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СЕРДЕЧНАЯ НЕДОСТАТОЧНОСТЬ У ДЕТЕЙ

HEART FAILURE IN CHILDREN

Учебно-методическое пособие

Минск БГМУ 2024

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А в т о р ы: А. В. Крылова-Олефиренко, И. А. Козыро, А. Г. Белькевич, А. М. Чичко

Р е ц е н з е н т ы: канд. мед. наук, доц., доц. 2-й каф. детских болезней Белорусского государственного медицинского университета А. Н. Башлакова; каф. педиатрии № 2 Витебского государственного ордена Дружбы народов медицинского университета

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Освещены вопросы этиологии, патогенеза, классификации и клинических проявлений сердечной недостаточности у детей. Приведены современные рекомендации по диагностике и лечению данного заболевания.

Предназначено для студентов 4-го и 6-го курсов медицинского факультета иностранных учащихся, обучающихся по специальности «Лечебное дело» на английском языке.

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ABBREVIATIONS

ACEIs — angiotensin converting enzyme inhibitors
ARBs — angiotensin receptor blockers
ARNI — angiotensin receptor and neprilysin inhibitor
BP — blood pressure
BR — breath rate
CHD — congenital heart disease
CO — cardiac output
DCMP — dilated cardiomyopathy
EDP — end-diastolic pressure
EDV — end-diastolic volume
EF — ejection fraction
FC — functional classes
HF — heart failure
HFmrEF — heart failure with mildly reduced ejection fraction
HFpEF — preserved ejection fraction heart failure
HFrEF — heart failure with reduced ejection fraction
HR — heart rate
LA — left atrium
LV — left ventricule
LVHF — left ventricular heart failure
PH — pulmonary hypertension
RAAS — renin-angiotensin-aldosterone system
RVHF — right ventricular heart failure
SCD — sudden cardiac death
SV — stroke volume

INTRODUCTION

Heart failure (HF) is referred to the condition, when the heart fails to ensure proper supply of organs and tissues with blood in order to meet metabolic demands.

HF develops when the cardiac output is insufficient to meet metabolic demands of the organism or when the heart cannot successfully manage the venous return. These lead to pulmonary congestion and plethora (in case of left ventricular (LV) HF (LVHF)), peripheral edema (in case of right ventricular HF (RVHF)), or both in case of total HF.

According to **ICD-10** HF is classified in section I — cardiovascular diseases:

I50.0 — congestive HF
I50.1 — LVHF
I50.9 — HF non-specified

New **ICD-11** classification encodes Heart Failure in the class 11 — Diseases of the circulatory system, 12 subclass which includes 8 clarifying diagnoses:

BD10 — Congestive heart failure
BD11 — Left ventricular failure (it contains 4 clarifying diagnoses)
BD12 — High output syndromes
BD13 — Right ventricular failure
BD14 — Biventricular failure
KB40 — Neonatal cardiac failure (it contains 4 clarifying diagnoses)
BD1Y — Other specified heart failure
BD1Z — Heart failure, unspecified

EPIDEMIOLOGY

Clinically manifested chronic HF in adult population is diagnosed in not less than in 1.5–2 %, in Russian Federation — near 7 %. Among children the data vary a lot and in general prevalence is estimated to be 0.87–3.0 cases per 100 000 children less than 18 years. According to British heart association 34 % of children with acute HF due to the myocardial disease need transplantation or die within one year from manifestation.

According to the cause prevalence of HF may vary a lot as well: it is 8–14 per 1000 children with congenital heart disease (CHD), diagnosed at the first year life, 10–20 per 1000 children with cardiac arrhythmias (AV-block, chronic tachycardia, etc), 0.65–4.0 per 100 000 children with cardiomyopathies.

ETIOLOGY

Causes of HF are divided in two major groups: cardiac and non-cardiac.

