GLOMERULONEPHRITIS IN CHILDREN
CHRONIC RENAL FAILURE

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2016
Scheme of normal glomerule

- Mezangium
- Epithelial cells (podocites)
- Pediculus
- Endothelium (1-2)
- Basal membrane
- Mezangial cell (1-2)
Glomerulonephritis

- is a group of kidney diseases characterized by inflammation of the glomeruli or small blood vessels in the kidneys that can result in damage to the basement membrane, mesangium, capillary endothelium
The primary glomerulopathies (glomerulonephritis, GN) are those disorders that affect glomerular structure, function, or both in the absence of a multisystem disorder.

The clinical manifestations are predominately the consequence of the glomerular lesion (such as proteinuria, hematuria, and reduced glomerular filtration rate).

The combination of clinical manifestations leads to a variety of clinical syndromes.
GN comprises 25-30% of all cases of end-stage renal disease (ESRD).

About ¼ of patients present with acute nephritis syndrome.

Most cases that progress do so relatively quickly, and end-stage renal failure may occur within weeks or months of acute nephritic syndrome onset.

Asymptomatic episodes of post-streptococcal GN (PSGN) exceed symptomatic episodes by a ratio of 3-4:1.

GN is treatable and preventable
Geographic and seasonal variations in the prevalence of PSGN are more marked for pharyngeally associated GN (serotype 12) than for cutaneously associated disease (serotype 49).

Postinfectious GN has no predilection for any racial or ethnic group. A higher incidence (related to poor hygiene) may be observed in some socioeconomic groups.

Acute GN predominantly affects males (ie, 2:1 male-to-female ratio).

Postinfectious GN can occur at any age but usually develops in children. Outbreaks of PSGN are common in children aged 6-10 years.
Acute glomerulonephritis consists of the abrupt onset of hematuria, proteinuria, edema, and hypertension (duration <1 year).

Rapidly progressive glomerulonephritis is characterized by features of nephritis and progressive renal insufficiency.

Chronic glomerulonephritis features proteinuria and hematuria with indolent progressive renal failure (duration >1 year).
Etiology

- Hereditary predisposition
- Streptococcal infection, Staphylococci, Tuberculosis, Malaria, Syphilis, Mycoplasma pneumonia
- Viral infections (Hepatitis B, C, cytomegalovirus, Epstein Barr virus, mumps, Coxsackie)
- Exogenous antigens (immune reactions of different types)
- Endogenous antigens - DNA, tumor.
- Toxic substances (lead, cadmium, organic solvents, Hg, medicines, drugs, alcohol)
- Disorders of metabolism (disorders of carbohydrate and uric acid metabolism – hyperuricosuria and hyperuricemia)
Pathogenesis and pathology

- Antibodies formed in response to the antigens combine with antigens to form immune complexes that are trapped in the glomeruli
- Complement activation, release of mediators of inflammation and glomerular injury
- Infiltration with polymorphs, proliferation of endothelial and mesangial cells
- Hypercoagulation
- Increase in permeability of basement membrane
- Activation of renin-angiotensin-aldosterone system
- Decrease in filtration

- Edema
- Hypertension
- Oliguria
- Proteinuria
- Hematuria
- Casturia
Pathogenesis

Edema
- Decrease in filtration
- Retention of sodium and water (activation of renin-angiotensin-aldosteron system)
- Decrease in oncotic pressure (hypoalbuminemia)

Hypertension
- Decrease in filtration
- Retention of sodium and water (activation of renin-angiotensin-aldosteron system)
- Increase in vasoconstrictors’ level
Glomerulonephritis

Non-Proliferative

Minimal Change Glomerulonephritis
Abnormal Podocytes
Seen on Electron Microscopy
Treat with Supportive care
+ Prednisolone
Most respond well

Membranous Glomerulonephritis (MGN)
Thickened Glomerular Basement Membrane
Usually idiopathic
1/3 have chronic MGN
1/3 go into remission
1/3 progress to renal failure

Focal Segmental Glomerulosclerosis
Segments of Glomeruli Develop Sclerosis
Presents with Nephrotic Syndrome
Genetic causes identified
Steroids often ineffective
50% Progress to Renal Failure

Proliferative

IgA Nephropathy
Most common type of GN in adults
Macroscopic haematuria
Appears 24-48hrs post URTI/GI infection
IgA deposits seen in the matrix

Membranoproliferative Glomerulonephritis
Primary (immune mediated)
Secondary (SLE, Hep)
Usually progresses to End Stage Renal Failure

Rapidly Progressive Glomerulonephritis (Crescentic)

Vasculitic Disorders

Wegeners Granulomatosis
Vasculitis
Lungs, Kidney & other organs
c-ANCA +ve
Treat with Steroids
+ Cyclophosphamide

