitor or antacids along with prednisolone to prevent this complication.

Acute Kidney Injury: (AKI)

Formerly called acute renal failure, acute kidney injury (AKI) is a clinical state when sudden deterioration in

kidney function results in the inability of the kidneys to excrete nitrogenous waste products and there is disturbance of fluid and electrolyte balance.

Acute kidney injury network (AKIN) categorizes the severity of AKI by rise in serum creatinine above the baseline:

- Stage 1 = Serum creatinim >1.5 times normal
- Stage 2 = Serum creatinim >2 times normal
- Stage 3 = Serum creatinim >3 times normal

Acronym RIFLE stands for Risk , Injury , Failure , Loss and End- stage renal disease.

Modified pediatric RIFLE (p RIFLE) Criteria:

CRITERIA Estimated CCL Urine output

Risk	eCCL decrease by 25% < 0.5ml/kg/hour for 8 hours
Injury	eCCL decrease by 50% < 0.5ml/kg/hour for 16 hours
Failure	eCCL decrease by 75% <0.3ml/kg/hour for 24hours Or eCCL 35ml/min /1.73m2 or anuric for 12 hours.
Loss	Persistent failure >4 wk
End-stage	Persistent failure > 3 mo

CCL = creatinim clearance (or GFR) eCCL = estimated creatinine clearance

Etiology:

AKI is classified into 3 categories according to the cause of AKI prerenal , intrinsic , and postrenal

Prerenal causes: Prerenal AKI occurs when there is inadequate renal perfusion due to:

- Diminished intravascular volume e.g. dehydration due to vomiting , diarrhea , hemorrhage, diabetic ketoacidosis , burns
- Decreased effective renal perfusion in heart failure and nephrotic syndrome
- Hypotension in septic shock
- Impaired renal blood flow due to drugs / radiocontrast agent e.g. cyclosporine, ACEI , ARBs.

Intrinsic Renal Causes:

- Glomerulonephritis
- Hemolytic Uremic Syndrome
- Acute Tubular Necrosis
- Renal vein Thrombosis
- Acute interstitial Nephritis
- Tumor Lysis Syndrome
- Rhabdomyolysis (Crush injuries)

Postrenal causes:

- Posterior urethral valves
- Bilateral ureterovesical junction obstruction
- Neuropathic bladder
- Bilateral obstructive renal / ureteric stones
- Tumor obstruction
- Hemorrhagic cystitis

Pathogenesis:

Prerenal AKI:

Due to hypovolemia , hypotension or decreased effective blood flow , there is hypoperfusion of the kidneys which results in decreased GFR. Hypovolemia stimulates antidiuretic hormone (ADH) and aldosterone production resulting in oliguria and concentrated urine. AKI due to prerenal cause responds to early volume replacement, If renal hypoperfusion is prolonged beyond a critical point , intrinsic renal damage (acute tubular necrosis) occur.

Intrinsic renal AKI:

- Prolonged untreated prerenal failure leads to ischemic acute tubular necrosis (ATN)

- In hemolytic uremic syndrome (HUS) there is thrombotic microangiopathy (TMA) due to circulating Shiga toxin
- Untreated septic shock leads to ischemic as well as toxic ATN
- In acute glomerulonephritis (AGN) there is small vessel thrombosis by activation of coagulation system
- In acute interstitial nephritis (AIN) there is a hypersensitivity reaction to a drug or infectious agent
- In tumor lysis syndrome, there is obstruction of renal tubules by uric acid crystals.

Postrenal AKI:

- Bilateral urinary tract obstruction causes back pressure to the kidneys to cause AKI
- Relieving this obstruction is urgently required for a better outcome.