1. Cardiac:

• infants: nearly 80 % of cases of HF are due to CHD. More rarely cardiac arrhythmias and myocarditis;

• 1 to 3 years of life: CHD, infectious myocarditis, cardiac arrhythmias or problems with conduction system;

• preschoolers and school-aged children: CHD, infectious or toxic myocarditis (i.e. anthracycline toxicity), cardiomyopathies, cardiac arrhythmias or problems with conduction system;

• adolescents: myocarditis (infectious, toxic, immune-mediated in systemic connective tissue or autoimmune diseases), pericarditis, congenital or acquired heart defects, cardiac arrhythmias or problems with conduction system, infective endocarditis, cardiomyopathies.

2. Non-cardiac (to fulfil the HF criteria there should be evidence of cardiac dysfunction together with non-cardiac problem):

• sepsis, respiratory diseases, chronic severe anemia, hyperhydration caused by non-cardiac issues (kidney disease), thyrotoxicosis, genetic diseases (inborn errors of metabolism, neuro-muscular diseases).

PATHOGENESIS

HF is referred to the pathophysiological syndrome when due to the various cardiovascular diseases and/or imbalance of vasoconstrictive and vasodilating neuro-humoral systems the ability of heart to maintain proper cardiac output decreases which leads to discrepancy between hemodynamical needs and ability to maintain them.

According to the initial mechanism types of HF are:

– with **primary impairment of myocardial metabolism** (hypoxia, myocarditis, inborn errors of metabolism and storage diseases);

– with **volume or pressure overload** or their **combination (**congenital or acquired cardiac defects, hyperhydration, severe arterial hypertension);

– **combination** of two types given above (over time HF of any type becomes mixed).

According to the predominant type of dysfunction HF is classified as:

• **Systolic dysfunction** — heart failure with reduced ejection fraction (HFrEF) — significantly reduced ejection fraction (EF) of LV < 40 % or heart failure with mildly reduced ejection fraction (HFmrEF) — ejection fraction of LV 41–50 %.

• **Diastolic dysfunction** — heart failure with preserved EF (HFpEF), diagnosed in patients with symptoms of HF, evidence of structural or functional abnormalities and elevated natriuretic peptides, in case the EF is found to be within normal range or slightly reduced.

Along with reduction of contractility the compensatory mechanisms are activated to maintain adequate perfusion. They include:

1. Sympathetic system activation (which has positive inotropic and chronotropic action on myocardium). As cardiac output (CO) linearly depends on stroke volume (SV) and heart rate (HR) (CO = SV × HR) in tachycardia CO can be maintained nearly normal even if the contractility is reduced.

2. Renin-angiotensin-aldosterone system (RAAS) activation in response to reduction of renal perfusion which via vasoconstriction and higher peripheral vascular resistance helps to maintain systemic pressure within normal range.

3. Frank-Starling mechanism (strength of contraction of cardiomyocytes increases with the stretching (i.e., with the rise of end-diastolic volume) which leads to rise of SV and CO.

4. Hypertrophy of myocardium (allows to an increase the strength of contractions in pressure overload).

5. Sodium and water retention (which results from activation of RAAS) helps to maintain systemic pressure in case of reduced CO.

All the mechanisms listed above allow to tolerate myocardial dysfunction and are beneficial if short standing. However, if they persist for a long period of time

they become the factors which further damage the myocardium and account for the HF progression.

Thus, sympathetic system activation leads to rise in peripheral vascular resistance which in its' turn defines elevated afterload and results in hypertrophy of myocardium. Also higher intensity of catabolic processes and higher demand in oxygen might be seen in prolonged hyperactivation of sympathetic system. Diaphoresis, one more consequence of adrenergic stimulation, can cause dehydration in severe cases. Finally, due to constant stimulation the density of β-adrenoreceptors on cardiomyocytes might lower and the loss of positive inotropic effect of catecholamines can occur.

RAAS activation leads to vasoconstriction and activation of sympathetic nervous system, enhances peripheral noradrenergic activity, stimulates aldosterone and vasopressin synthesis, myocardial remodeling and hypertrophy, proliferation of smooth muscle cells within vessels' wall. Retention of water and sodium mediated by aldosterone increases blood volume and heart preload.

Diastolic HF results from rigidity of myocardium and decreased relaxation, valvular heart defects or pericarditis. Elevated end-diastolic pressure (EDP) is seen in this case but end-diastolic volume (EDV) remains normal and contractility of myocardium is not affected. In severe cases (cardiac tamponade, hypertrophic cardiomyopathy) CO decreases significantly.

