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1-я КАФЕДРА ДЕТСКИХ БОЛЕЗНЕЙ

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Острая и хроническая почечная недостаточность (острое повреждение почки и хроническая болезнь почек) у детей

Acute and chronic renal failure (acute kidney injury and chronic kidney disease) in children

Учебно-методическое пособие

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Освещены вопросы этиологии, патогенеза, классификации, клинических проявлений острой и хронической почечной недостаточности у детей. Приведены современные рекомендации по диагностике и лечению острой и хронической почечной недостаточности у детей.

Предназначено для студентов 4-го и 6-го курсов медицинского факультета иностранных учащихся, изучающих педиатрию на английском языке.

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ABBREVIATIONS

ACE – angiotensin converting enzyme

AKI — acute kidney injury

ANA – anti-nuclear antibodies

ARF — acute renal failure

ARB – angiotensin II receptor blockers

BP – blood pressure

BUN – blood urea nitrogen

CBC – complete blood count

eGFR – estimated glomerular filtration rate

GFR – glomerular filtration rate

HUS — hemolytic uremic syndrome

TMA – thrombotic microangiopathy

TTP –thrombotic thrombocytopenic purpura

RAAS – renin-angiotensin aldosterone system

RDA – recommended daily allowance

RRT – renal replacement therapy

ACUTE RENAL FAILURE

Acute renal failure (ARF) is a sudden or rapidly progressing, potentially reversible clinical-laboratory syndrome, related to the acute loss of kidney function. Usually, but not always, ARF is accompanied by oliguria.

Oliguria is diagnosed, when diuresis is less than 0,5 ml/kg per hour (in infants under 1 year of age less than 1 ml/kg per hour).

Anuria is the diuresis less than 0,3 ml/kg per hour (in infants under 1 year of age less than 0,5 ml/kg per hour).

Polyuria is the diuresis over than 2,5 ml/kg per hour.

Oliguria is not equivalent to ARF, because ARF is addressed to the impared ability of kidneys to maintain homeostasis, whereas oliguria is the reduced urine output.

There are two criteria needed to be present to diagnose ARF:

- presence of oliguria/anuria;
- more than 50% of creatinine level rise from baseline or, in case the baseline is not known, from recommended upper limit for age.

The term ARF has recently been replaced by the term acute kidney injury (AKI). This is argumented by several reasons, first of which was the necessity to unify the criteria of the acute kidney injury/disfunction severity determination and stratification. As the time passed the new data has become available, which stated that even mild reversible increase in creatinine serum level is associated with significant rise of mortality. The diagnosis AKI is not included in International Disease Classification X (IDC-X), it is however recommended to specify it in casts just after the term ARF.

The term AKI enables to more efficiently cover patients at risk kidney injury, in particular in case of 25% from baseline estimated glomerular filtration rate (eGFR) deterioration and diuresis less than 0,5 ml/kg per hour during 8 hours and longer.

On an average ARF is varied from 3 to 8 cases per 1 million children aged 0-18 years, among them one third of cases is diagnosed in infants under 3 years old.

CAUSES OF ARF

There are 3 groups of ARF causes:

- prerenal,

- renal,
- postrenal.

Prerenal causes are of the greatest significance in childhood, being observed in 80% of all neonatal and early childhood cases of ARF.

Early stages of prerenal ARF are characterized by glomerular filtration rate (GFR) deterioration without pathomorphological features of glomerular lesion and tubular function preserved.

Prerenal causes of ARF include:

1. Systemic hemodynamics impairment;
   - hypovolemia (hemorrhage, severe burns, diarrhea and vomiting);
   - decreased effective circulating volume (circulatory failure);
2. Renal ischemia:
   - intrarenal blood redistribution (arterio-venouse intrarenal fistula);
   - decreased renal blood flow (renal artery or vein thrombosis);
3. Decreased cardiac output without (heart failure, cardiac tamponade);
4. Combination of any above;

Renal causes include:

1. Ischemia caused by renal injury (prolonged renal ischemia).
2. Renal parenchymal disease:

− Immune glomerulopathies: acute poststreptococcal glomerulonephritis, rapidly progressive glomerulonephritis, secondary glomerulopathies, ie systemic vasculitis (lupus nephritis, IgA glomerulonephritis in Schonlein-Henoch purpura, periarteriitis nodosa);

− Tubulointerstitial lesions (tubulointerstitial nephritis, acute pyelonephritis).

3. Toxic tubular lesions:

a) endogenouse, caused by:

− myoglobin (rhabdomyolis, severe trauma, crush-syndrome);

− hemoglobin (severe hemolyse, hemolytic-uremic syndrome (HUS), snake vapor, hemolytic transfusion reaction);

− uric acid (tumor-lysis syndrome);

б) exogenous, caused by:

− antibiotics;

− anaesthetics;

− heavy metals (lead, mercury);

− ethylene glycol, contrast media, alcohol surrogate.

4. Combined: Reie syndrome.

Postrenal causes of ARF are*:*

1. Urethral (valves, stricturae);

2. Bladder trauma, neoplasm;

3. Ureteral - stenosis, obstruction (by blood clot, stone):

− internal;

− external.

In children postrenal causes constitute nearly 10% of all ARF cases, with congenital abnormalities of urethra and ureter being the prevalent among them.

HEMOLYTIC UREMIC SYNDROME

HUS is one of the major causes of ARF in infants, therefore we will discuss it more deeply.

Associated with HUS mortality rate varies from 5% to 15%, in the Republic of Belarus ≈ 1–1,5 %.

HUS is a disorder characterized by acute renal failure, microangiopathic hemolytic anemia and thrombocytopenia. Typical HUS accounts for a majority of cases (60-80%). It develops secondary to gastrointestinal infection caused by verotoxin-producing strains of E.coli 0157:H7, Shigella dysenteriae, Salmonella typhi, Yersinia enterocolitica, Campilobacter jejuni et al. In typical HUS clinical

manifestations develop following a prodrome of bloody diarrhea, it therefore is referred to as D+ HUS or STEC-HUS. Usually it has a good prognosis.

Atypical HUS (aHUS) develops without preceding diarrhea. It can be sporadic (postinfectiuos - neuraminidase producing bacteria: Str. pneumoniae, Aeromonas hydrophila, Clostridium; Coxsackievirus, Influenza type A2, ECHO, adenoviruses; medicines (estrogen containing oral contraceptives, cyclosporin A); or vaccination associated (DTP, MMR, polio) and familial. Mutations in complement proteins are found in about half of patients with aHUS. These mutations lead to over activation of complement and cause complement-mediated thrombotic microangiopathy (TMA). aHUS is a chronic disease with recurrent course and high risk of multiple organs damage (permanent kidney damage, stroke, heart attack).

Thrombotic thrombocytopenic purpura (TTP, Moskowitz disease) shares many clinical signs with aHUS and formerly was considered to be a variant of aHUS. Today it is found to be a separate disease due to evidence of different pathogenetic mechanisms involved. TTP found to be a clotting disorder, associated with lack of protease that is responsible for breakdown of von Willebrand factor (VWF) multimers (this protease is designated as ADAMTS13 - A Disintegrinlike And Metalloprotease with ThromboSpondin type 1 motif 13). Low activity of ADAMTS13 is found to be caused by inhibiting autoantibodies in sporadic cases or mutations.

CLASSIFICATION

According to the cause:

1)prerenal;

2)renal;

3)postrenal.

According to the urine output:

1)without oliguria (non-oliguric ARF);

2)with oliguria/anuria (oliguric/anuric ARF).