Clinical Findings:

- The child with AKI may have altered mental status and convulsions due to advanced uremia or hypertensive encephalopathy.
- Breathing may be rapid and deep from acidosis
- There may be peripheral or pulmonary edema.
- History of fluid or blood loss with severe dehydration (ATN)
- Edema, hematuria and hypertension (GN)
- Dysentery, pallor, petechiae (HUS)
- Sudden passage of dark red urine, pallor and jaundice (intravascular hemolysis e.g. malaria)
- History of interrupted urinary stream, palpable bladder (PUVS)
- Abdominal/flank colic, hematuria, dysuria (Urinary tract calculi)
- Absolute anuria suggests urinary tract obstruction, ATN, bilateral renal vein thrombosis, severe GN or vasculitis
- Nonoliguric renal failure is seen in renal failure due to nephrotoxins. (e.g. Aminoglycosides, radiocontrast agents)
- AKI is sometimes superimposed on chronic kidney disease, growth retardation, renal osteodystrophy, anemia (CKD) and small shrunken kidney on ultrasound (normocytic, normochromic) and suggest CKD.

Investigations:

- CBC with peripheral film may show microangiopathic hemolysis, thrombocytopenia and reticulocytosis in HUS.
- **Renal function tests (RFTs):** BUN, creatinine are raised.
- Serum electrolytes may show low sodium, high potassium, low calcium and high phosphate. Uric acid is always raised
- Throat culture, ASO titer and serum C3 level are examined in suspected acute GN.
- In glomerular and vascular disease, proteinuria > 1 g/m²/d along with red cells and casts may be seen.

- Eosinophils in the urinary sediment suggest interstitial nephritis.
- The presence of renal tubular epithelial cells, cellular debris and muddy brown tubular cells support the diagnosis of ATN.
- **Abdominal ultrasound:** It will reveal renal size, structural defects, hydronephrosis, hydroureter, stones and bladder anatomy.
- **Plain X-ray abdomen:** It may reveal stone, spinal abnormalities

MCUG:

It is diagnostic test in posterior urethral valves and vesicoureteral reflux.

X-ray chest: It may reveal cardiomegaly and pulmonary edema

Renal biopsy:

It is done in AKI when:

- Etiology of AKI is not clear
- Unremitting AKI > 2-3 weeks where it may reveal crescentic GN or extent of renal damage e.g. ATN, cortical necrosis.

Management

General measures

- Establish a secure IV line.
- Draw blood samples for necessary investigations.
- Collect urine sample. Catheterize if bladder is palpable otherwise attach urine bag.
- Record blood pressure (one hourly if it is high; four hourly if it is normal).
- Careful intake and output record.
- Daily weight measurement.
- Urea, creatinine, serum electrolytes, and blood gases are estimated daily.
- Frequent ECG monitoring to detect hyperkalemia on time.
- In established renal failure, total fluid given per day is as follows:
 - 400 ml fluid/m²/day (insensible losses) + output (losses in urine, stool, vomiting)
 - In infants 15 ml/kg fluid plus output (losses in urine, stool, vomiting) is given.
 - Increase fluids by 10% for each 1°C rise in temperature.
- In general, glucose-containing solutions (10–25%) without electrolytes are used as maintenance fluids. The composition of fluid may be modified according to the state of electrolyte balance.
- At least 300 calories/m²/day are given to reduce catabolism. Main part of calories should be from carbohydrates and fat. Protein should be restricted to 0.5 g/kg/day (1.0–1.5 g/kg/day in infants) of high quality protein such as egg, chicken, etc. Oral intake is more appropriate to avoid the fluid overload.
- Reversible conditions that can be treated should be given prompt attention. Obstruction of the urinary tract should be corrected or bypassed.

- Avoidance or careful monitoring of blood levels of drugs excreted by the kidney and appropriately adjusting either the total dose or the dosing interval are very important.