***Respiratory changes in HF*.** In HF with LV systolic dysfunction or severe diastolic dysfunction elevated left ventricle EDP is noted. If HF develops acutely resistance of left atrium (LA) walls is rather high which leads to rise of EDP in LA. This pressure is transferred on pulmonary veins and might lead to the transudation of fluid into the interstitial space. The younger the child the higher the permeability of pulmonary vessels and interstitial edema is. Thus, interstitial and peribronchial edema occur both resulting in ventilation/perfusion (V/Q) mismatch and stimulation of respiratory drive (tachypnea). Pulmonary resistance is increased as well which contributes to restrictive changes (limited ability to expand) and bronchial obstruction develops due to peribronchial edema. Therefore, both phases of breathing are getting affected in HF.

Finally, the work of breathing rises significantly increasing the oxygen demand and at the same time the ventilatory cost of CO_2 eliminating.

Under normal conditions excess of fluid should be eliminated from lungs by increasing the lymphatic drainage but in HF compensatory mechanisms are overloaded and alveolar edema occurs. Thus, alveoli are becoming poorly ventilated which affects V/Q and PaO_2 decreases. Systemic hypoxemia stimulates respiratory drive and the vicious cycle of dyspnea, high demand in oxygen and V/Q mismatch is being initiated.

One of the important mechanisms for protection from pulmonary edema in pulmonary venous hypertension is Kitaevs' effect. Due to this effect reflectory spasm of pulmonary arteries occurs in pulmonary venous hypertension to prevent alveolar capillaries from excessive pressure. If this effect is being activated for

a prolonged period resistance of pulmonary arteria increases significantly resulting in right ventricle afterload rise and subsequent hypertrophy.

Summarizing all the above mentioned all the compensatory mechanisms activated in HF at the same time increase the work of heart and its oxygen demand. Resulting from combination of both underlying problems and adaptation mechanisms structural remodeling of myocardium occurs — hypertrophy, activation of collagen production, dystrophy, necrosis and apoptosis of cardiomyocytes. Dilation of heart chambers and decrease in contractility are observed then contributing to relative insufficiency of mitral and tricuspid valves. Congestion, ischemia and systemic inflammatory response due to immune imbalance cause dystrophic changes in target organs (liver, kidneys, brain etc.).

CLASSIFICATION

In school-aged children the classification of HF by Strazhesko–Vasilenko can be used (Table 1). It is based on structural changes in the heart and degree of physical activity limitations. Similar criteria are used in the American College of Cardiology/American Heart Association (ACC/AHA) classification and New-York Heart Association (NYHA).

Table 1

HF classification by Strazhesko–Vasilenko and NYHA

HF classification by Strazhesko–Vasilenko		**Functional classes of HF according to NYHA**	
I	Initial stage of cardiac disease. Hemodynamics is normal. Hidden HF	I	Physical activity is normal. Intensive physical activity is tolerated but dyspnea and/or fatigue may be observed
IIA	Clinically manifested stage of cardiac disease. Hemodynamical changes are moderate and predominantly affect one of the blood circuits	II	Mild limitation of physical activity: no symptoms at rest, daily physical activity is tolerated but causes fatigue, dyspnea and tachycardia
IIB	Severe cardiac disease. Moderate changes of hemodynamics in both blood circuits	III	Significant limitation of physical activity: mild symptoms at rest, even mild physical activity can cause worsening of general condition
III	End stage of heart disease. Pronounced changes of hemodynamics and severe irreversible changes of target organs (lungs, liver, kidneys, brain, vessels)	IV	Physical activity total intolerance; symptoms of HF are present at rest, minimal efforts cause significant worsening

In children of first years of life it is not always possible to assess their complaints. Classifications, which are based on objective signs and symptoms, are worked out — HF classification modified by N. A. Belokon; functional classes (FC) classification (NYHA) were modified by R. D. Ross (Table 2).