There are 4 stages in ARF course:

1) initial;
2) oligoanuric;
3) diuresis restoration and polyuria;
4) outcome.

AKI classification is presented in the table 1

Table 1

RIFLE AKI classification in children (A. Akcan-Arikan, M. Zappitelli, L. Loftis et al., 2007)

Class	GFR	Diuresis
Risk	eGFR decrease by 25 %	< 0,5 ml/kg/hour 8 hours and longer
Injury	eGFR decrease by 50 %	< 0,5 ml/kg/hour 16 hours and longer
Failure	eGFR decrease by 75 % or eGFR < 35 ml/min/1,73 m^2	< 0,3 ml/kg/hour 24 hours and longer or anuria > 12 hours
Loss	ARF persisting more than 4 weeks	
End Stage Renal Disease	ARF persisting more than 3 months	

AKI staging (KDIGO, 2012)

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline OR ≥ 26.5 µmol/l increase	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5 ml/kg/h for Ss 12 hours
3	3.0 times baseline	<0.3 ml/kg/h for >24 hours
	OR Increase in serum creatinine to ≥4.0mg/dl (≥353.6 µmol/l)	OR Anuria for >12 hours
	OR Initiation of renal replacement therapy OR decrease in eGFR to <35ml/min per 1.73 m2	

Estimated GFR (eGFR) is the GFR that is estimated using Schwartz equation:

$$\text{eGFR (ml/min/1,73 m}^2) = \frac{40 \text{ x } Height\ (sm)}{Serum\ creatinine\ (mcmol/l)}$$

PATHOGENESIS

Pathogenesis of ARF is uniform in all causes and includes following:

- renal vasoconstriction, which causes tissue ischaemia;
- decrease in glomerular capillaries permeability, which causes GFR reduction;
- tubular obstruction by desquamated epithelium;
- transepithelial filtrate backflow into peritubular space.

One of the most important points in AKI pathogenesis is given to hemodynamic factors, mediated by *tubuloglomerular feedback mechanism*. Under physiological conditions this mechanism functions to decrease blood flow and GFR in order to prevent tubular damage in case of their excessive volume overload. In AKI damage to proximal epithelium causes decrease in sodium and water reabsorption in proximal tubules. Juxtaglomerular apparatus reacts on increased sodium and water amount in distal tubules (which under normal conditions would mean water overload) and secrets vasoactive peptides, first of all renin, into blood flow. Activation of renin-angiotensin-aldosterone system causes and maintains the afferent arteriole constriction and therefore redistribution of renal blood flow, which consequently causes arteriole blood flow limitation and GFR decrease. These changes normally result in sodium and water excretion. But in case of AKI activation of *tubuloglomerular feedback mechanism* decreases renal blood flow and therefore exacerbates tubular ischaemic damage.

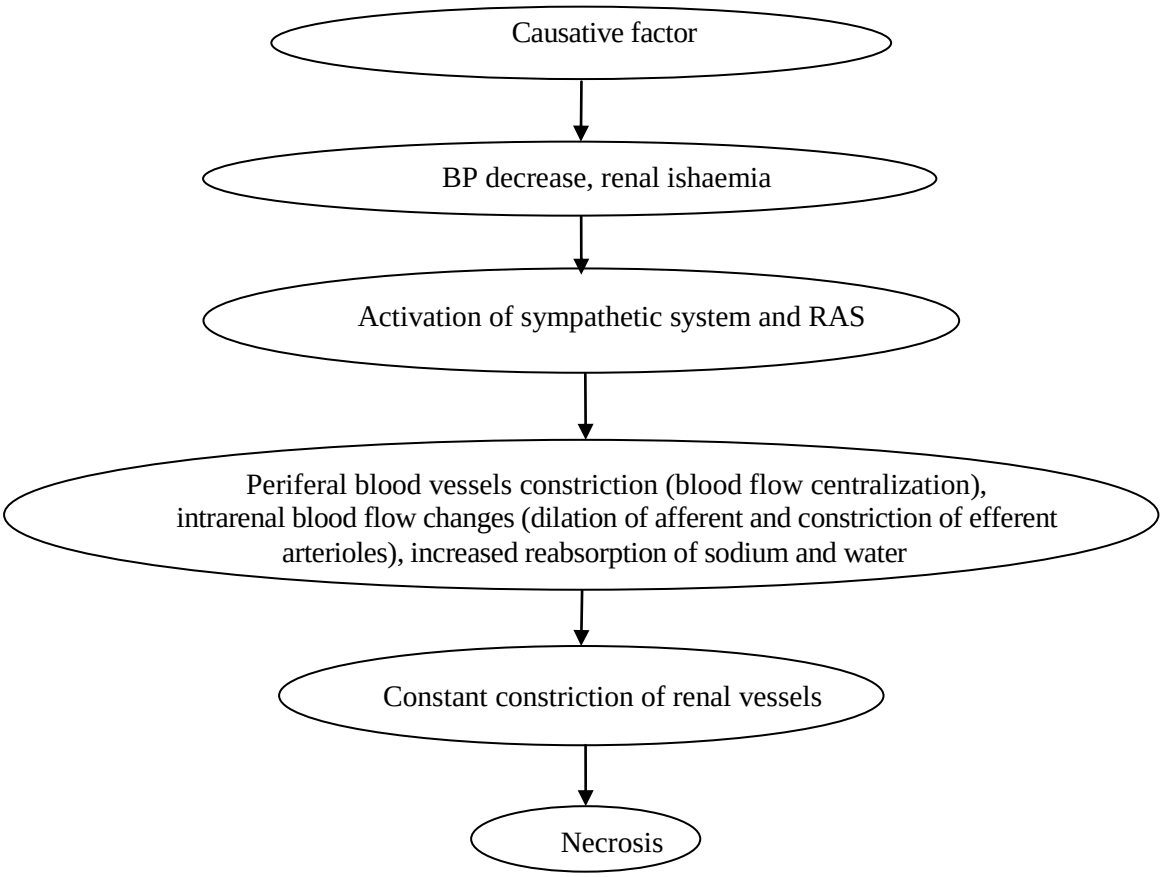
When oligoanuria develops, hemodynamic factor stops playing a key role, because tubular damage has already happened. At this stage attempts to enhance renal blood flow fail to result in GFR increase.

As a consequence of impaired tubular reabsorption water excretion increases. This is why after restoration of glomerular filtration polyuria develops.