Fluid therapy

Renal failure with dehydration

- If a patient with renal failure is severely dehydrated or is in shock, IV fluid therapy is mandatory. Push normal saline 20 ml/kg within ½ hour.
- After ½ hour, observe for hydration status and passage of urine. If hydration and shock is improved, now give 90 ml/kg of normal saline or ringers lactate slow in 3 hours and again observe the hydration status and urine output.
- If there is no urine output after 3 hours and hydration is improved, give frusemide 2 mg/kg/dose IV stat and observe for 2–3 hours. If urinary output is not increased, a second dose of frusemide may be given. If still there is no urine output, peritoneal dialysis is indicated.
- If hydration is good but blood pressure is low, dopamine infusion is given to improve renal perfusion and blood pressure.

Renal failure with fluid overload (pulmonary edema)

- No IV fluids are given. Give frusemide 2 mg/kg/dose IV stat. Assess after 2–3 hours. Dose of frusemide may be repeated.
- If there is no diuresis after 2 doses of frusemide, a single IV dose of 0.5–1.0 g/kg of mannitol may be given over 30 minutes.
- Dopamine (5 µg/kg/minute) may be given if there is no hypertension; this will increase renal cortical blood flow.
- Peritoneal dialysis is indicated if there is no response to the above treatment.

Management of complications

Hyperkalemia

- Hyperkalemia is defined as serum level greater than 6 mEq/l.
- Medicines used to decrease the serum potassium when serum potassium rises above 7 mEq/l (but that do not affect the total body potassium) are:
 - Calcium gluconate (10%) at 0.5–1.0 ml/kg given IV diluted and slow over 10 minutes
 - Sodium bicarbonate 1–2 mEq/kg given slow IV diluted in normal saline.
 - Glucose solution (25%) 2 ml/kg given with regular insulin 1 unit/5 g of glucose given IV over 1 hour.
 - Procedure to deplete potassium stores includes the use of Kayexalate, either orally or per rectum, at the dose of 1 g/kg mixed with sorbitol. It is given for potassium levels of 5.5 mEq/l or more. It exchanges sodium for potassium.
 - β-adrenergic receptor agonists such as salbutamol given by nebulization also acutely lower potassium levels.

- The duration of action of the above measures is just a few hours. Dialysis is the only definitive therapy for removal of potassium.

Acidosis

- Partial correction of acidosis (to raise the arterial pH to 7.20, serum bicarbonate level to 12 mEq/l) is recommended by using the following formula:

$$\text{mEq/l NaHCO}_3 \text{ required} = 0.3 \times \text{weight (kg)} \times (12 - \text{serum bicarbonate, mEq/l})$$
- The remainder of the correction is made by the oral administration of sodium bicarbonate.

Hypocalcemia

- Hypocalcemia and hyperphosphatemia may present as tetany or convulsions. Give 0.5–1.0 ml/kg IV calcium gluconate slow and diluted in 5–10 minutes under cardiac monitoring.

Hyponatremia

- This usually occurs due to fluid overload or hypotonic fluid administration, therefore fluid restriction is indicated.
- Hyponatremia below 120 mEq/l may require correction (elevated to 125 mEq/l) with hypertonic sodium chloride:
 - mEq/l of sodium required = $0.6 \times \text{weight (kg)} \times (125 - \text{serum sodium, mEq/l})$
- When there is congestive cardiac failure and hypertension due to extreme fluid overload, this is a contraindication to hypertonic saline administration. In such situation, dialysis to correct hyponatremia may be required.

Hypertension

- Hypertension is a common complication in acute renal failure as a result of volume overload, primary renal disease, or both.
- Nifedipine or diazoxide are used in acute hypertension. In severe hypertension, continuous IV infusion of sodium nitroprusside is given. For chronic hypertension, propranolol or captopril is given.

Seizures

- This is a rare complication due to primary renal disease, uremia, hyponatremia, hypocalcemia, and hypertension.
- Diazepam is the drug of choice to control such seizures.

Infections

- Children with acute renal failure are susceptible to infections following bladder catheterization or peritoneal dialysis.
- Broad-spectrum antibiotics should be used and nephrotoxic drugs should be avoided.

Anemia

- This is a common complication (the result of volume expansion), but is mild and does not require treatment.
- If Hb falls below 7 g/dl, blood (pack cells 10 ml/kg) should be given very slowly in 4–6 hours.