Microscopic Polyangitis
Small vessel vasculitis
p-ANCA +ve
Treat with long term steroids
+/- cytotoxic agents

Goodpastures Syndrome
Autoimmune
anti-GBM antibody
Glomerulus & Lung affected
Haematuria & Haemoptysis
Treat with steroids
+/- steroid sparing agents

Post Infectious Glomerulonephritis
Occurs weeks after URTI
Usually Strep Pyogenes
Supportive treatment
Resolves over 2-4 weeks
GLOMERULONEPHRITIS

Antigen-Antibody Complex in Glomeruli Causing:
- Inflammation
- ↓ Glomerular Filtration Rate

Antigen-Antibody Complex From Recent Strep Infection

- Headache
- ↑ BP
- Facial / Periorbital Edema
- Lethargic
- Low Grade Fever
- Weight Gain (Edema)

Proteinuria
Hematuria
Oliguria

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Clinical manifestations

Symptoms

Extrarenal

- Pallor (spasm of vessels)
- Edema - slight or severe (periorbital and/or pedal edema, pulmonary edema, ascites and pleural effusion)
- Hypertension
- Cardiovascular disorders (changes of heart borders, rhythm, sounds, murmurs)
- Mild fever, anorexia, nausea, vomiting, headache may be present

Renal

- Abdominal pain or pain in a loin region
- Oliguria (<1ml/kg/h), anuria
- Hematuria (microhematuria, macrohematuria – “cola-colored”)
- Proteinuria (mild or severe)
- Casturia (hyaline, granular, RBCs casts)
Complications

- **Heart failure and pulmonary edema** (circulatory overload) – dyspnea, orthopnea, pulmonary crepitation, enlarged tender liver

- **Hypertensive (angiospastic) encephalopathy** – irritability, headache, vomiting, blurring of vision, dimness of vision, temporary blindness, drowsiness, coma, generalized convulsions

- **Acute renal failure** – disturbed consciousness (drowsiness, stupor, coma), vomiting, diarrhea, air hunger, convulsions, severe oliguria or anuria, hyperkalemia, acidosis, hypercreatininemia

- **Thromboembolia, thrombosis** (Nephrotic syndrome)

- **Infections** (Nephrotic syndrome)
International classification of diseases
Code ICD – 10

- N00 – acute nephritic syndrome
- N01 – rapidly progressive nephritic syndrome
- N02 – recurrent persistent hematuria
- N03 – chronic nephritic syndrome
- N04 – nephrotic syndrome
- N05 - unspecified nephritic syndrome
- N06 – isolated proteinuria
- N07 - hereditary nephropathy, not elsewhere classified
- N08 - glomerular disorders in diseases classified elsewhere
PRIMARY GLOMERULAR LESIONS

- Minimal change disease
- Focal segmental glomerulosclerosis with hyalinosis
- Membranous glomerulonephritis
- Membranoproliferative glomerulonephritis
- Mesangial proliferative glomerulonephritis
- Crescentic glomerulonephritis
- Immunoglobulin A nephropathy
- Fibrillary and immunotactoid glomerulonephritis
- Collagenofibrotic glomerulopathy
- Lipoprotein glomerulopathy
# Clinical classification of glomerulonephritis in children (Vinnitsa, 1976)

<table>
<thead>
<tr>
<th>Syndromes and forms</th>
<th>Period of disease</th>
<th>Condition of renal functions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GN:</strong></td>
<td>• period of initial manifestations • Period of comprehensive manifestations • Period of reverse development • Transition to chronic GN</td>
<td>- without disorders of renal functions; - with disorders of renal functions; - acute renal failure</td>
</tr>
<tr>
<td>- with nephritic syndrome;</td>
<td></td>
<td></td>
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<tr>
<td>- with nephrotic syndrome;</td>
<td></td>
<td></td>
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<tr>
<td>- with isolated urinary syndrome;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- with nephrotic syndrome, hematuria and hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic GN:</strong></td>
<td>• Period of exacerbation • Period of partial remission • Period of full clinic and laboratory remission</td>
<td>- without disorders of renal functions; - with disorders of renal functions; - chronic renal failure</td>
</tr>
<tr>
<td>- nephrotic form;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- hematuric form;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- mixed form</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rapidly progressive GN</strong></td>
<td></td>
<td>-with disorders of renal functions; - chronic renal failure</td>
</tr>
</tbody>
</table>
## Clinical syndromes of acute GN

