UNIVERSITATEA DE STAT DE MEDICINĂ ȘI FARMACIE
"NICOLAE TESTEMIȚANU" DIN REPUBLICA MOLDOVA

Acute poststreptococcal glomerulonephritis in children

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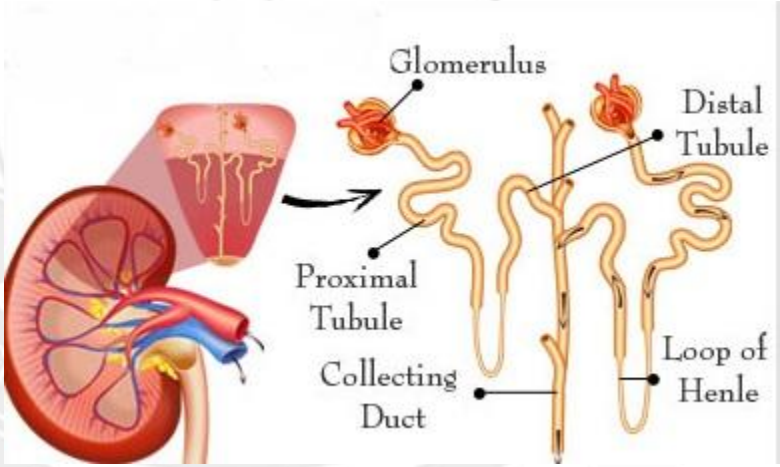
Departament of Pediatry

Goal

The goal of lesson: to know how to diagnose the acute glomerulonephritis and nephrotic sindrome in children on the base of anamnesis, clinical and laboratory-instrumental data, the treatment.

Definition

- **Acute glomerulonephritis** is a representative disease of ***acute nephritic syndrome*** in which inflammation of the glomerulus is manifested by proliferation of cellular elements secondary to an immunologic mechanism.



Epidemiology

- Acute poststreptococcal glomerulonephritis (APSGN) remains by far the most common glomerulonephritis in children worldwide.
- Its global burden has been estimated at well more than 450,000 cases annually, with most cases occurring in children.
- The reported annual incidence of PSGN in developing countries has been estimated at **9.3 cases per 100,000 persons,** with rates as high as 93 per 100,000 among Aboriginal Australian children.
- In developing countries APSGN, usually occurs in children, predominately males and often as epidemics.
- APSGN usually occurs as sporadic cases, but epidemic outbreaks have taken place in communities with densely populated dwellings that have poor hygienic conditions with a high incidence of malnutrition, anemia, and intestinal parasites.

- A strong seasonal variation is also noted; sporadic APSGN following upper respiratory tract infection, pharyngitis, and tonsillitis is more common in winter and spring in temperate areas, whereas skin infections are commonly found to precede APSGN in the more tropical and subtropical areas, with a peak incidence during summer and autumn.

Etiology

- APSGN results from an antecedent infection of the skin (impetigo) or throat (pharyngitis) caused by nephritogenic strains of **group A beta-hemolytic streptococci.**
- The M and T proteins in the bacterial wall have been used for characterizing streptococci.
- Nephritogenicity is mainly restricted to certain M protein serotypes (ie, 1, 2, 4, 12, 18, 25, 49, 55, 57, and 60) However, not all strains of a nephritis-associated M protein serotype are nephritogenic.
- However, not all strains of a nephritis-associated M protein serotype are nephritogenic.

- In addition, nontypeable group A streptococci are frequently isolated from the skin or throat of patients with glomerulonephritis, representing presumably unclassified nephritogenic strains.

Pathogenesis

- Most forms of **acute poststreptococcal glomerulonephritis** (APSGN) are mediated by an **immunologic process.**
- Cellular and humoral immunity is important in the pathogenesis of this disease, and humoral immunity particularly in APSGN.
- Nonetheless, the exact mechanism by which APSGN occurs remains to be determined.

The 2 most widely proposed theories include

Glomerular trapping of circulating immune complexes and

In situ immune antigen-antibody complex formation resulting from antibodies reacting with either streptococcal components deposited in the glomerulus or with components of the glomerulus itself, which has been termed “molecular mimicry.”

Immune complex-mediated mechanisms

Post-streptococcal Glomerulonephritis

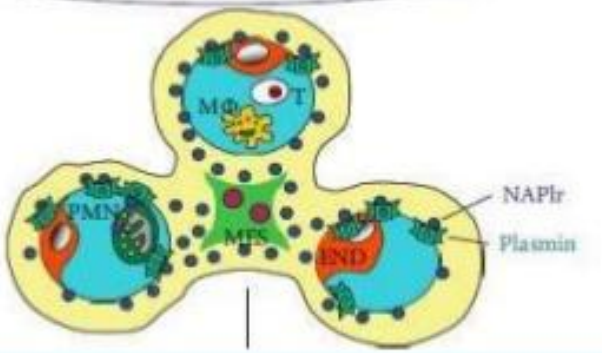
Pathogenesis

Nephritis-associated plasmin receptor (NAPLr)

Streptococcal Infection

Streptococcal proteinase exotoxin B (SPEB)

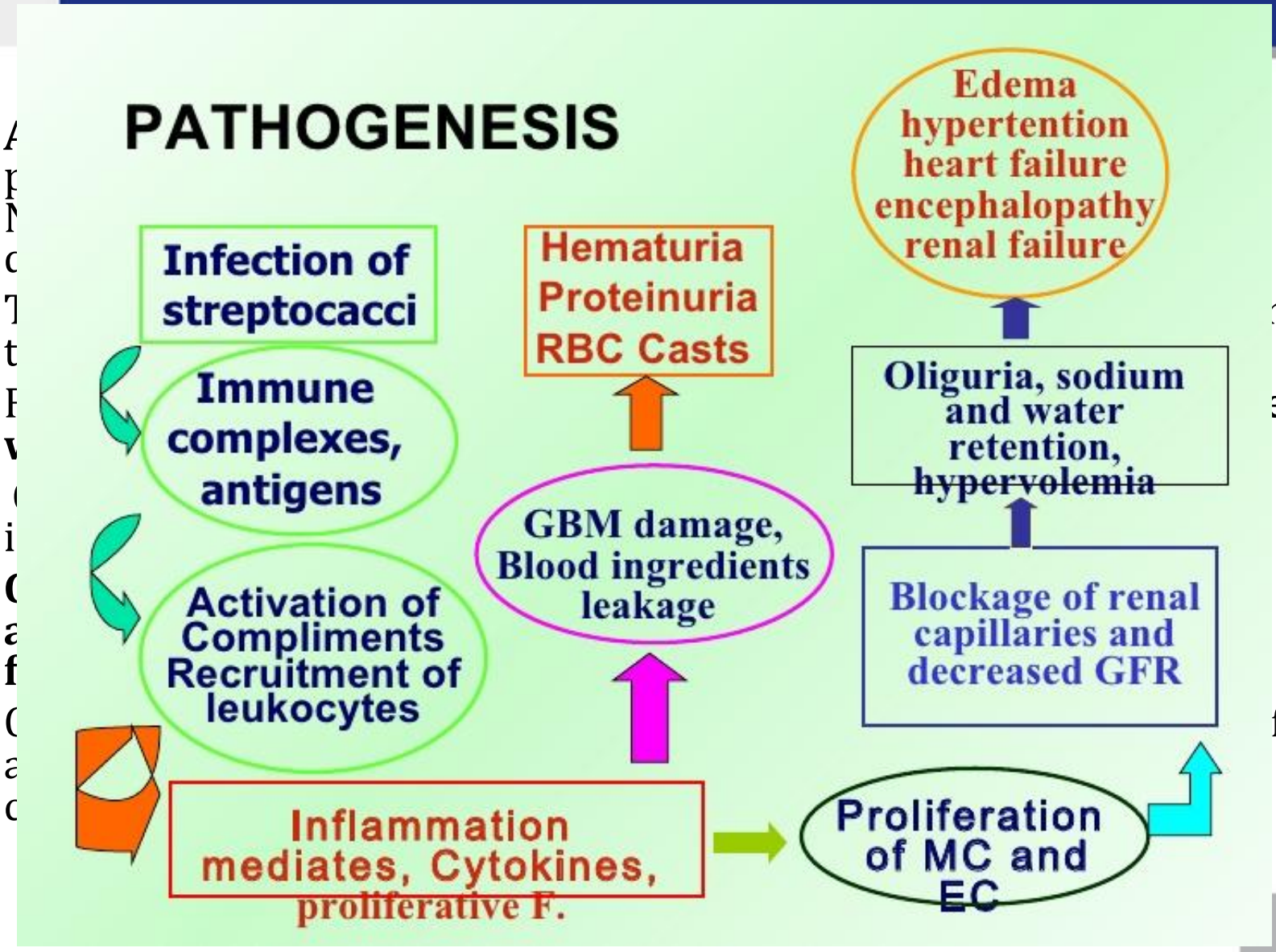
Deposition of NAPlr on the inner side of glomerular tufts, inducing plasmin-related endocapillary inflammation



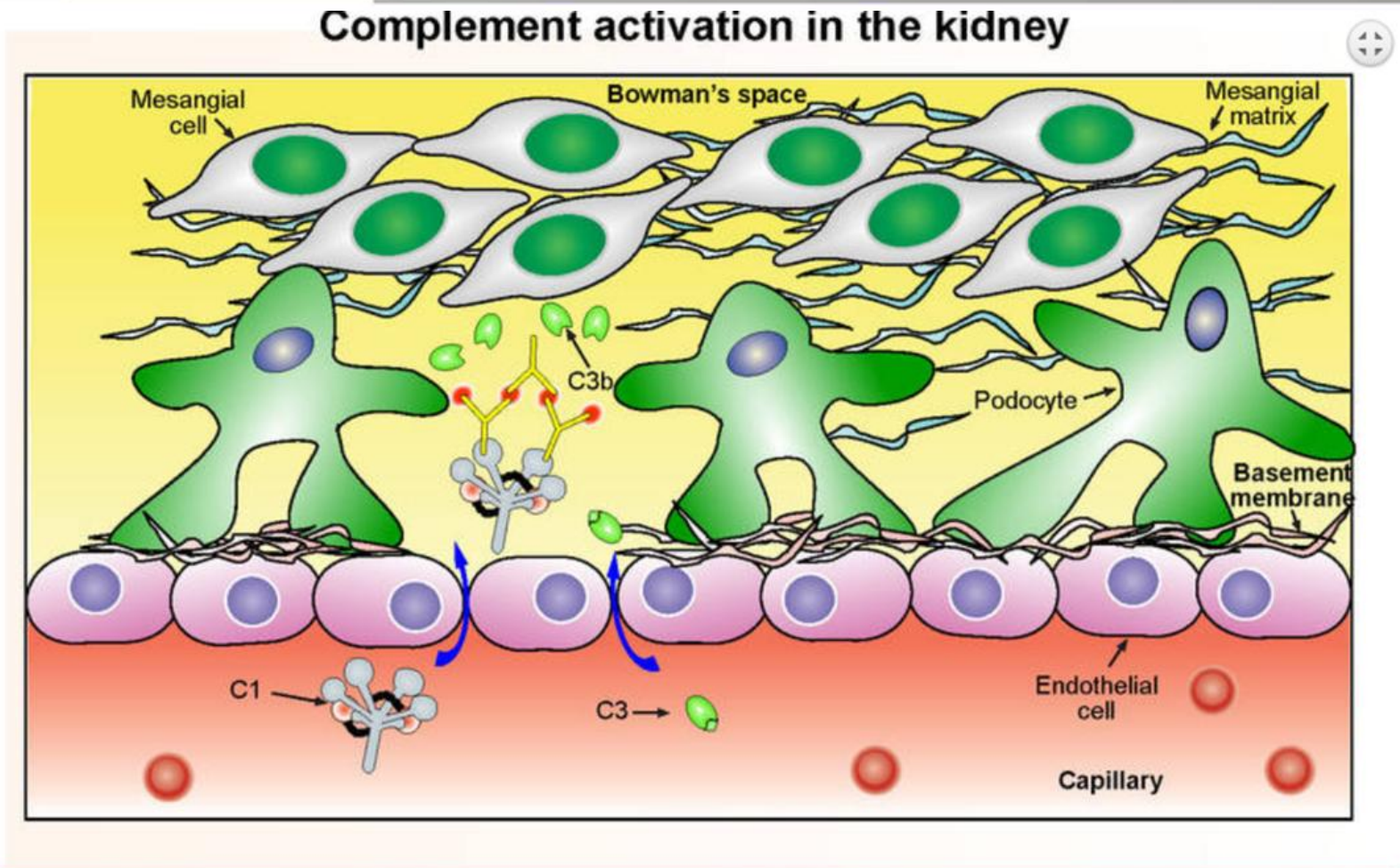
Development of circulating immune complexes

A local direct mechanism of glomerular inflammatory damage

it is not co-localized with complement or immunoglobulin


PATHOGENESIS
Infection of streptocacci
Immune complexes, antigens
Activation of Compliments Recruitment of leukocytes
Inflammation mediates, Cytokines, proliferative F.
Hematuria Proteinuria RBC Casts
GBM damage, Blood ingredients leakage
Edema hypertention heart failure encephalopathy renal failure
Oliguria, sodium and water retention, hypervolemia
Blockage of renal capillaries and decreased GFR
Proliferation of MC and EC

Complement activation



The deposition of immune complexes in the Bowman's space activates the classical complement system by recruitment of C1 proteins from plasma. A loss of plasma C3 levels correlates with complement activation and deposits of C3 proteins can be detected in the Bowman's space.