Table 2

Modified classifications of HF in children (by N. A. Belokon and R. D. Ross)

HF stages by N. A. Belokon	**Functional classes by R. D. Ross**

Stage	Left ventricular HF	Right ventricular HF	Class	
I	Symptoms are absent at rest and only appear following hard physical activity (tachycardia, dyspnea)		I	No symptoms, physical activity is not limited
IIA	Heart rate (HR) is elevated by 15–30 %, breath rate (BR) is elevated by 30–50 % from normal for age	Liver is enlarged, palpated 2–3 sm below costal margin	II	Mild tachypnea or diaphoresis while feeding in babies. Dyspnea while physical activity in older children
IIB	HR is elevated by 30–50 %, BR by 50–70 % above normal. Acrocyanosis +/–, obsessive cough, crackles on lung auscultation	Liver is enlarged, palpated 3–5 sm below costal margin, pastosity, neck veins bulging	III	Significant tachypnea or diaphoresis while feeding in babies which causes prolonged feeding and leads to malnutrition. Severe dyspnea while physical activity in older children
III	HR is elevated by 50–60 %, BR is elevated by 70–100 %. Clinical signs of pulmonary congestion	Hepatomegaly, peripheral edema, generalized edema (hydropericardium, ascites)	IV	At rest tachypnea, diaphoresis and grunting are observed

CLINICAL MANIFESTATIONS

I stage: exertional dyspnea and tachycardia. In babies — irritability or sleepiness, transient perioral cyanosis while breastfeeding.

Investigations reveal decreased cardiac output on functional tests (signs of decreased compensatory capacities of myocardium). According to presence of clinical manifestations *stage I* is now used to be divided into two subgroups: pre-clinical (IA) and clinical (IB).

IIA stage: tachypnea and tachycardia at rest, marked fatigue and mild to moderate decrease of blood pressure (BP). In predominantly right ventricular HF pastosity or transient peripheral edema can be observed, mild to moderate hepatomegaly. In left ventricular HF tachypnea and tachycardia, transient wet crackles at lung bases, periodical coughing are observed.

IIB stage: marked tachycardia and dyspnea at rest, perioral cyanosis, pallor or marble skin, decreased BP (both systolic and diastolic), cardiomegaly, muffled heart tones, liver and kidney function impairment.

At *stage IIB* HF usually involves both systemic and pulmonary circuits even though initially was either left ventricular or right ventricular. Venous congestion signs are observed in:

1) systemic circuit — jugular vein distention, cyanosis, hepatomegaly, stable peripheral edema, ascitis, hydrothorax, decreased diuresis;

2) pulmonary circuit — obsessive cough, dyspnea, intercostal retractions, diffuse wet crackles over lung fields, signs of pulmonary edema.

IIIA stage (end-stage) severe congestion in both pulmonary and systemic circuits (marked signes of pulmonary edema, abrupt progression of hepatomegaly

and generalized edema), cyanosis, abrupt decrease of BP, significant cardiomegaly, encephalopathy and signs of dystrophy in target organs (liver, kidney, brain etc.).

IIIB stage — irreversible dystrophy of organs and systems.

Factors which precipitate congestion signs and symptoms in children with compensated HF:

I. Conditions which lead to activation of metabolic processes and increase the demand to cardiac output:

– fever;
– infections;
– anemia;
– tachycardia;
– hyperthyroidism;
– increased circulating blood volume (rise in pre-load);
– excessive intake of salt and fluid;
– renal insufficience.

II. Conditions which lead to increased afterload:

– poor management of arterial hypertension;
– pulmonary embolism (right ventricular overload).

III. Conditions, which lead to decreased contractivity of myocardium:

– medicines with negative inotropic effect (high doses of beta-adrenoblockers);
– ischemia or myocardial infarction.

IV. Severe bradycardia.

DIAGNOSTICS

Two major goals:

1. To diagnose HF and its stage.
2. To determine the cause of HF.

HF diagnosis is based on:

1. *History* (cardiac diseases, sudden death among relatives, presence of risk factors, preciding illnesses, pregnancy course and growth parameters during the first years of life — often failure to thrive, sudden rise in body weight may be due to progression of edema) and *complaints* (difficulty breathing, skipped, irregular or fast heart beats, physical exercise intolerance, paroxismal nocturnal dyspnea or cough, fatigue, decreased appetite, in infants and babies — difficulties with feeding, prolonged feeding).