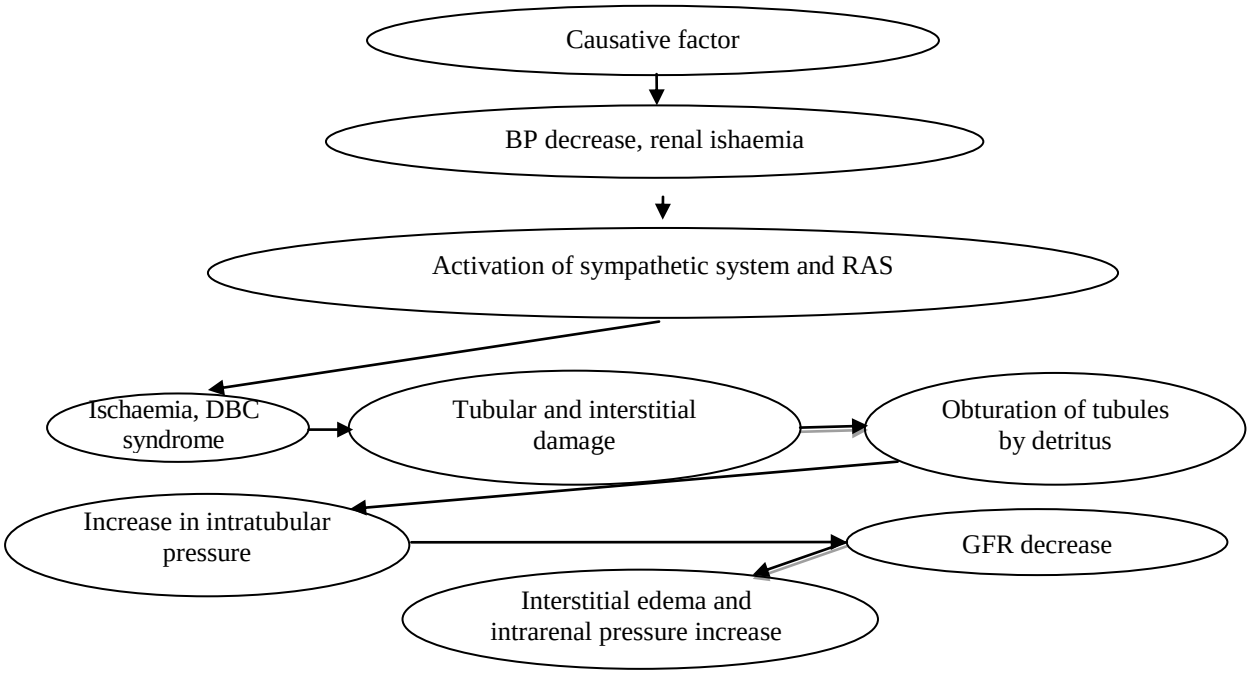
At the outcome stage renal hemodynamics is considered to play the major role. Increase in renal blood flow consequently causes GFR increase and leads to higher diuresis.

Pathogenesis of ARF according to the cause (prerenal, renal and postrenal) is

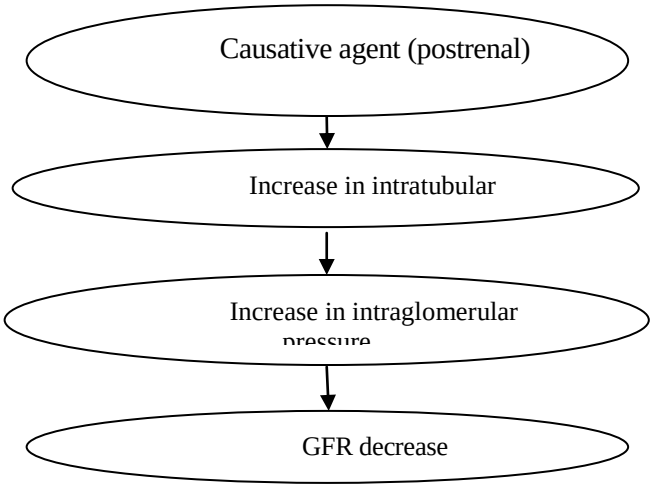
schematically shown at the pictures 1,2 and 3.



Pic.1. Pathogenesis of prerenal ARF



Pic.2. Pathogenesis of renal ARF



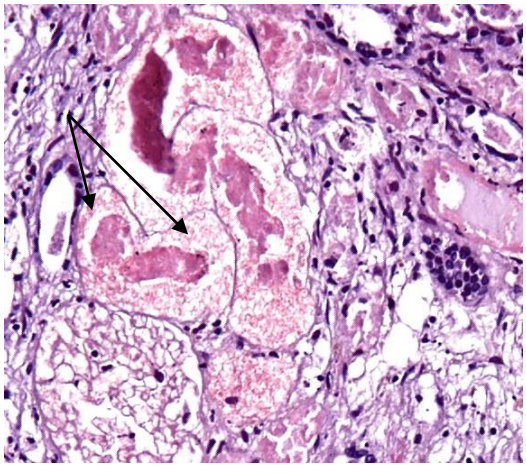
Pic.3. Pathogenesis of postrenal ARF

PATHOLOGY

Tubules and interstitium are mostly affected. Glomeruli are intact or minimally affected (except ARF developed in patients with glomerulonephrites). Tubular damage is characterized by:

− tubular necrosis (necrosis of tubular epithelium with undamaged tubular basement membrane), ie toxic nephropathies (pic. 4);

− tubulorrhexis (destuction of tubular basement membrane in addition to necrosis of tubular epithelium), ie «schok kidney» (pic. 5).



Pic. 4. Necrosis of tubular epithelium with undamaged tubular basement membrane (HE, x40)

Pic. 5. Tubulorrhexis (HE, x40)

Tubular epithelium distrophy and dilation of tubules are caused by reduction in water reabsorption, increase in intratubular pressure and therefore disruption or disfunction of tubules. Tubulonecrosis (necrosis of tubules) develops within first 48 hours of causative agent action. Epithelial cells of proximal tubules are most sensitive to ischaemia.

Cortical necrosis is the most severe and often irreversible condition, because necrosis is seen also in glomeruli (glomerular capillaries and mesangium) and Bowmen capsule.

CLINICAL PRESENTATION

ARF is the cyclic condition, which classically undergoes 4 consequent stages:

- initial (manifestation);
- oligoanuric;
- diuresis restoration and polyuria;
- outcome.

Symptoms of ARF include:

1) absolutely or relatively decreased diuresis, less often - polyuria (typical symptom of the stage III);
2) decreased specific gravity of the urine;
3) various changes in urinalyses, which depend on the cause of the ARF (proteinuria, hematuria, hemoglobinuria, leucocyturia, cylindruria);
4) changes of blood biochemical tests:
   - rise in serum creatinine level (which happens more rapidly than rise in urea level), (N up to 88 mcmol/l);
   - elevated blood urea level (N up to 8.35 mmol/l);

- increased level of blood potassium (N 3,7 - 5,2 mmol/l), which is observed approximately in 60 % of patients (note, that acidosis enhances hyperkalemia and alkalosis reduces it);
- increased concentration of Mg (N 0,78 - 0,99 mmol/l) and P (N 0,65 - 1,62 mmol/l);
- decrease in blood concentration of Ca (N 2,0- 2,8 mmol/l), Cl (N 96 - 107 mmol/l), Na (N 135 - 145 mmol/l);

5) Acid-base balance changes: metabolic acidosis and respiratory alkalosis;

6) Complete blood count (CBC): changes depend on underlying cause and may include anemia, trombocytopenia, low hematocrit, high neutrophils with left shift, low lymphocytes, low monocytes and eosinophils;

7) Coagulation changes:

- hypercoagulation;
- increased fibrinogen level;
- rise in fibrinogen-degradation products (FDP test);
- diminished fibrinolysis.

There are such novel markers used to diagnose early stages of ARF available as:

- increased level of Cystatin C can be observed as early as 6-8 hours upon initiation of ARF. Rise in blood concentration of Cystatin C is the marker of glomerular injury, and rise in urine concentration of Cystatin C is the marker of tubular injury. Cystatin C is the marker of functional, not the structural lesion;
- NGAL («renal troponin» or lipocalin-2) level rises in 2 hours after initiation of ARF and is considered to be the biomarker of structural damage. Increased concentrations of NGAL are observed in blood and urine as well;

- NAG (N-acetyl-β-D-glucosaminidase) is the brush border enzyme of proximal tubules epithelial cells, which is also very early marker of ARF.

Both NGAL and NAG appear to be the most sensitive markers of AKI.