Nonimmune complex-mediated mechanisms

- Other nonimmune complex mediated mechanisms have been proposed for the development of APSGN, such as **delayed-type hypersensitivity, superantigens, and autoimmune phenomena**.
- A role for delayed-type hypersensitivity has been implicated in the pathogenesis of this disease.
- Early in the course of APSGN, resident endothelial and mesangial cells are predominantly proliferated, and this is accompanied by infiltration with polymorphonuclear leukocytes and monocytes.
- Macrophages are effector cells that cause resident cellular proliferation.
- The infiltration of macrophages in the glomeruli is mediated by complement-induced chemotaxis and, most likely, by an antigen-specific event related to delayed-type hypersensitivity mediated by helper/inducer T cells.

Clinical Presentation

- Three phases of the disease can be identified:

- the latent phase
- the acute phase
- and the recovery phase

- **The latent** period of **7-21 days between onset of the streptococcal infection** and development of clinical glomerulonephritis is characteristic.

- This latent period, more clearly defined after pharyngeal infections than after pyoderma, averages approximately 10 days.

- The median age of presentation in childhood is age 6-8 years, with the condition being extremely rare prior to age 2 years.

- In very young children, it is postulated that APSGN is rare because of the low rate of streptococcal pharyngitis in this age group and an immature immune response.

Clinical Examination

To include:

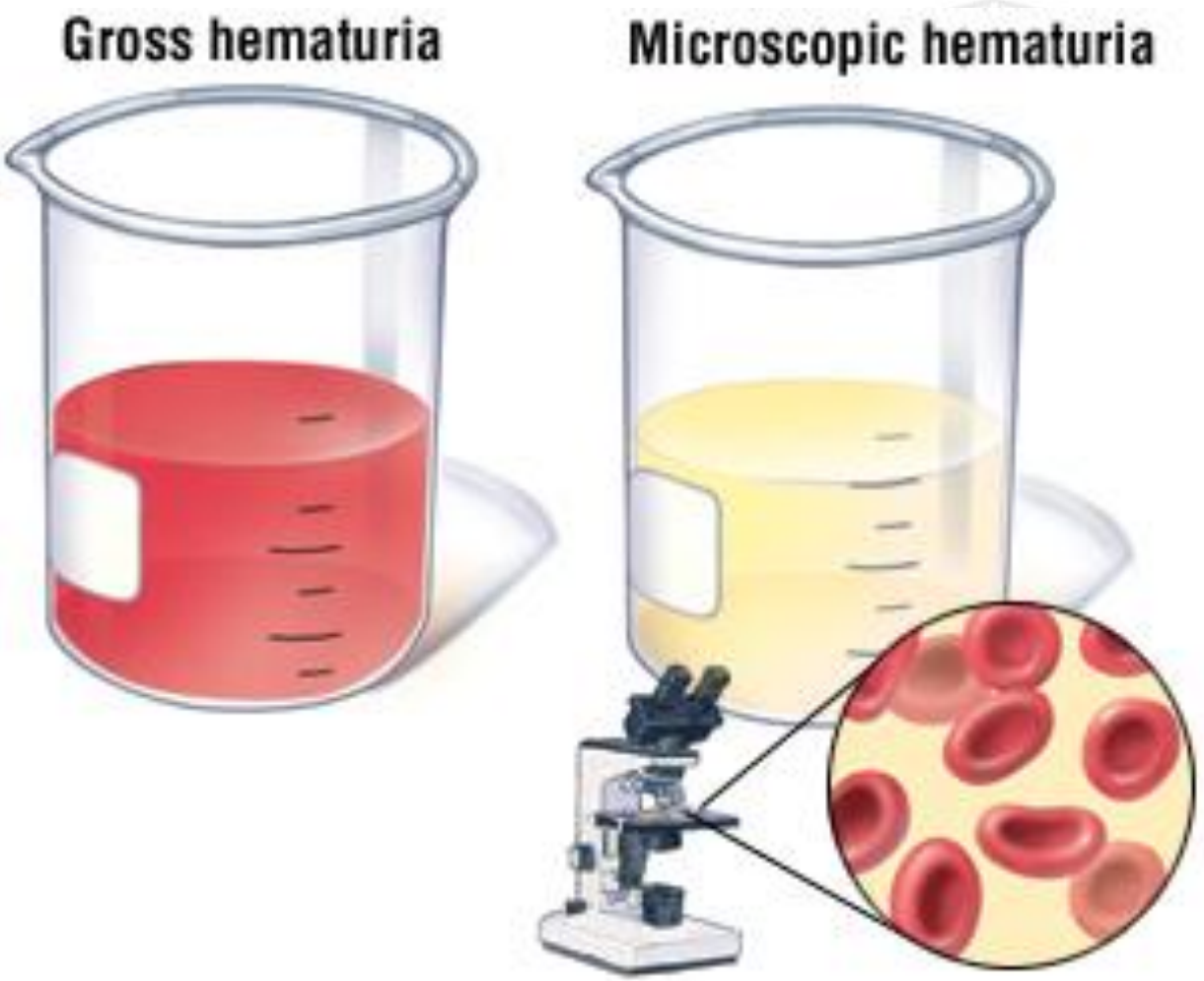
- **Height, weight, estimated body surface area** (an estimate of dry weight will give a more accurate surface area estimate)
- **Blood pressure**
- **Assessment of oedema** (usually mild - lower limb, sacral, ascites, scrotal, pleural
- effusions)
- **Cardiovascular status** and perfusion (volume status):
- **Indicators of fluid overload**: tachycardia, hypertension, respiratory distress, warm peripheries, hepatomegaly, raised JVP
- **Indicators of hypovolaemia**: tachycardia, hypertension, cool peripheries, delayed capillary refill time
- **Examination of the whole body for rashes** (esp lower limbs for purpura of HSP and face for butterfly rash of SLE)

Triad of edema, hematuria, and hypertension

- **The triad** **ic for APSGN.**
- **Edema an** **on clinical presentati** **on.**
- **Edema** is t finding. According nately 85% of patients.
- Edema usu bital area, but it may be ger
- The degree of factors, including t take, and the degree of h
- One or both findings usually appear abruptly and may be associated with various degrees of malaise, lethargy, anorexia, fever, abdominal pain, and headache.

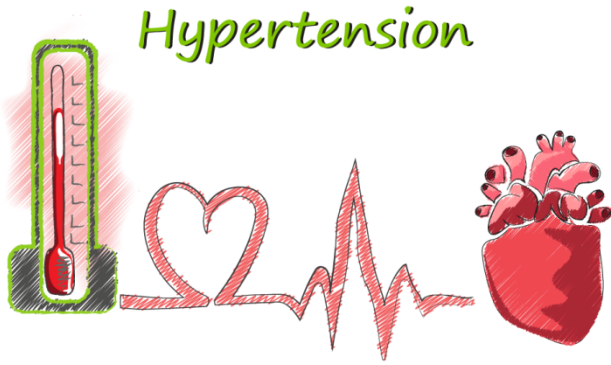
Gross hematuria

- Gross
  child
  glom
  hospi
- The u
  cola
  is usu
  prese
- Obse



Hypertension

- **Hypertension** is the third cardinal feature of poststreptococcal acute glomerulonephritis and is reported in **50-90% of children who are hospitalized with acute glomerulonephritis.**
- The magnitude of the increase in blood pressure widely varies; however, systolic pressures greater than 200 mm Hg and diastolic pressures greater than 120 mm Hg are not unusual. Hypertension usually resolves in 1-2 weeks and rarely requires long-term treatment.



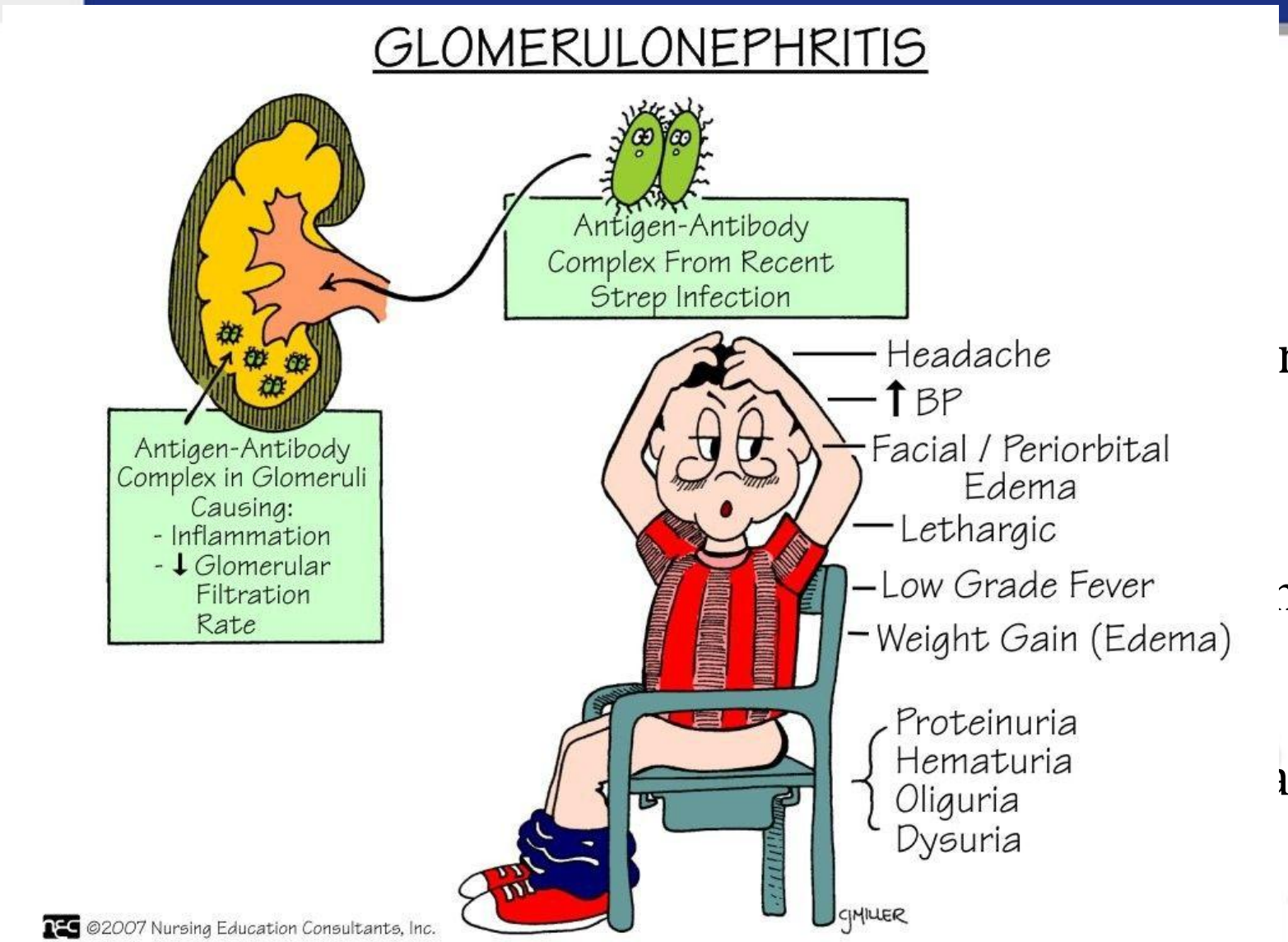
Hypertensive encephalopathy

- **Hypertensive encephalopathy** can be the presenting feature of postinfectious glomerulonephritis.
- This condition has been reported in approximately **5% of hospitalized children and is the most serious early complication of this disease.**
- In these patients, hypertension is usually severe and is accompanied by signs of central nervous system (CNS) dysfunction such as headache, vomiting, depressed sensorium, confusion, visual disturbances, aphasia, memory loss, coma, and convulsions.

- The mechanism of hypertension is most likely retention of sodium and water with resulting expansion of the extracellular space.

- Hypertensive encephalopathy has been reported in the occasional individual with minimal or no edema and with minimal urinary abnormalities.

Circulatory congestion



Laboratory testing

Urine for:

- Dipstick urinalysis
- Urine culture
- Urine microscopy for casts (often not seen unless extremely fresh specimen)
- Urine protein:creatinine ratio (confirm with early morning specimen) if proteinuria on Dipstick

Blood for:

- Paediatric renal profile to include urea, electrolytes, creatinine, calcium, phosphate,
- chloride, bicarbonate and albumin
- Full blood count
- Antistreptolysin titre
- Ask lab to store blood for Anti-DNAse B and Antihyaluronidase titres if ASOT negative
- C3 and C4 levels
- Anti-nuclear antibody (ANA)
- Throat swab
- CXR if hypertensive or fluid overloaded

Laboratory testing

- Confirmation of GAS pharyngitis at the time of acute infection is obtained **by throat culture or rapid streptococcal antigen testing** because culture results are only positive 20% to 25% of the time when checked at the later onset of nephritic symptoms.
- Elevated serum titers against GAS proteins have long been used to indicate possible infection, with **antistreptolysin O (ASO) titers** being the most commonly used.
- ASO titers typically will peak approximately 2 to 4 weeks after an episode of pharyngitis and remain elevated for several months.
- ASO titers also do not typically rise in GAS skin infections because streptolysin may be bound by lipids in the skin.
- Finally, elevated ASO titers may persist in a convalescent phase for up to 6 months in some individuals and could be potentially misleading in someone much further removed from their GAS infection.
- Titers against other GAS antigens may also be used to make the diagnosis, especially when checked in combination with ASO titers.