- Blood should be fresh to decrease the amount of potassium administered.

Gastrointestinal bleeding

- This may be prevented by giving calcium carbonate antacids, or IV cimetidine (5–10 mg/kg/12 hour).

Dialysis

- If the oliguria is prolonged or clinical or metabolic deterioration occurs in spite of careful conservative management, then peritoneal dialysis or occasionally hemo-dialysis is required.
- Following are the indications for dialysis:
 - Hyperkalemia unresponsive to medical therapy
 - Acidosis unresponsive to medical therapy
 - Fluid overload unresponsive to fluid restriction or to diuretics
 - Symptoms and signs of uremia
 - Hypertension or congestive heart failure not responding to medical treatment
- Peritoneal dialysis is generally safe, simple and more effective.
- For peritoneal dialysis pediatric catheter is selected, bladder emptied and abdomen surgically prepared and catheter inserted 2 cm below the umbilicus in the midline under local anesthesia. The entire perforated segment of catheter must lie intra-peritoneally and catheter fixed with tape. A peritoneal dialysate is infused at a rate of 30 ml/kg and allowed to remain in peritoneal cavity for 30 minutes and allowed to drain in a bag by gravity method. If fluid is not recovered fully, then place the child in upright position at an angle of 45°. Dialysis is continued for 48 hours or rarely for 7 days and then catheter is removed. Start with isotonic fluids but if edema or fluid overload is present, alternate two cycles of isotonic with one cycle of hypertonic solution. Heparin can be added to dialysate to prevent clotting in the catheter (500 units/l solution). Antibiotics are added to the dialysis fluids; gentamicin 10 mg/l or cefotaxime 250 mg/l.
- The complications of catheter insertion and peritoneal dialysis are bleeding from insertion site, bowel perforation, peritonitis, respiratory distress, dehydration or hypervolemia, hyperglycemia, electrolyte imbalance, and failure to obtain adequate return of fluid.

Recovery phase

- Recovery from acute renal failure often involves a period of brisk urine output (diuretic phase or recovery phase of acute renal failure).
- This diuresis reflects excretion of water that accumulates in the earlier oliguric phase.

Electrolyte and fluid imbalance may occur in this phase.

Use of medications in AKI

- Avoid nephrotoxic agents eg aminoglycosides, NSAIDs, radiocontrast studies
- Avoid agents that reduce renal perfusion eg ACEI, ARBs

- Dose of agents medications should be adjusted according to GFR (usually taken as $<15\text{ml/min}/1.73\text{m}^2$) consult dose adjusting tables.
- Dopamine: Dopamine at low doses cause renal vasodilatation and may induce modest natriuresis.

Prevention of AKI:

- Prompt rehydration in acute diarrhea
- Judicious use of nephrotoxic drugs
- Careful hydration before radiocontrast diagnostic procedure
- Forced diuresis along with allopurinol to prevent AKI during tumors lysis (at start of chemotherapy)
- High index of suspicion in situations with high risk of AKI e.g post cardiac surgery, sepsis, ventilatory support, use of vasopressors and inotropes.

Prognosis

- Prognosis depends upon the cause. In patients with acute tubular necrosis, the period of anuria or oliguria usually lasts 7–10 days.
- Oliguria lasting longer than 3 weeks, or anuria, makes a diagnosis of acute tubular necrosis very unlikely.
- Prognosis is good (90% complete remission) in acute tubular necrosis, hemolytic uremic syndrome, and other causes responsible for prerenal failure.
- It is poor when renal failure results from rapidly progressive glomerulonephritis, bilateral renal vein thrombosis or bilateral cortical necrosis (less than 10% recovery), and may require chronic dialysis and eventual renal transplantation.