At *the initial stage* of ARF clinical presentation include first of all symptoms of the underlying disease. The initial stage duration may vary from hours to days, which depends on the etiology and manifests with reduced (or sometimes increased) diuresis and general symptoms. Vomiting, abdominal pain, stupor, progressive decrease of diuresis and decline of specific gravity of the urine are commonly seen at the initial stage of ARF. This stage is potentially reversible after restoration of renal blood flow and resolution of interstitial edema. That is why early diagnosis and intervention are of great importance in managing patients with ARF.

At t*he oligoanuric stage* all the typical symptoms of ARF are seen. Duration of this stage may vary from days to weeks depending on cause and adequacy of treatment performed, especially at the initial stage. As the disease progresses typical uremic symptoms are observed:

- most patients experience nausea, vomiting and diarrhea;
- neuromuscular irritability and spasms, convulsions, drowsiness, stupor or coma;
- arterial hypertension, muffled heart sounds, systolic murmur;
- peripheral or generalized edema.

Major laboratory changes at the oligoanuric stage include elevation of blood urea nitrogen (BUN) and serum creatinine levels, hyperkalemia and metabolic acidosis.

At this stage following complications may be observed:

- cardiac arrest caused by hyperkalemia;
- severe volume overload and pulmonary/cerebral edema;

- uremic encephalopathy, which can progress to coma.

Recovery (polyuric) stage is characterized in, that glomerular filtration gradually restores with consequent rise in urine production, while tubular reabsorption remains impaired. Patient's condition remains severe, muscle hypotonia, weakness are often seen. This stage can also be divided in two periods: early (rise in diuresis, but elevation of BUN and serum creatinine is still observed) and late (normalization of nitrogen homeostasis occurs). Low specific gravity of urine is characteristic of the polyuric stage, also proteinuria, leucocyturia, hematuria (according to the cause of ARF) may be seen. BUN and serum creatinine levels remain elevated, later start to gradually decrease. Dehydration and hypokalemia due to high tubular losses of electrolytes and water are common at the polyuric stage.

Duration of the polyuric stage varies between 1 to 3 months. Most common complications include:

- dehydration;
- loss of electrolytes;
- infections.

Lethal outcome at this stage can be caused by severe disturbances of water-electrolytes homeostasis and infections.

The outcome stage is diagnosed upon normalization of BUN and serum creatinine levels. At this stage gradual restoration of kidney functions happens, which can take up to 3 years. At the same time chronic renal disease can gradually develop.

DIAGNOSIS

ARF work up should include:

- Careful patients' medical history (look for diarrhea, vomiting, hypoxia, medicines, possible toxins exposure);

- Physical examination (drowsiness, fever, skin discoloration, rash, arterial hypertension/hypotension, fluid balance - dehydration or volume overload, urine output estimated hourly);
- Laboratory tests:
  - ✓ CBC and erythrocyte sedimentation rate (ESR);
  - ✓ Urinalysis;
  - ✓ Blood chemistry tests (total protein, urea, creatinine, electrolytes, bilirubin, transaminases, lactate dehydrogenase, amylase, lipase, C- reactive protein (CRP);
  - ✓ Coagulation tests;
  - ✓ Acid-base balance;
  - ✓ eGFR;
  - ✓ NGAL, NAG, Cystatine C;
  - ✓ Blood culture;
- Imaging:
  - ✓ Urinary tract ultrasound (in majority of cases of ARF kidneys appear to be enlarged and echo bright)
    - to exclude obstruction,
    - look for signs of CRF – small or cystic kidneys. In majority of cases of ARF kidneys are enlarged and echo bright;
  - ✓ Doppler ultrasound – to assess if there any abnormality of renal blood flow present.

Approach considerations

In case of HUS following tests should additionally be administered:

- Stool culture;
- Verotoxin producing E.coli detection tests (O157:H7);

- Haptoglobin test;
- Complement test (if atypical D- HUS is considered).

If acute nephritis is considered, additionally should be investigated:

- Strep test;
- Throat (or wound) swab culture and sensitivity;
- Antistreptolysin O test;
- Complement C3 and C4, IgA, IgM, IgG; ANA.

If etiology remains unclear kidney biopsy should be considered.

TREATMENT

General guidlines:

1) Treat the cause;
2) Proper diet according to usage und the type of the renal replacement therapy (RRT);
3) Restore effective circulating volume and effective renal blood flow;
4) Manage anemia, electrolyte disturbances, acidosis, uremia;
5) Stimulation of diuresis (with caution);
6) Prophylaxis and treatment of infectious complications (consider dose adjustment of antimicrobials and antifungals based on guidelines according to the eGFR and use of the RRT);
7) Control BP (hypotensive therapy);
8) Symptomatic treatment:
   - Antipyretics if febrile;
   - Anticonvulsants;
   - Digestive enzymes supplementation if needed;
9) Physical therapy and rehabilitation.

At the oligoanuric stage management of ARF should ultimately be started with accurate assessment of patients' fluid volume status. Treatment should be intended to keep a patient in a euvolemic status (table 2).

Table 2

Fluid volume status assessment and correction

Volume status	Clinical signs	Management
Dehydration	Tachycardia, cold limbs, central-peripheral temperature gradient above 2 °C, capillary refill time (CRT) > 3 seconds, low BP, dry skin and mucous membranes, sunken eyes, altered skin turgor	Replace fluid: i/v infusion of 10-20 ml/kg of isotonic solution within 30 minutes, than assess diuresis and repeat infusion if needed
Euvolemia	—	I/v infusion of 10-20 ml/kg of isotonic solution within an hour, than i/v furosemide 2–4 mg/kg
Volume overload	Tachycardia, gallop rhythm of the heart, high BP and central venous pressure, hepatomegaly	I/v furosemide 2–4 mg/kg, RRT if no effect observed

Restoration of the effective circulating volume is the main goal of conservative treatment at early stages of ARF:

1) blood products transfusion to treat hemorrhage;
2) 20% albumin for nephrotic syndrome;
3) hypertonic sodium chloride if the salt-wasting condition is observed;
4) any crystalloid solution can be used (normal saline, dextrose, Ringer's lactate).

Patient's weight should be measured twice daily and urine output should be controlled hourly. Volume correction depends on fluid volume status of a patient and urine output:

Fluid volume = insensible losses 400ml/m²/24 hours (or 30 ml/kg/24 hours)
+ 100% urine replacement (if euvolemic)
or restrict to 50-75% (if overloaded)

+ current losses replacement (hemorrhage, diarrhea, vomiting, tachypnoe).

Diuretics are administered if no intravascular fluid volume deficit is observed. Furosemide and mannitol are most often used. Furosemide is administered i/v in a single dose 2-4mg/kg 3 to 6 times per 24 hour or i/v infusion 5-10 mg/kg within 30-60 minutes. Following after administration of furosemide rise in urine production doesn't mean restoration of kidney function or predict better outcome, but is still very important to manage fluid overload and hyperkalemia.

If no effect is observed upon administration of 10 mg/kg following use of furosemide is contraindicated. Initiation of RRT should thus be considered.

Mannitol can be only administered in presence of diuresis in patient. Infusion of 20% solution is administered as a single dose 0,2–0,5 g/kg within 30–60 minutes. In case the positive effect is seen (rise of urine output) mannitol can be administered at a dose 0,5-1,0 g/kg per 24 hours as continuous 24 hours infusion. Efficacy is best observed when administered before or at the time of initiation of renal ischaemia.

