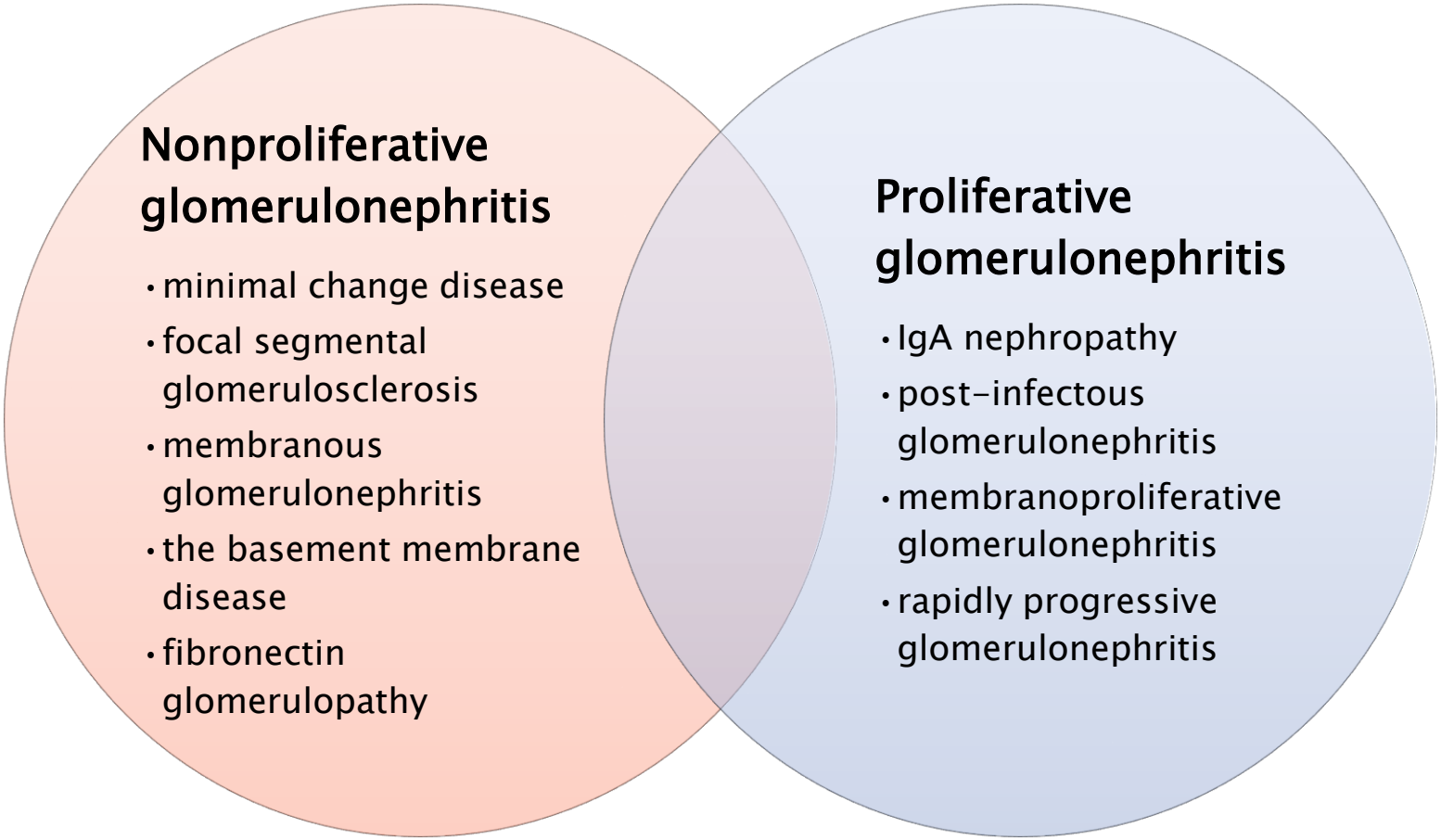
Nephrotic and nephritic syndrome

Nephrotic vs nephritic syndrome

- causes are **glomerulonephritis/nephrosis**
  - **nephritic** affect basement membrane/endothelium injury which leads to hematuria
  - **nephrotic** affect podocytes
    - cause proteinuria

Nephrotic vs nephritic syndrome



Nephrotic syndrome

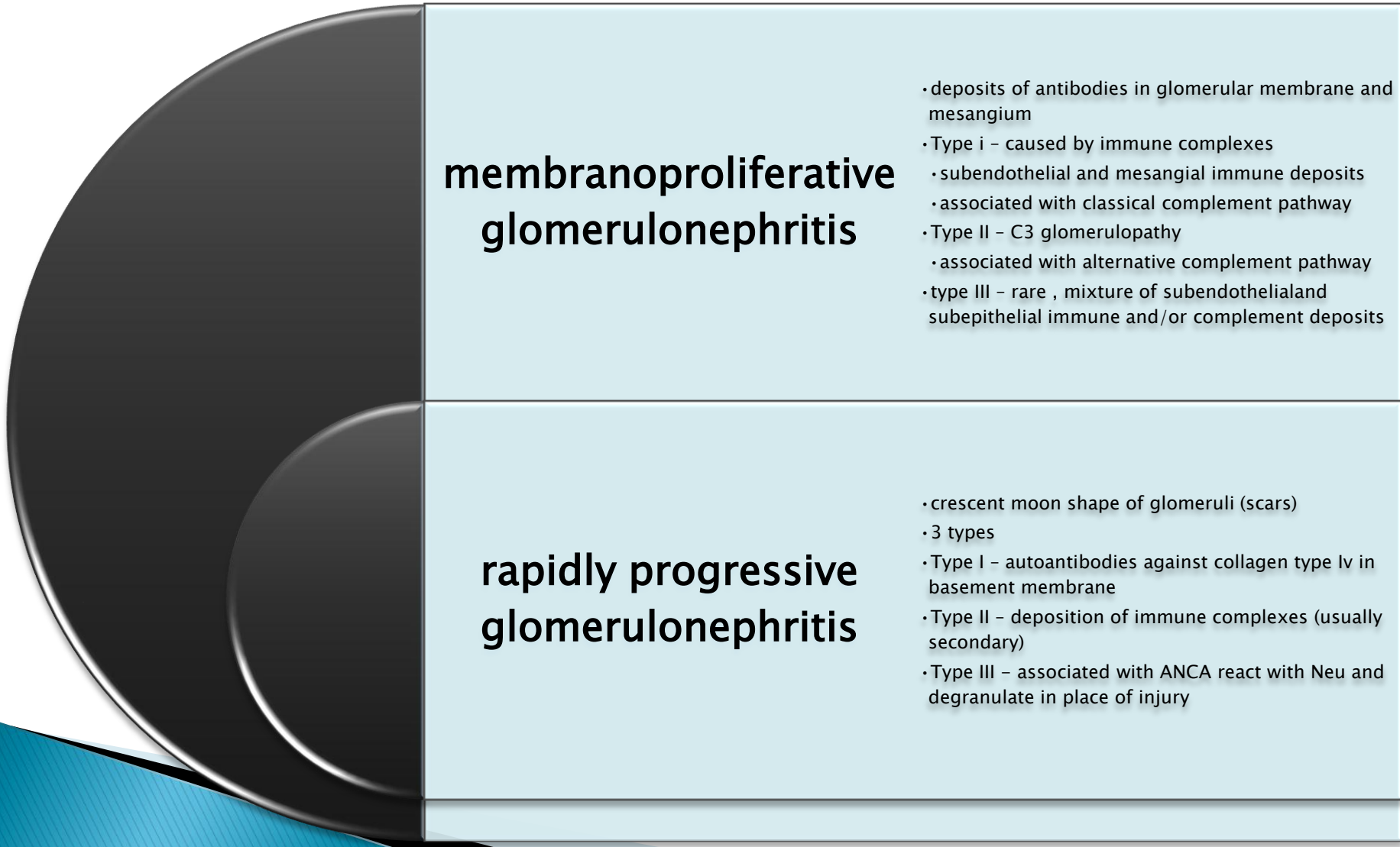
causes

- *primary*
  - minimal change disease
  - focal segmental glomerulosclerosis
  - membranous nephropathy
  - according histology:
    - focal segmental glomerulosclerosis
    - membranous glomerulonephritis
    - membranoproliferative glomerulonephritis
    - rapidly progressive glomerulonephritis
- *secondary*
  - DM
  - SLE
  - syphilis, sarcoidosis, MM, cancer, genetic disorders, drugs

Nephrotic syndrome

minimal change disease	• idiopathic • unknown pathomechanism • loss of visceral epithelial cells foot processes (podocyte effacement) • vacuolisation • growth of microvilli
focal segmental glomerulosclerosis	• only some of glomeruli are afected (sclerosis) • damage of renal podocytes • associated with gene defects • NPHS1 (encodes protein nephrin) • NPHS2 (encodes podocin) • INF2 (encodes actin-binding protein formin)
membranous glomerulonephritis	• inflammation of glomerulal membrane (suspected is autoimmune mechanism) • 85% are primary • accumulation of immune compexes in basement mambrane • activation of complement response

Nephrotic syndrome



Nephrotic syndrome

secondary causes:

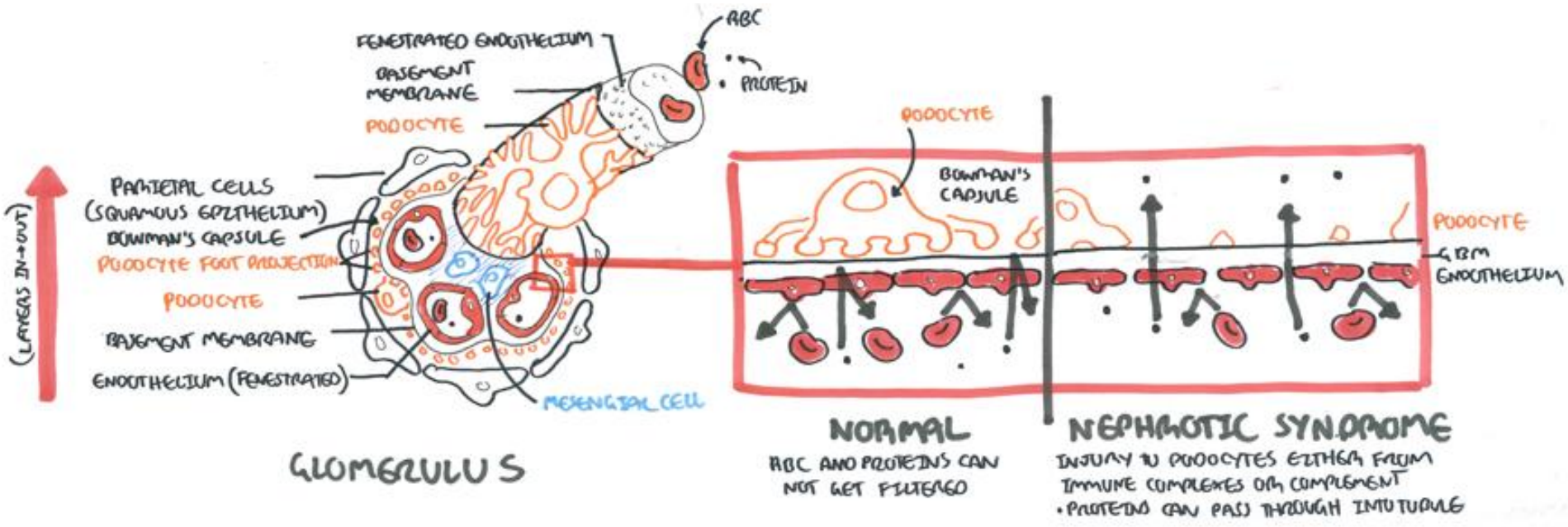
- **Minimal change disease**
  - associated with Hodgkin lymphoma, allergy, NSAIDs
- **Focal segmental glomerulosclerosis**
  - toxins (steroids, heroin)
- **Membranous glomerulonephritis**
  - SLE
  - syphilis, malaria, hepatitis B and C, HIV
  - drugs (captopril, NSAIDs, penicilin, anti-TNF...)
  - cancer
- **Membranoproliferative glomerulonephritis**
  - hepatitis C, SLE, rheumatoid arthritis, ccleroderma, celiac disease, Sjoörgen's syndrome
- **Rapidly progressive glomerulonephritis**
  - Type I – Goodpasture syndrome
  - Type II – SLE, Henoch-Schönlein purpura, IgA nephropathy
  - Type III – ANCA-associated vasculitis