<table>
<thead>
<tr>
<th>Sign</th>
<th>Isolated urinary syndrome</th>
<th>Nephritic syndrome</th>
<th>Nephrotic syndrome</th>
<th>Nephrotic syndrome with hematuria and hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>-</td>
<td>+/-/+</td>
<td>++/+++</td>
<td>++/+++</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>N</td>
<td>↑</td>
<td>N or ↓</td>
<td>↑</td>
</tr>
<tr>
<td>Oliguria</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Daily proteinuria</td>
<td>&lt; 1-2 g (&lt;50mg/kg)</td>
<td>&lt; 1-2 g (&lt;50mg/kg)</td>
<td>&gt;1-2 g (&lt;50mg/kg, 1g/m², 40 mg/m²/h)</td>
<td>&gt;1-2 g (&lt;50mg/kg, 1g/m², 40 mg/m²/h)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Casturia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Leucocyturia</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Albumins</td>
<td>↓</td>
<td>↓</td>
<td>&lt; 30-25g/l</td>
<td>&lt; 30-25g/l</td>
</tr>
<tr>
<td>α-2-globulins</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>γ-globulins</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Lipids</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Classification</td>
<td>Definition</td>
<td></td>
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<tr>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Edema, uPCR ≥2000mg/g (≥200mg/mmol), or ≥300mg/dl, or 3+ protein on urine dipstick, hypoalbuminaemia ≤2.5g/dl (≤25g/l)</td>
<td></td>
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</tr>
</tbody>
</table>
### Definitions of nephrotic syndrome in children

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>uPCR X2000mg/g (≥200mg/mmol) or ≥3+ protein on urine dipstick for 3 consecutive days</td>
</tr>
<tr>
<td>Infrequent relapse</td>
<td>One relapse within 6 months of initial response, or one to three relapses in any 12-month period</td>
</tr>
<tr>
<td>Frequent relapse</td>
<td>Two or more relapses within 6 months of initial response, or four or more relapses in any 12-month period</td>
</tr>
<tr>
<td>Steroid dependence</td>
<td>Two consecutive relapses during corticosteroid therapy, or within 14 days of ceasing therapy</td>
</tr>
<tr>
<td>Late nonresponder</td>
<td>Persistent proteinuria during 4 or more weeks of corticosteroids following one or more remissions</td>
</tr>
</tbody>
</table>

uPCR, urine protein:creatine ratio
NEPHRITIC or NEPHROTIC

NEPHRITIC SYNDROME

- Inflammation of the glomeruli
- HTN
- Cola-colored urine (hematuria)

NEPHROTIC SYNDROME

- Hypoalbuminemia
- Hyperlipidemia
- Oliguria
- Berger's disease (IgA nephropathy) is the most common cause of primary glomerulonephritis
- Peripheral edema
- Massive proteinuria

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Clinical forms of chronic GN

- **Hematuric form** – hematuria, mild proteinuria, casturia.

- **Nephrotic form** is an equivalent of nephrotic syndrome of acute GN, course is recurrent, persistent proteinuria is unfavorable prognostic sign.

- **Mixed form** is characterized by combination of nephrotic syndrome, hypertension and hematuria, course is progredient, chronic renal failure is often.
Obligatory investigations:

- blood test;
- urine examination;
- proteinogram; cholesterol, lipids;
- Reberg’s test, GFR;
- Zimnitsky’s test;
- antistreptolosin-O, IgM, IgG, IgA, immune complexes, C3-complement;
- ECG;
- ultrasound examination;
- biopsy – if necessary (atypical presentation, persistent hematuria or oliguria or hypertension >3 weeks, family history of hereditary nephritis, nephrotic syndrome)
The urine dipstick test offers a qualitative assessment of urinary protein excretion. Dipsticks primarily detect albuminuria and are less sensitive for other forms of proteinuria (low molecular weight proteins, Bence Jones protein, gamma globulins).

The dipstick is reported as

- negative,
- trace (10–20 mg/dL = 0,01-0,02 g/l),
- 1+ (30 mg/dL = 0,03 g/l),
- 2+ (100 mg/dL = 0,1 g/l),
- 3+ (300 mg/dL = 0,3 g/l),
- 4+ (1000–2000 mg/dL = 1-2 g/l).
Factors contributing to the progression of GN

- inflammation mediators;
- processes of coagulation;
- systemic and intraglomerular hypertension;
- metabolic disorders:
  - lipid disorders;
  - free radical processes;
  - lipid peroxidation;
  - excess deposition of calcium;

- Tubular and interstitial disorders
Symptoms that worsen the prognosis of GN

- leucocytutia expressed in the debut of disease;
- extrarenal symptoms persisting more than 1 month;
- combination of hematuria with proteinuria;
- recurrence of hematuria within 3 months;
- the presence of tubulo-interstitial component;
- reduction of tubular functions more than 6 months from onset;
- increase in kidney more than 60\% of the norm;
- frequent acute respiratory infections (ARI), scarlet fever, enteric infections in history;
- the presence of chronic foci of infection;
- allergic dermatitis;
- hereditary predisposition
Risk factors that increase the likelihood of development and progression of GN

Unmodifiable:

- **Age** - puberty;  
  **gender** - male;  
  **Race** - African;  
  **renal dysplasia** (congenital reduction in the number of nephrons);  
  **genetic factors**.