CHRONIC RENAL FAILURE (CRF) Chronic Kidney Disease

CASE

A 10-year-old boy presents with **growth failure**, headache, progressive **pallor**, lethargy, anorexia, **facial puffiness**, and bone and joint pain for last one year. On laboratory investigation, blood urea is 40 mg/dl, **creatinine 7 mg/dl**, Na 146 mEq/l, K 6.5 mEq/l (**hyperkalemia**), Ca 8.5 mg/dl, PO₄ 10 mg/dl.

The term chronic renal failure (CRF) and chronic renal insufficiency (CRI) have now been replaced by more appropriate title of Chronic Kidney Disease (CKD)

Definition:

CKD is defined as evidence of kidney damage for >3 months or a decrease in $\text{GFR} < 6 \text{ ml/min}/1.73\text{m}^2$ for >3 months.

Evidence of kidney damage include:

- Albuminuria $>30\text{mg}/24\text{hr}$.
- Microscopic hematuria with abnormal urine sediment e.g abnormal RBCs morphology.
- RBCs, WBCs or granular casts
- Abnormal imaging e.g. polycystic kidney, dysplastic kidneys, hydronephrosis due to obstruction, cortical

scarring with vesicoureteral reflux, renal masses, renal artery stenosis, small hyperechoic kidneys.

- Abnormal histology e.g FSGS, lupus nephritis etc.

Staging of CKD:

This staging of CKD is proposed by National Kidney Foundation-Kidney Disease Outcome Quality Initiative NKF-KDOQI. CKD is classified into 5 stages based on GFR.

- GFR is calculated by Schwartz formula:

$$\text{GFR}(\text{ml}/\text{min}/1.73\text{m}^2) = \frac{\text{Height}(\text{cm}) \times \text{K}}{\text{Serum creatinine (mg/dl)}}$$

The 2012 Clinical practice Guideline of the Kidney Disease Improving Global outcomes (KDIGO) proposed a revised classification of CKD categories based on GFR, albuminuria and showing overall prognosis.

Table 23.2: Stages of chronic renal disease.

Stage	Residual Renal Function	Treatment Suggestions
Impaired renal function	40–80%	Usually not needed.
Chronic Renal Insufficiency (CRI)	25–50%	Any major stress may lead to acute renal failure. Aim of treatment is to preserve the renal function.
Chronic Renal Failure (CRF)	<30%	Aim of treatment is to prevent metabolic complications.
End-Stage Renal Disease (ESRD)	Usually <10%	Dialysis is needed to maintain quality of life.

Albuminuria is included as an additional risk factor because it marks the severity of injury and is associated with progression of kidney disease.

Causes of CKD:

Congenital anomalies of Kidneys and Urinary tract (CAKUT)

- Posterior urethral valves
- Renal hypo dysplasia
- Reflux nephropathy
- Bilateral pelviureteric junction or ureterovesical junction obstruction

Glomerular Disease

- **Glomerulonephritis:** Idiopathic, with SLE, HSP, Hepatitis B or C, HIV
- Focal segmental Glomerulosclerosis (FSGS)
- Alport Syndrome
- Congenital Nephrotic Syndrome

Cystic Kidney Disease

- Nephronophthisis
- Autosomal recessive and dominant Polycystic Kidney Disease

Following AKI

- Hemolytic uremic syndrome
- Acute cortical necrosis

Tubulointerstitial Disease

- Inherited Cystinosis, primary hyperoxaluria, Barter syndrome, Dent, disease.
- **Acquired: Nephrolithiasis**
- There may be hyponatremia due to tubular damage or use of diuretics. Conversely, hypernatremia may be seen in oligoanuria.

Hypertension:

It is due to sodium and water overload and excessive renin production. It may cause hypertensive heart failure or seizures.

Bleeding Tendency

Main cause is defective platelet function and thrombocytopenia.

Uremic gastric ulceration and pericarditis are late features.