Nephrotic syndrome

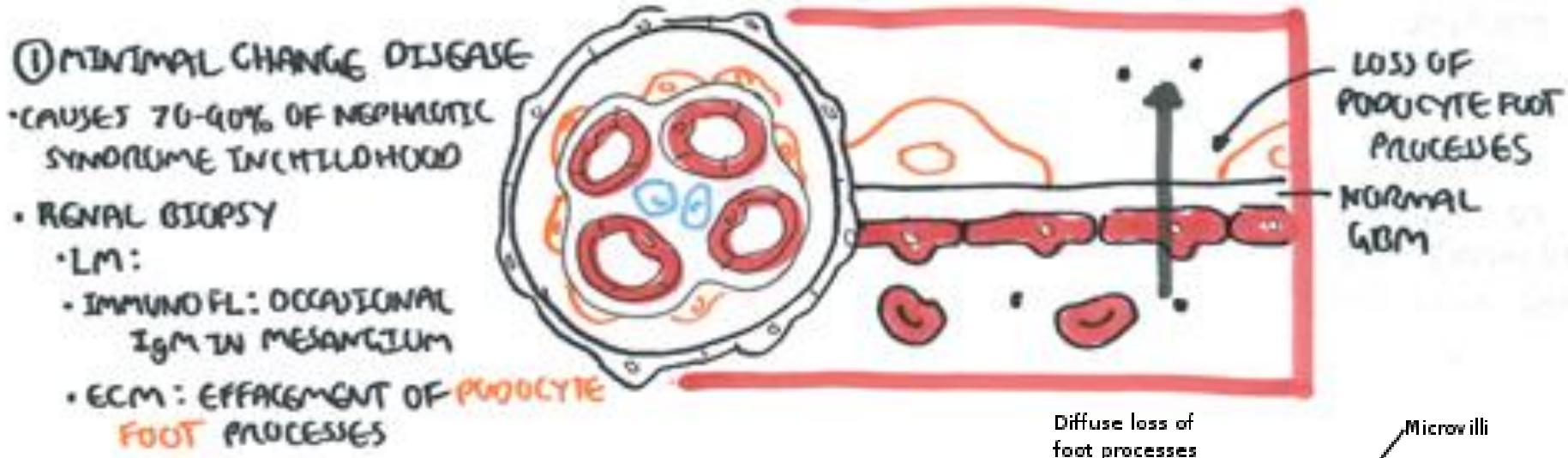
According histology:

- **Membranous nephropathy**
  - Sjörgen's syndrome
  - SLE
  - DM
  - sarcoidosis
  - drugs (gold, corticosteroids, heroin..)
  - cancer
  - leprosy syphilis
  - malaria
- **Focal segmental glomerulosclerosis**
  - hypertensive nephrosclerosis
  - HIV
- **Minimal change disease**
  - drugs (NSAIDs)
  - Hodgkin's lymphoma
  - allergies
  - bee sting
- **Membranoproliferative glomerulonephritis**
  - hepatitis C

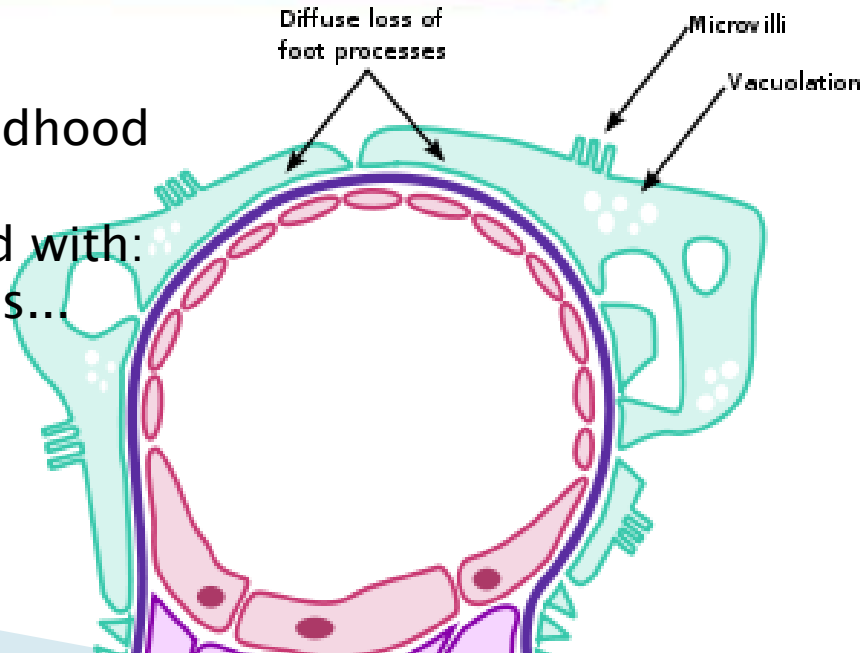
Nephrotic syndrome



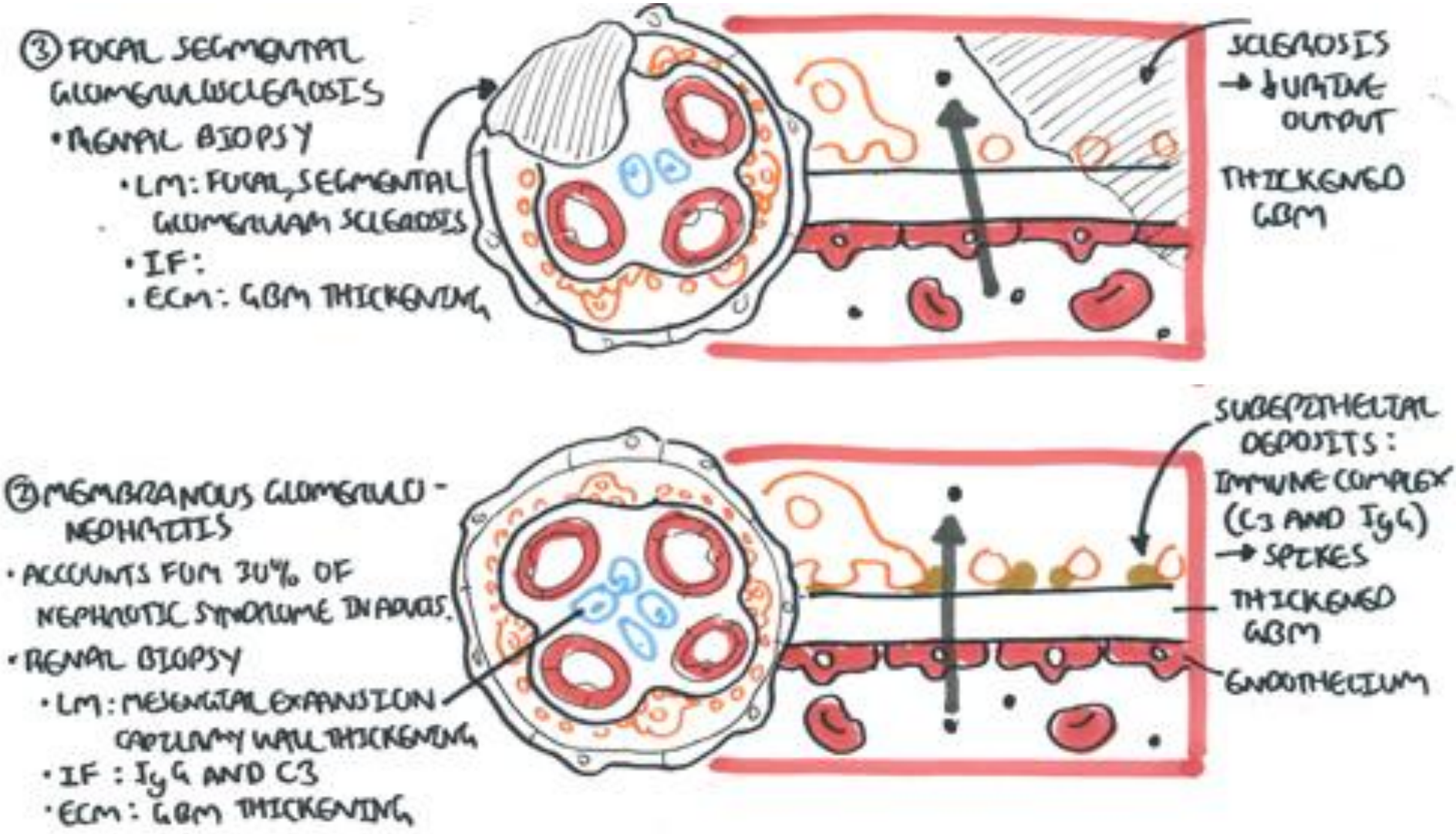
Nephrotic syndrome



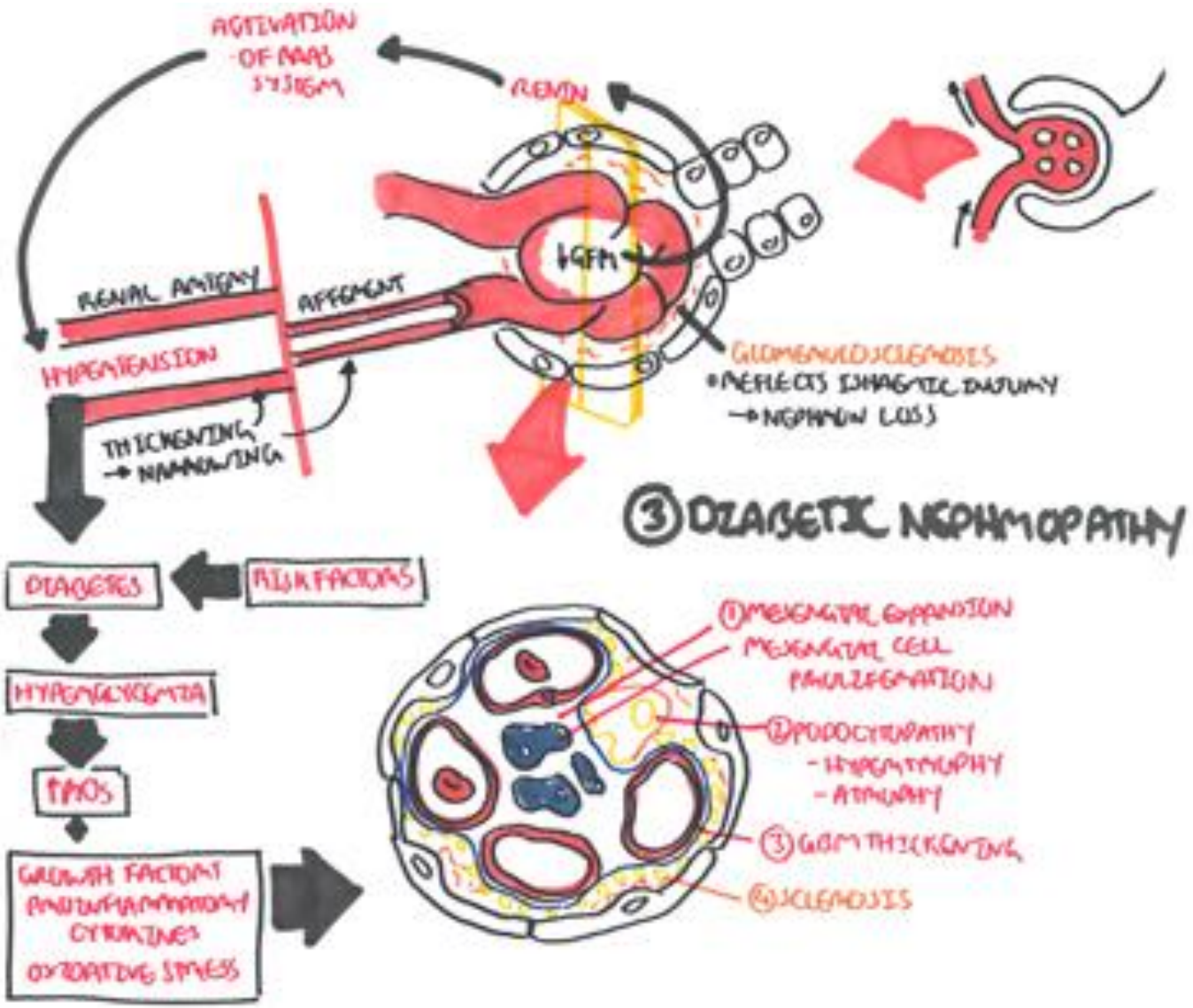
70-90% of nephrotic syndrome in childhood
only 10-15% in adults
usually primary, but can be associated with:
allergies, Hodgkins lymphoma, NSAIDs...



Nephrotic syndrome



Nephrotic syndrome

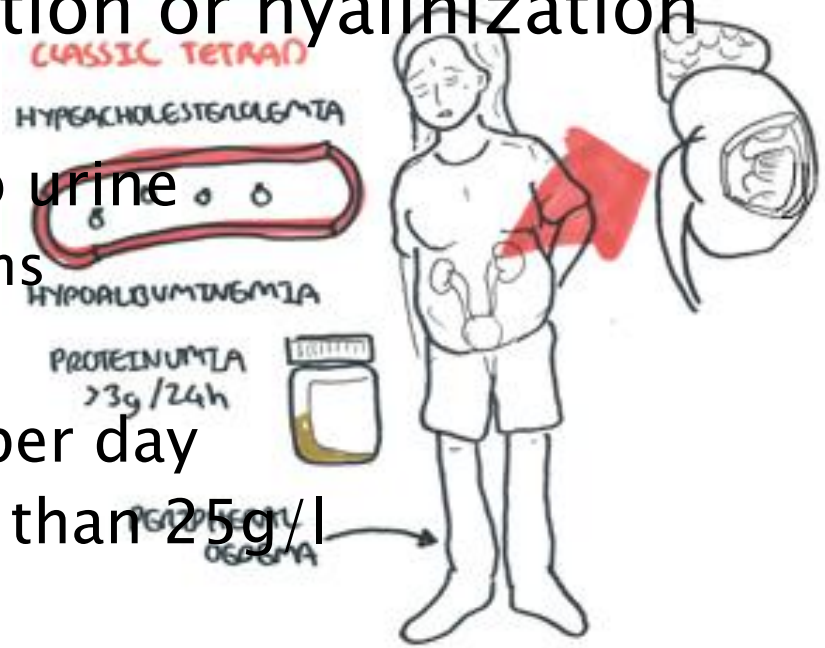


Nephrotic syndrome – DM

Staging	
Class I	Isolated glomerular basement membrane thickening. There is no evidence of mesangial expansion, increased mesangial matrix, or global glomerulosclerosis involving >50 percent of glomeruli.
Class II	Mild (class IIa) or severe (class IIb) mesangial expansion.
Class III	At least one Kimmelstiel-Wilson lesion (nodular intercapillary glomerulosclerosis) is observed on biopsy and there is <50 percent global glomerulosclerosis.
Class IV	Advanced diabetic sclerosis. There is >50 percent global glomerulosclerosis.