2. *Physical examination* — skin (cyanosis, marble skin, pallor in syndrome of low cardiac output, capillary refill time greater than 3 sec.); edema (ankles, scrotum, coccyx), arrythmias, tachycardia, arterial hyper/hypotension, tachypnea, diffuse apex beat, cardiac borders shift, muffled heart tones, pathological S3 (gallop rhythm), hepatomegaly, hepatojugular reflux (jugular veins bulging when pressure over the right upper quadrant of the abdomen is applied), decreased diuresis.

3. *Laboratory data:*

• CBC;

• Urine test;

• Blood biochemistry (urea, creatinine, electrolytes, glucose, bilirubin, ALT, AST, LDH and myocardial fraction (HBDH), creatinkinase and myocardial fraction, troponin, iron, ferritin, transferrin, lipids);

• Hormonal studies (thyroid gland function);

• Coagulation tests, INR, D-dimers — hypercoagulation is possible, especially in polycythemia;

• Acid-base studies and blood gases (metabolic lactate acidosis as the result of tissue hypoxia);

• Natriuretic peptides:

– NT-proBNP < 125 pg/ml — HF is unlikely;

– NT-proBNP 200–400 pg/ml — HF stage I;

– NT-proBNP 400–1000 pg/ml — HF stage IIA;

– NT-proBNP >1000 pg/ml — HF stage II B–III.

• If acute myocarditis is suspected — additionally test for viral DNA, RNA, serology tests; complement components C3, C4; IgA, IgM, IgG; antinuclear antibodies.

4. *Instrumental studies:*

• ECG (arrhythmias, blockades, LV hypertrophy, wide and deformed QRS, ST segment depression and T wave changes — ischemic changes in myocardium);

• Echocardiogram (EF, End-diastolic pressure and volume, pulmonary artery pressure, structural abnormalities, hypokinesis);

• Chest X-ray (cardiomegaly, pulmonary congestion);

• Functional tests (6-minute walk — distance is assessed when walking in comfortable regimen) — additional method used in school aged children:

– FC I: from 426 m to 550 m,

– FC II: from 300 m to 425 m,

– FC III: from 150 m to 300 m,

– FC IV: < 150 m.

• MRI (structural and functional characteristics of myocardium to diagnose storage diseases (Fabry, hemochromatoses, glycogen storage diseases), non-compact myocardium, cardiomyopathies). Additional method of EF assessment if Echocardiogram is not informative (poor acoustic window); MRI with contrast (gadolinium) — detects fibrose changes in myocardium;

• Coronary angiography if coronary arteries anomalies suspected;

• Cardiac catheterisation;

• PET CT scan, cardiac scintigraphy with 99m Tc-labelled diphosphonates.

MANAGEMENT

Major goals of treatment are:

• To relieve symptoms;

• To protect target organs (brain, kidneys, vessels, liver);

• To improve quality of life;
• To reduce the number of hospital admissions;
• To improve the prognosis and to reduce the rate of progression.

Diet. Reduced amounts of salt, sugars, caffeinated drinks, fried, smoked foods or those rich in saturated fats are recommended depending on stage. Patients should be encouraged to have more food rich in potassium (dried fruits, bananas), polyunsaturated fats, and overall more homemade than processed food in their diet.

At advanced stages dietary salt intake should be limited up to 1–1.5 g/day for 5 to 7 days to stabilize the patient. These strict limitations should not be prolonged because of risk of electrolyte imbalance. In children of the first years of life there is no need to limit salt in diet as specialised milk formulas allow to control it's intake.

Daily need in calories is higher in HF patients compared to their healthy pears. Children of the first year of life should get **150 kcal/kg/day**. If breast feeding is possible bottle breast feeding is preferred to prevent tiredness, prolonged feeding and failure to thrive. Number of feedings should be increased and the volume of each feeding decreased. Nutritional status and growth should be regularly monitored. If malnutrition is observed breast milk fortifiers or energy dense formulas with partial or complete hydrolysis of protein can be used. If failure to thrive persists, it is possible to use partial (at night) or full tube feeding.