Laboratory testing

- Elevated **DNAse B levels** may also be seen with GAS pharyngitis, but, unlike ASO, they become elevated with pyodermal infections as well.
- Checking more than one GAS antigen titer has greater specificity than a single antigen test. There are several commercially available tests that check **multiple antigen titers** (Streptozyme-ASO, DNAse B, streptokinase, and hyaluronidase), but they also have high (25%–50%) false-negative rates.
- Perhaps the test of greatest diagnostic value in the diagnosis of PSGN, as well as in most other postinfectious glomerulonephritides, is serum C3, especially because **C3 is a component** of the actual pathogenesis of the disease. C3 levels are decreased in more than 90% of all cases of PSGN.

Laboratory testing

- Other recommended testing, as should be performed in any renal disease, includes:
- **urinalysis with microscopy,**
- **complete blood cell count,**
- **electrolyte levels,**
- **renal function testing.**

Laboratory testing

- **Urine dipstick** test results will often reveal large amounts of blood and protein, whereas leukocyte esterase test results may also be positive.
- **Microscopic examination of the urine** often yields some leukocytes being present and at times even white blood cell casts.
- In a freshly voided specimen, visualized **red blood cells** in the urine may appear dysmorphic, and **red blood cell casts** may also be seen.
- The presence of red blood cell casts is not specific for PSGN but is pathognomonic of glomerular disease in general.

Laboratory testing

- **The blood cell count** may reveal leukocytosis and somewhat decreased platelet and hemoglobin levels.
- Elevated *white blood cell* counts may be seen secondary to the recent GAS infection or the generalized inflammation with PSGN.
- *Platelet counts* may be mildly decreased from serum dilution, but extremely low levels (<50 B 103/mL [50 B 109/L]) may prompt concern about other pathologic mechanisms causing platelet consumption or destruction.
- **Hemoglobin levels** may be mildly or moderately low, with almost onethird of patients having a hemoglobin level less than 10 g/dL (<100 g/L).

Laboratory testing

- Increase in **blood urea nitrogen level**
- However, if there is a significant **elevation creatinine** (rise of >50% above normal), serial monitoring of creatinine every 12 hours is indicated because there are rapidly progressive forms of nephritis that may require emergency interventions.
- **Electrolyte levels** are often normal, but hyponatremia may be seen from dilution with total body fluid overload.
- Hyperkalemia and anion gap acidosis could be seen if renal function is significantly impaired.

Imaging studies

- Ultrasonography: Kidneys are enlarged only in a few patients.
- The chest x-ray may show heart failure

Histologic studies

Renal biopsy is not recommended for diagnosing patients with PSGN and is performed only when other glomerular pathologies are suspected.

Renal biopsy is indicated when:

- Renal function is worsening
- Patient has anuria
- There is no latent period between the acute glomerulonephritis and streptococcal infection
- Complement levels are normal
- There is no rise in antistreptococcal antibodies
- There is persistent hypertension
- **Light microscopy:** all glomeruli show hypercellularity (endothelial, mesangial, and inflammatory cells). These findings are non-specific and are present in other glomerular pathologies.
- **Electron microscopy:** the most characteristic finding by electron microscopy is the presence of humps; which are electron-dense deposits in the subepithelial space near the glomerular basement membrane.
- **Immunofluorescence microscopy:** shows deposits of IgG and C3 if the tissue sample was taken in the first 2 to 3 weeks of the disease.

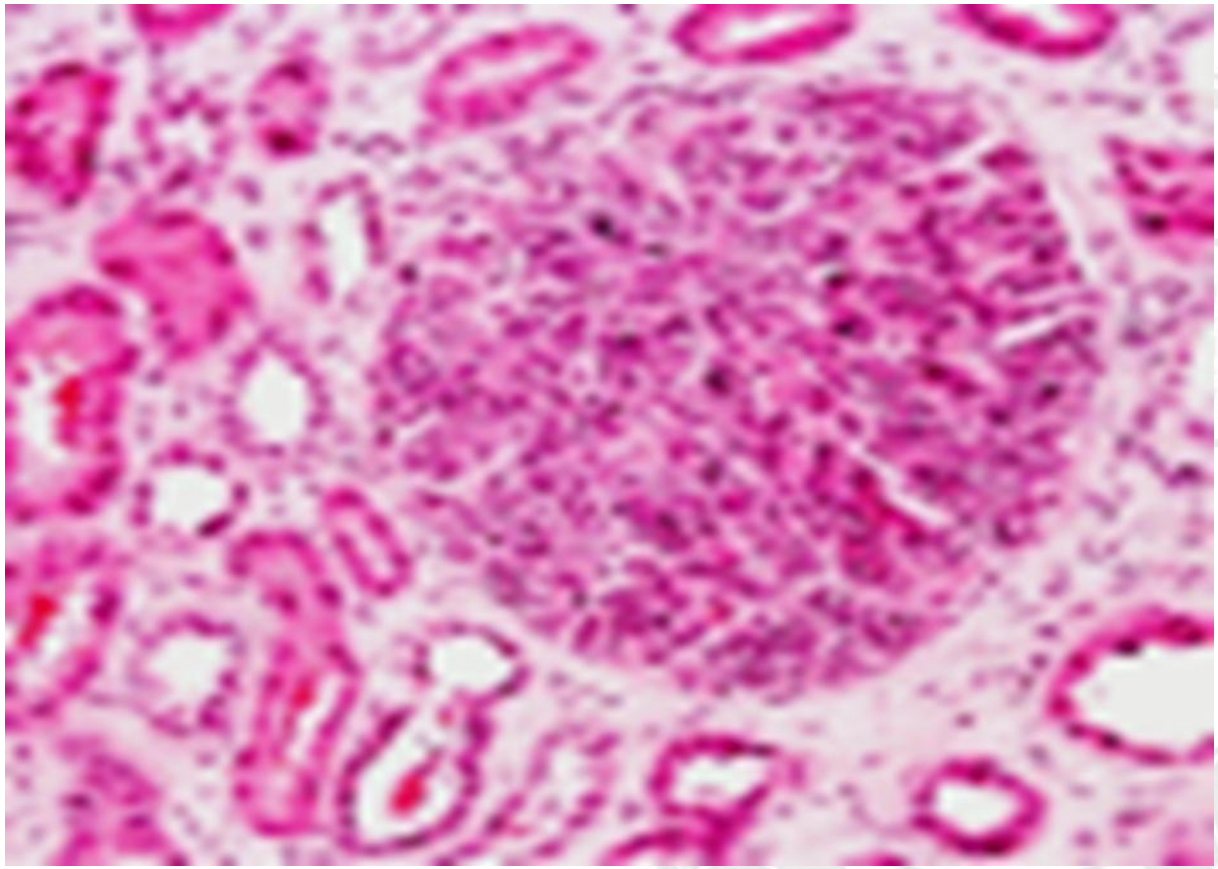


Figure 1.

Acute post-streptococcal glomerulonephritis (GN) with severe proliferative and exudative GN. The glomerulus is enlarged and markedly hypercellular with a large number of neutrophils. Note the red blood cells in some tubular lumens. Hematoxylin and eosin.

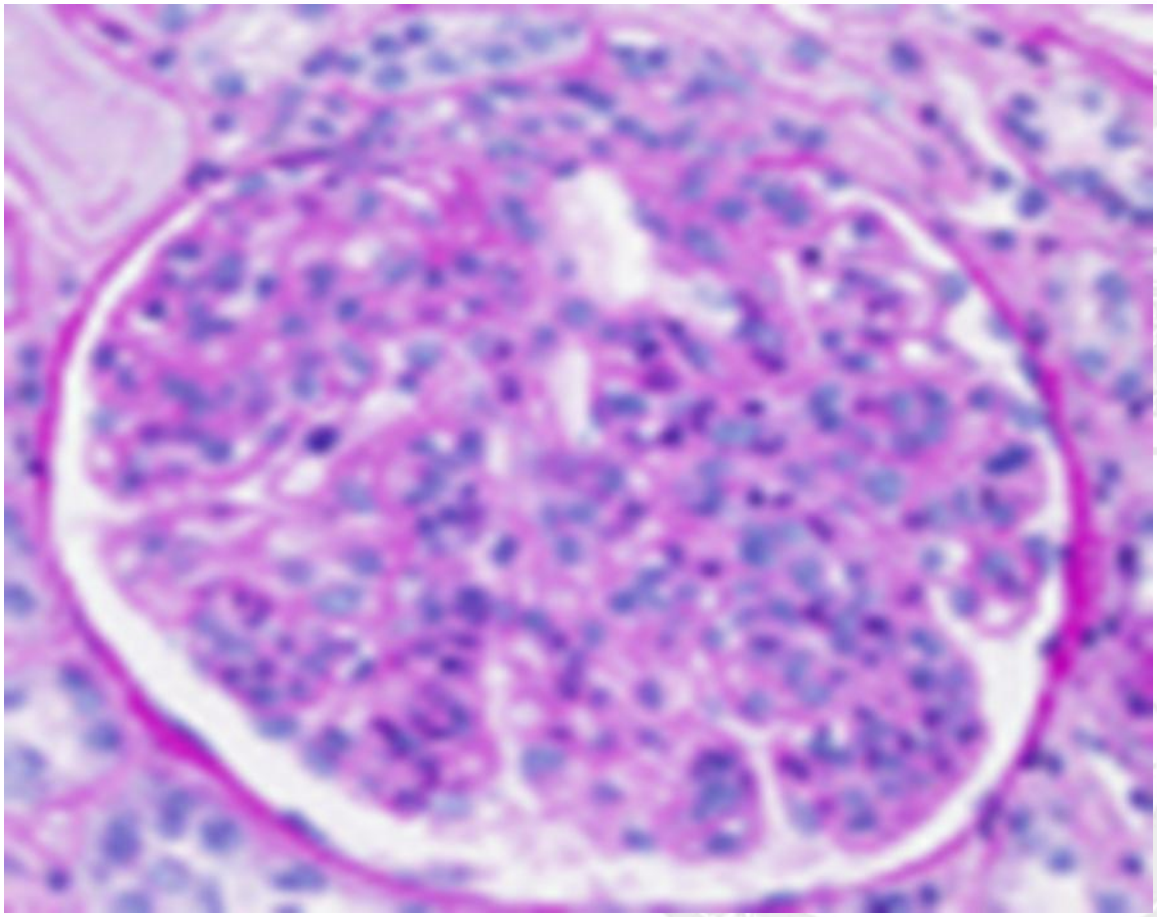


Figure 2.

Acute post-streptococcal GN with proliferative and exudative GN. The glomerulus shows endocapillary hypercellularity with multiple neutrophils, although far fewer than the glomerulus in Figure 1

Imunofluorescence microscopy

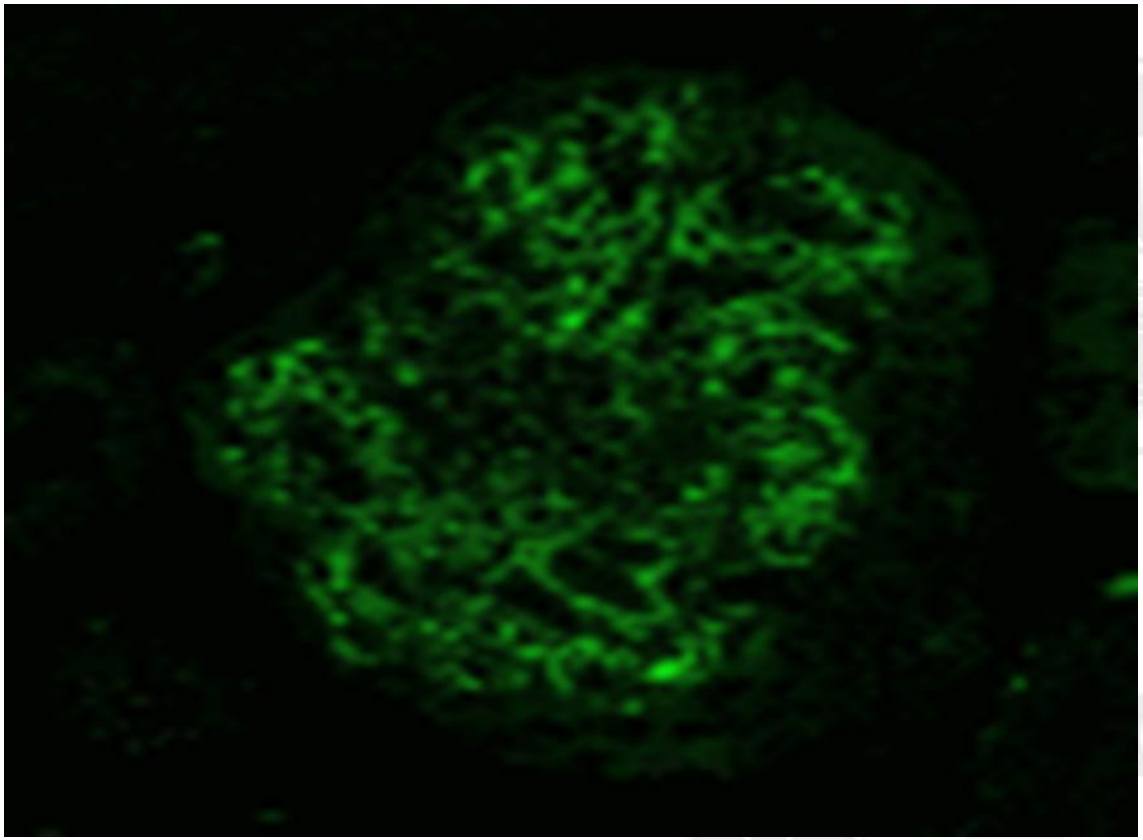


Figure 3.

