Nephrotic syndrome:
- It is a clino-laboratory syndrome featured by

1) Edema

2) Heavy selective proteinuria protein: creatinine ratio of >2-3: 1 (protein excretion > 40mg/m²/hr)

3) Hypoproteinemia

4) Hyperlipidemia.

Etiology:
- Most children with nephritic syndrome have idiopathic nephritic syndrome. Glomerular lesions associated with idiopathic syndrome include minimal changes disease (the most common), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, membranous nephropathy and diffuse mesangial proliferation.

Pathophysiology
- Increased permeability of the glomerular capillary wall → massive proteinuria -
  → hypoalbuminemia.
- There is extensive effacement of podocyte foot processes (the hallmark of idiopathic nephrotic syndrome).
- Idiopathic nephrotic syndrome is associated with complex disturbances in the immune system, especially T cell-mediated immunity.
- The mechanism of edema: massive urinary protein loss → hypoalbuminemia, → decrease in plasma oncotic pressure and transudation of fluid from the intravascular compartment to the interstitial space.
The reduction in intravascular volume decreases renal perfusion pressure → activating the renin-angiotensin-aldosterone system, which stimulates tubular reabsorption of sodium.

The reduced intravascular volume also stimulates the release of antidiuretic hormone, which enhances the reabsorption of water in the collecting duct (so more and more edema).

Serum lipid levels are elevated for 2 reasons. 1) Hypoalbuminemia stimulates generalized hepatic protein synthesis, including synthesis of lipoproteins and coagulation factors.

Coagulation factors are increased, increasing the risk of thrombosis and blood viscosity.

2) Lipid catabolism is diminished as a result of reduced plasma levels of lipoprotein lipase related to increased urinary losses of this enzyme.

Patients with nephrotic syndrome are at increased risk of infections (sepsis, peritonitis, pyelonephritis), especially with encapsulated organisms such as Streptococcus pneumoniae and Haemophilus influenzae.

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Some reasons for this include loss of opsonins, and immunoglobulins in the urine and use of immunosuppressive medications to treat nephrotic syndrome.

Nephrotic syndrome is a hypercoagulable state resulting from multiple factors:

vascular stasis

—an increase in hepatic production of fibrinogen and other clotting factors

decreased serum levels of anticoagulation factors

increased plasma platelet production

increased platelet aggregation.

Clinical picture

More common: "pitting edema", which is initially noted around the eyes and in the lower extremities then becomes generalized.

Anorexia, irritability, abdominal pain, and diarrhea are common.

Important features of minimal change idiopathic nephrotic syndrome are the absence of hypertension and gross hematuria and no renal failure.

Nephritic syndrome can initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema.

N.B: non pitting edema is seen in hypothyroidism.
kwashiorkor | Minimal changes nephrotic syndrome
---|---
Both have edema
In the first 2 years | 2-6 years
Hyproproteinemia due to decreased intake | Hyproproteinemia due to loss in urine
no ascite nor hyperlipedemia | With ascites, pitting edema and hyperlipedemia

Laboratory diagnosis
- The urinalysis reveals 3+ or 4+ proteinuria
- A spot urine protein: creatinine ratio exceeds 2.0, and urinary protein excretion exceeds 40 mg/m2/hr.
- The serum creatinine value is usually normal
- The serum albumin level is <2.5 g/dL, "massive proteinuria"
- Serum cholesterol and triglyceride levels are elevated.
- Serum complement levels are normal.
- A renal biopsy is not routinely performed if the patient fits the standard clinical picture of MCNS.

Pathology (Renal biopsy)
- Light microscopy:
  - No change
- Electron microscopy:
  - Fusion of epithelial foot processes