Potentially modifiable:

- Systemic arterial hypertension;
- Activation of sympathetic nervous system;
- **Decrease in the number of functioning nephrons** (hypertrophy, hyperfiltration, intraglomerular hypertension);
- **Activity of the main disease** (proteinuria);
- High protein diet;
- **Dyslipoproteidemia**;
- **Deposits of calcium, phosphorus, uric acid in kidneys**;
- **associated diseases / factors** - infection, obstruction of upper urinary tract, obesity, use of analgesics and other nephrotoxins, smoking, pregnancy.
The spectrum of glomerular diseases

SLE

IgA nephropathy

Minimal change nephropathy

FSGS

Diabetic nephropathy

Membranous nephropathy

Amyloidosis

MCGN

Post-streptococcal glomerulonephritis

Anti-GBM disease

Small vessel vasculitis

Haematuria

Proteinuria

Nephrotic

Mechanism

- Injury to podocytes
- Changed architecture:
  - Scarring
  - Deposition of matrix or other elements

Nephritic

Mechanism

- Inflammation
- Reactive cell proliferation
- Breaks in GBM
- Crescent formation
Targets of treatment:

- Detection and elimination of etiological factor (etiotropic treatment),
- Suppression of activity, stabilization of clinical course and deceleration speed of progression (pathogenetic treatment),
- Decrease in symptoms’ severity (symptomatic treatment)
Treatment

Activity

- Recommend bed rest until signs of glomerular inflammation and circulatory congestion subside. Prolonged inactivity does not benefit in the patient recovery process.

- NB! Bed rest in case of nephrotic syndrome – risk of thrombosis!!!
Diet (N7a → 7 → 5)

- **Sodium and fluid restriction** - For treatment of signs and symptoms of fluid retention (e.g., edema, pulmonary edema)
- **Sodium restriction** – edema, hypertension (≈ 2 weeks or more)
- **Control of fluid’s intake** (Fluid intake = perspiration loss of water + daily diuresis of previous day + pathological loss of water)
- **Protein restriction** for patients with azotemia (1 wk or more) - If no evidence of malnutrition
Etiotropic treatment

- **Antibiotics** (penicillins, cephalosporins of 2-3 generations, macrolids) 2-4 weeks + antihistamines (if necessary);
- **Antiviral drugs**;
- **If HCV, HBs Ag** – interferons;
- **Antisyphilitic, antimalarial, antituberculous drugs**.
Patogenetic treatment

Influence on immune factors:
- Corticosteroids
- Cytostatic drugs
- Immunosuppressive agents
- Plasmaferesis

Influence on nonimmune factors:
- Inhibitors of angiotensin-converting enzyme (iACE)
- Hypolipidemic drugs
- Anticoagulants
- Chloroquinum
- Antiaggregants
- Ca-channel blockers
- Antioxidants
Signs of GN’s activity

- Nephrotic syndrome;
- acute nephritic syndrome;
- Strengthening of proteinuria and hematuria;
- High blood pressure;
- Renal insufficiency and strengthening of azotemia;
- Intravascular coagulation;
- Increase ESR;
- hyper-alfa2-globulinemia
Indications for treatment with prednisone:

- Nephrotic syndrome;
- Rapidly progressive GN;
- High activity and progressing course of GN;
- Secondary GN (lupus nephritis)
Prednisone

- 1.5-2 mg/kg/d (≤60 mg/d) p.o. or 3-4mg/kg/d i/v 6-8 weeks;
- then supporting treatment 6-15 mo., initial dose – 30-50% of maximal,
- (+ + + - - - -) or (+ -) during 6-8 mo.
- Then dose goes down by 1-2,5mg every 4-6-8 weeks to 2,5-5 mg.

In case of intercurrent infections - 12,5-20 mg/d during 10-15 days, then return to initial dose
- Ps-therapy with methylprednisone (30 mg/kg i/v)
Indications for treatment with cytostatic and immunosuppressive agents:

- Steroid resistant GN;
- In adolescents;
- Relapsing of nephrotic syndrome

- *Chlorbutin* - 0.15-0.2 mg/kg/d 8-12 weeks, supporting dose - \( \frac{1}{2} \) of initial 6-15 mo.
- *Cyclophosphamide* - 2-3 mg/kg/d 8 weeks
- Cyclosporine A - 3-5-6 mg/kg/d 6-12 mo
- *Acidum mycophenolicum (cellcept)* 500-600 mg/m\(^2\) 9-12 mo
KDIGO Clinical Practice Guideline for Glomerulonephritis (2012)