Immunofluorescence staining for C3 in acute post-streptococcal GN. There is granular staining in the glomerular capillary walls and mesangium, in a "starry-sky" pattern.

Electron Microscopy

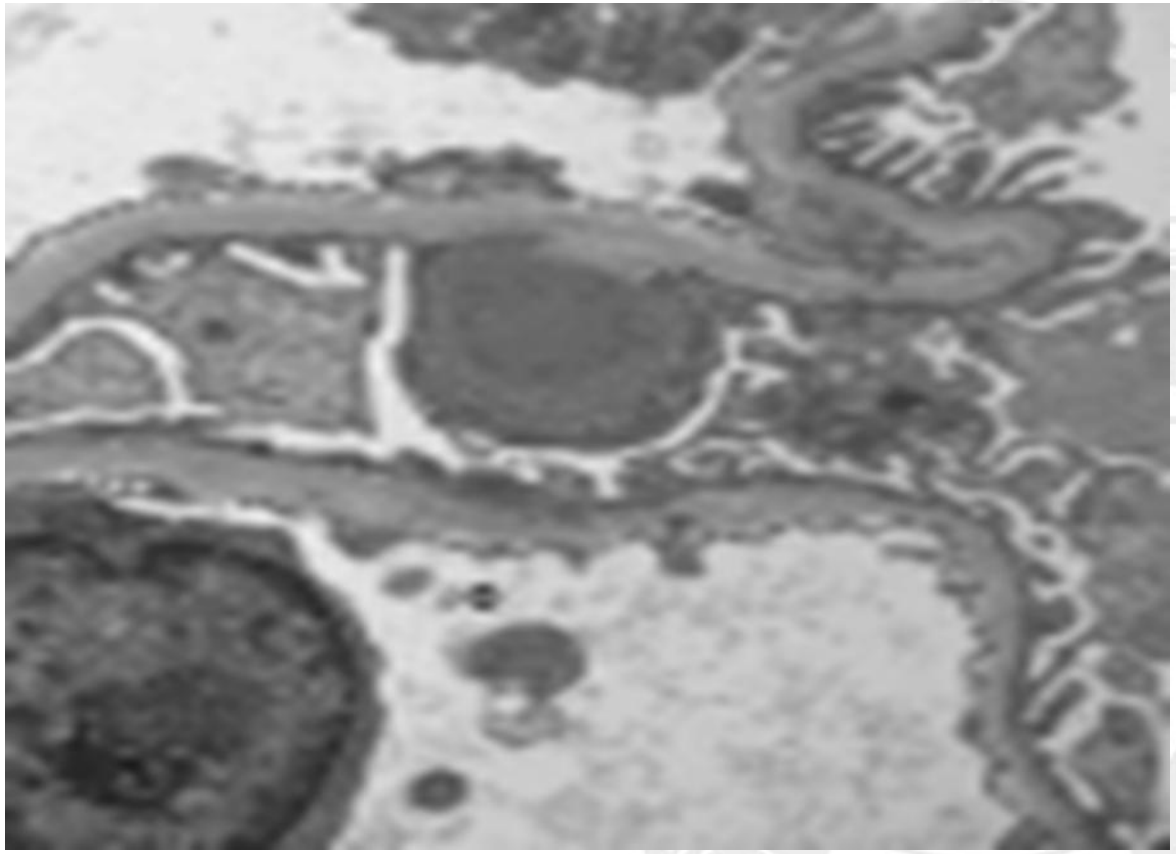


Figure 4.

Electron-microscopy in acute post-streptococcal GN. Note the large, "hump"-like subepithelial deposit. The periphery of this deposit is slightly less electron-dense than its center, indicating very early resorption.

Differential diagnosis

- The **differential diagnosis of PSGN** includes most other types of childhood glomerulonephritides, which also tend to present acutely, including **primary glomerular diseases**, such as IgA nephropathy, membranoproliferative glomerulonephritis, hereditary nephritis (commonly called Alport syndrome), and, importantly, other forms of postinfectious glomerulonephritis.

- Also on the list of differential diagnoses are **secondary glomerulonephritides,** such as systemic lupus erythematosus nephritis, Henoch-Schenlein purpura nephritis, Goodpasture disease, and glomerulonephritis as part of antineutrophil cytoplasmic antibody–associated vasculitides, as well as hemolytic uremic syndrome, all conditions in which the kidneys are only one organ system that may be involved.

- **IgA Nephropathy:** usually occurs after an upper respiratory tract infection, but it differs from PSGN in the shorter latency period it takes to appear after the episode of infection.
- **Membranoproliferative glomerulonephritis:** also presents with a nephritic picture and hypocomplementemia following respiratory tract infection. Complement levels take a longer time to return to normal than in PSGN.
- **Lupus nephritis:** sometimes PSGN presents with a picture similar to lupus nephritis. Laboratory testing for antibodies specific to each of the diseases can help in the diagnosis.
- **Nephrotic syndrome**

Treatment

General measures:

- Salt and water restriction is the initial step to control edema.

Fluid Balance

Fluid input and urine output should be closely monitored.

- All children should be weighed daily.
- All patients should be on a no added salt diet.
- If oliguric (<0.5 ml/kg/hr) restrict fluid input to replacement of insensible losses (400 ml/m2/day) plus previous days urine output

Antibiotics

Phenoxymethyl Penicillin

Doses are as follows:

- 1 – 5 yr 125 mg four times a day for 10 days
- 6 – 12 yr 250 mg four times a day for 10 days
- > 12 yr 500 mg four times a day for 10 days

Diuretics

- **Thiazide diuretics** may be effective first-line agents, whereas loop diuretics should be considered in those with more significant edema or some degree of renal dysfunction to ensure potency of action because thiazides are not as effective when renal function is less than 30 mL/min/1.73 m2.

- The 2 may be paired as well, but **potassium-sparing diuretics** should be avoided because of the existing risk of hyperkalemia in PSGN.

- **Loop diuretics** alone have been proven to be more effective than othsingle antihypertensive agents.

Hypertension

- **Calcium channel blockers** have been associated with fluid retention and edema and thus should not be the sole agent used, but they are likely to be effective when used in combination with a diuretic. b-Blockers can contribute to hyperkalemia and should therefore be used with vigilant laboratory monitoring.
- **Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers** are often viewed warily in the setting of PSGN. Theoretically, they may not be as effective with fluid overload because these patients have low serum renin and aldosterone levels.
- However, intrarenal renin levels are likely to be elevated in patients with PSGN who have decreased glomerular capillary perfusion.
- However, the concern with the use of these agents remains the potential for further worsened glomerular filtration and hyperkalemia, so caution is warranted.

Prognosis

- The **short-term prognosis** of APSGN in children is excellent;
- The **long-term prognosis**, as related to the development of chronic kidney disease, is also different in children and in adults.
- Volume overload resolves rapidly, typically within 10 days, and serum creatinine levels return to baseline within 3 to 4 weeks.
- Any associated proteinuria often tends to resolve shortly after this, whereas microscopic hematuria can linger for several months to a few years.
- Fortunately, recurrence of PSGN is extremely rare, although there have been case reports of this occurring, mainly with pyoderma from different nephritogenic strains.

- ***Persistent urinary findings***, either hematuria or proteinuria, have been reported in as few as 5% but up to 20% of PSGN patients after 10 years.
- ***Hypertension*** is less prevalent but seen in 3% of patients, whereas azotemia from chronic kidney disease is noted in less than 1% in several cohorts.
- ***Normal complement levels***, the findings of nephrotic syndrome, and biopsy findings of crescent formation are all predictors of worse long-term prognosis.

Long term Monitoring

- Long-term follow-up for a patient following APSGN primarily consists of blood pressure measurements and urine examinations for protein and blood.
- In general, examinations are performed at 4- to 6-week intervals for the first 6 months and at 3- to 6-month intervals thereafter, until both hematuria and proteinuria have been absent and the blood pressure has been normal for 1 year.
- Documenting that the low C3 has returned to normal after 8-10 weeks may be useful.

Follow up at 0-6 weeks as frequently as necessary to determine the following

- Hypertension has been controlled.
- Edema has started to resolve.
- Gross hematuria has resolved.
- Azotemia has resolved.
- Follow up at 8-10 weeks after onset to assess the following:
- Azotemia has subsided.
- Anemia has been corrected.
- Hypertension has resolved.
- C3 and C4 concentrations have returned to normal.
- Follow up at 3, 6, and 9 months after onset to check the following:
- Hematuria and proteinuria are subsiding gradually.
- Blood pressure is normal.
- Follow up at 12 months after onset to evaluate that proteinuria and microscopic hematuria have disappeared.
- Follow up at 2, 5, and 10 years after onset to check the patient's urine, blood pressure, and serum creatinine level are normal.

Case study

- A 5-year-old boy with a history of autism spectrum disorder was seen in his pediatrician's office approximately 3 weeks ago for a honey-crusted rash on his face, the dorsal aspect of his hands, and his legs.
- At that time, he was diagnosed as having impetigo and given a prescription for triple antibiotic cream to place on the skin lesions for the next 2 weeks.
- The lesions improved, but several weeks after the impetigo was diagnosed, the boy became less active and developed swelling of his eyelids, face, and hands.
- His condition culminated with notably decreased oral intake for a few days and the appearance of coffee-colored urine noted in the toilet, prompting the family to bring the boy to the local emergency department.

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Examination

On examination, the child is not toxic appearing and does not engage the physician but will interact with his parents.

He is afebrile, with a heart rate of 92 beats per minute and a blood pressure (BP) at rest of 138/87 mm Hg.

There is slight fullness to his eyelids, but he appears otherwise normocephalic.

His lung, heart, and abdominal examination findings are normal, but he has leg edema (1+).

His genitourinary examination findings are normal, although the physician notes that the patient pauses from playing when percussing over his costovertebral angles.

His skin lesions have healed.

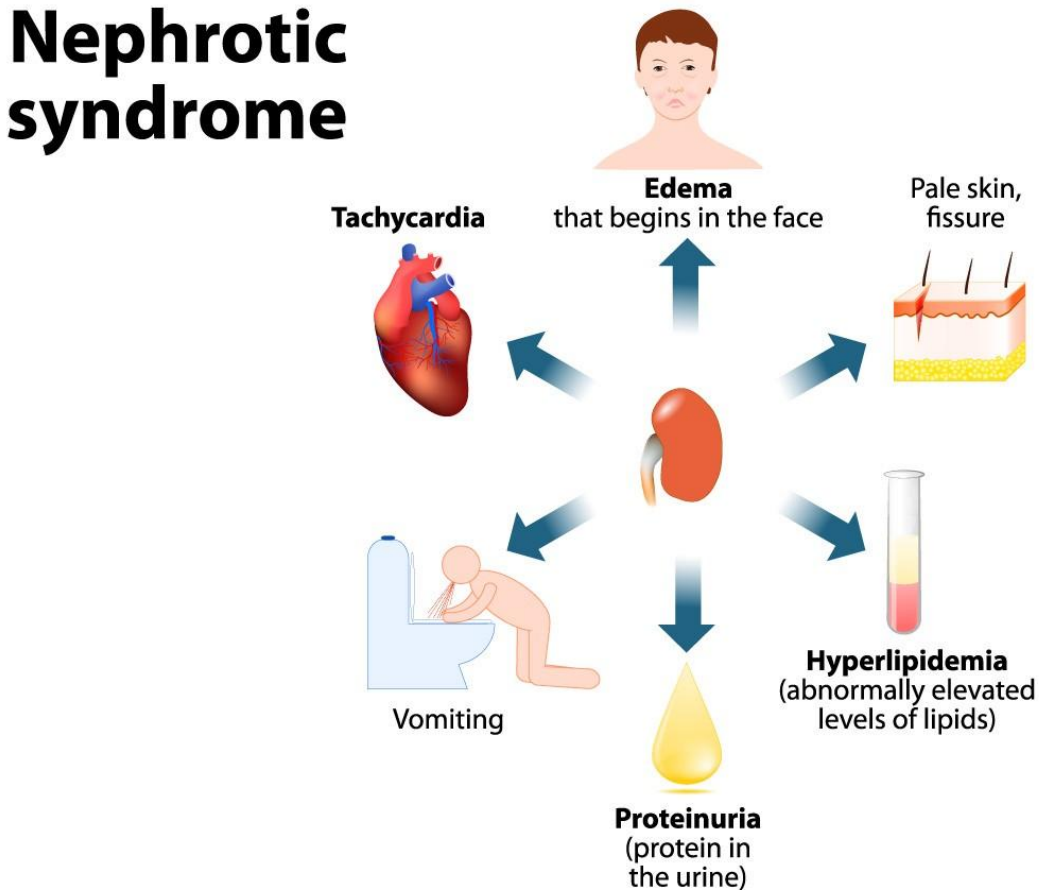
Laboratory evaluation

- Laboratory evaluation reveals red urine with large amounts of blood, 0.1 g/dL (1 g/L) of protein, and small amounts of leukocyte esterase, but no nitrites apparent on dipstick testing.
- *Microscopic examination* reveals 30 to 49 red blood cells, 5 to 9 white blood cells, and 3 to 4 hyaline casts per high-powered field.
- A *complete blood cell* count reveals 13,600 white blood cells, a hemoglobin level of 8.2 g/dL (82 g/L) (reference range, 11.5–13.5 g/dL [115–135 g/L]), and 278,000 platelets.
- *Renal function test* results are normal, with a serum creatinine level of 0.47 mg/dL (42 μmol/L) (reference range, 0.29–0.48 mg/dL [26–42 μmol/L]), but the serum albumin level is decreased at 2.7 g/dL (27 g/L) (reference range, 3.5–4.7 gm/dL [35–47 g/L]).
- The emergency department physician is considering next steps in this child's evaluation and treatment.