Treatment
- Prednisone should be administered at a dose of 60 mg/m2/day for 4-6 consecutive wk.
- About 80-90% of children respond to steroid therapy (clinical remission, diuresis, and urine trace or negative for protein for 3 consecutive days) within 3 wk.
- After the initial 6-wk course, the prednisone dose should be tapered to 40 mg/m2/day given every other day as a single daily dose for at least 4 wk. The alternate-day dose is then slowly tapered and discontinued over the next 1-2 mo. "or can be stopped suddenly"
- In children with large pleural effusions, ascites, or severe genital edema → sodium restriction and fluid restriction may be necessary if the child is hyponatremic.
- Diuresis may be augmented by furosemide (loop diuretic) orally or IV, with extreme caution as it can lead to intravascular volume depletion and a significantly increased risk of intravascular thrombosis.
- IV administration of 25% albumin as a slow infusion followed by furosemide is sometimes necessary.
• children who continue to have proteinuria (2+ or greater) after 8 wk of steroid therapy are considered **steroid resistant**, and a diagnostic renal biopsy should be performed.
• a subset of patients relapse while on alternate-day steroid therapy or within 28 days of completing a successful course of prednisone therapy. such patients are termed **steroid dependent**. patients who respond well to prednisone therapy but relapse ≥ 4 times in a 12 mo period are termed **frequent relapses**.
• Steroid-dependent patients, frequent relapsers, and steroid-resistant patients:
  - **Cyclophosphamide**: given as a single oral dose for a total duration of 8-12 wk. side effects are (neutropenia, disseminated varicella "chicken box", hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy)
  - **Cyclosporine** or **tacrolimus**: side effects include hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia.
  - **Mycophenolate**
  - **Levamisole** an antihelminic agent with immunomodulating effects.

**Complications**

• **Spontaneous bacterial peritonitis** is a common infection, although sepsis, pneumonia, cellulitis, and urinary tract infections may also be seen. *Streptococcus pneumoniae* is the most common organism causing peritonitis.

• Thromboembolic complication

• Hyperlipidemia may be a risk factor for cardiovascular disease.

• no renal failure

**Prognosis**

Most children with steroid-responsive nephritic syndrome have repeated relapses, which generally decrease in frequency as the child grows older.

Chronic kidney disease (CKD) is defined as renal injury (proteinuria) and/or a glomerular filtration rate <60 mL/min/1.73 m² for >3 mo.

**Causes**

CKD in children <5 yr old is most commonly a result of
  - congenital abnormalities such as renal hypoplasia, dysplasia, or obstructive uropathy
  - congenital nephrotic syndrome
  - focal segmental glomerulosclerosis
  - polycystic kidney disease
  - renal vein thrombosis, and hemolytic uremic syndrome.

**After 5 yr of age, acquired diseases**

  - various forms of glomerulonephritis including lupus nephritis) and inherited disorders (familial juvenile nephronophthisis, Alport syndrome) predominate.
CKD related to metabolic disorders (cystinosis, hyperoxaluria) and certain inherited disorders (polycystic kidney disease) can occur throughout the childhood years.

### Pathophysiology

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<th>Manifestation</th>
<th>Mechanisms</th>
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<td>Accumulation of nitrogenous waste products</td>
<td>- Decrease in glomerular filtration rate</td>
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<tr>
<td></td>
<td>- Decreased ammonia synthesis</td>
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<td></td>
<td>- Impaired bicarbonate reabsorption</td>
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<td>- Decreased net acid excretion</td>
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<tr>
<td>Sodium retention</td>
<td>- Excessive renin production</td>
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<td>- Oliguria</td>
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<td>Sodium wasting</td>
<td>- Solute diuresis</td>
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<td>- Tubular damage</td>
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<td>Urinary concentrating defect</td>
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<tr>
<td>Hyperkalemia</td>
<td>- Decrease in glomerular filtration rate</td>
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<td></td>
<td>- Metabolic acidosis</td>
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<td>- Excessive potassium intake</td>
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<td></td>
<td>- Hyporeninemic hypoaldosteronanism</td>
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<tr>
<td>***Renal osteodystrophy</td>
<td>- Impaired renal production of 1,25-dihydroxycholecalciferol (active form of vit D)</td>
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<tr>
<td></td>
<td>- Hyperphosphatemia</td>
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<tr>
<td></td>
<td>- Hypocalcemia</td>
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<td></td>
<td>- Secondary hyperparathyroidism</td>
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<tr>
<td>***Growth retardation</td>
<td>- Inadequate caloric intake</td>
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<tr>
<td></td>
<td>- Renal osteodystrophy</td>
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<tr>
<td></td>
<td>- Metabolic acidosis</td>
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<td></td>
<td>- Anemia</td>
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<td></td>
<td>- Growth hormone resistance</td>
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<tr>
<td>***Anemia</td>
<td>- Decreased erythropoietin production</td>
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<td></td>
<td>- Iron deficiency</td>
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<td></td>
<td>- Folate deficiency</td>
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<td>- Vitamin B12 deficiency</td>
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<td></td>
<td>- Decreased erythrocyte survival</td>
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<tr>
<td>Bleeding tendency</td>
<td>- Defective platelet function</td>
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</tbody>
</table>
Infection
- Defective granulocyte function
- Impaired cellular immune functions
- Indwelling dialysis catheters