Treatment of the initial episode of SSNS

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 60mg/m²/d or 2mg/kg/d to a maximum 60mg/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 40mg/m² or 1.5mg/kg (maximum 40mg on alternate days) (1D) and continued for 2–5 months with tapering of the dose. (1B)
3.2: Treatment of relapsing SSNS with corticosteroids

3.2.1: 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 60mg/m² or 2mg/kg (maximum of 60mg/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 (40mg/m² per dose or 1.5mg/kg per dose: maximum 40mg on alternate days) for at least 4 weeks. (2C)
3.2.2: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)

3.2.2.4: 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)
3.3: Treatment of FR and SD SSNS with corticosteroid-sparing agents

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 (2mg/kg/d) be given for 8–12 weeks (maximum cumulative dose 168mg/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 (0.1–0.2mg/kg/d) may be given for 8 weeks (maximum cumulative dose 11.2mg/kg) as an alternative to cyclophosphamide. (2C)

3.3.2.4: We suggest that second courses of alkylating agents not be given. (2D)
3.3.3: We recommend that levamisole be given as a corticosteroid-sparing agent. (1B)

3.3.3.1: We suggest that levamisole be given at a dose of 2.5mg/kg on alternate days (2B) for at least 12 months (2C) as most children will relapse when levamisole is stopped.

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 4–5mg/kg/d (starting dose) in two divided doses. (2C)

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

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 1200mg/m^2/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)

3.3.7: We suggest that mizoribine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (2C)

3.3.8: We recommend that azathioprine not be used as a corticosteroid-sparing agent in FR and SD SSNS. (1B)
3.4: Indication for kidney biopsy

3.4.1: Indications for kidney biopsy in children with SSNS are (Not Graded):

- late failure to respond following initial response to corticosteroids;
- a high index of suspicion for a different underlying pathology;
- decreasing kidney function in children receiving CNIs.
3.5: Immunizations in children with SSNS

3.5.1: To reduce the risk of serious infections in children with SSNS

- Give pneumococcal vaccination to the children.
- Give influenza vaccination annually to the children and their household contacts.
- Defer vaccination with live vaccines until prednisone dose is below either 1mg/kg daily (<20mg/d) or 2mg/kg on alternate days (<40mg on alternate days).
- Live vaccines are contraindicated in children receiving corticosteroid-sparing immunosuppressive agents.
- Immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child but avoid direct exposure of the child to gastrointestinal, urinary, or respiratory secretions of vaccinated contacts for 3–6 weeks after vaccination.
- Following close contact with Varicella infection, give nonimmune children on immunosuppressive agents varicella zoster immune globulin, if available.
Inhibitors of ACE

Effects –
- hypotensive
- antiproteinuric
- antisclerotic

Indications
- hypertension
- proteinuria without biochemical activity of GN
- Decrease in renal functions
Indications for treatment with anticoagulants

- high risk of thrombosis (nephrotic syndrome, nephrotic syndrome with hematuria and hypertension, rapidly progressive GN);
- acute renal failure;
- prolonging course of GN
Membranostabilisators (antioxidants)

- in acute period (cell membranes’ destruction)
- As a supporting therapy
- vit A, E, Dimephosphon, Essentiale at al.
Infusion therapy (indications)

Nephritic syndrome
- Elimination of edema
- Improvement of rheology
- Correction of electrolytic disorders
- Desintoxication

Nephrotic syndrome
- Elimination of edema
- Improvement of rheology
- Correction of hypovolemia
- Risk of disseminated intravascular coagulation syndrome
- Syndrome of inadequate secretion of antidiuretic hormone
Infusion therapy in nephritic syndrome

- 5% glucose, 0,9% sodium chloride (1:1) – 10 ml/kg
- Rheosorbilact 5-8 ml/kg (carefully in osmolarity >310 mosm/l – risk of acute renal failure)
- Xilate 10 ml/kg
- Diuretics (torasemid 0,8-1 mg/kg or furosemid 2-3 mg/kg + hidrochlorthiasid 2-3 mg/kg )
- Dopamin 0,5-1,5 mkg/kg/min
Infusion therapy in nephrotic syndrome

- Voluven (hydroxyethylamylum) – 5-10 ml/kg/d or dextranum (polyglucinum, reopolyglucinum) 5-8 ml/kg/d
- Albuminum 20% (or 5%) - 5 ml/kg/d
- Rheosorbilactum 5-10 ml/kg
- Fresh frozen plasma (risk of disseminated intravascular coagulation syndrome) – 5-10 ml/kg/d
- Diuretics (torasemid 0.8-1 mg/kg or furosemid 2-3 mg/kg + hidrochlorthiasid 2-3 mg/kg or verospiron 5-10 mg/kg)
Azotemia

- Infusion therapy and forcing of diuresis;
- Enterosorption;
- Medicines which decrease level of azotemia (Lespenephryl, Chophytol);
- Lack of effect – extracorporal methods of detoxication (dialysis).
Chronic renal failure (insufficiency)

Chronic kidney failure is the most significant result of chronic kidney disease. Treated chronic kidney failure, also called end-stage renal disease (ESRD), is the most feared consequence of kidney disease.
Chronic renal insufficiency, chronic renal failure, and end-stage renal disease (ESRD): Terms describing the continuum of increasing renal dysfunction and decreasing glomerular filtration rate (GFR). Because of the progressive nature of kidney disease, these terms represent successive stages of disease in most patients.