Question

- What is the diagnosis of this child ?
- What is further examination should be done?
- The principles of this child treatment?

Nephrotic syndrome in children



- Idiopathic nephrotic syndrome (INS) is a common chronic illness characterized by massive proteinuria and hypoalbuminemia in children.

- **Nephrotic syndrome** (NS) is characterized by heavy proteinuria (urine protein:creatinine ratio ≥2000 mg/g or ≥300 mg/dL, or 3+ protein on urine dipstick), hypoalbuminemia (≤2.5 g/dL), and edema.

EPIDEMIOLOGY

- It has an incidence of 2 to 7 per 100,000 population and a prevalence of 16 per 100,000 population, well above the 1 per 1 million incidence of chronic renal failure in children.
- Age at initial presentation also has an important say on the disease distribution frequency, 70% of MCNS patients are younger than 5 years; 20 to 30% of adolescent patients have MCNS.
- FSGS develops in children around 6 years and during the first year of life, congenital and infantile genetic disorders and congenital infections are more common than MCNS and FSGS and not all cases of MCNS or FCGS are idiopathic.

- The International Study of Kidney Disease in Childhood reported that **84.5%** of children with INS had minimal change nephrotic syndrome (MCNS),
- ✓ **9.5%** had focal segmental glomerulosclerosis (FSGS),
- ✓ **2.5%** had mesangial proliferative glomerulonephritis,
- ✓ **3.5%** had membranous nephropathy or other diseases leading to nephrotic-range proteinuria.
- Eighty to ninety percent of children with INS respond to steroid treatment.
- Unfortunately, 60%–80% of the children with steroid-responsive nephritic syndrome relapse, but they almost never develop end-stage renal disease (ESRD).
- Resistance to immunosuppressant therapy, occurs in 50% of FSGS cases and 10% of MCNS cases, which is associated with progression to ESRD.

Classification

- Childhood NS is classified into three groups:

Idiopathic	Secondary	Congenital
• INS 90% of cases	• 10%	• <1%

Classification:

Nephrotic syndrome is primarily classified as:

1. ***Primary NS*** that is not associated with systemic disease and accounts for 90% of childhood cases.

2. ***Secondary NS***: that occurs as a part of systemic disease or is related to a drug or other toxin.

Etiological classification of nephrotic syndrome

- **A. Acquired**
- **B. Congenital**

Again, both of the cases of nephrotic syndrome may be primary and secondary.

A. **Acquired causes**

a. **Primary - 90%**

- Idiopathic (90%)
- Minimum change nephrotic syndrome (MCNS) -85%
- Mesangioproleferative nephrotic syndrome (MPNS) -5%
- Focal sclerosis nephrotic syndrome (FSNS) -10%
- Some form of GN (10%)
- Membranous GN
- Membranoproliferative GN

b. **Secondary - 10%**

- Post infectious
- Virus - BV, Human immunodeficiency
- virus (HIV) others
- Bacteria - Syphilis,

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- Spuntaneous bacterial endocarditis (SBE)
- *Systemic Disease*
- Collagen Vascular - Systemic lupus nephritis (SLE),
- Henoch schonlein purpura (HSP),
- Polyasteritis nodosa (PAN)
- *Disease*
- Diabetic Nephropathy
- Sickle cell disease
- Wegner's granulomatosis
- Good pasteur's syndrome
- Hereditary Nephritis - (Alport's syndrome)
- Drugs
- Penicillamine
- Captopril
- Warfarin

Etiological classification of nephrotic syndrome

- Lithium
- Gold
- Trimethodione
- Probenecid etc.
- Malignancy- Leukemia, Lymphoma,
- Wilm's tumor
- Amyloidosis

Etiological classification of nephrotic syndrome

B. Congenital nephrotic Syndrome- nephrotic syndrome that presents in the first 3 months of life.

a. Primary

1. Infantile microcystic disease
• Finish Type - AR
• Non finish type
2. Diffuse Mesangial sclerosis
3. Minimal -Lesion Nephrotic syndrome
4. Focal segmental glomerulosclerosis

b. Secondary

1. Intrauterine infection - toxoplasmosis, CMV, Rubella, Syphilis
2. Gonadal dysgenesis
3. Nail patella syndrome
4. Lowe's syndrome

DEFINITIONS

TABLE 1. Definitions Used in Idiopathic Nephrotic Syndrome

Classification	Definition
Nephrotic syndrome	Edema, proteinuria > 40 mg/m2/hr or protein/creatinine ratio > 0,2 g/mmol (> 2 g/g) or 50 mg/kg/day or 3-4 + on urine dipstick, hypoalbuminemia < 25 g/L (< 2,5 mg/100ml)
Remission	Urinary protein excretion ≤ 4 mg/m2/hr or 0-trace of protein on urine dipstick or protein/creatinine ratio < 0,02 g/mmol (< 2 g/g) for 3 consecutive days
Initial responder	Attainment of complete remission within initial 8 weeks of corticosteroid therapy
Initial nonresponder/steroid resistance	Failure to achieve remission during initial 8 weeks of corticosteroid therapy
Relapce	Urinary protein > 40 mg/m2/hr or protein/creatinine ratio> 0,2 g/mmol (> 2 g/g) or 2 + protein or more on urine dipstick for 3 consecutive days
Infrequent relapce	One relapce within 6 months of initial response or one to three relapses in any 12-months period
Frequent relapce	Two or more relapses within 6 months of initial response or four or more relapses in any 12- months period
Steroid dependence	Two consecutive relapses during corticosteroid therapy or within 14 days of ceasing therapy
Late nonresponder	Proteinuria for > 8 weeks following one or more remissions

Clasification response to steroid

- **Steroid-Sensitive Nephrotic Syndrome:** Patients who enter remission in response to corticosteroid treatment alone are referred to as having steroid-sensitive nephrotic syndrome (SSNS).
- **Steroid-Dependent Nephrotic Syndrome:** some patients respond to initial corticosteroid treatment by entering complete remission but develop a relapse either while still receiving steroids or within 2 weeks discontinuation of treatment following a steroid taper.

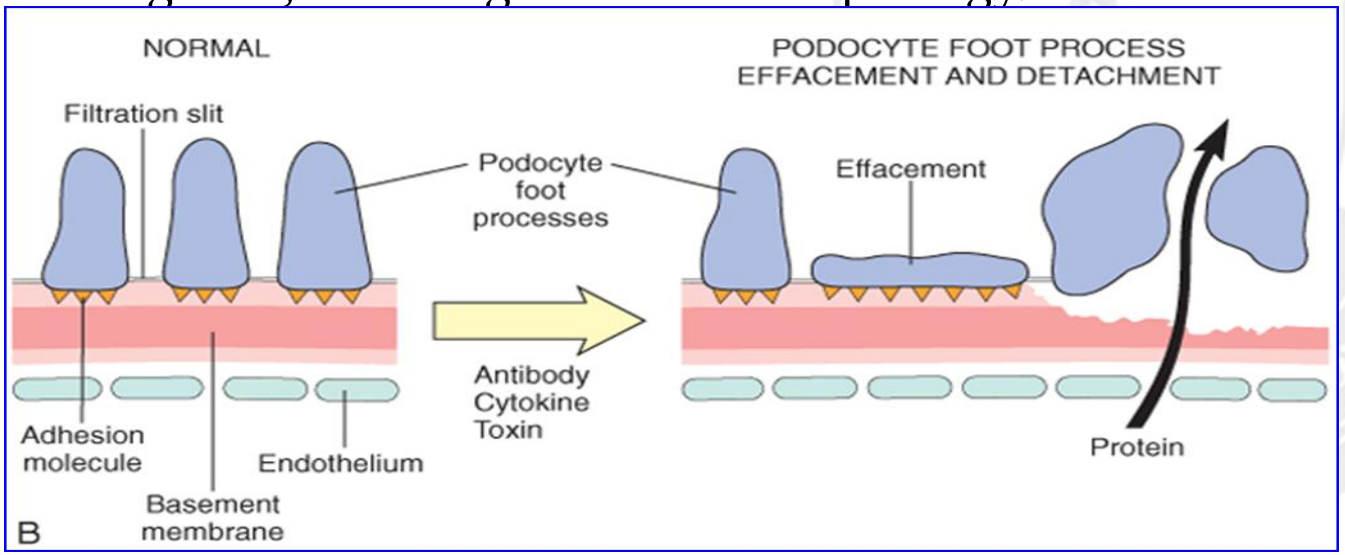
Clasification response to steroid

- **Steroid-Resistant Nephrotic Syndrome:**

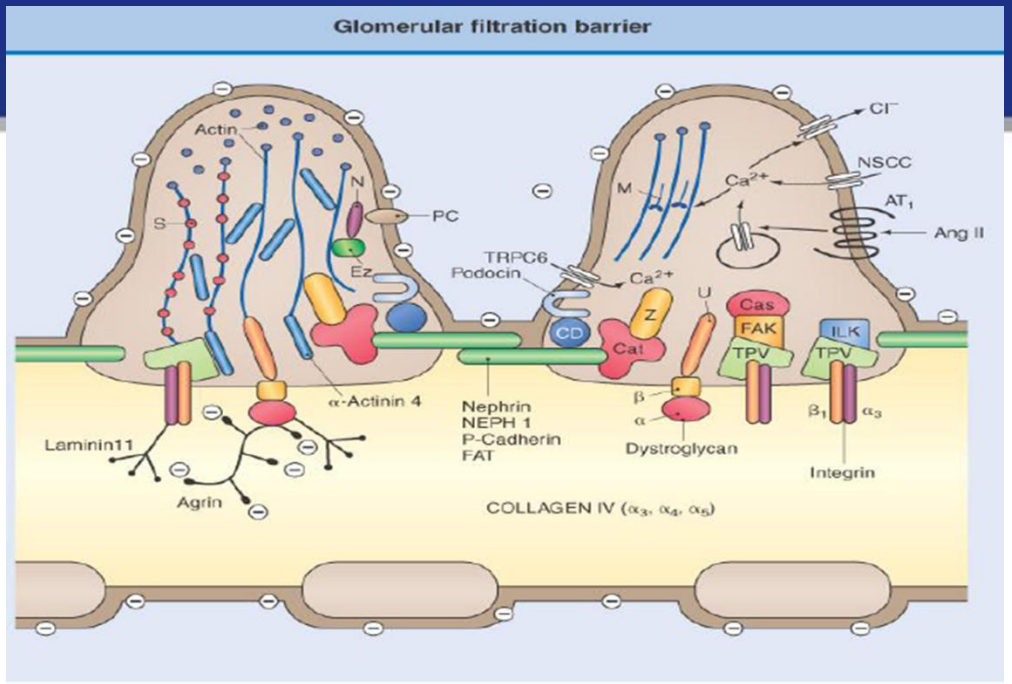
No urinary remission following 4 weeks of prednisone 60mg/m2/day followed by three intravenous pulses of methylprednisolone (500 mg/m2) and another two weeks of prednisone at the dose of 60 mg/m2/day

PATHOGENESIS

- **Primary Glomerular Defect**
- The glomerular capillary wall consists of three structural elements that constitute the permselectivity barrier:endothelial cells separated by fenestrae, the glomerular basement membrane containing matrix proteins, and podocytes (specialized epithelial cells).
- Normally, larger proteins (>69 kD) are excluded from filtration; but in nephrotic syndrome, glomeruli appear greatly changed, adjacent podocytes are fused together, assuming a foot-like morphology.



- ***Mutations in several podocyte proteins*** have been identified in families with inherited nephrotic syndrome; a plasma factor may alter glomerular permeability, especially in patients with steroid-resistant nephrotic syndrome and lastly altered T-lymphocyte responses, in that the T-cells could result in the production of a permeability factor that can interfere with the expression, function or both to cause proteinuria



(Modified from English K, Kriz W, Witzgall R: Update in podocyte biology. Curr Opin Nephrol Hypertens 2001;10:331–340.)

- Nephrin was the first slit-diaphragm protein

identified12-22 and mutations in this transmembrane protein cause congenital (Finnish-type) nephrotic syndrome that occurs with a frequency of 1 per 8,200 live births in Finland.

- Among children with inherited nephrotic syndrome, investigators have identified mutations in other genes that encode podocyte proteins.

Permeability Factor

- The role of a systemic circulating factor has been hypothesized in patients with MCNS and FSGS. The clinical response toward immunosuppressive drugs and also lack of inflammatory changes in renal parenchyma suggest an extrarenal factor as causative agent for proteinuria.

Permeability Factor

- Various vascular permeability factors have been implicated including *vascular endothelial growth factor, heparanase and hemopexin*.
- ***Vascular endothelial growth factor*** is a potent permeability factor produced in vivo by normal glomerular podocytes, and receptors for the factor are located on glomerular endothelial and mesangial cells.
- ***Heparanase*** is postulated to increase the permeability of glomerular capillary wall by degrading heparin sulfate glucosamino glycans.