Neurologic symptoms (fatigue, poor concentration, headache, drowsiness, memory loss, seizures, peripheral neuropathy)
- Uremic factor(s)
- Aluminum toxicity
- Hypertension

Gastrointestinal symptoms (feeding intolerance, abdominal pain)
- Gastroesophageal reflux
- Decreased gastrointestinal motility

Hypertension
- Volume overload
- Excessive renin production

Hyperlipidemia
- Decreased plasma lipoprotein lipase activity

Pericarditis, cardiomyopathy
- Uremic factor(s)
- Hypertension
- Fluid overload

Glucose intolerance
- Tissue insulin resistance

Clinical manifestations
Clinical presentation of CKD is varied and depends on the underlying renal disease.

- children and adolescents with CKD from chronic glomerulonephritis can present with Edema, hypertension, hematuria, and proteinuria.

- infants and children with congenital disorders such as renal dysplasia and obstructive uropathy can present in the neonatal period with failure to thrive, polyuria, dehydration, urinary tract infection, or overt renal insufficiency.

- Short stature and the bony abnormalities of renal osteodystrophy in patients with long-standing untreated CKD.

Lab findings
- Elevated blood urea nitrogen and serum creatinine
- Hyperkalemia, hyponatremia (if volume overloaded), acidosis, hypocalcemia, hyperphosphatemia, and an elevation in uric acid
- Patients with heavy proteinuria can have hypoalbuminemia.
- A complete blood cell count shows a normochromic, normocytic anemia.
- Serum cholesterol and triglyceride levels are often elevated.
In children with CKD caused by glomerulonephritis, the urinalysis shows hematuria and proteinuria.

**Treatment**  ***essay question***

- Children with high blood pressure, edema, or heart failure can require sodium restriction and diuretic therapy.

**Fluid restriction** is rarely necessary in children with CKD until the development of end-stage renal disease (ESRD) requires the initiation of dialysis.

- **Hyperkalemia** may be treated by restriction of dietary potassium intake, administration of oral alkalinizing agents, and/or treatment with Kayexalate.
- **Metabolic acidosis** can be treated with Bicitra or sodium bicarbonate tablets or solution may be used to maintain the serum bicarbonate level >22 mEq/L.
- **Protein intake** should be 2.5 g/kg/24 hr and should consist of proteins of high biologic value that are metabolized primarily to usable amino acids rather than to nitrogenous wastes. The proteins of highest biologic value are those of eggs and milk, followed by meat, and fish.
- **Water-soluble vitamins** should be routinely supplied.

- **Zinc and iron supplements** should be added only if deficiencies are confirmed.

- Recombinant human GH (rHuGH) at a dose 0.05 mg/kg/24 hr SC for children who remains less than -2 SD for height.
- for children with renal osteodystrophy should follow a low phosphorus diet and receive Vitamin D therapy ergocalciferol 0.01-0.05 ug/kg/24hr of calcitriol

- **Anemia**: Recombinant human erythropoietin (rHuEPO) is administered when the patient’s hemoglobin concentration falls below 10g/dl, at a dose of 50-150 mg/kg/dose SC 1-3 times weekly.
- **Hypertensive children**: with suspected volume overload should follow a salt-restricted diet (2-3 g/24hr) and can benefit from Thiazide diuretics. Angiotensin-converting enzyme (ACE) inhibitors are the antihypertensive medications of choice in all children with proteinuric renal disease.

- **Immunizations**
- **Immunosuppressant drugs**
- **other therapeutic modalities** include chronic dialysis and renal transplantation
Definition

**Hypertension** is defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) ≥95th percentile for age, sex, and height on ≥3 occasions. **Prehypertension** was defined as average SBP or DBP that are ≥90th but <95th percentile.