Chronic renal insufficiency: The stage in chronic kidney disease in which damage to the kidney already has resulted in significant impairment of renal function, but systemic manifestations are minimal. Most patients who have chronic renal insufficiency are asymptomatic. Chronic renal insufficiency usually is identified because the serum creatinine is slightly elevated. The serum creatinine test is insensitive and does not identify all persons who have chronic renal insufficiency. Although precise GFR limits cannot be assigned to this stage of disease, typically patients with chronic renal insufficiency have a GFR between 30 ml/min and 75 ml/min.
Chronic renal failure: The stage in chronic renal disease in which renal dysfunction has progressed to a level resulting in systemic manifestations. These manifestations include a rise in the blood concentration of urea, creatinine, and phosphate, which are removed by the kidneys, and other problems, such as anemia, bone disease, acidosis, and salt and fluid retention. Growth failure may be seen in children. Most patients with chronic renal failure progress to treated chronic kidney failure (end-stage renal disease).

End-stage renal disease (ESRD) (referred to in this focus area as treated chronic kidney failure): The stage in chronic renal disease in which renal replacement therapy, dialysis, or kidney transplantation is needed to sustain life. Treated chronic kidney failure is generally an irreversible state. The glomerular filtration rate is usually less than 10ml/min.
Causes of CRF

- Primary and secondary glomerulopathy
- Tubulointerstitial diseases
- Obstructive nephropathy
- Metabolic diseases (diabetes mellitus, amyloidosis)
- Congenital kidney diseases
Conceptual model of CKD
Am.J.Kidney Dis. 2009; 53:S4-16

Complications

N → R → D → ↓GFR → ESRD → EOL

Screening for CKD risk factors
CKD risk factors reduction, screening for CKD
Diagnosis and treatment, treat comorbid conditions, slow progression
Estimate progression, лечение treat complication, prepare for replacement
Replacement by dialysis and transplant
Chronic kidney disease (CKD)
(Kidney Disease Outcome Quality Initiative - KDOQI, 2002)

1. Kidney damage for 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either:
   - Pathological abnormalities; or
   - Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests

2. GFR <60 mL/min/1.73m² for 3 months, with or without kidney damage
Current Chronic Kidney Disease (CKD) Nomenclature used by KDIGO (2012) (Kidney Disease Improving Global Outcomes)

- CKD is defined as abnormalities of kidney structure or function, present for ≥ 3 months, with implications for health
- and CKD is classified based on cause, GFR category, and albuminuria category (CGA).
### Stages of chronic kidney disease (CKD) and chronic renal failure (insufficiency) (CRF) in children

<table>
<thead>
<tr>
<th>Stage of CKD</th>
<th>Stage of CRF</th>
<th>GFR ml/min/1,73 m²</th>
<th>Creatinine, mmol/l</th>
<th>Maximal specific gravity of urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>-</td>
<td>≥90</td>
<td>≤0.104</td>
<td>&gt;1.018</td>
</tr>
<tr>
<td>II</td>
<td>I (tubular)</td>
<td>≥90</td>
<td>≤0.104</td>
<td>≤1.018</td>
</tr>
<tr>
<td></td>
<td>I (compensative)</td>
<td>89-60</td>
<td>0.105-0.176</td>
<td>&lt;1.018</td>
</tr>
<tr>
<td>III</td>
<td>II (subcompensative)</td>
<td>59-30</td>
<td>0.177-0.351</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>III (decompensative)</td>
<td>29-15</td>
<td>0.352-0.440</td>
<td>&lt;1.018</td>
</tr>
<tr>
<td>V</td>
<td>IV (terminal)</td>
<td>&lt;15</td>
<td>&gt;0.440</td>
<td></td>
</tr>
</tbody>
</table>
Criteria for CKD (either of the following present for > 3 months)

Markers of kidney damage (one or more)

- Albuminuria (AER >30mg/24 hours; ACR >30mg/g [>3mg/mmol])
- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

Decreased GFR

GFR < 60ml/min/1.73 m² (GFR categories G3a–G5)
The plasma level \((P)\) of an endogenous filtration marker is determined by its generation \((G)\) from cells and diet, extrarenal elimination \((E)\) by gut and liver, and urinary excretion \((U \times V)\) by the kidney.