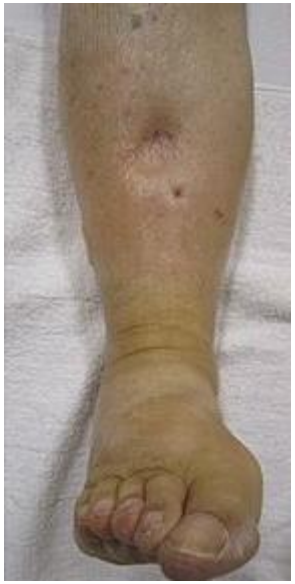
Nephrotic syndrome

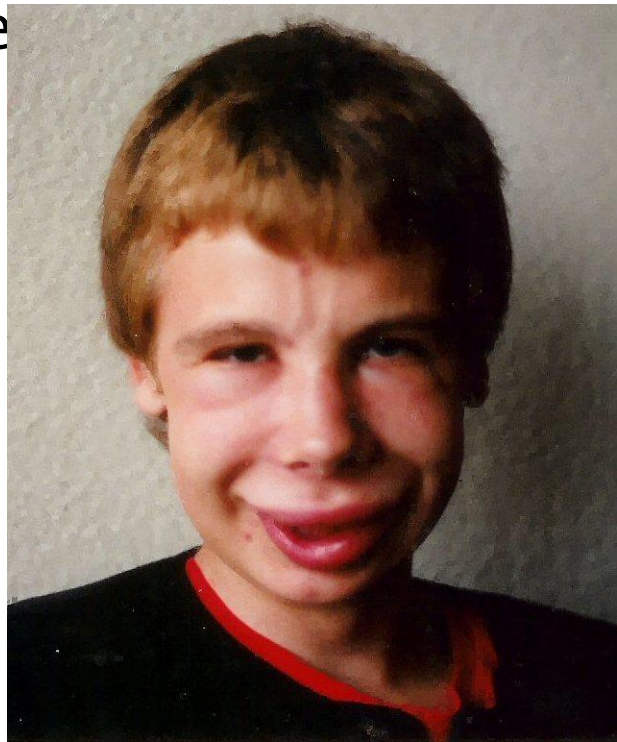
- in normal circumstances larger molecules (over 40 kDa) are not able to be filtered to urine
- because of inflammation or hyalinization defect of podocytes
  - filtration of proteins to urine
    - a lot of types of proteins
- **Main findings:**
  - proteinuria over 3,5g per day
  - hypoalbuminemia less than 25g/l
  - hypercholesterolemia
  - edema



Nephrotic syndrome

- **edema**
  - is result of:
    - decreased oncotic pressure
    - affected sodium metabolism
  - puffiness around the eyes in the
  - pitting edema of legs
  - pleural effusion
  - ascites
  - anasarca





Nephrotic syndrome

- **hyperlipidemia**
  - decreased levels of lipoprotein lipase = decreased lipid catabolism
  - stimulation of lipprotein synthesis because of hypoproteinemia
- **normotension or hypertension**
- **anemia** because of transferrin loss (iron resistent microcytic hypochromic anemia)
- **dyspnea** (pleural effusion)
- **foamy urine**
- **Muehrcke's nails**

Nephrotic syndrome

- **thrombophilia**
  - decrease levels of antithrombin III
  - increased risk of thromboembolism
- **lipiduria**
- **Complications**
  - infections
    - loss of immunoglobulins
  - kidney failure
    - hypovolemia

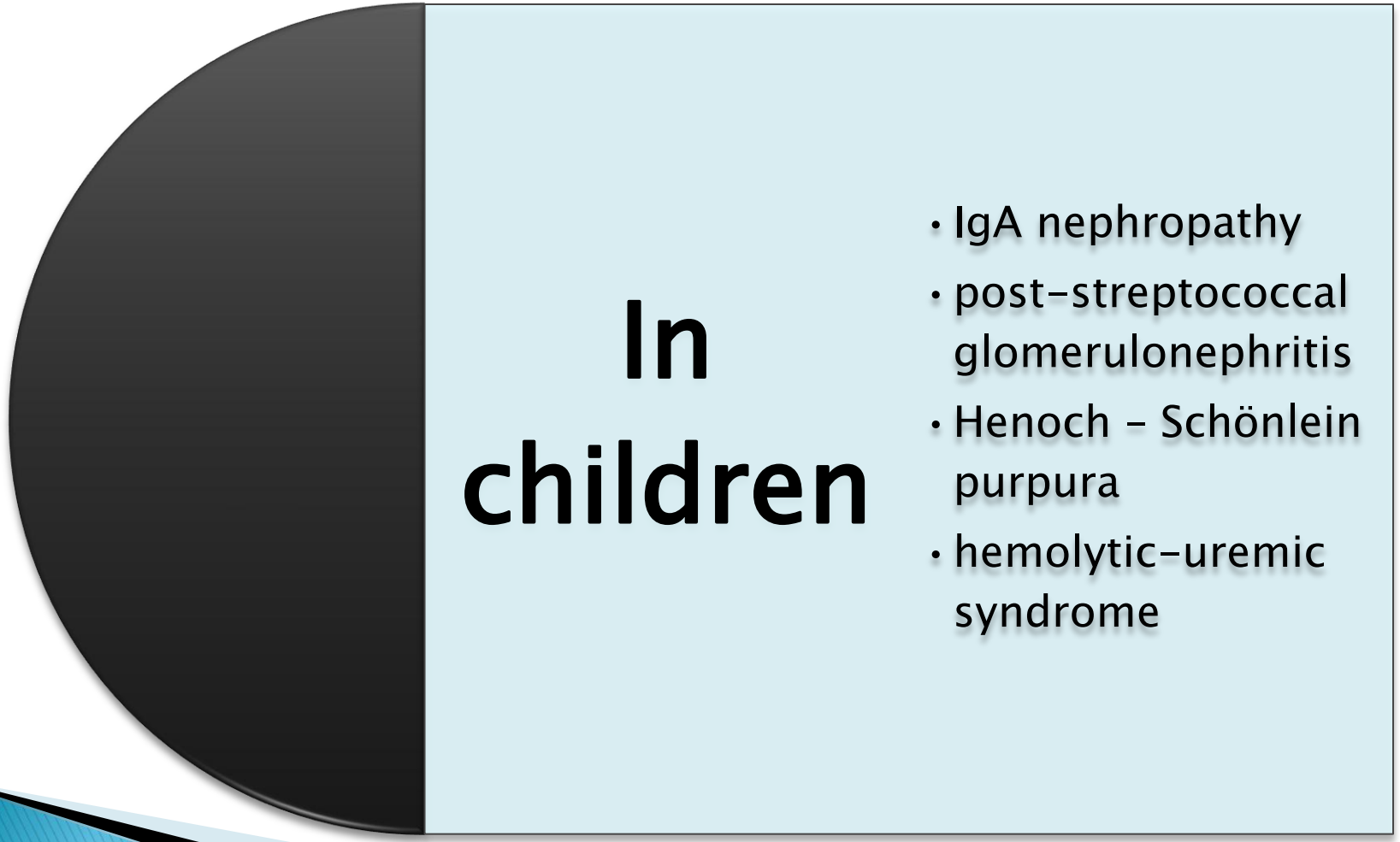
Nephrotic syndrome

- **pulmonary edema**
- **hypothyroidism**
  - lack of thyroglobulin
- **vitamin D deficiency**
  - loss of vitamin D binding protein
- **hypocalcemia** as result of hypovitaminosis D
- **growth retardation**

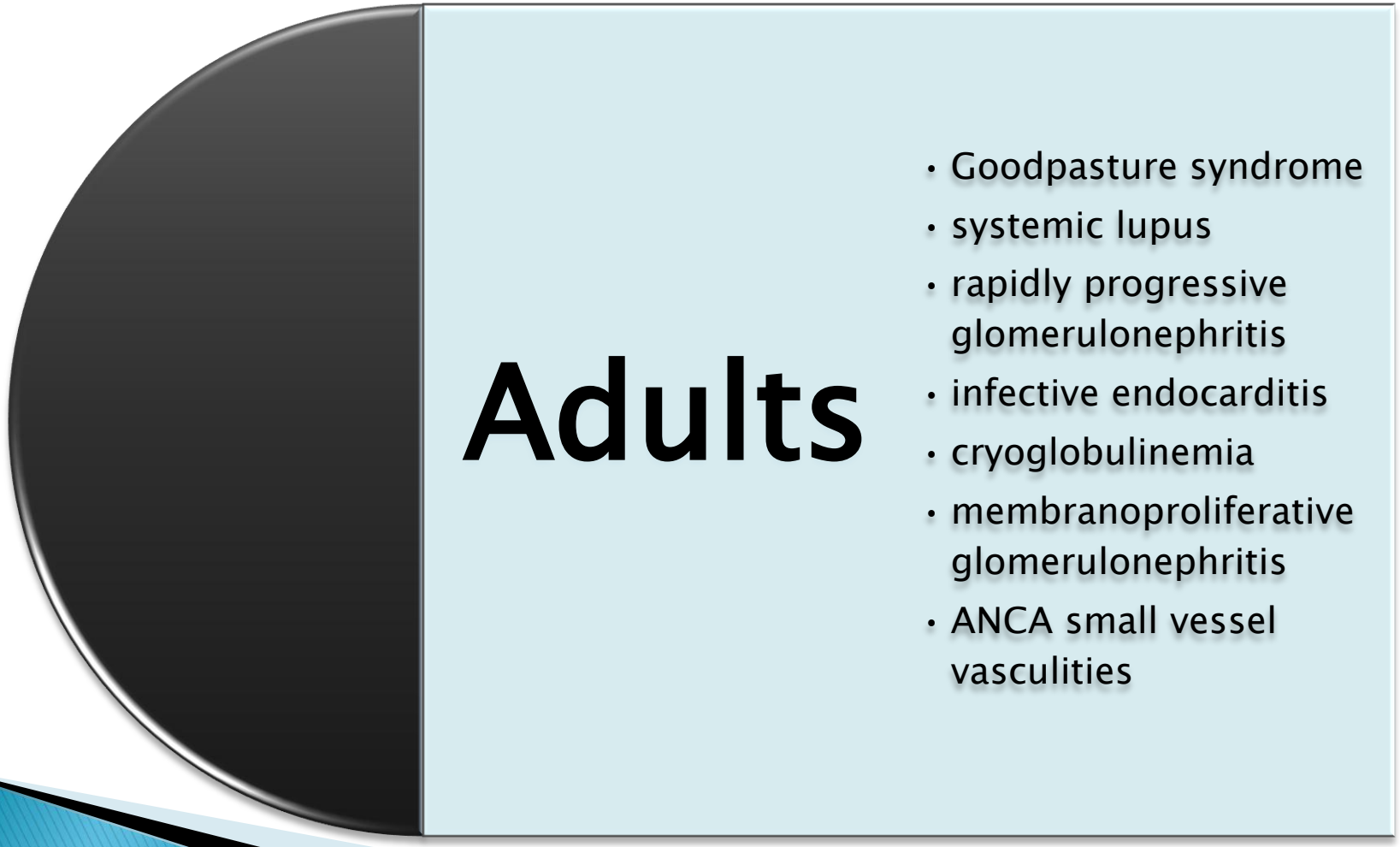
Nephritic syndrome

- affect glomerular basement membrane (thinning) and podocytes (small pores)
- **Causes**
  - main mechanism is **inflammation**
    - infection, autoimmunity or thrombosis