Immunological Basis

- Recent knowledge shows that antigen presentation to T-lymphocytes results in a polarized immune response, which may be type I (dominated by gamma interferons, interleukin-2) or type II (IL-4, IL-10, or IL-13).
- Type I cytokines predominate in cell-mediated immunity and type II in humoral immunity and are particularly associated with atopy and class switching of B cells for production of IgG4 and IgE.
- The findings of increased plasma levels of IgE, IgG4 and association with atopy suggest type II cytokine bias in patients with MCNS.
- Further increased systemic production of representative cytokines, chiefly, IL-4 is also reported. In vitro studies suggest that podocytes express receptors for IL-4 and IL-13.
- Activation of these receptors, by respective cytokines, might disrupt glomerular permeability resulting in proteinuria.

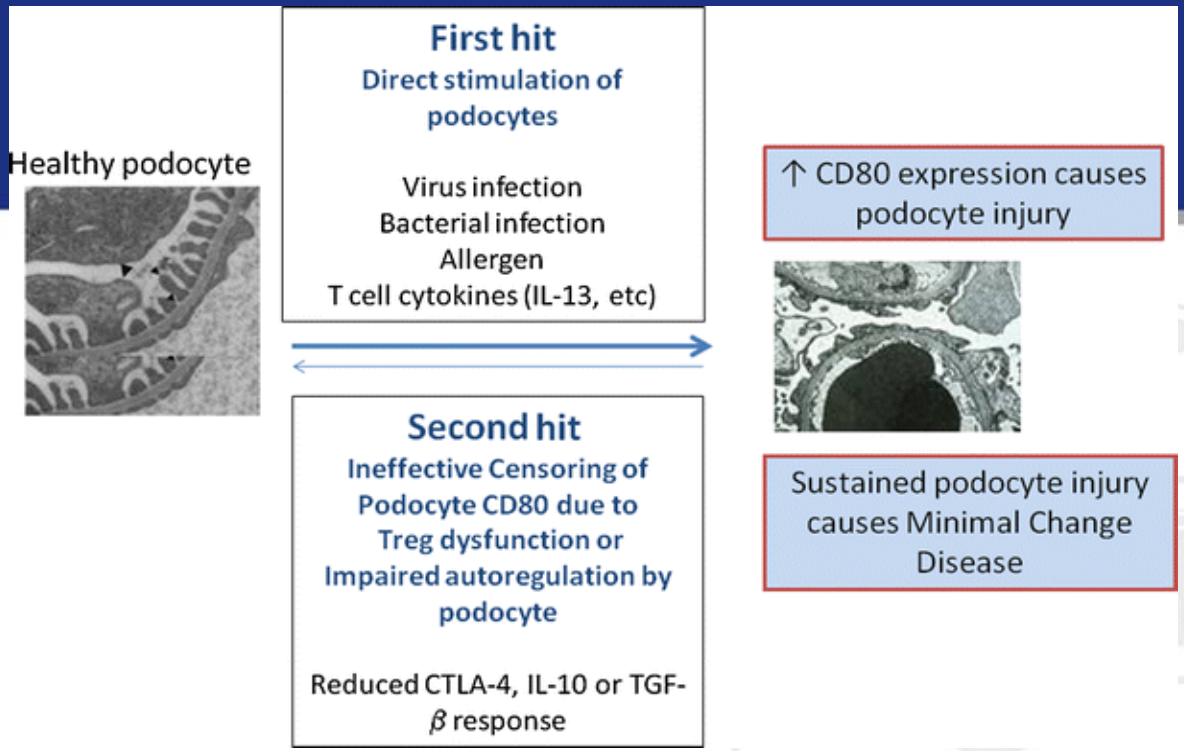
New paradigm for the pathogenesis of MCD

- A new paradigm for the pathogenesis of MCD has emerged since the discovery by Kestila et al. in 1998 **that mutations in the gene *NPHS1*, which encodes the podocyte-expressed immunoglobulin superfamily protein nephrin, cause congenital NS in humans.** This landmark study led to a substantial increase in our understanding of glomerular biology and physiology.
- Additionally, the development of proteinuria in lipopolysaccharide (LPS)-injected severe combined immunodeficient mice, which are devoid of T- and B-cells, suggests that this mouse model of MCD may be independent of T- or B-cells.
- Based on these findings, visceral glomerular epithelial cells (podocytes) have attracted particular attention as a key player in the pathogenesis of MCD.

Podocyte ultrastructure is the final barrierto urinary protein loss

- Podocytes are terminally differentiated cells that line the outer aspect of the glomerular basement membrane (GBM).
- Podocytes form the final barrier to urinary protein loss by the formation and maintenance of podocyte foot processes (FPs) and the interposed slit diaphragms (SDs).

- The SDs are the main selectively permeable barrier in the kidney.
- Podocyte foot processes (FPs) contain a contractile and dynamic apparatus consisting of actin, myosin II, α-actinin-4, talin, vinculin, and synaptopodin.
- The FPs are anchored to the GBM via α3/β1-integrin and dystroglycans. Our knowledge of SD structure is based on genetic studies of familial NS, which led to identification of SD proteins such as podocin, nephrin, α-actinin-4, and TRPC6.
- The genes for these proteins may be mutated in inherited NS.
- In contrast, no mutation has been found in MCD characterized by selective albuminuria associated with FP effacement, where the expression of these proteins is unchanged or downregulated.
- It is easily understandable that various proteins can leak from the impaired SD between podocytes due to reduced nephrin expression in congenital NS of the Finnish type or podocyte detachment in FSGS.
- However, it remains unclear how albumin can diffuse across the effaced podocyte FP in MCD.



- **Fig. 1.** Two hit theory in podocyte immune disorder. IL, interleukin; CTLA-4, cytotoxic T-lymphocyte antigen 4; TGF, transforming growth factor. Adapted from Shimada et al. Pediatr Nephrol 2011;26:645-9, with permission of Springer[6)].

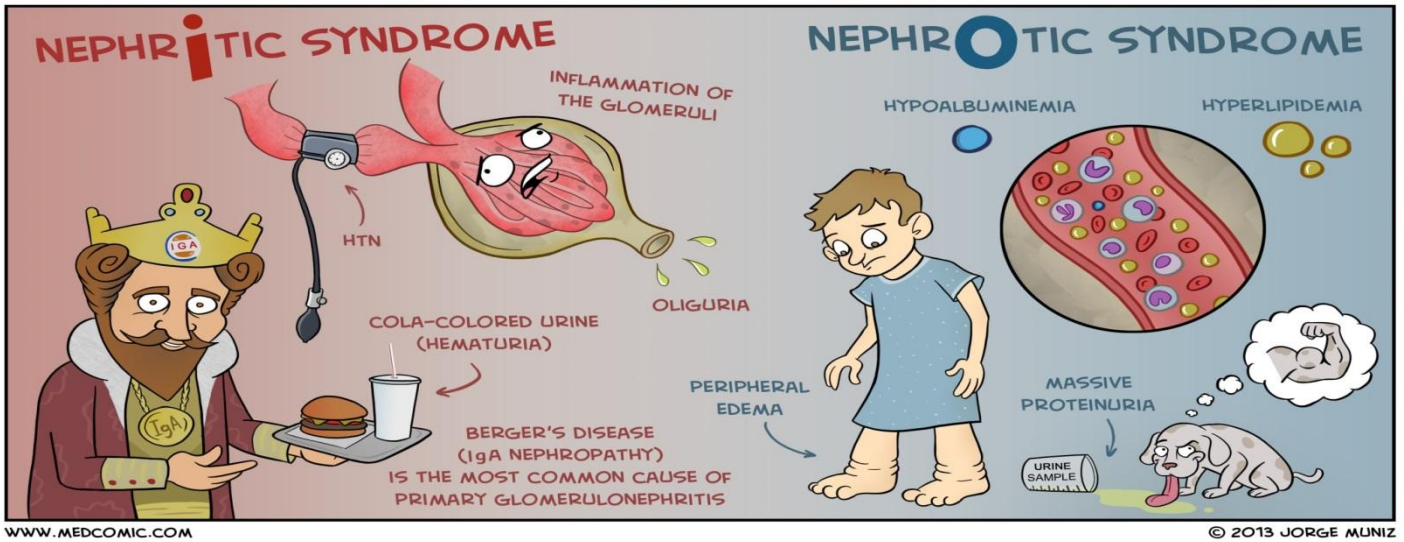
Recently, Shimada et al. proposed a "two-hit" theory that included the induction of CD80 (or B7-1) and regulatory T-cell (Treg) dysfunction, with or without impaired autoregulatory function of the podocytes.

Pathophysiology of edema in nephrotic syndrome

- Edema is a predominant clinical feature of NS which occurs with variable severity, from moderate edema localized in particular areas of the body (face, legs, abdomen, genitals) to massive generalized edema.
- The classical explanation for edema formation is a decrease in plasma oncotic pressure, as a consequence of low serum albumin levels, causing an extravasation of plasma water into the interstitial space.
- The resulting contraction in plasma volume (PV) leads to stimulation of the renin-angiotensin-aldosterone axis and antidiuretic hormone.
- The resultant retention of sodium and water by the renal tubules contributes to the extension and maintenance of edema.

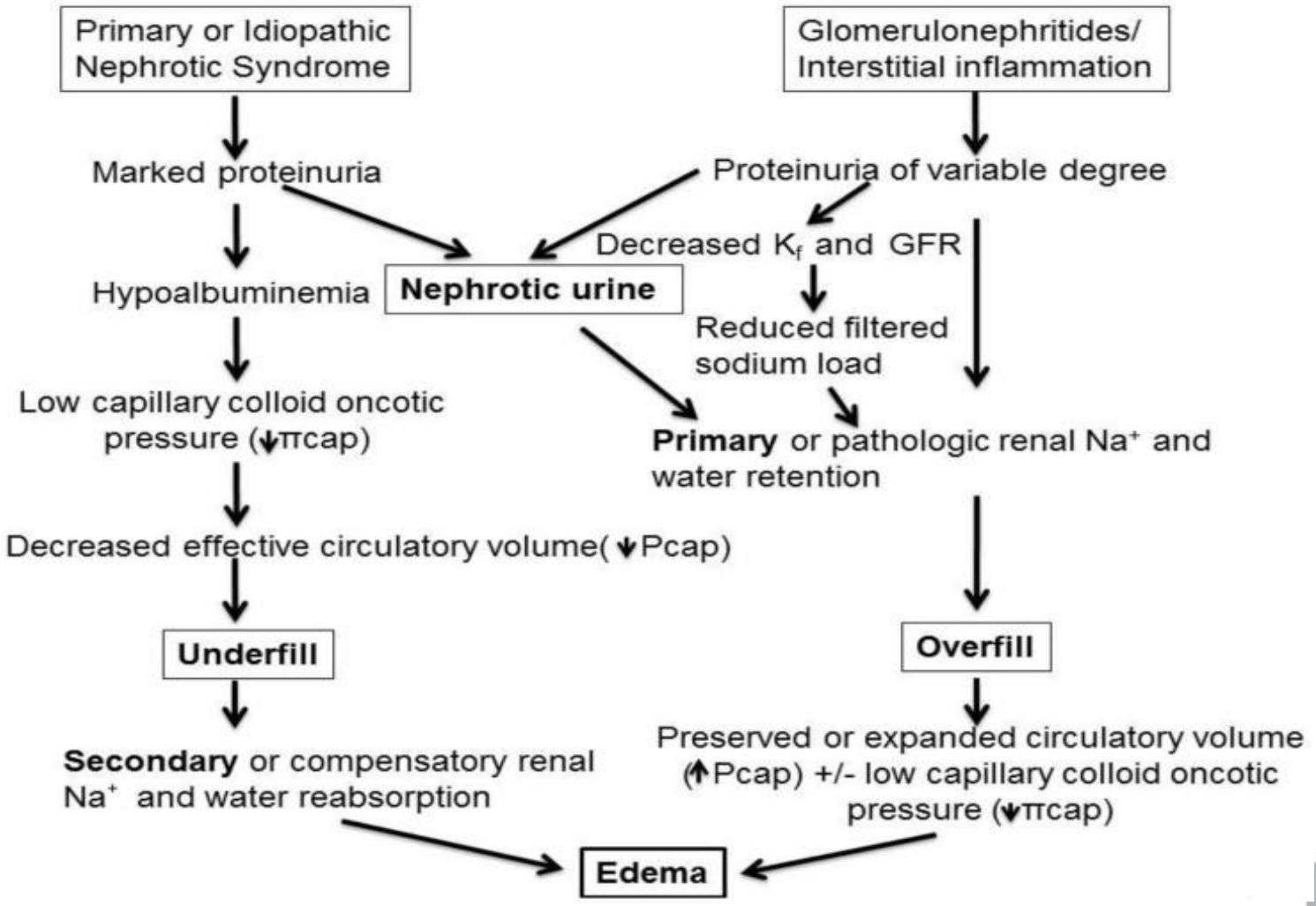
Pathophysiology of edema in nephrotic syndrome

- According to the **underfill mechanism**, the urinary loss of albumin leads to a decrease in plasma oncotic pressure which, with increased capillary ultrafiltration of sodium and water, leads to edema formation.
- Therefore, the retention of sodium chloride in NS could be a consequence of the activation of the reninangiotensin-aldosterone system (RAAS) secondary to plasma volume reduction.