Management algorithm in case ARF is suspected:

1) Urine output per hour should be accurately monitored;
2) Fluid administration as a 10-20 ml/kg infusion of isotonic solution within 2 hours according to the fluid volume status of a patient;
3) Furosemide at a single dose 2-4 mg/kg i/v;
4) than:
    a. if diuresis reaches 1 ml/kg/hour, prerenal ARF is most likely;
    b. no response:
        - ✓ continue rehydration therapy 5-15 ml/kg/hour with accurate monitoring of urine output per hour and volume status of a patient;
        - ✓ if oliguria still present repeat furosemide at the same single dose twice - in 2 and 4 hours after the first injection;

- ✓ if peripheral edema or central venous pressure above 8 cm H_2O are observed infusion should be terminated;

c. if upon 6 hours of rehydration therapy and three injections of furosemide restoration of diuresis is not observed, renal ARF is most likely and the patient should be transferred to the center, providing RRT.

Euphyllinum administration at a dose 0,4–0,8 mg/kg/hour or 10-20 mg/kg/24 hours can also be beneficial due to improvement of renal peripheral blood flow.

Hyperkalemia correction is necessary when serum level of potassium is above 5,5 mmol/l. Low potassium diet is prescribed (foods that are high in potassium include most fresh fruits and vegetables, such as bananas, oranges and orange juice, spinach and greens (collard, kale), potatoes). Potassium-containing solutions and medicines should be avoided. Table 3 illustrates an emergency management of hyperkalemia.

Table 3

Emergency treatment of hyperkalemia

Medicine	Dosage
Salbutamol (aerosolum 0,1 mg per single dose)	every 20 minutes within an hour
Calcium gluconate (10% solution)	0,5–1 ml/kg i/v slowly within 10 minutes t.i.d. or q.i.d.
Sodium hydrocarbonate (8,4% solution (1 ml contains 1 mmol $NaHCO_3$))	single dose 2–3 mmol/kg (dilute in 10% dextrose) iv within 10–30 minutes
Glucose (10% solution) with insulin	Glucose 0,5–1 g/kg/hour + insulin 1 ED per 4 g of pure glucose
Cation exchange resin	0,5–2 g/kg/day orally or rectally (with 30–50 ml 10% glucose solution)
Lactulose	Age adjusted dose

Moderate decrease of blood *sodium* level in patients with oliguria or anuria usually appears to be secondary to administration of hypotonic solutions. If the level

of Na is lower than 118 mmol/l *hyponatremia* becomes symptomatic. Clinical presentations include vomiting, seizures and encephalopathy and are caused by cerebral edema and hemorrhages. Management of hyponatremia requires water restriction and RRT. In polyuric patients hyponatremia may be caused by excessive urinary loss of electrolytes, which can be assessed by electrolytes measurement in urine. In this case correction with glucose solutions and 3% sodium chloride solution is performed:

$$Na\ (mmol) = (125 - Na_{patient}) \times weight\ (kg) \times 0{,}6$$

RRT should be started if patient has a serum sodium level is higher than 160 mmol/l or lower than 125 mmol/l.

Correction of *metabolic acidosis* should be performed gradually if the bicarbonate level is lower than 18 mmol/l because of significant risk of adverse effects (acid pH of cerebrospinal fluid when treated rapidly with sodium bicarbonate infusions; faster rate of tissue lactate production).

8,4% solution of sodium hydrocarbonate is prescribed orally or intravenously. The dose depends on the level of HCO_3 and is defined using following formulation:

$$NaHCO_3\ (mmol) = (18 - HCO_{3\ patient}) \times weight\ (kg) \times 0{,}5$$

If using intravenous infusion the defined amount of the 8,4% sodium hydrocarbonate solution is diluted in 0,9% solution of sodium chloride or 5% glucose and is infused slowly (over a period not less than 1 hour). Correction (especially if performed rapidly) of acidosis may be accompanied by decrease in Ca2+ concentration, thus its level should be closely monitored.

Severe metabolic acidosis with the level of HCO_3 lower than 10 mmol/l is considered to be an indication for RRT because of the risk of complications if large amounts of sodium hydrocarbonate are required.

Hypertension in ARF is usually a consequence of increased amount of extracellular volume. Treatment is started with limiting liquids and sodium intake.

Diuretics and hypotensive drugs are concomitantly used: furosemide is administered intravenously 1-5 mg/kg per day; sodium nitroprusside is administered as slow intravenous infusion at a low initial rate 0,3-0,5 mcg/kg/min with upward titration up to 8 mcg/kg/min until the desired effect is achieved. Single dose of sublingual nifedipine (0,05–0,5 mg/kg) can also be used.

As normal food intake is usually limited in patients with ARF, enteral (tube feeding) or parenteral nutrition should be prescribed to prevent undernutrition. In a majority of cases hypertonic glucose solutions (10% to 20%) with insulin are administered intravenously at an initial rate 0,2-0,25 g/kg/hour. Amino acids are also used (0,15 g/kg/hour). If administering amino acids supplementation sufficient calories intake should be maintained (to utilize 1 g of nitrogen 200-300 kcal are required).

RRT is used to correct electrolyte disturbances, fluid overload, acid-base balance disturbances, to lower urea and creatinine concentrations. There are two modalities available to provide acute dialysis - peritoneal dialysis and hemodialysis. The choice is made according to age of the patient, complications observed, hemodynamics stability and condition of the patient.

To initiate acute hemodialysis the central venous catheter is placed and heparinization is needed, which can produce adverse effects in case hypocoagulation is observed. Peritoneal dialysis doesn't cause serious changes of hemodynamics, thus enabling its use in infants and hemodynamically unstable patients. Indications for emergent dialysis in ARF are shown in Table 4.

At the polyuric stage free access to water and salt is prescribed to prevent dehydration and excessive loss of electrolytes. Additional potassium supplementation is administered. Body weight, daily fluid intake and diuresis, serum level and urinary excretion of electrolytes should be monitored to provide proper correction. Diet slowly returns to normal, calories intake rises. Protein intake can be slowly increased to the level 1,5-2 g/kg within several weeks, under the close control of serum urea level.

Table 4

Indications for emergent dialysis in ARF

Clinical signs of uremia	Value
Anuria	> 24 hours
Oliguria	> 36–48 hours
Serum level of urea	> 30 mmol/l
Serum level of creatinine	> 350 mcmol/l
Hypercatabolic ARF with increase of urea level	> 10 mmol/l per 24 hours
Following conditions in case of ineffectiveness of conservative interventions	
Severe fluid overload (pulmonary/cerebral edema, hypertension, pericarditis), neurological manifestations of uremia or electrolyte disturbances	—
Hyperkalemia	> 6 mmol/l
Hyponatremia	< 125 mmol/l
Hypernatremia	> 160 mmol/l
Metabolic acidosis with pH	< 7,2
Metabolic acidosis with HCO_3 level	< 10 mmol/l
Hypocalcemia with seizures and high serum level of phosphates	—

PROGNOSIS

Renal survival prognosis depends on the cause of ARF and the age of a patient. Complete recovery of renal functions can be observed if prerenal ARF was diagnosed and treated properly. Among causes of renal ARF most favorable prognosis are considered to have tubulointerstitial nephritis and ischemia caused renal damage. Postrenal ARF may have favorable course if the cause is treated timely (urological intervention is needed in majority of cases).

Chronic renal failure develops in 10 to 20% of patients within 3 to 5 years after renal ARF. Regular follow-ups with accessing of kidney function (laboratory tests and instrumental investigations) are therefore required.