Nephritic syndrome



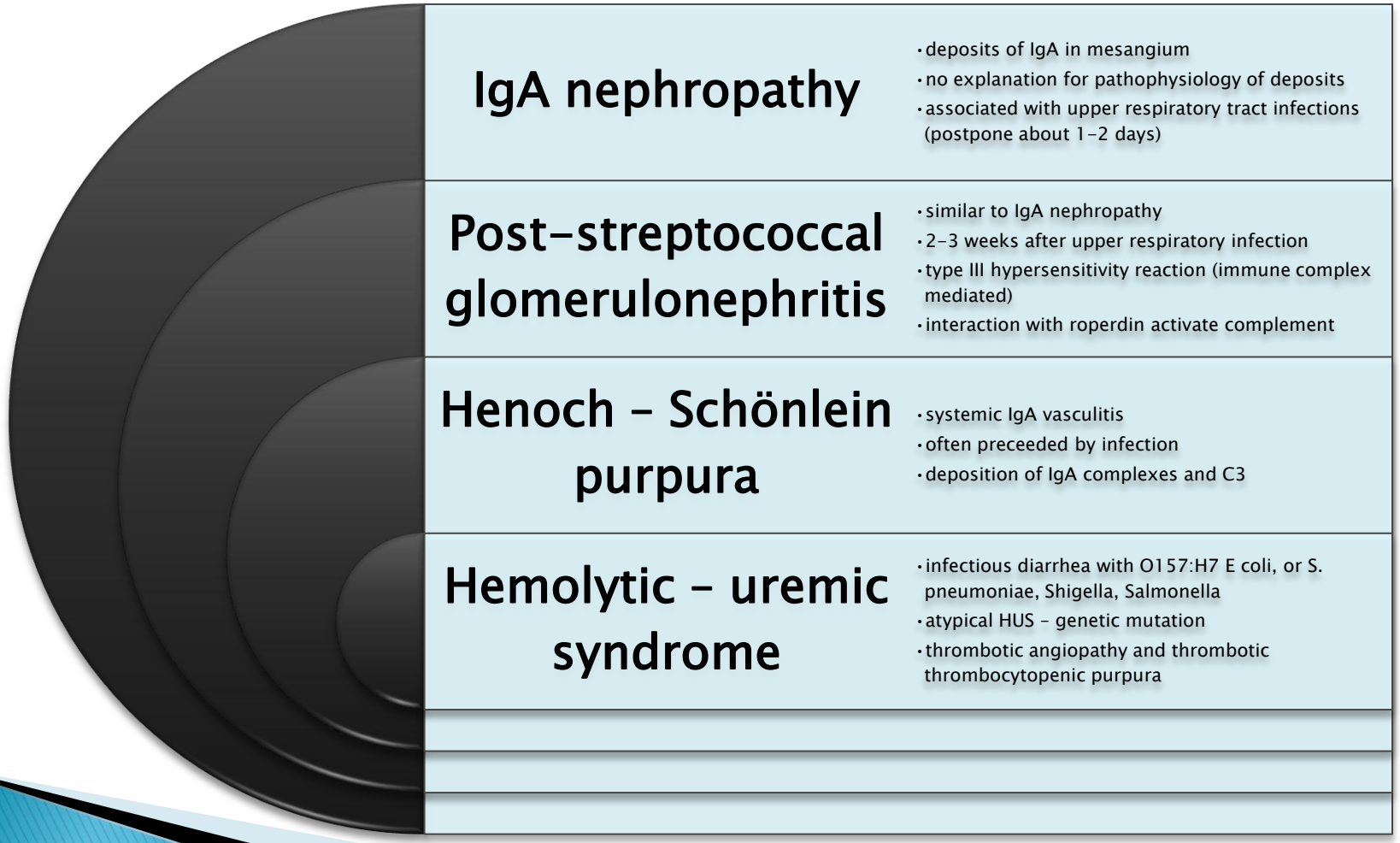
Nephritic syndrome



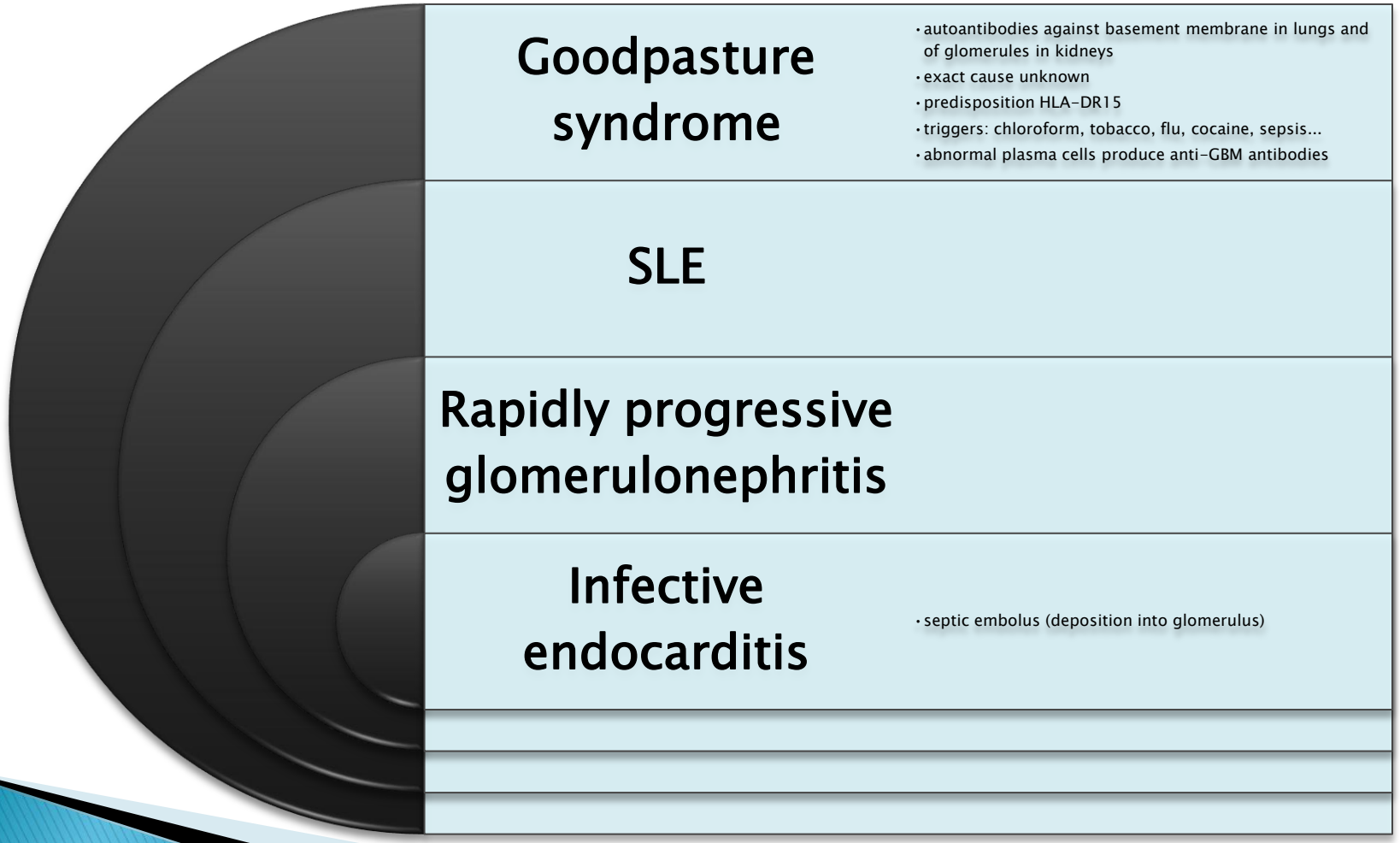
Nephritic syndrome

- pathomechanism is dependent of disease which cause it
- because of demage of different parts of glomerulus
- but all leads to defect of basal membrane and enlargement of pores in podocytes