Uremic Encephalopathy

Infants and young children are more likely to develop encephalopathy due to high azotemia

Diagnosis of CKD

- Detailed history should be taken for main CKD systemic features.
- History to evaluate the etiology of CKD is to be individualized.
- Family history of renal disease should be obtained.
- Clinical examination should include measuring BP, weight and height, pubertal development. Anemia and features of MBD should be looked for.
- **Investigations assess the severity of CKD:**
 - CBC with peripheral smear
 - RFTs, Serum electrolytes, calcium, phosphate, alkaline phosphatase, total protein, albumin, uric acid.
 - Arterial blood gases to look for blood pH and bicarbonate level.
 - Intact PTH (fasting)
 - X-ray left hand and wrist for bone age and MBD.
 - Chest X-ray, ECG and echocardiography to assess left ventricular hypertrophy and function
 - Calculate GFR by Schwartz formula.

Specific Investigation

- These are to find out the cause of CKD and tailored to the suspected etiology e.g. ultrasound, KUB, MCUG, DMSA ,MAG3 or DTPA scans, urinalysis and urine culture, C3, C4, ANA, anti DNA antibody, renal biopsy, 24 hour oxalate level, white cell cysteine level etc.

Pathophysiology and Systemic feature:

- Clinical features in advanced CKD (stage 3-5) include anorexia, growth failure, fatigue, anemia, hypertension and bone disease.
- The late feature (when GFR falls $<15\text{ml/min}/1.73\text{m}^2$) are itching, severe acidosis, hyperkalemia, left ventricular failure and pulmonary edema, pericarditis and altered sensorium.

Growth Retardation:

- Causes include poor nutrition (due to anorexia), metabolic acidosis, anemia and bone disease.
- Decreased growth hormone (GH) secretion and decreased insulin like growth factor (IGF)-I
- Secondary hyperparathyroidism: high PTH levels destroy growth plate architecture
- Delayed puberty is due to decreased gonadotrophins.
- Fluids and electrolyte losses in patients with renal dysplasia tubular disease also contribute to growth failure.
- Prolonged use of corticosteroids in glomerular disease also cause retardation of linear growth.

Anemia:

- Anemia causes easy fatigability and exertional dyspnea.
- Anemia is mostly normocytic and normochromic but superadded iron deficiency is often present.
- Main cause of anemia is lack of erythropoietin production.
- Other contributing factors include uremic bone marrow suppression, decreased RBC lifespan, iron and folate deficiency, and myelofibrosis.

Metabolic Acidosis and Dyselectrolyemia:

- Metabolic acidosis is due to bicarbonate wasting, decreased acid secretion and decreased acid ammonia synthesis
- Acidosis leads to anorexia, vomiting and worsening growth failure.
- Hyperkalemia is a complication of advanced CKD.

Mineral Bone Disease (MBD)

- In CKD, when GFR declines to 50% of normal, there is decreased production of activated vit.D ($1,25(\text{OH})_2$ cholecalciferol). This causes decreased intestinal absorption of calcium, hypocalcemia, increased PTH production and increased bone resorption
- Later, when GFR falls below 20-25% of normal there is decreased phosphate excretion from kidneys, resulting hyperphosphatemia further promotes hypokalemia and increase PTH secretion.
- Secondary hyperparathyroidism causes osteitis fibrosa cystica, bone resorption, fracture and deformities. Deficiency of $1,25$ dihydroxy cholecalciferol leads to rickets/osteomalacia.
- Infants show rachitic rosary, widened wrist and knees, and Harrison sulcus.
- Older children show genu valgum, anterior bowing of tibia, scoliosis, thoracic abnormalities and pathologic fractures.

Management

- The aims of treatment in CRF prior to dialysis are to preserve any remaining renal function and to avoid and treat complications.