CHRONIC RENAL FAILURE AND CHRONIC KIDNEY DISEASE

Chronic renal failure is defined as a permanent and irreversible reduction of glomerular filtration rate below the normal range (90-120 ml/min/1,73m2).

The term chronic kidney disease (CKD), being referred to more wide range of conditions, replaces formerly used term chronic kidney failure. Whatever the underlying etiology, once the loss of nephrons and reduction of functional renal mass reaches a certain point, the remaining nephrons begin a process of irreversible sclerosis that leads to a progressive decline in the GFR.

In the early stages, there may be few signs or symptoms and CKD may not be apparent. When CKD reaches an advanced stage, which means that significant percentage of nephrons is lost, dangerous levels of fluid, electrolytes and wastes can build up in a body. Adverse outcomes of chronic kidney disease can often be prevented or delayed through early detection with routine laboratory measurements. and treatment. Early stages of chronic kidney disease can be detected through routine laboratory measurements.

The guidelines define CKD as either kidney damage or a decreased eGFR as per Schwartz equation (p.8) of less than 60 mL/min/1.73 m2 for at least 3 months, irrespective of the underlying etiology (diagnosis).

Individuals are classified as having CKD if one following criteria is present for at least 3 months:

- any pathologic abnormalities or markers of kidney damage in blood or urine tests, irrespective of the level of eGFR;
- any markers of kidney damage, proven by imaging studies or biopsy;

- decreased eGFR of less than 60 mL/min/1.73 m2, with or without other signs of kidney damage.

eGFR is the main criteria to grade CKD. Grading of CKD according to eGFR level is shown in Table 5.

Table 5

Grading of CRF

Grade	GFR (ml/min/1.73 $m^{2)}$	Features
1	>90 - kidney damage with normal or increased GFR	renal parenchymal disease present
2	90-60 - kidney damage with mild decrease of GFR	usually no symptoms but blood biochemistry abnormalities
3	60-30 - moderate decrease of GFR	biochemistry abnormalities, poor growth, appetite
4	30-15 - severe decrease of GFR	more severe symptoms
5	<15 - kidney failure	requires RRT

As shown in the Table 5, any chronic disease with renal parenchymal lesion and preserved or slightly reduced eGFR can be referred to as CKD grade 1 or 2 (chronic glomerulonephritis, obstructive uropathy, early asymptomatic stages of diabetic nephropathy). The rationale for including individuals with eGFR $\geq$ 60 mL/min/1.73 m^2 is that eGFR may be normal or even increased (due to hyperfiltration in preserved glomeruli) despite substantial kidney damage and that patients with kidney damage are at increased risk of the two major outcomes of CKD: loss of kidney function and development of cardiovascular disease. At these stages specific treatment of the underlying cause can prevent or slow down further loss of nephrons and progression to CRF (which is referred to Grades 3-4 of CKD). Once CKD progresses to Grades 3-4, further progression to end-stage renal disease (ESRD) is considered to be unavoidable. At these stages treatment is prescribed to manage complications of CRF - anemia, osteodystrophy et al.

ETIOLOGY

Distribution of kidney diseases leading to ESRD in children:

- 40% - CAKUT – congenital anomalies of kidneys and urinary tract, structural malformations
- 25% - glomerulonephritis
- 20% - hereditary GP
- 10% - systemic diseases
- 5% - miscellaneous / unknown.

The definitive diagnosis of the underlying cause requires biopsy or imaging studies, which can be associated with risk of complications. Therefore, these procedures are often avoided in patients with grades 3 or higher of CKD unless a definitive diagnosis would change either the treatment or prognosis.

Guidelines recommend to assess and manage *risk factors* of progression of CKD. Some of them can be modified (obesity, hypertension, proteinuria), others can not (genetic predisposition, race, age, gender).

Obesity is often associated with hypertension, albuminuria and dyslipidemia. Any of these factors can potentially influence on progression of CKD. Obesity leads to glomerular hyperperfusion and hyperfiltration, hypertension enhances hyperperfusion and hyperfiltration in unaffected nephrons. Proteinuria leads to direct injury to podocytes and tubular epithelial cells.

Low birth weight or prematurity are associated with congenital reduction in nephron number and predisposition to arterial hypertension and CKD in future.

Puberty is a critical period for individuals with CKD. Rapid decrease of kidney function is often observed in adolescents with CKD (activity of sex hormones, disbalance between number of functioning nephrons and rapidly increased height and body weight during growth spurt).

Individuals that have factors of risk and progression of CKD and GFR over 90 ml/min/m2 without markers of kidney damage are classified by guidelines as additional group - "at increased risk" of CKD. Such actions as screening and CKD risk reduction are recommended. Factors of initiation and progression of CKD are shown in Table 6.

Table 6

Factors of initiation and progression of CKD

Factors, that can initiate CKD	Factors, that lead to progression of CKD
Persisting activity of underlying cause (autoimmune diseases, diabetes, urinary tract infection, obstructive uropathy etc)	Proteinuria (microalbuminuria)
	Hyperglycemia
	Arterial hypertension
	Dyslipoproteinemia
Arterial hypertension	Hyperhomocysteinemia
Drugs toxicity	Anemia
	Acidosis
Obesity	Abnormalities of calcium and phosphorus homeostasis
	Smoking

PATOPHYSIOLOGY

With the progression of CKD complications of reduced kidney function develop.

In the course of CKD following common complications develop:

- anemia;
- hyperparathyroidism and bone disease;
- acidosis;
- AH;
- growth retardation and puberty delay.

Anemia

Anemia in patients with CKD result from the loss of erythropoietin synthesis in the kidneys. Other causes include: functional or absolute iron deficiency, blood loss (either occult or overt), the presence of uremic inhibitors (eg, parathyroid hormone (PTH), spermine, etc), reduced half life of circulating blood cells, deficiencies of folate or Vitamin B_{12} etc. Anemia causes anorexia, weakness, cardiovascular disease and therefore worsens prognosis in individuals with CKD.

CKD – mineral and bone disorder(CKD-MBD)

Bone disease is the common complication of CKD. It results from disorders of calcium-phosphorus metabolism and secondary hyperparathyroidism with high bone turnover or osteomalacia and dynamic bone disease (with normal or low PTH level).

During progression of CKD kidneys lose their ability to excrete phosphorus, which leads to elevation of the serum level of phosphorus. Thus production of active metabolite of vitamin D (calcitriol) results from either reduced kidney mass or direct suppression by elevated serum phosphorus. Lower than normal levels of calcitriol lead to reduced absorption of calcium in GI tract and hypocalcemia. Hypocalcemia, reduced calcitriol synthesis, and elevated serum phosphorus levels stimulate the production of PTH, stimulation of osteoblasts and result in high bone turnover with decreased cortical bone and increased risk of fracture.

Acidosis

Metabolic acidosis is a common complication of CKD, which develops with decrease of kidney mass usually in individuals with eGFR less than 30-40 ml/min/1,73m2. It results from inability of kidneys to excrete acids that are produced through ammoniagenesis. If tubular lesion is severe, there can also be loss of bicarbonates in urine observed. Patients with tubular-interstitial disease as underlying cause of CKD usually have more severe acidosis, which can be observed even if eGFR is over 30 ml/min/1,73m2.

Acidosis itself is associated with numerous sequelae – mineral bone disease, altered protein metabolism, skeletal muscle protein breakdown and decreased synthesis of albumin, nutritional problems resulting from nausea and loss of appetite, chronic inflammation, impaired cardiac function and may contribute to progressive decline of eGFR.