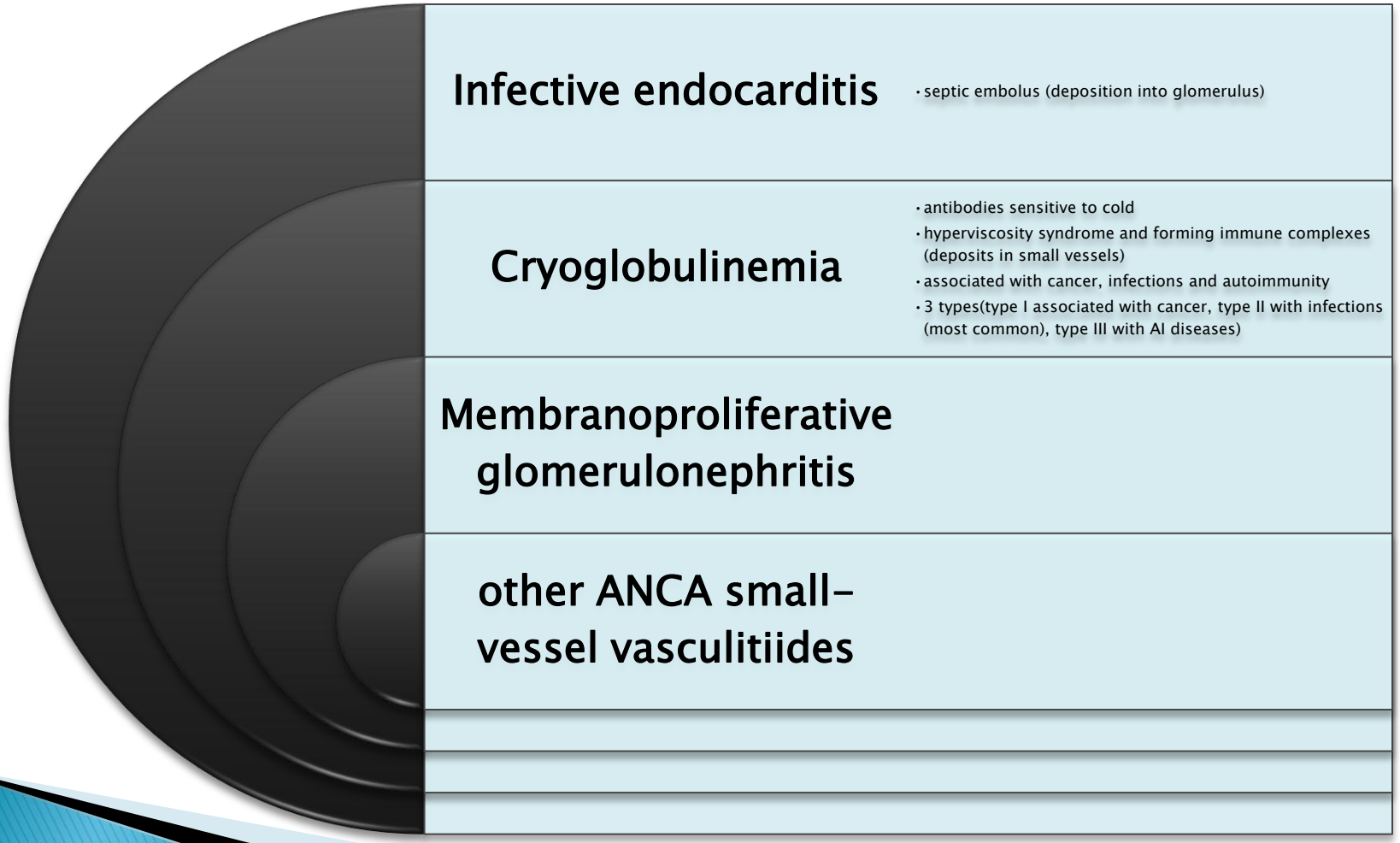
Nephritic syndrome – children

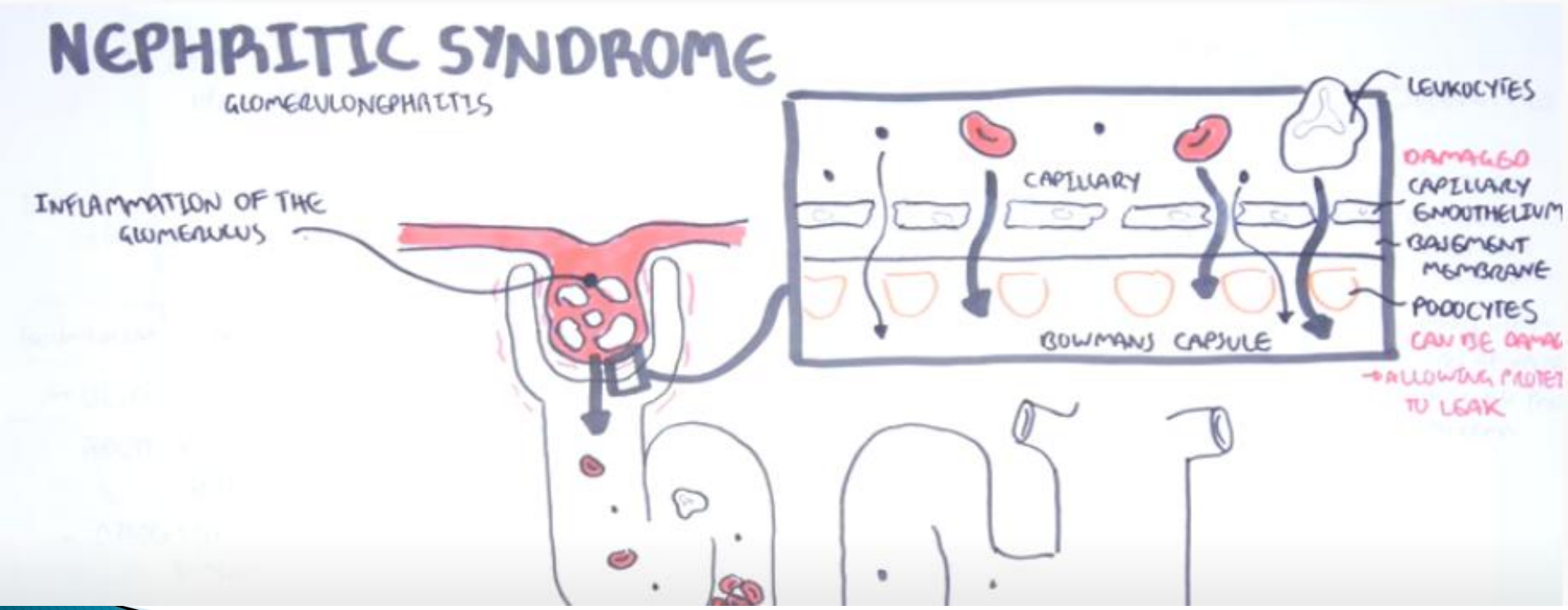


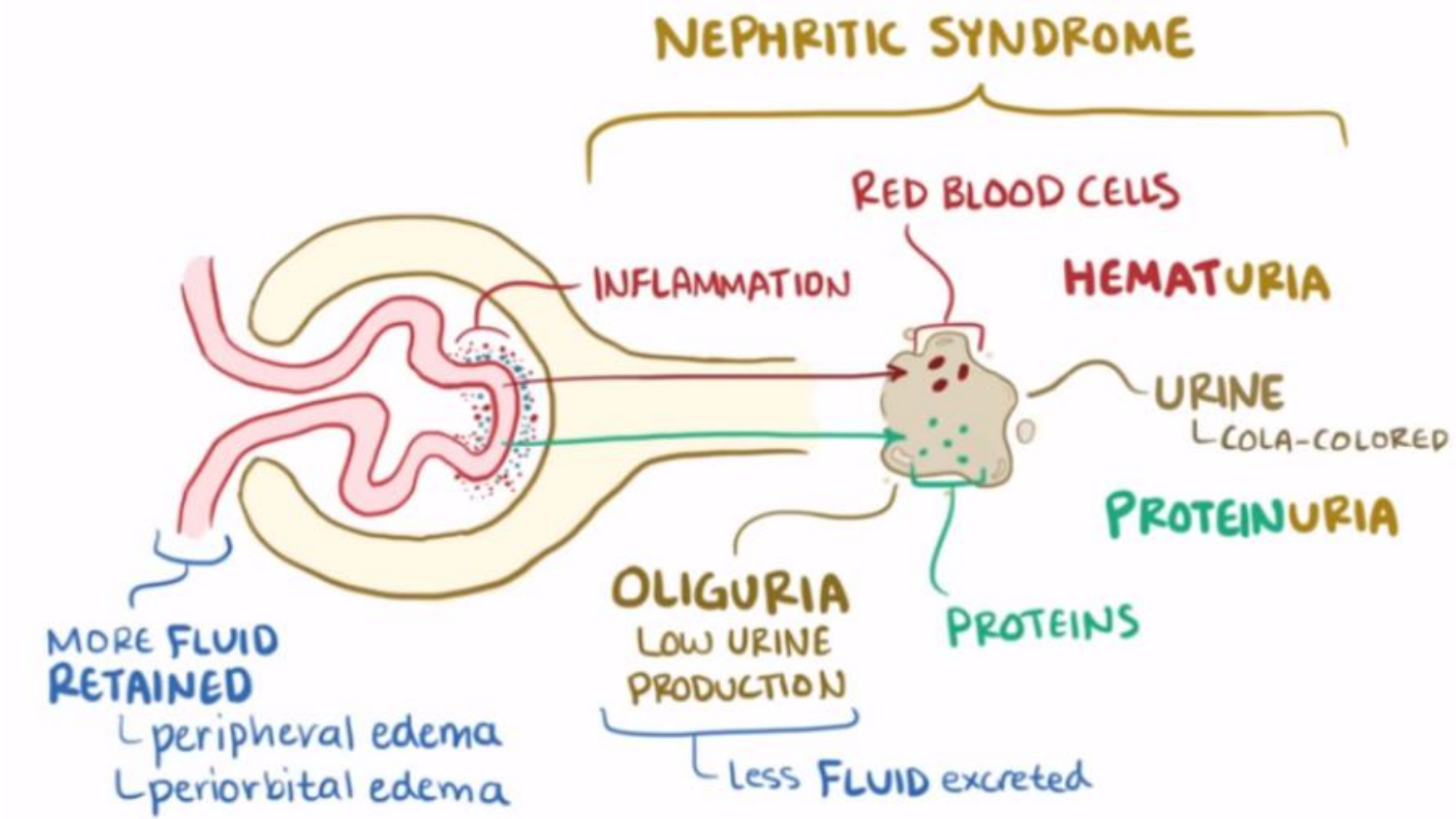
Nephritic syndrome – adults



Nephritic syndrome – adults

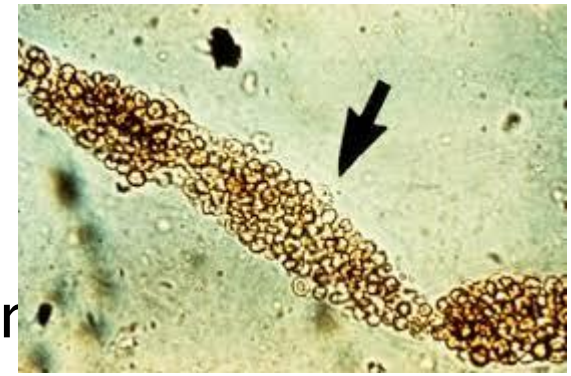


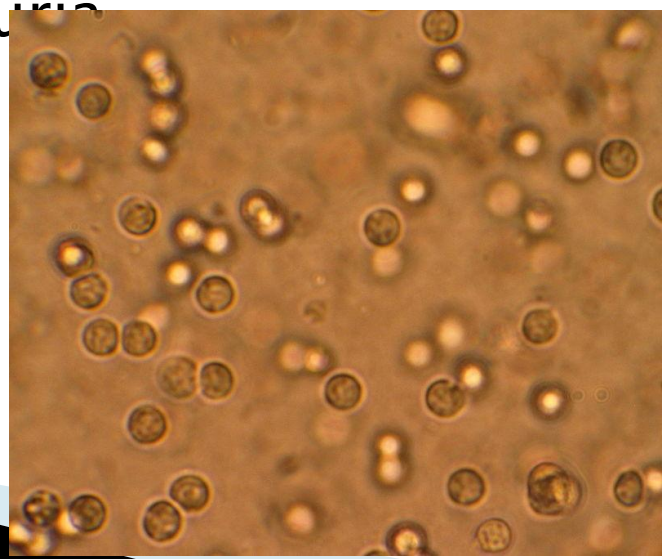

NEPHRITIC SYNDROME
GLOMERULONEPHRITIS
INFLAMMATION OF THE GLOMERULUS
CAPILLARY
BOWMANS CAPSULE
LEUKOCYTES
DAMAGED CAPILLARY ENDOTHELIUM
BASEMENT MEMBRANE
PODOCYTES
CAN BE DAMAG
→ALLOWING PROTEI
TO LEAK


NEPHRITIC SYNDROME
RED BLOOD CELLS
INFLAMMATION
HEMATURIA
URINE
COLA-COLORED
PROTEINURIA
OLIGURIA
LOW URINE PRODUCTION
PROTEINS
MORE FLUID RETAINED
peripheral edema
periorbital edema
less FLUID excreted

Nephritic syndrome

- **Symptoms**
  - **hematuria**
  - **hypertension**
  - oliguria (under
  - **red blood cell casts**
  - **pyuria**
  - mild proteinuria
  - **edema**
  - azotemia





Glomerulopathies

Glomerulopatie s nefritickým obrazom

- **Acute nephritic syndrome**
  - **characterized by a sudden onset, with the appearance of blood, erythrocyte casts, and proteinuria in the urine**
  - This finding is associated with **worsening kidney function, oliguria, retention of salt and water**, and varying degrees of **hypertension**
  - It is present **in acute glomerulonephritis** (the prototype for this type of glomerulopathy), in **other types of glomerulonephritis**
  - also occurs in systemic lupus erythematosus and cryoglobulinemia

Glomerulopathies with nephritic manifestations

- **Acute glomerulonephritis (poststreptococcal)**
  - **is caused by immune complexes**
  - this is typically exogenous in nature, but can also be endogenous
  - often occurs after an infectious disease of the skin or pharynx
  - **most often** occurs **in children**
  - the onset is manifested by **oliguria, hematuria, edema and varying degrees of hypertension**
  - usually occurs on the 6th – 21st day after infection
  - **hematuria** may only be microscopic
  - **proteinuria** is usually moderate up to 3.5 g per 24 hours
  - **erythrocyte casts** in the sediment – **the most important for the diagnosis of glomerulonephritis**

Glomerulopathies with nephritic manifestations

- leukocytes, tubular cells, hyaline and glomerular casts may also be present
- glomerular filtration (creatinine clearance) is reduced
- creatinine elevation is mild and albumin levels are normal
- but there is a clear tendency for fluid retention and edema
- glomerulonephritis results from the formation of antibodies directed against Streptococcus pyogenes type I antigens
  - these cross-react with the autoantigen vimentin – soluble immune complexes are formed
  - deposits are found in the mesangium and subendothelial spaces
  - soluble complexes are present in the circulation

Glomerulopathies with nephritic manifestations

- in a favorable case, phagocytosis of immune complexes in deposits may begin with gradual adjustment of renal function
- in other cases, the damage is irreversible
- fibrosis develops at the sites of damage
- persistence of this type is associated with proteinuria and hematuria
- in the histological picture, all glomeruli are affected
- glomeruli are enlarged and there is a pronounced hypercellularity of the glomeruli
- increased cellularity is caused by proliferation and edema of endothelial and mesangial cells and the presence of neutrophils and monocytes

Glomerulopathies with nephritic manifestations

- along the basement membrane and in the mesangium there are deposits of IgG and C3 fragment of complement
- sometimes there are thrombi in the lumen and necrosis in the capillary wall
- these findings are in a very unfavorable development of the disease
- in a favorable case, diuresis increases spontaneously in 1–2 weeks
- cure may be without consequences
- sometimes hypertension and proteinuria persist
- **Postinfectious nonstreptococcal glomerulonephritis**
  - acute glomerulonephritis can also occur with other infections
  - staphylococci, pneumococci, Klebsiella pneumoniae, meningococcal infections, syphilis, leptospirosis, herpes virus, mononucleosis, hepatitis B, rubella, etc.
  - clinic and histology as in streptococcal infection

Glomerulopathies with nephritic manifestations

- **Glomerulonephritis in infective endocarditis**
  - patients may present with hematuria, proteinuria, and deterioration of renal functions
  - this finding occurs in patients with negative blood cultures
  - histological findings are similar to poststreptococcal nephritis
- **Glomerulonephritis in visceral abscess**
  - most common in patients with lung abscess
  - histologically tends toward proliferative glomerulonephritis

Glomerulopathies with nephritic manifestations

- **Rapidly progressive glomerulonephritis**
  - deterioration of renal function up to complete failure
  - precondition for making the diagnosis is an increase in serum creatinine level with simultaneous finding of proteinuria and hematuria
  - erythrocyte casts are present in the sediment
  - half-moon-shaped formations of fibrin are present in about 50% of glomeruli
    - the cause of fibrinogen leakage through the capillary walls is changes in the basement membrane
    - from it fibrin deposits are formed in Bowman's capsule
    - deposits stimulate proliferation of parietal epithelial cells of Bowman's capsule and act as an attractant for circulating monocytes

Glomerulopathies with nephritic manifestations

- therefore, the cellularity of the glomeruli increases
- large deposits compress the capillaries and act as an obstruction on the proximal tubules to the point that the nephron is completely disabled

- extracapillary cells are gradually replaced by fibroblasts
- at least three types can be distinguished by immunofluorescence techniques:
- **1. type – autoantibodies against the basement membrane (IgG or IgA) are formed**
  - deposits are formed along the basement membrane
  - similar antibodies occur in 90% of patients
  - the alveocapillary network of the lungs may also be affected
  - Goodpasteur syndrome is clinically manifested by hemoptysis

Glomerulopathies with nephritic manifestations

- **Type 2 – granular deposits of immunoglobulins and complement**
  - deposition along capillaries and in the mesangium
  - vasculitis often develops – manifests as purpura
  - soluble immune complexes and cryoglobulins
  - are detected in the blood along with reduced complement activity
- **Type 3 – immunofluorescence-negative rapidly progressive glomerulonephritis**
  - such a picture arises because all deposits have already been eliminated by macrophages or there is a completely different pathological mechanism (unexplained)
  - occurs in older men and is often associated with systemic vasculitis
- **2. typ – granulárne depozity imunoglobulínov a komplementu**
  - ukladanie pozdĺž kapilár a v mezangiu
  - často sa vyvíja vaskulitída – prejavuje sa ako purpura
  - v krvi sa zisťujú solubilné imunokomplexy a kryoglobulíny súčasne so zníženou aktivitou komplementu
- **3. typ – imunofluorescenčne negatívna rýchlo progredujúca glomerulonefritída**
  - takýto obraz vznikne tým, že všetky depozity sú už zlikvidované makrofágmi alebo ide o celkom iný patologický mechanizmus (neobjasnený)
  - vyskytuje sa u starších mužov a býva spojený so systémovou vaskulitídou

Glomerulopathies with nephritic manifestations

- Complement levels are usually unchanged.
- Antineutrophil antibodies – ANCA – are very often present.

- Glomeruli are normocellular or hypercellular, often with segmental necroses.
- Linear deposits of IgG and C3b, less commonly IgA
- Subepithelial, subendothelial, and mesangial deposits may be present
- A consistent finding is the presence of gaps in the glomerular capillary basement membrane
- Prognosis is poor
- Without therapy, renal failure develops within several weeks to months
- Immune complex–mediated disease with granular deposits has a better prognosis
- Hypertension, azotemia, and worsening histological findings are indicators of poor prognosis

Glomerulopathies with nephritic manifestations

- **Slowly Progressive Glomerulonephritis (Membranoproliferative Glomerulonephritis)**
  - A group of glomerulonephritides with many synonyms:
  - Mesangiocapillary, nodular, chronic mesangioproliferative, hypocomplementemic
  - There are two types:
    - **Type 1** –
      - Characterized by decreased levels of circulating complement.
      - Subendothelial and mesangial deposits are present → immune complex–mediated pathogenesis.
      - Proteinuria or a nephrotic syndrome picture is present.
    - **Type 2** –
      - Complement activation caused by C3 nephritic factor.
      - Intramembranous deposits are present.
      - Proteinuria or a nephritic syndrome picture is present, similar to rapidly progressive glomerulonephritis.

Glomerulopathies with nephritic manifestations

- The clinical presentation is similar in both types. The onset of the disease is extremely variable:
  - One-third of patients present with a nephritic picture,
  - One-third with nephrotic syndrome,
  - One-third with proteinuria and hematuria.
- It encompasses a group of disorders characterized by mesangial cell proliferation, thickening of the basement membranes with a double contour, and variable disruption of glomerular architecture.
- Immunofluorescence reveals C3b deposits:
  - In Type 1, these are subendothelial,
  - In Type 2, they are within the thickened basement membrane (ribbon-like).
- The course of the disease is variable.
  A nephrotic syndrome picture and hypertension are associated with poor prognosis.
- The disease usually progresses to kidney failure over several decades.