Nutritional management

- Inadequate caloric intake once renal function falls below 50% is a major cause of growth failure in children.
- Caloric intake of at least 100% of the Recommended Dietary Allowance (RDA) for age should be provided to children with CRF.
- Protein restriction is important in severe uremia. High biologic value protein (fish, chicken, eggs) is given $0.50\text{--}0.75\text{ g/kg/day}$ or 5% of total calories. In growing children $1.0\text{--}1.5\text{ g/kg/day}$ of protein is given to protect growth retardation.
- Caloric requirements are met primarily by carbohydrates (75%) and fats (20%).
- Milk intake can be reduced if there is phosphate overload.
- Water-soluble vitamins are recommended to avoid deficiency states.

Fluid balance

- Fluid restriction is rarely necessary in CRF as renal concentrating ability is lost unless oliguria or heart failure is present.
- When fluid is restricted, it should be sufficient to compensate for insensible losses ($400\text{ ml}/\text{m}^2/\text{day}$) plus losses in urine, vomitus, and stools.

Sodium balance

- Generally, no added salt in food is recommended. Most children with renal insufficiency will maintain normal sodium balance with sodium derived from diet.
- Patients with high blood pressure, edema, or congestive heart failure may need more strict sodium restriction.
- Poor weight gain and muscle cramps need sodium supplements. This is especially needed in some patients whose renal insufficiency is a consequence of anatomic abnormalities leading to sodium waste in urine.

Potassium balance

- This usually is not a problem in chronic renal failure, but hyperkalemia can be a potentially life-threatening situation.
- Avoid excessive use of high potassium food (banana, citrus fruits and juices, etc); restrict such food in a case of severe renal failure.
- Hyperkalemia may be controlled by adding oral alkalinizing agents and kayexalate (an oral resin that binds to and removes potassium from the intestine). It is given in a dose of 1 g/kg/dose.

Acidosis

- It develops in all children with CRF but treatment is required only if serum bicarbonate falls below 20 mEq/l.
- Sodium bicarbonate (soda mint) tablet may be given 1–2 tablets orally every 6 hours.

Anemia

- There is normocytic, normochromic anemia and it occurs mainly as a result of inadequate erythropoitin production. In addition, iron deficiency is also seen. Severe cases, requires blood transfusion (pack cells) given very slowly.
- The recent availability of recombinant erythropoitin has provided effective treatment for anemia.

Hypertension

- Blood pressure should be controlled gradually, but in hypertensive crisis nifedipine (0.25–0.5 mg/kg) should be given sublingually or diazoxide (hyperstat) 1–3 mg/kg IV.
- Routine treatment of hypertension includes salt restriction, diuretics, and beta-blockers. Captopril may produce hyperkalemia.

- When severe hypertension is associated with circulatory overload, 2–4 mg/kg of frusemide may also be administered along with the above treatments.

Drug dosages

- Renal excretion is a major route of excretion for many drugs; their dosages must be modified in chronic renal failure.

Renal osteodystrophy

- The plasma calcium and phosphate level should be kept as near normal as possible. Hyperphosphatemia should be controlled by giving low-phosphate milk and by giving oral calcium carbonate, which binds phosphate in the intestinal tract. It should be given with each meal and before going to bed.
- If serum calcium still remains low after correction of serum phosphorus, then oral calcium should be supplemented in a dose of 500–1000 mg/day.
- In addition, alfacalcidol (1 α Leo) may be given and regular monitoring of calcium level is done to prevent the risk of hypercalcemia. The dose is 0.05–0.10 μ g/kg/day. The dose is progressively increased until serum calcium and alkaline phosphatase levels are normal and healing of rickets is seen radiologically. Then dose is reduced to initial level.

Infections

- Antibiotics are given to control infections especially UTI which is the most common infection in such patients.

Growth retardation

- In spite of adequate nutritional intake and correction of osteodystrophy, electrolyte abnormalities, acidosis, and anemia, many children with chronic renal failure have growth retardation.
- Growth in these patients may be accelerated with recombinant human growth hormone therapy.