- In contrast, in the **overfill mechanism** the primary intra-renal sodium and water retention caused by resistance to atrial natriuretic peptide (ANP) and the activation of epithelial sodium channel (ENaC) in the inner medullary collecting duct leads to an expansion of the intravascular compartment and edema.

Pathophysiology of edema formation in NS



Mechanism of edema formation in nephrotic syndrome: *"underfilling".*

Clinical characteristics

Neuromuscular weakness, pallor, cool extremities, tachycardia, and other signs and symptoms of orthostatic hypotension, abdominal pain secondary to gut edema, abdominal compartment syndrome, or thrombosis of vena cave or renal veins

Laboratory findings

Reduced urine volume

$FE^{Na+} < 0.2\%$

$UK^{+}/UK^{+} + Na^{+} > 60\%$ (increased TTKG index)

Reduced urinary Na^{+} and high potassium concentration

Very low serum albumin (≤2 g/dL)

Low serum creatinine level

GFR > 75 mL/min/1.73 m^2

Hemoconcentration

High circulating PRA, aldosterone, vasopressin, and norepinephrine

Low ANP concentration

Mechanism of edema formation in nephrotic syndrome: *"overfilling"*.

Clinical findings

Normal or elevated BP without tachycardia or orthostatic symptoms, and no signs to indicate distal extremity hypoperfusion

Laboratory findings

FE^{Na+} > 0.5% while on no salt restricted diet

$UK^{+}/UK^{+} + UNa^{+}$ < 60% (decreased TTKG index)

Hematuria and cellular casts

Serum albumin >2 g/dL

Elevated serum creatinine and BUN

GFR < 50 mL/min/1.73 m^2

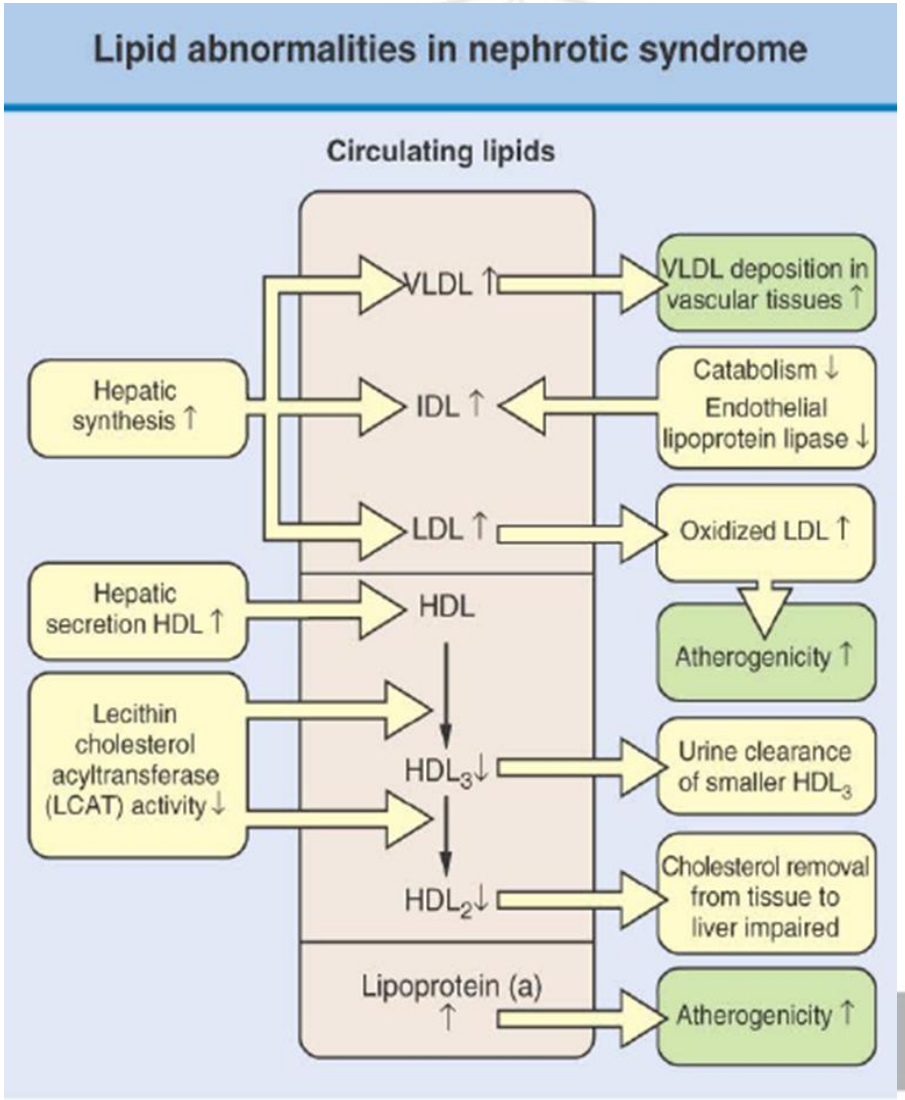
Decreased vasopressin

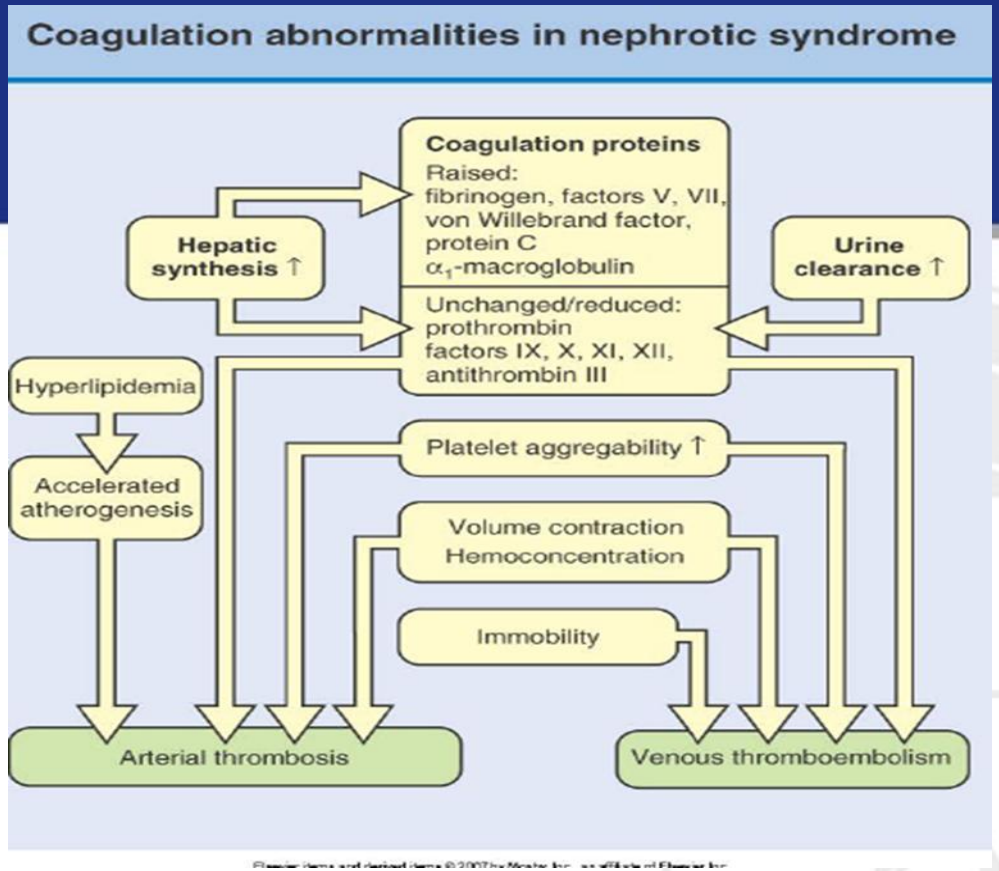
Low circulating PRA and norepinephrine

Low or normal plasma aldosterone

High ANP

- Increase liver synthesis
- Decrease function of regulatory enzymes
  - Decrease clearance of cholesterol in the periphery





- Nephrotic syndrome is a hypercoagulable state. The increased risk of thrombosis can be attributed to 2 basic mechanisms:
- **1. urine losses of antithrombotic proteins and**
- **2. increased synthesis of prothrombotic factors.**
- Abnormalities described in INS include decreased antithrombotic factors and increased synthesis of pro-thrombotic factors.

Clinical examination

- To include:
- Height, weight, estimated body surface area (NB – an estimate of dry weight will give a more accurate surface area estimate)
- Blood pressure
- Assessment of oedema (lower limb, sacral, ascites, scrotal, pleural effusions?

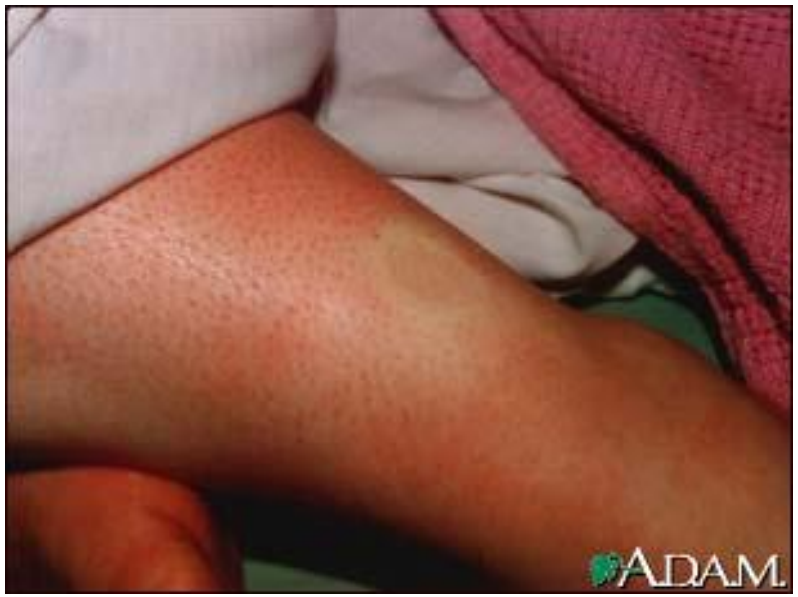
✓ Cardiovascular status and perfusion (volume status):

✓ Indicators of fluid overload: tachycardia, hypertension, respiratory distress, warm peripheries, hepatomegaly, raised JVP

✓ Indicators of hypovolaemia: tachycardia, hypertension, cool peripheries, delayed capillary refill time

Signs and symptoms

- Pitting edema is the presenting symptom in about 95% of children with nephrotic syndrome. It is typically found in the lower extremities, face and periorbital regions, scrotum or labia, and abdomen (ascites).
- Other signs and symptoms of nephrotic syndrome may include the following:
- Respiratory tract infection - A history of a respiratory tract infection immediately preceding the onset of nephrotic syndrome is frequent.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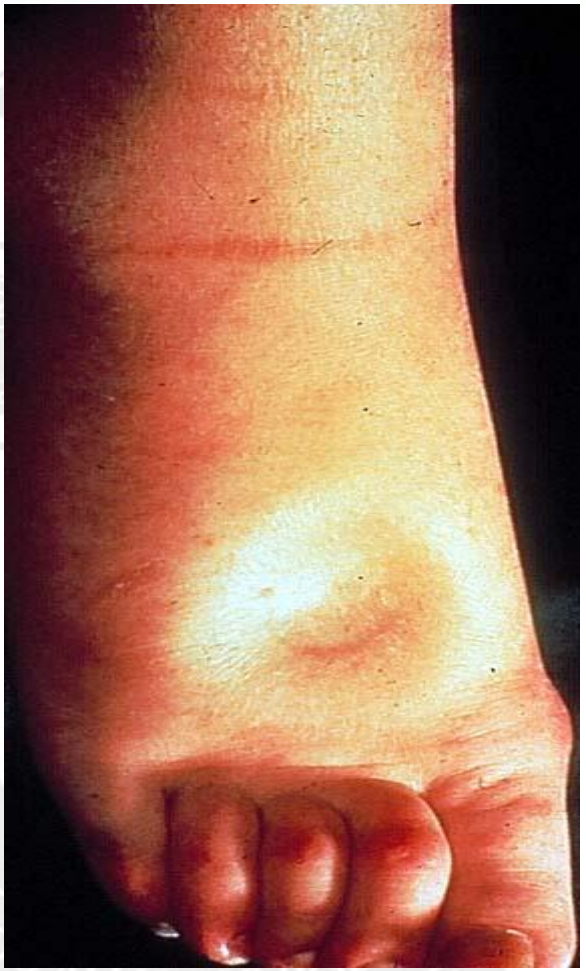


Signs and symptoms

- Allergy - Approximately 30% of children with nephrotic syndrome have a history of allergy [3]
- Macrohematuria
- Symptoms of infection - Such as fever, lethargy, irritability, or abdominal pain due to sepsis or peritonitis
- Hypotension and signs of shock - Can be present in children presenting with sepsis
- Respiratory distress - Due to either massive ascites and thoracic compression or frank pulmonary edema, effusions, or both.