Nefrotic syndrome

- It is defined as proteinuria of such severity that it causes hypoalbuminemia and leads to edema, hyperlipidemia with lipiduria, and hypercoagulability.
  - Proteinuria represents a loss of proteins exceeding 3.5 g/day per 1.74 m^2.
- The cause may be immunopathological mechanisms.
  In many patients, idiopathic nephrotic syndrome occurs.
- The cause of proteinuria is damage to the glomerular capillary basement membrane and podocytes.
- It is not the only cause of hypoalbuminemia.
  - Contributing factors include increased albumin catabolism in the renal vascular endothelium and proximal tubular epithelium.
  - Increased hepatic synthesis cannot compensate for the losses.

Nefrotic syndrome

- **Edema** is the main symptom.
  - It is localized in tissues with low tissue pressure.
  - The extent of edema corresponds to the degree of hypoalbuminemia.
  - Most pronounced in the morning, around the eyes.
  - In very severe cases: anasarca, pleural and pericardial effusions, and ascites.
- **Two theories explain edema**:
  - **Hypoalbuminemia theory** – decreased plasma albumin reduces oncotic pressure.
  - **Sodium retention theory** – associated with impaired renal sodium excretion.
    - The result is increased blood volume and blood pressure.
    - Hydrostatic pressure rises → edema formation.
    - Resistance to atrial natriuretic peptide is likely present.

Nefrotic syndrome

- Attempts to reduce edema with diuretics may lead to decreased plasma volume and renal failure.
  - Persistent proteinuria has catastrophic consequences:
  - It stimulates the release of cytokines, growth factors, and other mediators that trigger interstitial inflammation and subsequent fibrosis.
  - Loss of plasma proteins leads to decreased IgG and IgA concentrations and an increase in IgM.
  - Proteins excreted in the urine include vitamin D–binding protein, CSBG (corticosteroid-binding globulin), TBG (thyroid-binding globulin), and transferrin.
  - Low vitamin D levels result in hypocalcemia and secondary hyperparathyroidism.

Nefrotic syndrome

- Usually, there is no deficiency of T3 and T4.
- Microcytic anemia may result from transferrin deficiency.
- Anemia can also be caused by erythropoietin deficiency.
- Deficiency of IgG and complement explains the increased susceptibility to infections.
- In severe nephrotic syndrome, malnutrition and loss of muscle mass may occur.

- **Hyperlipidemia**
  - A result of lipid metabolism abnormalities in nephrotic syndrome.
  - The liver increases the synthesis of lipoproteins, including apolipoproteins.
  - Triggers for this synthesis are protein losses, reduced oncotic pressure, and hypoalbuminemia.

Nefrotic syndrome

- A certain contribution comes from disruption of the lipoprotein regulatory system.
  - LDL and cholesterol increase, and with more severe decreases in oncotic pressure, VLDL and triglycerides also rise.

- **Lipiduria**
  - Associated with the presence of lipid casts.
  - Under the microscope, they exhibit a “Maltese cross” appearance.
  - **Coagulation abnormalities**
  - Hypercoagulability is caused by urinary losses of coagulation inhibitors (antithrombin III, proteins C and S), increased hepatic synthesis of fibrinogen and factors V and VIII, increased platelet aggregability, and impaired fibrinolysis.

    Hemoptysis and dyspnea are negative prognostic signs.

Nefrotic syndrome

- **Minimal Change Glomerulopathy (Lipoid Nephrosis)**
  - Idiopathic nephrotic syndrome occurring mainly in children.
  - Associations are known with immunization, atopy, viral infections, and Hodgkin's disease.
  - Can occur after administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and in toxin-induced interstitial nephritis.
  - Pathogenesis is unclear.
  - Proteinuria is usually of significant degree, sometimes associated with microscopic hematuria.
  - Reduction in effective circulating volume can lead to prerenal azotemia.
  - This condition may progress to reversible renal failure.

Nefrotic syndrome

- The core abnormality is increased glomerular permeability to proteins.
- Histological changes are minimal.
- Mortality in the pre-steroid era was up to 50%.

- **Focal (Segmental) Glomerulosclerosis (FSGS)**
  - Some patients with idiopathic nephrotic syndrome show focal and segmental lesions in the glomeruli.
  - Likely represents a continuation of mesangioproliferative glomerulonephritis.
  - Nonselective proteinuria is not pronounced.
  - Marked hematuria and hypertension are present.
  - Erythrocyte casts are never observed.

Nefrotic syndrome

- Glomerular damage is uneven
- Certain segments of the glomeruli show increased cellularity
- Hyaline with lipid vacuoles is present in these segments
- Lesions begin in juxtamedullary glomeruli; cortical glomeruli may appear normal
- In sclerotic segments, IgG and C3 deposits are found
- Mesangial matrix is increased in the glomeruli
- Foam cells and degeneration of capillary epithelial cells are present
- Persistent proteinuria and hypertension may continue for years
- Prognosis is better in children

Nefrotic syndrome

- **Membranous Glomerulopathy (Nephropathy)**
  - The most common cause of nephrotic syndrome in adults.
  - Characterized by diffuse thickening of the glomerular capillary walls with accumulation of electron-dense material on the subepithelial side of the membrane.
  - Can occur in various disorders.
    - Antigens may be viral in origin or associated with cancers such as lung or colorectal carcinoma, among others.
  - Glomeruli show increased mesangial cells and matrix.
  - Deposits contain C3b, and less frequently IgA and IgM.
  - The disease progresses slowly.
  - All patients exhibit proteinuria; 40% have hematuria.
  - Hypertension and renal failure develop later.
  - Can occur in patients with malignancies.

Nefrotic syndrome

- **IgA Nephropathy (Berger's Disease)**
  - Patients present with mild proteinuria and hematuria, which worsen during fever and physical exertion.
  - The most common cause is IgA nephropathy.
  - Histologically: mesangioproliferative glomerulonephritis with deposits of IgA and C3, sometimes IgM or IgG.
  - Deposits are located in the mesangium.
  - Clinically, it most often manifests during viral infections.
  - Soluble complexes containing IgA are present in the blood.
  - In Henoch–Schönlein purpura, the kidney shows almost identical changes.
    - Later, it was recognized that IgA nephropathy is one of its forms.

Nefrotic syndrome

- **Glomerulopathies Associated with Systemic Diseases**
  - Renal syndromes can occur in various systemic diseases.
  - Histological findings are characteristic for each disorder type.
  - **Systemic Lupus Erythematosus (SLE)**
    - Clinically manifests in only 60% of patients, but renal involvement is found in all.
    - Typical kidney disease occurs in 30% of cases.
    - Deposits of IgG, IgM, and IgA, along with complement proteins, are present.
    - Deposits may also be found along the tubular basement membranes.
    - Renal involvement in SLE can be the most serious complication.
    - **WHO Classification of Lupus Nephritis – Classes I to VI:**
      - Normal glomeruli
      - Mesangial glomerulonephritis
      - Focal proliferative nephritis
      - Diffuse proliferative nephritis
      - Membranous nephropathy
      - Glomerular sclerosis

Nefrotic syndrome

- **Wegener's Granulomatosis (Granulomatosis with Polyangiitis)**
  - Disease of the upper and lower respiratory tracts.
  - Renal involvement with ANCA positivity and systemic vasculitis.
  - Rapidly progressive course.
  - Marked hematuria and proteinuria.
  - Often leads to renal failure.
- **Polyarteritis Nodosa (PAN)**
  - Involves medium-sized arteries of the kidneys and other organs.
  - Most pronounced changes occur in interlobar arteries.
  - Juxtamedullary apparatus is hyperplastic.
  - Deposits in glomeruli may be present.
  - Can lead to renal failure.
  - **Hypersensitivity Angiitis (Microscopic Polyangiitis)**
    - A microscopic variant.
    - Can develop as progressive glomerulonephritis.

Renal failure

Acute kidney injury

- Definition: **fast decrease in kidney functions which leads to accumulation of nitrogen substances in organism**
- **Causes::**
  - prerenal
  - renal
  - postrenal
- **According occurance:**
  - States connected with kidney hypoperfusion
  - Obstructive uropathies
  - Primary kidney diseases
  - Therapy of other diseases

Acute kidney injury

- The most common cause is renal ischemia
- **causes:**
  - Fast hemorhagia
  - Marked decrease of circulating blood
  - Perioperative hypotension
  - Cardiogenic shock
  - Surgical operations connected with interruption of blood circulation
- Duration of hypoperfusion is limited factor
  - Can cause reversible or irreversible changes
- **During mild hypoperfusion**
  - Leads to prostacyclin and NO production – dilation of aferent arterioles
  - Angtiotensin II cause peripheral vasoconstriction and mainly vasa effrens = increase of intraglomerular pressure

Acute kidney injury

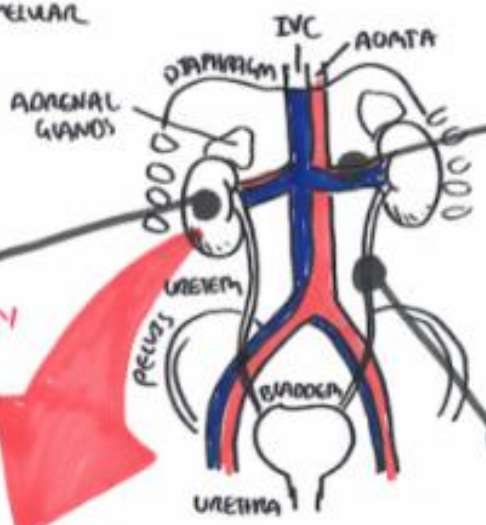
- **During strong hypoperfusion** this mechanism **doesn't funcion**
- Acute failure can be caused by **nephrotoxic substances**
  - E. g. heavy metal or solvents organic
  - Here belongs some drugs or their combinations
    - Aminoglycosidic ATB in combination with cyclosporins or cisplatina, some anestetics, **contrast substances**
- Can occur **in last trimester or after birth**
- **After birth** as consequance of acute bleeding
- **In liver disease** without visible cause
  - Mild oliguria with moderate findings
    - Most commonly in hepatal cirhosis with icterus, ascites and encephalopathy

Acute kidney injury

- Release of huge amount of myoglobin **(rhabdomyolysis)**
  - crush syndrome, non-traumatic in heat shock, extreme muscle work, hypokalemia, hypophosphatemia, hyperlipidemia therapy by fibrates, genetic defects
  - Myoglobin alone has not nephrotoxic effect
  - Negative efect has its precipitation
- **Intravascular hemolysis**
  - Hb is not nephrotoxic
  - Bigger influence have substances which are released from Ec stroma + hypoperfusion
- **In acute kidney injury dominates nitrogen substances = azotemia**

ACUTE RENAL FAILURE

"REVERSIBLE" DECREASE IN GLOMERULAR FILTRATION RATE



① PRE RENAL

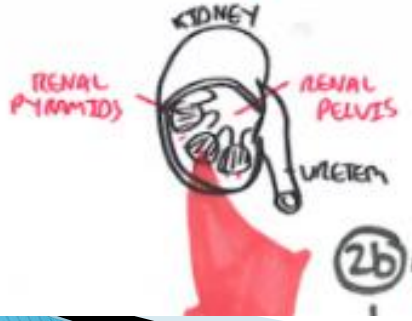
SUDDEN OR SEVERE DROP IN BP
FLOW OBSTRUCTION TO KIDNEYS
- ARTHEROSCLEROSIS
- ISCHEMIA