**Measurement of BP in children:**

- The preferred method is by auscultation and a BP cuff appropriate for the size of the child’s arm should be used.
- Elevated readings should be confirmed on repeat visits (3 times at least) before determining that a child is hypertensive.
- The BP should be measured with the child in the sitting position after a period of quiet for at least 5 min.
- Blood pressure should be measured with cubital fossa at heart level. The arm should be supported.
- Careful attention to cuff size is necessary to avoid over diagnosis, as a cuff that is too short or narrow artificially increases BP readings.
- A wide variety of bladder sizes should be available in any medical office where children are routinely seen. An appropriate sized cuff has an inflatable bladder that is at least 40% of the arm circumference at a point midway along the upper arm. The inflatable bladder should cover at least two thirds of the upper arm length and 80-100% of its circumference.
- Ambulatory blood pressure monitoring (ABPM) is a procedure where the child wears a device that records BP frequently, usually every 20-30 min, throughout a 24 hr period while the child goes about usual daily activities, including sleep.
- The stethoscope bell is placed over the brachial artery pulse, proximal and medial to the cubital fossa, below the bottom edge of the cuff.

The cuff bladder should cover 80% to 100% of the circumference of the arm.
Etiology

1. **Essential or primary hypertension**, hereditary, die, stress and obesity may play a role in the development of primary hypertension.

2. **Secondary hypertension** is the most common in infants and younger children.

**Conditions associated with chronic hypertension in children**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>Coarctation of thoracic or abdominal aorta, umbilical artery catheterization with thrombus formation.</td>
</tr>
<tr>
<td>Renal disease <em><strong>most common cause in children</strong></em></td>
<td>Reflux nephropathy, pyelonephritis, chronic pyelonephritis, chronic glomerulonephritis, hydronephrosis, congenital dysplastic kidney, systemic lupus erythematosus (other connective tissue diseases)</td>
</tr>
<tr>
<td>Renovascular</td>
<td>Renal artery lesions (stenosis, fibromuscular dysplasia, thrombosis, aneurysm)</td>
</tr>
<tr>
<td>Catecholamine excess</td>
<td>Pheochromocytoma, neuroblastoma</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Corticosteroid excess, primary aldosteronism</td>
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<tr>
<td>CNS disease</td>
<td>Tumor (intracranial mass), trauma, hemorrhage</td>
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<tr>
<td>Medication</td>
<td>Decongestants, exogenous steroids</td>
</tr>
<tr>
<td>other</td>
<td>Burns, traction, urologic surgery</td>
</tr>
</tbody>
</table>

**Clinical manifestation**

- Children and adolescents with primary hypertension are usually **asymptomatic**, the BP elevation is usually mild and is detected during a routine examination. These children may also be obese.
- **Headache, dizziness, epistaxis, anorexia, visual changes, and seizures may occur.**

- Hypertensive encephalopathy is suggested by the presence of vomiting, temperature elevation, ataxia, stupor, CT abnormalities, and seizures.
- Cardiac failure, pulmonary edema, and renal dysfunction (malignant hypertension) may occur in the face of marked hypertension.
- **Hypertensive crisis** may manifest with decreased vision (retinal hemorrhages of hypertensive retinopathy) and papilledema, encephalopathy (headache, seizures, depressed level of consciousness), heart failure, or accelerated deterioration of renal function.
Treatment

• Weight loss in obesity related hypertension.
• Diet increased in fresh fruits, fresh vegetables, fiber, and nonfat dairy and reduced in sodium.
• Regular aerobic physical activity for at least 30-60 min on most days along with a reduction of sedentary activities to less than 2 hr per day is recommended.
• Indications for pharmacologic therapy include symptomatic hypertension, secondary hypertension, hypertensive target organ damage, diabetes (types 1 and 2), and persistent hypertension despite nonpharmacologic measures.
• Start by single agent at low dose. The dose can then be increased until the goal BP is achieved. Once the highest recommended dose is reached or if the child develops side effects, then a second drug from a different class can be added.

• Acceptable drug classes for use in children include ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics.

Urinary tract infections

• Urinary tract infections (UTIs) occur in 1-3% of girls and 1% of boys (girls are more affected as urethra is short).

• In girls, the first UTI usually occurs by the age of 5 yr, with peaks during infancy and toilet training.