Urinary excretion is the sum of filtered load \((GFR \times P)\), tubular secretion \((TS)\), and reabsorption \((TR)\).

In the steady state, urinary excretion equals generation and extrarenal elimination. By substitution and rearrangement, \(GFR\) can be expressed as the ratio of the non-\(GFR\) determinants \((G, TS, TR, \text{ and } E)\) to the plasma level.
Updated “Bedside” Schwartz equation: KDIGO 2012

- $eGFR(\text{ml/min}/1.73m^2) = 41.3(\text{height}/SCr)$, where height is in meters and SCr is in mg/dl.

mg/dl x 88.4 = mmol/l

$eGFR(\text{ml/min}/1.73m^2) = \frac{36.5 \times \text{height (cm)}}{\text{SCr(mmol/ml)}}$
### Prognosis of CKD by GFR and Albuminuria

**Categories:** KDIGO 2012

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73m²)</th>
<th>Description and range</th>
<th>Persistent albuminuria categories</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G1</strong></td>
<td>Normal or high ≥ 90</td>
<td>A1 Normal to mildly increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A2 Moderately increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3 Severely increased</td>
</tr>
<tr>
<td><strong>G2</strong></td>
<td>Mildly decreased 60-89</td>
<td>A1 Normal to mildly increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A2 Moderately increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3 Severely increased</td>
</tr>
<tr>
<td><strong>G3a</strong></td>
<td>Mildly to moderately decreased 45-59</td>
<td>A1 Normal to mildly increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A2 Moderately increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3 Severely increased</td>
</tr>
<tr>
<td><strong>G3b</strong></td>
<td>Moderately to severely decreased 30-44</td>
<td>A2 Moderately increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3 Severely increased</td>
</tr>
<tr>
<td><strong>G4</strong></td>
<td>Severely decreased 15-29</td>
<td>A3 Severely increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3 Severely increased</td>
</tr>
<tr>
<td><strong>G5</strong></td>
<td>Kidney failure &lt; 15</td>
<td>A3 Severely increased</td>
</tr>
</tbody>
</table>

Persistent albuminuria categories:
- **A1**: Normal to mildly increased
- **A2**: Moderately increased
- **A3**: Severely increased

- < 30 mg/g < 3 mg/mmol
- 30-300 mg/g 30-300 mg/mmol
- > 300 mg/g > 30 mg/mmol
The graph illustrates the stages of Chronic Kidney Disease (CKD) and the corresponding loss of kidney function, as well as associated symptoms:

- **Stage 1**: Below normal to mild loss of kidney function, often no symptoms.
- **Stage 2**: Mild to moderate loss of kidney function, high blood pressure (B/P), protein in urine.
- **Stage 3**: Moderate to severe loss of kidney function, anemia, early bone disease.
- **Stage 4**: Severe loss of kidney function, fatigue, swelling, nausea, vomiting.
- **Stage 5**: Kidney failure—Dialysis.

The percentage of kidney function remaining decreases as the stage of CKD progresses.
STAGES OF CHRONIC KIDNEY DISEASE

1. KIDNEY DAMAGE WITH NML OR INCREASED GFR
   GFR ≥ 90
   DX/RX OF UNDERLYING CONDITION AND COMORBIDITIES

2. MILD
   GFR 60 TO 89
   ESTIMATE THE RATE OF PROGRESSION

3. MODERATE
   GFR 30 TO 59
   EVALUATE AND TREAT COMPLICATIONS

4. SEVERE
   GFR 15 TO 29
   PREPARE FOR RENAL REPLACEMENT THERAPY

5. KIDNEY FAILURE
   GFR < 15 OR DIALYSIS
   DIALYSIS OR TRANSPLANTATION IF UREMIC

GFR: ML/MIN/1.73M²
Chronic renal disease

Progression of renal disease
Decreased renal perfusion
Decreased filling pressures
Heart failure
Cardiomyopathy
Myocyte death

Erythropoietin

Chronic kidney disease—Mineral and Bone Disorder

Cardiovascular disease

High output state
Pressure and volume overload
LVH and LVD

Anaemia

Other factors:
 hyperparathyroidism,
fistula,
malnutrition

CKD-MBD
Factors associated with CKD progression

- cause of CKD
- level of GFR
- level of albuminuria
- age, sex, race/ethnicity
- elevated BP
- anemia, calcium-phosphorus disorders
- hyperglycemia, dyslipidemia
- smoking, obesity, history of cardiovascular disease
- ongoing exposure to nephrotoxic agents, and others.
Signs and symptoms