② INTRA RENAL

- DIRECT DAMAGE TO KIDNEY
- INFLAMMATION
- INFECTION
- DRUG
- AUTOIMMUNE DISEASE

③ POST RENAL

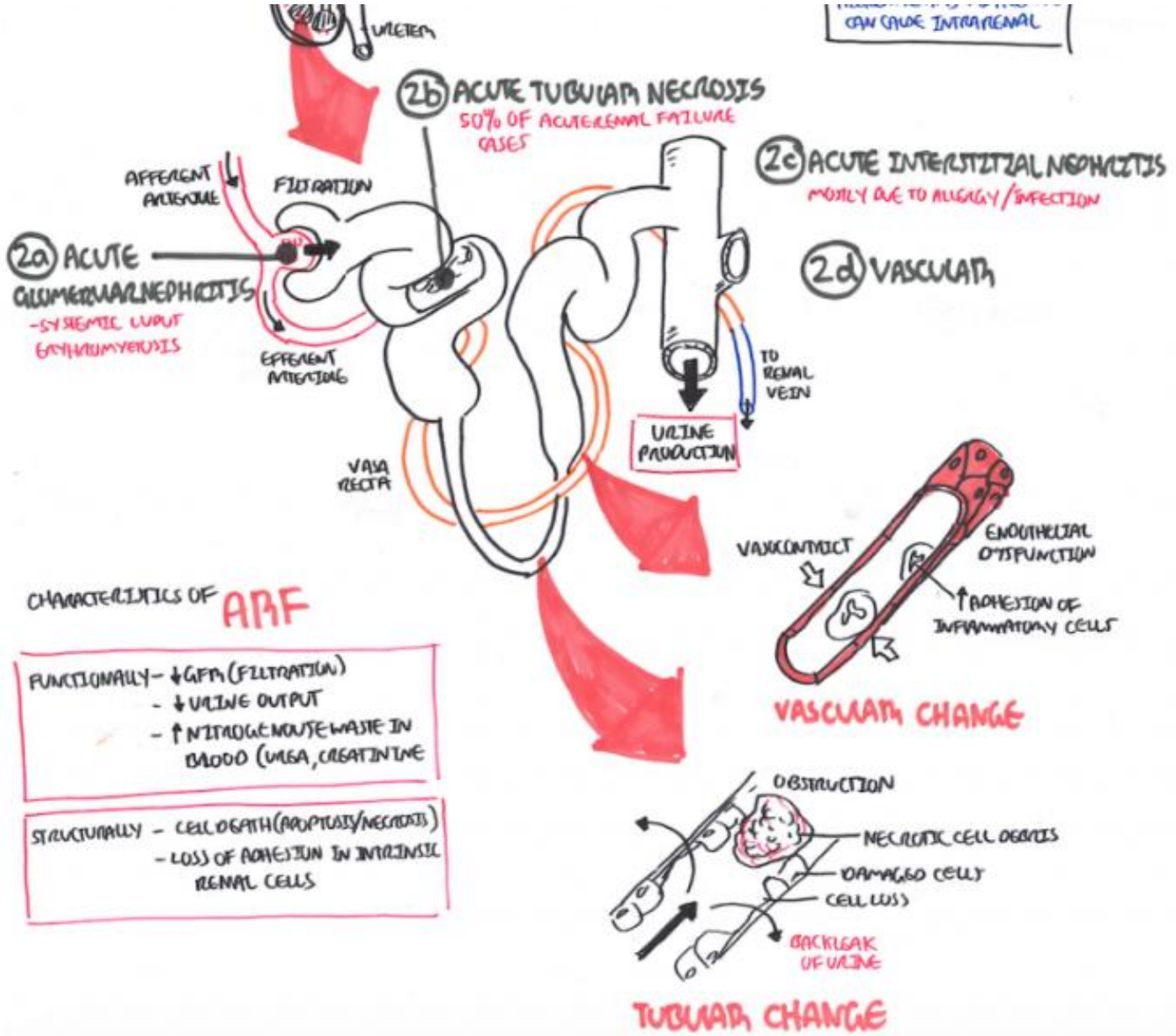
OBSTRUCTION OF URINE FLOW
- BENIGN PROSTATIC HYPERPLASIA
- KIDNEY STONES
- BLADDER INJURY OR TUMOUR



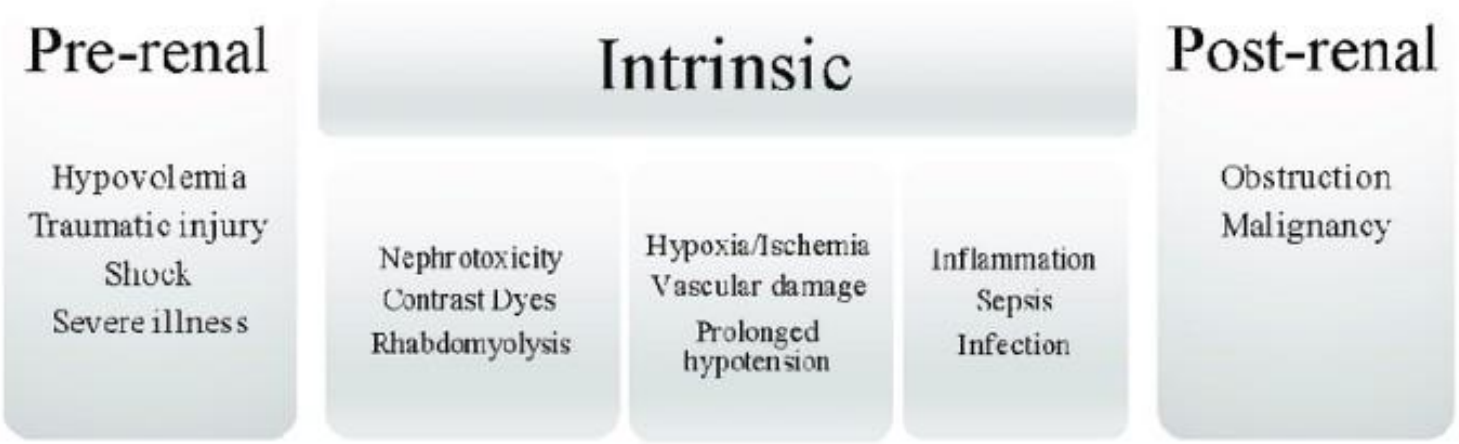
2b ACUTE TUBULAR NECROSIS

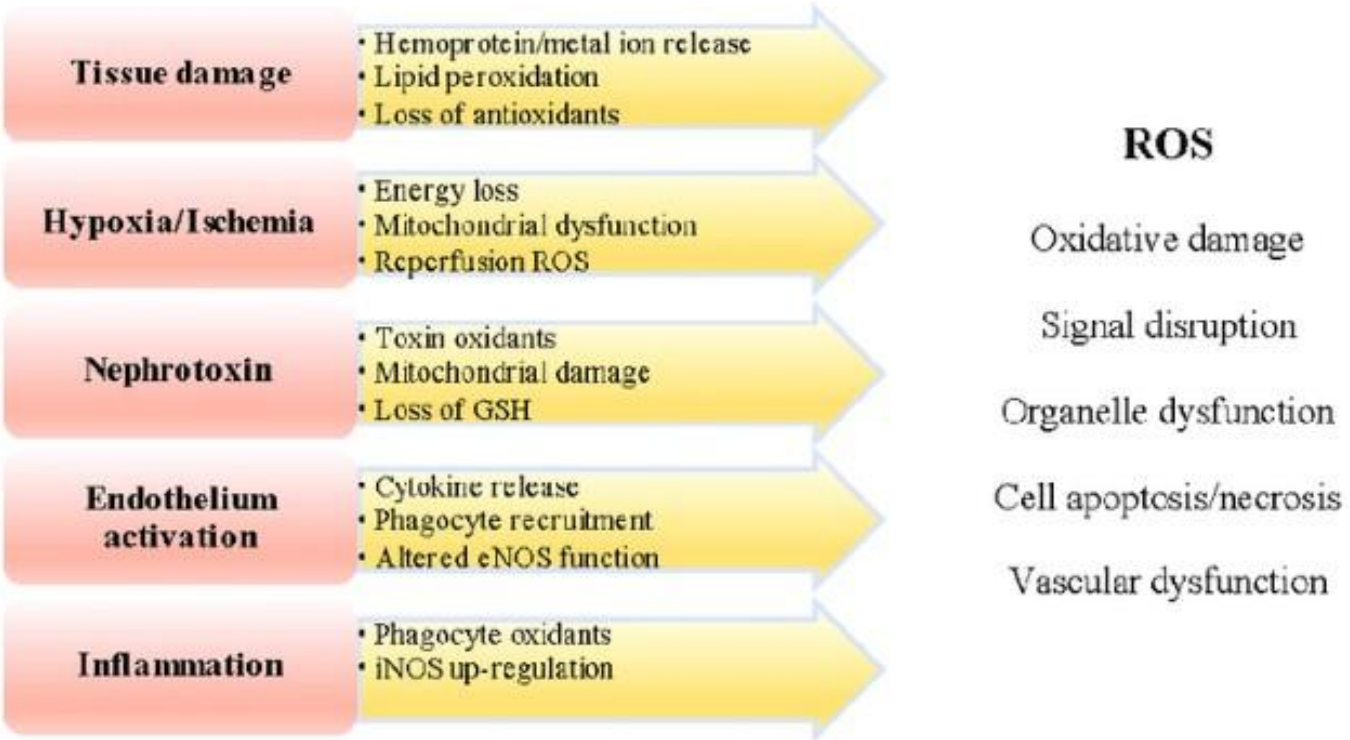
50% OF ACUTE RENAL FAILURE

PRERENAL AND POSTRENAL CAN CAUSE INTRARENAL


URETER
CAN CAUSE INTRARENAL
2b ACUTE TUBULAR NECROSIS
50% OF ACUTE RENAL FAILURE CASES
2c ACUTE INTERSTITIAL NEPHRITIS
MOSTLY DUE TO ALLERGY / INFECTION
AFFERENT ARTERIOLE
FILTRATION
2a ACUTE GLOMERULAR NEPHRITIS
-SYSTEMIC LUPUS ERYTHEMATOSUS
EFFERENT ARTERIOLE
2d VASCULAR
TO RENAL VEIN
URINE PRODUCTION
VASA RECTA
CHARACTERISTICS OF ARF
FUNCTIONALLY - ↓GFR (FILTRATION)
- ↓URINE OUTPUT
- ↑NITROGENOUS WASTE IN BLOOD (UREA, CREATININE
STRUCTURALLY - CELL DEATH (APOPTOSIS/NECROSIS)
- LOSS OF ADHESION IN INTRINSIC RENAL CELLS
VASCONSTRICT
ENDOTHELIAL DYSFUNCTION
↑ADHESION OF INFLAMMATORY CELLS
VASCULAR CHANGE
OBSTRUCTION
NECROTIC CELL DEBRIS
DAMAGED CELL
CELL LOSS
BACKLEAK OF URINE
TUBULAR CHANGE

Pathophysiology of Acute Kidney Injury





Acute kidney injury

- **Prerenal causes of azotemia**
  - **hypovolemia**
    - Bleeding, burns, bleeding to GIT, osmotic diuresis, pancreatitis, trauma, hypoalbuminemia, peritonitis, diarhoe, vomiting
  - **Decrease in minute cardiac output**
    - Myocardial diseases, heart tamponade, lung embolia
  - **Change in ratio of systemic and renal vessel resistance**
    - Vasodilation in sepsis, anaphylaxis, anestesis, cirhosis with ascites
  - **hyperviscosity syndrome**
    - Polycytemia, macroglobulinemia

Acute kidney injury

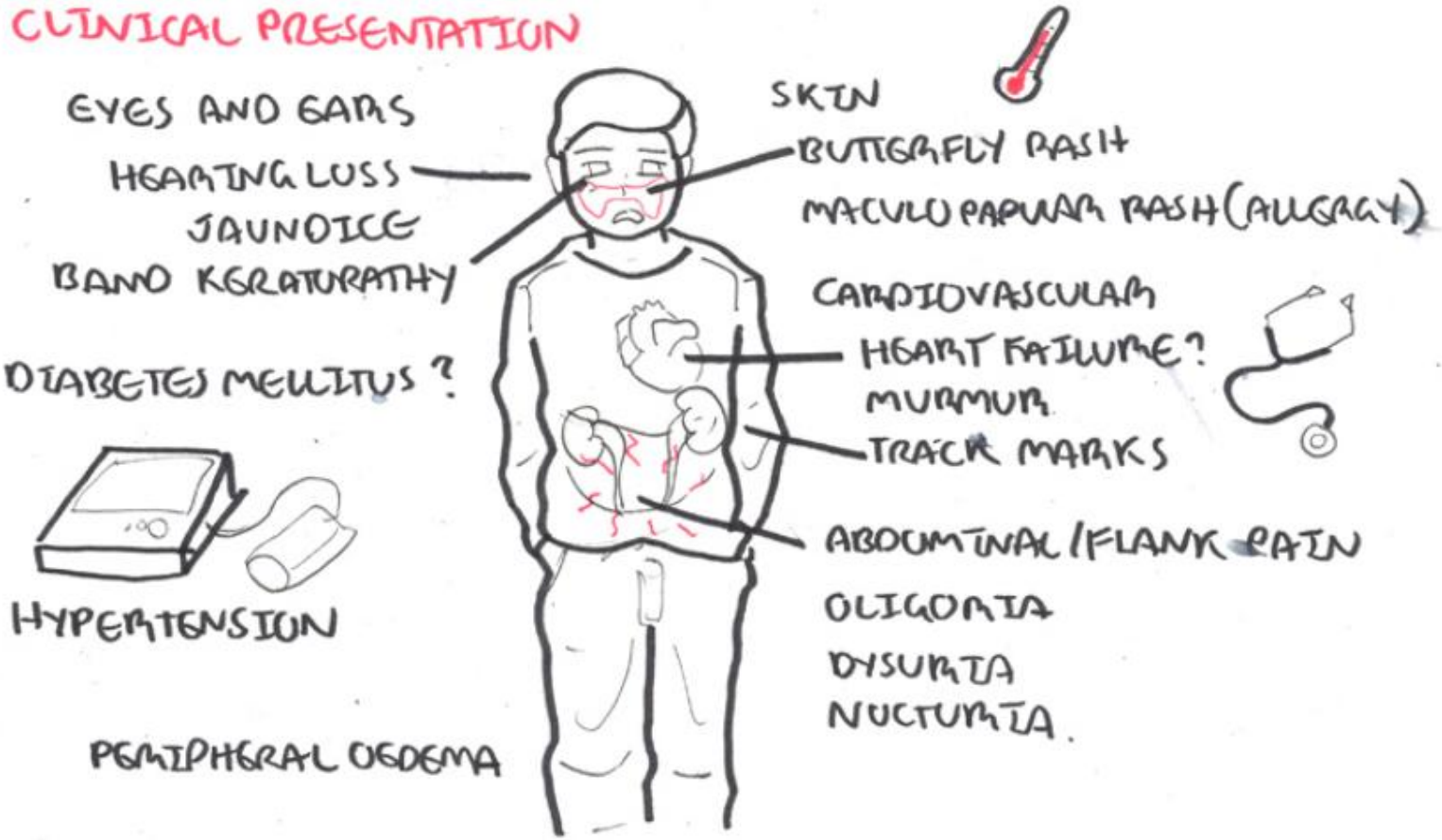
- **Renal causes of azotemia**
  - **Disorders of big renal vessels**
    - Trombosis, embolia, aneurysma dissecans, venous obstruction, vasculitis, compresion
  - **Disorders of renal circulation**
    - Glomerulonephritis, vasculitis, hemolytic-uremic syndrome, DIC, trombotic trombocytopenic purpura, radiation nephritis, toxemia in pregnancy
  - **Ischemia and nephrotoxic substances**
    - Bleeding, complication of pregnancy after birth, radiocontrast substances, cyclosporin, cisplatina, hemolysis, aminoglycosidic ATB
  - **Tubulointerstitial diseases**
    - Acute and chronic tubulointerstitial nephritis, infections, leucocytary infiltration, diuretics, acute tubular necrosis, intratubular obstruction
  - **Rejection of transplant kidney**

Acute kidney injury

- **Postrenal causes of azotemia**
  - **Ureters obstruction**
    - Stones, extrarenal compresion, retroperitoneal fibrosis
  - **Urine bladder and uretra**
    - Prostatic hypertrophy, strictures, neoplasia, neurogenic causes

Acute kidney injury

- **Symptoms**
  - ARI starts with **oliguria**
    - Is main symptom but not necesseraly present in all patients
    - Azotemia can develops in patients without oliguria too
    - Last 10-14 days
  - In oliguric patients **creatinin and urea increased**


CLINICAL PRESENTATION
EYES AND EARS
HEARING LOSS
JAUNDICE
BAND KERATOPATHY
DIABETES MELLITUS ?
HYPERTENSION
PERIPHERAL OEDEMA
SKIN
BUTTERFLY RASH
MACULOPAPULAR RASH (ALLERGY)
CARDIOVASCULAR
HEART FAILURE?
MURMUR
TRACK MARKS
ABDOMINAL / FLANK PAIN
OLIGOMIA
DYSURIA
NUCTURIA.