Treatment of end-stage renal disease

- When the renal function is unable to sustain a stable milieu or serum creatinine is at 10 mg/dl, dialysis or renal transplantation is considered.
- The excretory function of the kidney can be partially replaced by peritoneal dialysis. It is only a holding measure until a suitable renal transplant becomes available. Continuous ambulatory peritoneal dialysis is the most common renal replacement therapy. Hemodialysis is another important method of replacing renal function.
- **Renal transplantation** has been very successful in children, even in those less than 1 year of age. Living related donor kidney transplantation has the best outcome.

Factors aggravating the pre-existing renal failure

- Uncontrolled hypertension
- Congestive heart failure
- Hypovolemia due to any cause
- Urinary tract infection
- Hypokalemia or hypercalcemia
- Nephrotoxic drugs
- Obstruction by renal calculus

Counseling and education:

- Parents should be informed about the nature of disease, role of preventive and therapeutic measures and likelihood of disease progression.
- The child should be encouraged to participate in activities and attend regular school. The need and availability of renal replacement therapy should be discussed in advance. Social support is also important.
- Immunizations: Ensure age appropriate immunization.

RENAL TUBULAR ACIDOSIS**CASE**

A 5 month-old child has **poor weight gain** although his feeding is adequate. The child has had no illness, though mother noticed that baby is very thirsty, irritable most of the time and his pampers are too wet. The examination is normal except for the child's very low weight (failure to thrive). Laboratory investigations show normal blood counts. BUN and creatinine are normal. Serum electrolyte show sodium 137 mEq/l, chloride 110mEq/l, potassium 2.9mEq/l, and bicarbonate 17mEq/l. **Urinalysis** reveals a **pH of 6.8, specific gravity 1.009**. Plain abdominal X-ray and renal ultrasound shows bilateral **nephrocalcinosis**.

Findings suggestive of Renal Tubular Acidosis (RTA)

- Growth retardation, Failure to thrive
- Polyuria
- Polydipsia
- Refractory rickets (usually proximal RTA)
- Renal calculi, nephrocalcinosis (distal RTA)
- Hyperchloremic, hypokalemic metabolic acidosis
- Hypercalciuria with normal serum calcium (distal RTA)

Types

- There are three types of renal tubular acidosis (RTA): distal (type I), proximal (type II), and hyperkalemic (type IV).

Distal RTA (dRTA)

- The most common form of distal RTA in childhood is the hereditary form.
- The clinical presentation is one of failure to thrive, anorexia, vomiting, dehydration and constipation. There is history of polyuria, polydipsia. An occasional patient may present with acidotic breathing.
- Work up reveals hypokalemia, hyperchloremia, metabolic acidosis along with hypercalciuria, nephrolithiasis or nephrocalcinosis.
- Patients with distal RTA cannot acidify their urine. They have a urine pH >5.8 despite a systemic metabolic acidosis.

Proximal RTA (pRTA) / Fanconi syndrome

- Proximal RTA is the second common form of RTA in childhood.
- It may be present in isolation.
- Mostly, pRTA is part of **Fanconi syndrome** (a generalized dysfunction of the proximal tubule) leading to:
 - Excessive bicarbonate loss
 - Glycosuria
 - Aminoaciduria
 - Excessive urinary losses of phosphate and uric acid
- The presence of a low serum uric acid level, glycosuria, and aminoaciduria is helpful diagnostically.
- Chronic hypophosphatemia leads to rickets in children.
- Rickets and/or failure to thrive may be the presenting complaint.
- The ability to acidify the urine is intact in proximal RTA. Thus, untreated patients have a urine pH <5.5.

Fanconi syndrome causes

- Important causes are as follows:

Neonatal

- Galactosemia
- Mitochondrial disorders
- Tyrosinemia

Infancy

- Fructosemia
- Cystinosis
- Fanconi-Bickel syndrome
 - Lowe's syndrome

Childhood

- Cystinosis
 - Wilson's disease
 - Dent's disease

Acquired causes

- Aminoglycosides
- Sodium valproate
- FSGS
- Recovery phase of ATN
- Acute interstitial nephritis

Management

- Bicarbonate replacement is the main treatment.