Arterial hypertension

Arterial hypertension can be both a cause and a complication of CKD. Major factors that cause AH in CKD are salt and water retention due to impaired ability to excrete sodium and increased vascular resistance due to activation of the renin-angiotensin system (RAS) (resulting from scars formation or compression of vessels by cysts), activation of sympathetic nervous system, imbalance of vasoactive substances (vasoconstrictor and vasodilator prostaglandins, reduced synthesis of nitric oxide, increased endothelin production).

If not controlled AH is a factor for CKD progression and cardiovascular disease. On its turn, CKD is an independent risk factor for cardiovascular morbidity and mortality. Increased intraglomerular pressure causes glomerular hyperfiltration and contributes to proteinuria and further damage to nephron and therefore to progressive decline in renal function.

Growth retardation

Malnutrition and growth retardation can both result from and lead to other consequences of CKD, such as metabolic acidosis, anemia and osteodystrophy. Wasting and stunting are associated with greater risk of morbidity and mortality.

Children with CKD are at significant risk of protein-energy malnutrition. Nutrition is a major factor driving growth in infants, whereas growth and sex hormones in addition to nutrition influence on growth in childhood and adolescence. Spontaneous calorie, water and electrolytes intake is often inadequate in children with CKD, especially in infants, which has a great impact on their growth and

development. The earlier the age at which kidney failure occurs, the more likely growth will be affected. Growth and developmental deficits that arise from infancy not always can be fully corrected in future.

CLINICAL PRESENTATION

Signs and symptoms of CKD develop over time if kidney damage progresses slowly. May include:

- Nausea, vomiting;
- Loss of appetite;
- Fatigue and weakness, sleep problems;
- Changes in diuresis (oliguria/anuria or polyuria);
- Arterial hypertension;
- Cognitive impairment;
- Muscle twitches and cramps;
- Swelling of feet and ankles;
- Persistent itching;
- Chest pain, shortness of breath, if fluid builds up in the lungs.

Signs and symptoms of kidney disease are often nonspecific, meaning they can also be caused by other illnesses. Kidneys are highly adaptable and able to compensate for lost function, signs and symptoms may not appear until irreversible damage has occurred. For example, patients often don’t complain of headaches even if severe hypertension is present.

TREATMENT OF CKD

The major goal of treatment of CKD – patients should look, feel and behave like their healthy peers. Conservative treatment is to delay progression of CKD and to postpone RRT as long as possible.

When managing this group of patients the main principle “do not harm” should be applied:

- spare the vascular bed;
- avoid (nephro)toxic drugs;
- surgery can wait;
- improve growth before RRT;
- dialysis can wait.

For every individual with CKD an individual plan of care should be provided by multidisciplinary team based on the CKD grade, course and complications, nutritional status and growth, comorbidities and previous treatment. This plan should include measures to identify progression of CKD and complications, general lifestyle recommendations, nutrition and medical therapy.

Lifestyle modification

Management of pediatric CKD patients aims for them to live a life as normal as possible. Children with CKD usually have reduced physical activity and social functioning compared with peers. These may lead to obesity, depression and poor quality of life, and is associated with higher risk of cardiovascular morbidity and mortality.

CKD individuals are to be incouraged to undertake physical activity (according to their health and tolerance), optimally for at least 30 minutes 5 times per week, preferably leisure sports, no competitions are allowed.

Education is an important part of the childrens' development. Pediatric CKD patients should receive all necessary classes. Education should be adapted to be well tolerated and children to feel as involved in social and school life and communication with peers as possible.

Nutrition

Guidlines recommend to monitor closely patients growth and development, frequently reevaluate and modificate the nutrition plan of care for chidren with CKD stages 2 to 5.

Alterations to fluid or dietary intake of protein, carbohydrate and/or fat, phosphorus, sodium, potassium, or calcium may be required. Vitamin, mineral, or trace element supplements also may be needed.

Energy intake should be 100-120% of RDA for chronological age, with following adjustment according to response (ie, weght gain or loss). If no response – early intervention with supplemental nutritional support (preferably oral intake of energy-dense diet and commercial supplements) should be initiated. When energy requirements cannot be met with oral supplementation, tube feeding should be considered.

No limitation of protein is required in individuals with eGFR higher than 25 ml/min/m2. Children with CKD do not significantly benefit from low-protein diet. Moreover, such diet can produce negative effect on the growth rate of the patient. With the progression of CKD and decrease of GFR lower than 25 ml/min/m2 protein restriction is needed, because it reduces metabolic acidosis due to reduction in daily acid load, reduces hyperparathyroidism due to lowering of phosphorus intake, counteracts polyuria because of the reduction in osmotic load.

Diet should be balanced and contain healthy fat and carbohydrates.

Sodium intake restriction is recommended for children with CKD, especially those who have hypertension. Sodium intake should not exceed the age based RDI.

Restriction of potassium, phosphorus or water intake is recommended based on complications observed (for patients who have CKD-MBD, hyperkalemia or oliguria and volume overload, accordingly). If water restriction is needed, energy-dense diet is prescribed to provide sufficient calorie intake.

Conversely patients with polyuria are at risk of dehydration and electrolyte disturbances. When managing this group of patients, free water access and salt supplementation (NaCl 1-3 mmol/kg per day) under close control of blood chemistry may be needed.

Medical treatment

When prescribing any medicine physician should take into account GFR of the patient. Potentially kidney toxic drugs should be avoided.

Patients with CKD G1-G2 may benefit from specific treatment of the causative disease. Additionally assessment and diminishment of risk factors are performed to postpone the progression of the disease. Early detection and management of comorbidities is also important. When prescribing any medicine physician should take into account GFR of the patient. Potentially kidney toxic drugs should be avoided.

Management of patients with CKD G3-G5 is based on monitoring of CKD progression and its complications. Early and correct treatment of the complications and comorbidities plays the pivotal role in the care of the CKD patients.

Hypertension

BP-lowering agents are recommended in children with CKD and blood pressure (BP) consistently above 90th percentile for age, height and sex. Treatment regimens are to be tailored taking into consideration daily rhythms of BP (as per ambulatory blood pressure monitoring (ABPM)). Target BP is BP consistently lower than 50th percentile for age, height and sex. Five main classes of hypotensive agents are used. They are:

- - angiotensin-converting enzyme inhibitors (ACE inhibitors);
- - angiotensin II receptor blockers (ARB);
- - calcium channel blockers;
- - beta-blockers;
- - diuretics.

Interruption of the RAAS is one of the major goals when treating hypertension, therefore ACE inhibitors and ARB are considered to be the first-line hypotensive agents irrespective of the level of proteinuria. When considering administration of

ACE inhibitors eGFR should be taken into account. In patients with eGFR lower than 25 ml/min/m^2 their use is contraindicated.

It is preferred that hypotensive agents (if BP not properly controlled) to be titrated upward up to max daily dose according to BP. Only after that additional drug should be prescribed. Drugs that can be administered as single daily dose should be preferred.

Table 7 shows the most commonly used antihypertensive drugs.