Acute kidney injury

- **Hyponatremia, edemas and lung congestion** develop
  - Hyponatremia is result of water retention and edemas are result of Na^+ retention
- **Decreased kalium elimination**
  - Increase over 6,5 mmol/l changes in ECG
  - Deviation of electric axis to left, peaked T waves, prolonged QRS and PQ interval and decrease of P wave
  - Bradycardia and heart arrest can occur
- **Hyperphosphatemia** because of decreased excretion of phosphates
  - Not enormous values
  - Connected with hypocalcemia and hypermagnesiemia
- **Metabolic acidosis**
  - Retention of organic acids causes decrease in plasma bicarbonates

Acute kidney injury

- **hyperurikemia**
  - Decreased excretion of uric acid
  - Slight increase in its concentration
- **Anemia from multifactorial causes**
  - Decreased production of EPO, hemolysis, bleeding, hemodilution, short life of Ec
  - **Normocytic normochromic anemia**
  - Thrombocytes decreased because of blood marrow depression
  - Lc count increased
- **Cardiovascular complications**
  - Most important: hypertension, arhytmias, pericarditis
  - Increased load of circulation causes water and Na retention
  - Not marked hypertension, occurs around second week of ARI
  - Cause is mainly water retention
  - Often occurs supraventricular arhytmias

Acute kidney injury

- **Metabolic changes**
  - Mainly in older patients cause neurologic complications
  - Lethargy, somnolency, confusion
- **Nearly in all cases detection of GIT changes**
  - Anorexia, nausea, vomitus, ileus, diffuse abdominal pain
  - Complication is bleeding in GIT
- **infection**
  - Serious complications are lethal

- In benign cases **after oliguric period we can detect increase in diuresis and glomerulal filtration (polyuric phase)**
  - It is sign of recovery
- Complications can persist (improvement in 1–2 weeks)

Acute kidney injury

- Improvement of changed functions up to 1 year
- Can stay small changes in kidney functions and hypertension
- It differs from chronic failure by affected kidney ability excrete nitrogen substances
- Causes are different but this is not permanent structural change of kidney as in chronic kidney failure
- **ARI is functional failure in dynamics**
- **CKF is progressive decrease of functional parenchyma**

Chronic kidney failure

- Kidney diseases are dangerous because of destructive processes which lead to nephrones destruction
- Result is chronic kidney failure which one clinic picture is uremia
  - The most important finding
- It is clear that it is defect of more mechanisms which cause changes in whole organism
- The final result depends on reduction of nephrones count and how fast they are destructed
- **CKF is state of ireversible and progressive kidney defect**
  - Is consequence of big spectrum of kidney defects

Chronic kidney failure

- In majority of patients glomerular filtration is lower than 25ml/min
- Clinical manifestation usually occurs after decrease of function under 10%
- **Picture of CRF:**
  - Decrease of glomerular filtration
  - Retention of nitric substances
  - Disability to regulate metabolism of water and electrolytes
  - Defect of kidney endocrine functions
- It differs from acute failure not by duration but by different clinical development

Chronic kidney failure – staging

Chronic kidney disease (CKD) staging - CKD G1-5 A1-3 glomerular filtration rate (GFR) and albumin/creatinine ratio (ACR)						
				ACR		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30	30-300	>300
GFR	G1	Normal	90+	1 if kidney damage present	1	2
	G2	Mildly decreased	60-89	1 if kidney damage present	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	4+	4+
	G5	Kidney failure	<15	4+	4+	4+

Numbers 1 - 4 indicates risk of progression as well as frequency of monitoring (number of times a year).

Kidney Disease Improving Global Outcomes - KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [46]

Chronic kidney failure

- **CKF is irreversible structural change of kidney which causes loss of basic functions of kidney (to hold equilibrium of internal environment)**
- Difficult and pathological process
- at the beginning the cause is present and known, causes damage and destruction of nephrones
  - Destruction is compensated by decrease in proglomerular vessel resistance
  - It increases flow in but pressure gradient too in glomerular capillaries
  - It ensure hyperfiltration still functional glomeruli

Chronic kidney failure

- Hyperfiltration lead to consequent nephrones failure
- Circulus vitiosus – less functional glomeruli lead to increased hyperfiltration and it lead to increased glomeruli destruction

- If systemic hypertension is present, progression is very fast
- ACE inhibitors have protective effect
- Progression is most boosted by growth factor TGF-β
  - It is polypeptid which has influence to chemotaxis, regulation of other growth factors, inhibition of T and B cells and induction of cell proliferation and fibrinogenesis
  - Stimulates cell production of extracellular matrix and decreases production of matrix degradated proteases
  - This way activates process of fibrinogesis

Chronic kidney failure

- angiotensin II acts as growth factor and induces expresion of TGF-β in smooth muscle cells and mesangial cells
- PDGF (plateled derived growing factor) is next growth factor which has influence to production of collagen by mesangial cells
  - This effect is accelerated by hypoglycemia
- IGF-1 stimulates cell hyperplasia – increased production of mesangial matrix
- Probably system of protease inhibitors is involved

Chronic kidney failure

- Serum from uremic patient has toxic influence to biological systems
  - Toxic effect have metabolites of proteins and aminoacids
  - Products of protein metabolism are excreted mainly by kidneys
  - Urea presents 80% of nitrogen which is excreted by urine in patients with CRF
  - Next important substances are guanidine substances
    - Guanidin, metyl- and dimetylguanidin, creatine, creatinin, guanidinsuccinyl acid
- Clinical symptomps:

  Anorexia, fatique, vomitus, headache

Chronic kidney failure

- Some metabolites are no toxic but can have influence to other substances which under their effect become toxic
- During uremia there is retention of nitrogen substances
- There is increase of polypeptidic hormones in plasma
  - Parathormon, insulin, glucagone, growth hormone, luteinizing hormone, prolactin
    - Participate kidney defect + increased secretion

Chronic kidney failure- manifestation

- **Fluids and electrolytes**
  - fluids overload/hypervolemia
  - edemas
  - hyperkalemia
  - Metabolic acidosis
- **calcium, phosphorus and bones**
  - hyperphosphatemia
  - hypocalcemia
  - Secondary hyperparathyreoidism
  - Renal osteodystrophy
- **Hematological changes**
  - anemia
  - Hemorhagic diatesis

Chronic kidney failure- manifestation

- **Cardiopulmonal changes**
  - hypertension
  - Congestive heart failure
  - Lung edema
  - Uremic pancreatitis
- **Gastrointestinal changes**
  - nausea and vomiting
  - GIT bleeding
  - Esophagitis, gastritis, colitis
- **Neuromuscular changes**
  - myopathies
  - Peripheral neuropathy
  - encephalopathies

Chronic kidney failure- manifestation

- **Dermatological changes**
  - Yellow discoloration of skin
  - pruritus
  - dermatitis
- Uremia is connected with changes in intracellular and extracellular fluids
- Uremic toxins damage ion transports, mainly sodium transport
  - Natrium is permanently in increased concentration in extracellular compartment
  - Uremia inhibits change of Na with K in cells (activity of Na+K+ATPasis)

Chronic kidney failure- manifestation

- Most highlighted change is in Ec, Lc and in bone muscle cells
- Defects of ion exchange are seen mainly in membrane potential of excitatory tissues
- Worsen Na transport is cause of osmotic hyperhydration of cells – different stage
  - Because of this reason there is water retention
  - Successfull dialysis causes rapid decrease of weight
- Retention of Na in cell participate on development of heart failure, hypertension and ascites
- Decrease in volume of extracellular water worsen kidney function

Chronic kidney failure- manifestation

- urea and next toxins cause hypotermia
  - Active transport of Na through membrane is proportional with basal energy production
- Ability to metabolize glucose is worse
  - Production of insuline decreases and its degradation increases (in plasma)
  - Glucose intolerance is effect of peripheral resistance to insulin action
  - Production of glucagon decreases
- Uremic patients have increased levels of TAG and lipoproteins
  - Lipase activity is decreased and hepatal production of VLDL is increased
  - Abnormalities in sugar and lipid metabolism are risk factors of atherosclerosis development

Chronic kidney failure– manifestation

- Intracellular kalium is decreased
  - Extracellular kalium is in normal level or increased
  - Most common reason for kalium transfer from cells is metabolic acidosis
  - Transfer of kalium to cell is subdued
  - Oliguria can lead to hyperkalemia with serious heart rhythm disorder
- Phosphate concentration increases
  - If glomerular filtration decreases under 20% of norm
  - Increase of phosphates increase Ca transfer to bones = **hypocalcemia**

Chronic kidney failure- manifestation

- Hypocalcemia is cause of increased level of parathormon in blood plasma
- Hypocalcemia is caused by lack of active form of vit. D
- There is no occurance of tetany

- Uremic osteodystrophy starts to occure
  - Include osteomalacia, osteosclerosis, osteofibrosis and disorders in children growth
  - Clinical symptoms occur only in 10% of patients, histological in 35-95%
  - Cause of bone changes is increased production of parathormon, disorders in vit. D metabolism, chronic metabolic acidosis and high loss of calcium via faeces
  - Spontaneous fractures can occur
- Joint pain
  - Increased accumulation of calcium deposits in bursae and periarticular structures

Chronic kidney failure

- **Consequences of changes in CRF**
  - Retention of fluids presents huge load for heart
    - Progresively develops ARDS
  - Very common complication is **arterial hypertension**
    - Can be present without water and salts retention
      - In this case increased renin activity is detected
      - In rare cases can continue to malignant hypertension
      - Systolic and diastolic pressure increase, renin activity increases, occurance of hypertension encephalopathy, changes of retina and papilar edema
      - In these cases therapy is ineffective
      - Only bilateral nephrectomy is helpfull
  - Progressive uremia causes pericarditis
  - Despite hemodialysis, atherosclerosis develops

Chronic kidney failure

- Affects coronary, brain and peripheral vessels
- Factors like hyperlipidemia, hypertension, glucose intolerance and metastatic vascular calcification participate

◦ Normocytic normochromic anemia develops

- Kidneys are not able synthetize EPO
- Depression of erythropoiesis (toxins+lack of EPO)
- Premature hemolysis of blood is caused by toxic substances
- Blood loss in GIT
- Loss is accelerate by heparin administration because of hemodialysis
- Bleeding to GIT, pericardium, subdural and intracerebral bleeding
- There is prolonged time of bleeding (decrease of platelet factor 3) – connected with increased concentration of guanidinsuccinyl acid)

Chronic kidney failure

- Affected production and function of Lc
  - Occur lymphopenia and atrophy of lymphatic tissue
  - Neu are less affected
  - All types of Leu are affected
  - Chemotactic response is decreased
  - Despite serious infection there is no occurence of fever
  - Infection development helps acidosis, hyperglycemia, azotemia, decreased Ig and complement
- CNS disorders
  - Discrete changes and sleep disorders
  - Later affected concentration, loss of memory, neuromuscular inability
  - Twitching of large/big muscles

Chronic kidney failure

- **Peripheral neuropathy**
  - Affects more lower than upper limbs
  - Is signal of worsening of status
  - In chronic dialysis signs of dialasing dementia
  - Probably Is connected with increased concentration of Al
  - symptoms: dysartria, myoclonus, dementiia
- **anorexia, singultus, nausea, vomiting**
- Urea is excreted via saliva, here is decomposed to ammonia and is cause of **uremic smell**
- In all GIT can occur mucosa ulcerations
  - Ulcerations and enteritis are causes of blood loss
  - Common are peptic ulcers (in 25% of patients)
  - Causes of origin are: gastric hyperacidity, increase gastric secretion, secondary hyperparathyereoidism

Chronic kidney failure

- Anemia together with urochromes retention is cause of typical skin color
- Urea is excreted by sweat
- Can participate on skin pruritus occurance

- Patients most common die because of:
  - CVS complications (50%)
  - sepsis (25%)