Signs and symptoms

- Tachypnea - To compensate for mechanical restriction to breathing
- Seizure - Due to cerebral thrombosis
- Anorexia
- Irritability
- Fatigue
- Abdominal discomfort
- Diarrhea
- Hypertension

Laboratory evaluation

- Therefore, initial laboratory testing should include the following:
- Urinalysis
- Urine protein quantification
- Serum albumin
- Lipid panel

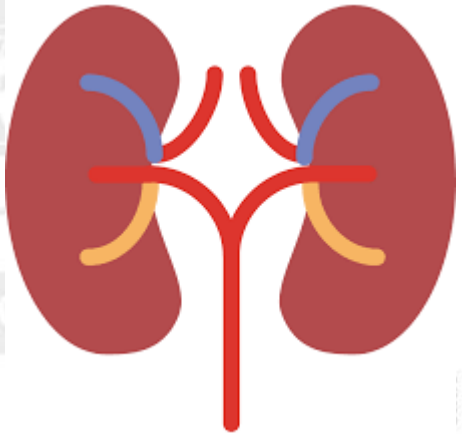
Laboratory evaluation

- Complete blood count (CBC)
- Metabolic panel - levels of serum electrolytes, calcium, phosphorus, and ionized calcium, as well as of blood urea nitrogen (BUN) and creatinine
- Testing for HIV
- Testing for hepatitis B and C
- Complement studies (C3, C4)
- Antinuclear antibody (ANA), anti–double-stranded DNA antibody (in selected patients)

Laboratory evaluation

Other tests and procedures in selected patients can include the following:

- Genetic studies;
- Kidney ultrasonography;
- Chest radiography;
- Mantoux test;
- Kidney biopsy.



Renal Biopsy

- Is general, renal biopsy is indicated only in the setting of atypical features such as age at onset (less than 1 year or m than 10);
- SDNS or SRNS;
- gross or persistent microscopic hematuria or presence of red cell casts, abnormal serologies, or significant persistent renal failure.

- **Diagnosis of nephrotic syndrome** is confirmed by the triad of generalized edema, proteinuria, albuminuria (> 2+ on dipstick or urine protein/creatinine ratio (>2mg/mg), and hypoalbuminemia (serum albumin < 2,5 g/dl), although hypercholesterolemia is also commonly present.

Treatment

- **Dietary advice -** A balanced no added salt diet is recommended while the patient is in relapse. The dietetic advice to achieve this is to avoid the addition of salt in cooking and at the table.
- To reduce the intake of processed foods parents should select foods which contain <0.5 g Na per 100 g weight of food.
- Compliance with a no added salt diet will aid adherence to the fluid restriction and encourage good blood pressure control.
- The diet should be nutritionally balanced with an emphasis on healthy eating and the avoidance of a high saturated fat intake.

Steroid-sensitive nephrotic syndrome in children

Treatment of the initial episode of SSNS

Dosing of prednisone

Prednisone doses of 60 mg/m2/day and 2 mg/kg/day are the internationally accepted standard doses for children with NS.

3.1.1: We recommend that corticosteroid therapy (prednisone or prednisolone)* be given for at least 12 weeks. (1B)

3.1.1.1: We recommend that oral prednisone be administered as a single daily dose (1B) starting at 60 mg/m2/d or 2 mg/kg/d to a maximum 60 mg/d. (1D)

3.1.1.2: We recommend that daily oral prednisone be given for 4–6 weeks (1C) followed by alternate-day medication as a single daily dose starting at 40 mg/m2 or 1.5 mg/kg (maximum 40 mg on alternate days) (1D) and continued for 2–5 months with tapering of the dose. (1B)

Kidney International Supplements (2012) 2, 143–153; doi:10.1038/kisup.2012.13

Treatment of relapsing SSNS

Corticosteroid therapy for children with infrequent relapses of SSNS:

3.2.1.1: We suggest that infrequent relapses of SSNS in children be treated with a single-daily dose of prednisone 60 mg/m2 or 2 mg/kg (maximum of 60 mg/d) until the child has been in complete remission for at least 3 days. (2D)

3.2.1.2: We suggest that, after achieving complete remission, children be given prednisone as a single dose on alternate days (40 mg/m2 per dose or 1.5 mg/kg per dose: maximum 40 mg on alternate days) for at least 4 weeks. (2C)

Kidney International Supplements (2012) 2, 143–153; doi:10.1038/kisup.2012.13

Corticosteroid therapy for frequently relapsing (FR) and steroid-dependent (SD) SSNS

3.2.2.1: We suggest that relapses in children with FR or SD SSNS be treated with daily prednisone until the child has been in remission for at least 3 days, followed by alternate-day prednisone for at least 3 months. (2C)

3.2.2.2: We suggest that prednisone be given on alternate days in the lowest dose to maintain remission without major adverse effects in children with FR and SD SSNS. (2D)

3.2.2.3: We suggest that daily prednisone at the lowest dose be given to maintain remission without major adverse effects in children with SD SSNS where alternate-day prednisone therapy is not effective. (2D)

3.2.2.4: We suggest that daily prednisone be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone. (2C)

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Treatment of FR and SD SSNS with corticosteroid-sparing agents

3.3.1: We recommend that corticosteroid-sparing agents be prescribed for children with FR SSNS and SD SSNS, who develop steroid-related adverse effects. (1B)

3.3.2: We recommend that alkylating agents, **cyclophosphamide or chlorambucil,** be given as corticosteroid-sparing agents for FR SSNS. (1B) We suggest that alkylating agents, cyclophosphamide or chlorambucil, be given as corticosteroid-sparing agents for SD SSNS. (2C)

3.3.2.1: We suggest that **cyclophosphamide (2 mg/kg/d) be given for 8–12 weeks** (maximum cumulative dose 168 mg/kg). (2C)

3.3.2.2: We suggest that cyclophosphamide not be started until the child has achieved remission with corticosteroids. (2D)

3.3.2.3: We suggest that **chlorambucil (0.1–0.2 mg/kg/d) may be given for 8 weeks** (maximum cumulative dose 11.2 mg/kg) as an alternative to cyclophosphamide. (2C)

3.3.2.4: We suggest that second courses of alkylating agents not be given. (2D)

Kidney International Supplements (2012) 2, 143–153; doi:10.1038/kisup.2012.13

Treatment of FR and SD SSNS with corticosteroid-sparing agents

3.3.4: We recommend that the calcineurin inhibitors cyclosporine or tacrolimus be given as corticosteroid-sparing agents. (1C)

3.3.4.1: We suggest that cyclosporine be administered at a dose of 4–5 mg/kg/d (starting dose) in two divided doses. (2C)

3.3.4.2: We suggest that tacrolimus 0.1 mg/kg/d (starting dose) given in two divided doses be used instead of cyclosporine when the cosmetic side-effects of cyclosporine are unacceptable. (2D)

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Treatment of FR and SD SSNS with corticosteroid-sparing agents

3.3.4.3: Monitor CNI levels during therapy to limit toxicity. (Not Graded)

3.3.4.4: We suggest that CNIs be given for at least 12 months, as most children will relapse when CNIs are stopped. (2C)

3.3.5: We suggest that MMF be given as a corticosteroid-sparing agent. (2C)

3.3.5.1: We suggest that MMF (starting dose 1200 mg/m2/d) be given in two divided doses for at least 12 months, as most children will relapse when MMF is stopped. (2C)

3.3.6: We suggest that rituximab be considered only in children with SD SSNS who have continuing frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents, and/or who have serious adverse effects of therapy. (2C)

Kidney International Supplements (2012) 2, 143–153; doi:10.1038/kisup.2012.13

Treatment recommendations for SRNS

4.2.1: We recommend using a calcineurin inhibitor (CNI) as initial therapy for children with SRNS. (1B)

4.2.1.1: We suggest that CNI therapy be continued for a minimum of 6 months and then stopped if a partial or complete remission of proteinuria is not achieved. (2C)

4.2.1.2: We suggest CNIs be continued for a minimum of 12 months when at least a partial remission is achieved by 6 months. (2C)

4.2.1.3: We suggest that low-dose corticosteroid therapy be combined with CNI therapy. (2D)

4.2.2: We recommend treatment with ACE-I or ARBs for children with SRNS. (1B)

4.2.3: In children who fail to achieve remission with CNI therapy:

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Treatment recommendations for SRNS

4.2.3.1: We suggest that mycophenolate mofetil (2D), high-dose corticosteroids (2D), or a combination of these agents (2D) be considered in children who fail to achieve complete or partial remission with CNIs and corticosteroids.

4.2.3.2: We suggest that cyclophosphamide not be given to children with SRNS. (2B)

- Kidney International Supplements (2012) 2, 143–153; doi:10.1038/kisup.2012.13

Pharmacological Management of Nephrotic Edema

Albumin Infusion

Albumin: Is indicated in clinical hypovolemia and symptomatic edema. A low serum albumin is not an indication for intravenous albumin. If there is evidence of hypovolemia, give 1 gm/kg 20% albumin (5 ml/kg) over 4 to 6 hours.

Children should be closely monitored during albumin infusions, and where possible should be administered during working hours.

Mild edema

- Since treatment with corticosteroids usually leads to diuresis within 4–8 days, a mild edema (weight gain <7-10%) can be managed simply with dietary sodium restriction (<1-2 g/day or <35 mg/kg/day) and moderate fluid restriction (initial restriction of fluid intake to an equivalent volume of the patient's insensible losses plus his/her urine output).
- Mild edema be managed with salt and fluid restriction only.

Moderate edema

- In patients with persistent edema and a weight gain of 7-10%, a loop diuretic such as oral **furosemide (1–3 mg/ kg/daily**) is recommended, in addition to salt and water restriction.
- Additional treatment with **potassium-sparing diuretics (e.g. spironolactone, 1–3 mg/kg daily)** should be given to patients requiring higher doses and prolonged treatment with furosemide.
- Blood pressure should be monitored frequently and a gradual reduction of the edema over a period of one week is preferable.

Severe/refractory edema

- Severe/refractory edema In patients with a weight gain >10% and severe edema who do not respond to maximum doses of oral furosemide (and spironolactone), the co-administration of a thiazide diuretic (e.g. hydrochlorthiazide) may be indicated; furosemide might be better administered intravenously by bolus injections, under careful monitoring.
- For patients with refractory edema, infusions of albumin (20% albumin, 0.5–1 g/kg, over 3–4 h) with an i.v. bolus of furosemide (1 mg/kg intravenously) administered during or at the end of the infusion, are indicated.
- As the effect of these infusions is transient, patients with severe edema might require repeat infusions.
- All patients receiving albumin should be observed for respiratory distress, hypertension and congestive heart failure.
- Albumin should be administered with caution in patients with renal failure and is contraindicated in most patients with pulmonary edema. In these patients, acute hemodialysis with or without infusion of albumin should be considered.

Infection

- Loss of complement components and immunoglobulins may result in an increased risk of infection.
- Prophylactic Phenoxymethylpenicillin (Pen. V) should be given whilst patients have significant proteinuria.
- Phenoxymethylpenicillin

✓ Child under 1 year 62.5 mg twice daily

✓ Child 1–5 years 125 mg twice daily

✓ Child 5–18 years 250 mg twice daily

Gastroprotection

- We do not recommend the routine use of prophylactic proton pump Inhibitors (PPIs) in combination with steroid therapy in NS.
- We suggest that PPIs should be used only in
- selected cases manifesting with gastric symptoms
- resistant to treatment with malgadrate or alginate, or with any other risk factor (gastroesophageal reflux, esophageal disease, concomitant need for other gastrotoxic therapies).

Supplementation with calcium and vitamin D

- Steroids cause osteoporosis through the inhibition of osteoblasts and by increasing bone resorption and the duration of steroid therapy and its cumulative dose correlate with bone density moreover, low levels of 25-hydroxycholecalciferol [25(OH)D3] due to the urinary loss of both vitamin 25(OH)D3 itself and its binding protein can be noticed at onset and during relapses.
- We do not suggest calcium and vitamin D supplementation in children at first episode or in SSNS unless vitamin D deficiency has been predicted or demonstrated.

Treatment of hyperlipidemia

The majority of patients with NS or nephrotic-range proteinuria have hyperlipidemia, which can be explained by an increase in the hepatic synthesis of very low density lipoprotein (VLDL) and an accumulation of low density lipoprotein (LDL) correlated to the severity of hypoalbuminemia and proteinuria, leading to raised cholesterol levels similar to those seen in familial or congenital forms of dyslipidemia.

- We do not recommend the use of lipid-lowering treatments at INS onset In pediatric SRNS, some uncontrolled trials have demonstrated the safety and efficacy of statins and probucol in reducing cholesterol and triglycerides, yet the progression of renal insufficiency and proteinuria were unaffected, therefore the use of lipid-lowering drugs is not recommended in children.
- We do not recommend low fat diets for children at INS onset.

TABLE 2 Complications of Nephrotic Syndrome

Infectious	Peritonitis Cellulitis Disseminated Varicella Infection
Cardiovascular	Hypertension Hyperlipidemia Coronary artery disease
Respiratory	Pleural effusionPulmonary embolism

Hematologic	Venous (more common) or arterial (less common) thrombosis Anemia
Gastrointestinal	Intussusception
Renal	Acute renal failureRenal vein thrombosis
Endocrinologic	Reduced bone mineral densityHypothyroidism, clinical and subclinical (more common in CNS)
Neurologic	Cerebral venous thrombosis

Prognosis

- The single most important prognostic factor for maintenance of long-term normal renal function in nephrotic syndrome is the patient's initial response to corticosteroids.
- Although children who enter complete remission during an 8-week initial course of oral corticosteroids have an excellent prognosis, the prognosis for those who fail to enter remission is more guarded.
- Overall, close to 80 % of newly diagnosed children treated with corticosteroids will achieve complete remission.

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