• In boys, most UTIs occur during the 1st yr of life.
  • In girls, 75-90% of all infections are caused by *Escherichia coli*, followed by *Klebsiella spp* and *Proteus spp*.
  • In boys >1 yr of age, *Proteus* is as common a cause as *E. coli* in boys.

  • *Staphylococcus saprophyticus* and enterococcus are pathogens in both sexes.

• Adenovirus and other viral infections also can occur especially as a cause of cystitis.

Clinical manifestation:
The 3 basic forms of UTI are *pyelonephritis* (infection in renal parenchyma and pelvis), *cystitis* (infection in urinary bladder), and asymptomatic bacteriuria.

• Clinical pyelonephritis: abdominal, back, or flank pain; fever; malaise; nausea; vomiting; and, occasionally, diarrhea. *Fever may be the only manifestation*.

• Newborns can show nonspecific symptoms such as poor feeding, irritability, jaundice, and weight loss. *(same manifestation as septicemia)*

• Pyelonephritis is the most common serious bacterial infection in infants <24 mo of age who have fever without an obvious focus. Complication of pyelonephritis include scarring in renal parenchyma the lead to renal failure.
• **Cystitis** indicates that there is bladder involvement; symptoms include dysuria, urgency, frequency, suprapubic pain, incontinence, and malodorous urine. Cystitis doesn’t cause fever and doesn’t result in renal injury.

• **Asymptomatic bacteriuria** refers to a condition in which there is a positive urine culture without any manifestations of infection. It is most common in girls. The incidence is <1% in preschool and school-age girls and is rare in boys. This condition is benign and does not cause renal injury. Some girls are mistakenly identified as having asymptomatic bacteriuria, whereas they actually are experiencing day or night incontinence or perineal discomfort secondary to UTI

**Diagnosis:**

• a midstream urine sample usually is satisfactory in toilet-trained children.

  N.B: midstream urine sample: Procedure done after some urine has been voided into toilet but before bladder is fully emptied; this is done to exclude urethral contamination.

• In children who are not toilet-trained, a catheterized urine sample should be obtained.

• Sterile collection bag after disinfection of the skin of the genitals can be useful only if the culture is negative or if a single uropathogen is identified.

• A suprapubic aspirate generally is unnecessary.

• Pyuria(leukocyte "pus" in the urine) suggests infection, but infection can occur in the absence of pyuria; this finding is more confirmatory than diagnostic. **Sterile pyuria** (positive leukocytes, negative culture) occurs in partially treated bacterial UTIs, viral infections, inflammation near the ureter or bladder (appendicitis, Crohn disease).

• Nitrites and leukocyte esterase are positive in infected urine

• Microscopic hematuria is common in acute cystitis.

• White blood cell casts in the urinary sediment suggest renal involvement

• Urine culture: If the culture shows >100,000 colonies of a single pathogen, or if there are 10,000 colonies and the child is symptomatic, the child is considered to have UTI.

**Treatment**

• acute cystitis should be treated promptly to prevent possible progression to pyelonephritis. if the symptoms are severe, presumptive treatment is started pending results of the culture

• With acute renal infection, leukocytosis, neutrophilia, and elevated serum erythrocyte sedimentation rate and C-reactive protein are common. **(blood indices are also elevated)**

• **Acute cystitis**: 3 to 5 day course of therapy
- **trimethoprim-sulfamethoxazole** (TMP-SMX) is effective against *E.coli*.

- **Nitrofurantoin** (5-7 mg/kg/24 hr in 3-4 divided doses) also is effective and has the advantage of being active against *Klebsiella* and *Enterobacter* organisms.

- **Amoxicillin** (50 mg/kg/24 hr)

  - **pyelonephritis**, a 10 to 14 day course is preferable. Parenteral treatment with ceftriaxone (50-75 mg/kg/24 hr, not to exceed 2 g) or cefotaxime (100 mg/kg/24 hr), or **ampicillin** (100 mg/kg/24 hr) with an **aminoglycoside** such as gentamicin (3-5 mg/kg/24 hr in 1-3 divided doses) is preferable (the potential ototoxicity and nephrotoxicity of aminoglycosides should be considered).

  - in a child with recurrent UTIs, prophylaxis against reinfection , using TMP-SMX , or nitrofurantoin at 30 % of the normal therapeutic dose once a day , is helpful.