Table 7

Medical treatment of hypertension

Group	Drug	Dosage
ACE inhibitors	Enalapril	Initial 0,08 mg/kg/day PO or divided q12hr; may be increased q2weeks according to BP; not to exceed 0,58 mg/kg/day or 40 mg/day
	Captoprile	Infants: Initial 0,15-0,3 mg/kg/dose q6-24hr Children: Initial 0,3-0,5 mg/kg/dose; q6-12 hr Titrate upward to maximum 6 mg/kg/day
ARB	Losartan	Children ≥6 years Initial 0,7 mg/kg/day (not to exceed 50 mg/day), increase according to BP up to 1,4 mg/kg/day (or 100 mg/day)
CCB	Amlodipine	0,06-0,2 mg/kg/day
	Nifedipine	0,25-0,5 mg/kg/day
β-blockers	Metoprolole	1-2 mg/kg/day
	Atenolole	1 mg/kg/day
Diuretics	Furosemide	1-2 mg/kg qd or bid
	Hydrochlorthiazide	<6 months: 1-3 mg/kg/day PO q12hr (max 37,5 mg/day) 6-24 months: 1-2 mg/kg/day PO or divided q12hr (max 37,5 mg/day); ≥ 2 years: 1-3 mg/kg/day (max 100mg/day)
	Spironolactone	1-3,3 mg/kg/day PO or divided q12hr; not to exceed 100 mg/day

Anemia

Iron replacement therapy should be started as initial treatment of anemia in CKD patients. If no effect is seen treatment with erythropoietin is initiated 50 – 150

Units/kg IV/SC 3 times weekly initially. If the patient is on dialysis, IV route is preferred (at the end of dialysis session). If the level of hemoglobin approaches or exceeds 110 g/l, dose should be reduced or treatment interrupted.

CKD-MBD

Treatment of CKD-MBD is targeted on lowering of serum phosphorus if high and maintaining the level of calcium.

Dietary phosphate restriction is required in pediatric patients with hyperphosphatemia (plant-based phosphate is absorbed less than animal-based, avoid processed foods to avoid phosphorus-containing additives). It is suggested that dietary phosphorus intake be reduced to 80% of the AI or RDA.

Phosphate-lowering therapy with phosphate binders (calcium-free or calcium-containing) should be prescribed if persistent and progressive hyperphosphatemia is observed despite dietary phosphorus restriction. Aluminium-containing phosphate binders can only be recommended as the single course with duration up to one month.

Maintaining the target level of calcium in serum requires individualized approach, because of the adverse effects of both hypocalcemia and hypercalcemia. However adequate calcium intake is necessary for the development and growth during childhood. Recommended daily allowances (RDA) and age-specific ranges of blood level of calcium and phosphorus are shown in Table 8. As for calcium, intake up to 200% of RDA is considered to be relatively safe in children older than 1 year of life.

Vitamin D

If vitamin D deficiency (according to serum level of 25(OH)D) is observed, supplementation with vitamin D2 or D3 is required. If secondary hyperparathyroidism is found to be severe and progressive, substitution with active metabolites of vitamin D is prescribed:

- dihydrotachysterol (AT10) 15 – 45 μg/kg per day;

- alphacalcidol (One alpha Leo) 40 – 100 ng/kg;

- calcitriol (Rocaltrol) 20 – 60 ng/kg.

Treatment with vitamin D analogues should be started with low doses irrespective of the initial level of PTH. Then the dose is titrated upward gradually according to the response of PTH to avoid hypercalciuria.

Table 8

Age-specific normal ranges of blood levels and RDA of Calcium and Phosphorus

<table>
<tr><td rowspan="2">Age</td><td colspan="2">Calcium</td><td colspan="2">Phosphorus</td></tr>
<tr><td>Normal serum range, iCa, mmol/L</td><td>RDA, mg</td><td>Normal serum range, mmol/L</td><td>RDA, mg</td></tr>
<tr><td>0–6 months</td><td>1.22-1.4</td><td>210</td><td>1.68-2.71</td><td>100</td></tr>
<tr><td>7-12 months</td><td>1.20-1.4</td><td>270</td><td>1.62-2.52</td><td>275</td></tr>
<tr><td>1-3 years</td><td rowspan="2">1.22-1.32</td><td>500</td><td rowspan="2">1.45-2.10</td><td>460</td></tr>
<tr><td>4-5 years</td><td rowspan="2">800</td><td rowspan="2">500</td></tr>
<tr><td>6-8 years</td><td rowspan="2">1.15-1.32</td><td rowspan="2">1.16-1.87</td></tr>
<tr><td>9-12</td><td rowspan="2">1300</td><td rowspan="2">1250</td></tr>
<tr><td>>12 years</td><td>1.12-1.3</td><td>0.74-1.45</td></tr>
</table>

Poor growth

Management of growth failure includes first of all adequate nutrition and correction of metabolic disturbances. However, if growth retardation is observed despite the optimal nutritive support and good control of metabolic parameters and the patients' height is found to be less than 2 standard deviation (SD) for age below the mean for age and gender administration of recombinant human growth hormone in dosage 0,05 mg/kg/day or 30IU/m^2/week is needed. Patients' height should be

followed, treatment is considered to be ineffective and should be stopped if the growth rate increases for less than 2 cm per year compared to the previous year.

Metabolic acidosis

Oral bicarbonate supplementation is needed in CKD pediatric patients with serum bicarbonate concentrations <22 mmol/l. Initial dose of sodium bicarbonate is 1-3 mmol/kg/day PO divided q4-6hr. 1 g of baking soda contains 12 mmol of bicarbonate, 1 tsp – 44 mmol.

Other conditions

Additional treatment may be needed if other conditions and complications of CKD develop. These may include:

- treatment of neurological complications;
- correction of hyperuricemia;
- statins in case of hypercholesterolemia;
- fish oil or non-saturated fatty acids to correct hypertriglyceridemia;
- correction of mild hyperkalemia with cation exchange resin 0,5–2 g/kg/day PO or PR (administered with 30–50 ml 10% glucose solution) or lactulose in age-adjusted dose.

Vaccination

Pediatric CKD patients are to be provided with all recommended childhood vaccines with respect to their immune status (live viral vaccines are avoided in patients receiving immunosuppressive therapy).

The *influenza* vaccine should be given to all children with CKD annually. *Pneumococcal* vaccination is particularly important in children with nephrotic syndrome and those with CKD. Booster doses should be given every 5 years after initial dose.

All patients who are likely to require dialysis and before transplantation must be assessed for the level of Hepatitis B antibodies and if necessary given the *Hepatitis B* vaccination. Booster doses may be required, as the decline of antibodies titers may be observed in patients receiving RRT.

RRT

RRT is discussed and planned in all patients with progressive CKD and CKD less than 15 ml/min/m2. Appropriate education and counseling about different RRT modalities, transplant options, vascular access surgery are extremely important to improve patients' compliance and psychosocial development.

Three types of RRT are used: hemodialysis, peritoneal dialysis and transplantation, which can be from living donor or cadaver. The exact method is chosen according to the age, individual risks and health of the patient, ie causative disease, complications and comorbidities.

The absolute indications for initiation of RRT are:

- uremia associated neurologic consequences;
- hypertension that fails to respond to antihypertensive therapy;
- pulmonary edema unresponsive to diuretics;
- pericarditis;
- bleeding tendency;
- refractory nausea or vomiting.

Relative indications to initiate dialysis include less severe uremic symptoms, hyperkalemia, hyperphosphatemia, malnutrition, progressive severe CKD-MBD and growth failure.

Timing of living donor transplant

Transplantation is the major method of treatment of pediatric patients with CKD. Transplantation from living donor can be performed pre-emptively (when patient doesn't receive dialysis) or on dialysis. However, there is no strict guideline

available that provides indications for the timing of transplantation. Likelihood of improvement of patients' symptoms should be assessed and balanced with risks of transplant surgery and prolonged immunosuppression, required after transplantation.

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