- Initially it is without specific symptoms and can be detected as an increase in serum creatinine or protein in urine (in children – decrease in specific gravity)
- Blood pressure is increased (fluid overload, production of vasoactive hormones)
- Accumulation of urea – **azotemia or uremia** – lethargy, pericarditis, encephalopathy, “uremic frost” (urea is excreted by sweating and crystallizes)
- **Hyperkalemia** – malaise, muscles hypotonia, cardiac arrhythmias
- **Erythropoetin** synthesis is decreased – anemia, fatigue
- **Fluid volume overload** – edema, pulmonary edema
- **Hyperphosphatemia** – due to reduced phosphate excretion, associated with **hypocalcemia** (due to vit D deficiency) – tetany. Later – **hyperparathyroidism, renal osteodystrophy**
- **Metabolic acidosis** (accumulation of sulfates, phosphates, uric acid)
Early identification and referral of people with CKD has the potential to reverse, delay, or prevent progression of disease and is a key focus of international initiatives in the area of kidney disease.
The goals of early identification and referral are several-fold and include:

1. Provision of specific therapy based on diagnosis
2. Slowing/arresting CKD progression
3. Evaluation and management of comorbid conditions
4. Prevention and management of CVD
5. Identification, prevention, and management of CKD-specific complications (e.g., malnutrition, anemia, bone disease, acidosis)
6. Planning and preparation for RRT (e.g., choice of modality, access-placement and care, preemptive transplantation)
7. Psychosocial support and provision of conservative care and palliative care options where required
The goal of therapy – to slow down or halt the otherwise relentless progression of CKD to stage 5

- Treatment of original disease
- **Renoprotection** (normalization of BP, elimination of proteinuria, anemia, azotemia, hyperparathyroidism, normalization of acid-alkaline balance)
- **Renal replacement therapy** (transplantation, hemodialysis, peritoneal dialysis)
DIET THERAPY

- Protein restriction (0.5-0.8 g/d)
- Adequate intake of calories (30-35 kcal/kg/d)
- Fluid intake = urine volume + perspiration loss (500 ml)
- Low phosphate diet (600-1000 mg/d)
- Supplement of EAA (ketosteril)
Ketoacids:

- STIMULATE SYNTHESIS OF PROTEIN
- SUPPORT NITROGEN BALANCE
- INHIBIT CATABOLISM
- DECREASE PROTEINURIA

0,1 g/kg/ day

( ≈ 1 tab/ 5-6 kg / day) + low protein diet (≤0,6 g / kg / day)
### Conservative therapy of CRF (renoprotection)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>ACE inhibitors (ACEIs), angiotensin II receptors blockers (ARBs), diltiasem</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>(ACEi), (ARBs), diltiasem</td>
</tr>
<tr>
<td>Renal anemia</td>
<td>Erythropoetin, Iron, vit B12, folic acid</td>
</tr>
<tr>
<td>Renal hyperparathyroidism</td>
<td>Ca, phosphate binders, vit D</td>
</tr>
<tr>
<td>Disorders of acid-alkaline balance</td>
<td>Sodium bicarbonate, citric mixture</td>
</tr>
<tr>
<td>Azotemia</td>
<td>Diet, enterosorbtion, enteropassage, aminoacids (ketoacids), dialysis</td>
</tr>
</tbody>
</table>
Renal replacement therapy
When kidney function has deteriorated and is no longer adequate to sustain life and the process is considered irreversible, renal replacement therapy (RRT)—dialysis or transplantation—becomes necessary to maintain life.
Renal replacement therapy

- Appropriate preparation for RRT includes reduction in cardiovascular disease risk factors, treatment of anemia, optimum therapy to preserve residual renal function, consultation about nutrition, and patient education about RRT methods. Patients should be seen by a specialist in RRT at least 12 months prior to initiation of RRT for general counseling.
Renal replacement therapy

Renal transplantation is an important lifesaving renal replacement therapy and has been shown to offer many advantages when compared with dialysis.
Renal replacement therapy

**POST KIDNEY TRANSPLANT REJECTION SIGNS**

**Acute**
1 week to 2 years post OP
oliguria, anuria
↑ temp (> 37.8°C)
↑ BP
flank tenderness
lethargy
sp. gravity
fluid retention

**Chronic**
gradual over months to years
gradual in bun, ↑ creatinine
imbalance in electrolytes
fatigue

Hi, I'm Sydney, your new kidney!
Indications for hemodialysis

- Decrease in GFR < 10-15 ml/min or increase in serum creatinine > 0.44 mmol/l
- Hyperkalemia > 6.5-7.0 mmol/l
- Life-threatening complications (pulmonary edema, hypertension with symptoms of congestive heart failure, edema of brain, decompensated metabolic acidosis)
KIDNEY HEALTH IS IN YOUR HANDS