In children over one year old, the daily calorie requirement is **125–130 kcal/kg/day**, decreasing at school age to **80–100 kcal/kg/day**. If there are signs of malnutrition or decreased appetite, partial (up to $^1/_2$ daily calorie requirement) or full enteral nutrition with isocaloric or hypercaloric (when fluid restrictions are needed) formulas is recommended.

Water balance. Fluid restriction depends on the degree of heart failure, the severity of edema and decreased diuresis. As a rule, with HF stage I fluid intake restrictions are not required. Starting from stage IIA, diuresis, water balance (the difference between the volume of fluid intake and excretion), body weight changes are assessed. If there are signs of fluid retention, it is necessary to limit its intake to amounts no more than the volume of urine excreted the day before. Daily morning weighing allows to identify hidden swelling in the early stages and timely correct therapy.

Physical activity appropriate to the severity of heart failure is encouraged in all patients. Light exercise is recommended (for example, walking at a calm pace), as well as exercise therapy. In case of decompensation of heart failure, any exercise is contraindicated; physical rest is necessary. As the condition improves in the hospital, physical rehabilitation is prescribed which may include individually selected exercises, subject to regular monitoring of the ECG and the patient's condition.

Etiotropic treatment. In the presence of a correctable cause of HF (CHD, coronary vessels anomalies, myocarditis, etc.) etiotropic treatment is possible and is subject to a particular etiology.

Conservative therapy is prescribed long-term (often lifelong) and based on following principles:

• reducing the requirements for cardiac output (by limiting physical activity, providing thermal comfort, reducing peripheral vascular resistance);

• prevention of myocardial dystrophy and remodeling (by decreasing afterload and preload (regulation of blood volume);

– maintaining of adequate cardiac output (by use of inotropic agents);

– correction of homeostasis disorders and prevention/treatment of complications (correction of electrolyte balance and acid-base balance, prevention and treatment of hypercoagulation and thromboembolism).

The major groups of medications used in the treatment of heart failure include:

1) drugs that improve the patient's condition (diuretics, cardiac glycosides);

2) means to reduce the frequency of hospitalizations and improve survival:

– angiotensin-converting enzyme inhibitors (ACEIs);

– angiotensin II receptor blockers (ARBs) (if intolerant to ACEIs);

– angiotensin receptor-neprilysin inhibitor (ARNI);

– aldosterone receptor antagonists;

– beta blockers.

TREATMENTS TO REDUCE HOSPITALIZATIONS AND IMPROVE SURVIVAL

All patients, in the absence of contraindications (renal artery stenosis, angioedema, hyperkalemia, glomerular filtration rate less than 30 ml/min/1.73 m^2), should be prescribed an **ACEIs** at an initial dose of 20–25 % of the target (*enalapril* 0.05–0.08 mg/kg) followed by a gradual increase to the maximum tolerated over 4–8 weeks while monitoring blood potassium levels and renal function. ACEIs reduce the synthesis of angiotensin II and the breakdown of bradykinin, mediators that affect the sympathetic nervous system, endothelial function, vascular tone and myocardial functioning. Hemodynamic effects include dilation of arteries and veins, a sustained decrease in LV filling pressure during rest and exercise, a decrease in systemic vascular resistance and a direct beneficial effect on ventricular remodeling.

If side effects occur (obsessive dry cough, angioedema), it is possible to use an **ARBs** (*losartan* for children 6–16 years old weighing 20–50 kg, 25 mg per day once orally, maximum dose 50 mg per day once). In some cases, when using ACEIs in the maximal dosages the improvement is not achieved, it is possible to use a combination of ACEIs with ARBs but in this case the risk of side effects (ex. hyperkalemia) increases.

A new group of drugs is **ARNI**, a combination drug containing an *angiotensin II receptor blocker and a neprilysin inhibitor* (sacubitril). Neprilysin is an enzyme involved in the breakdown of natriuretic peptides. By inhibiting the activity of neprilysin, ARNI increase natriuretic peptides concentration. Effects include decreased blood pressure, decreased afterload and increased natriuresis. ARNI can be prescribed to children aged 1 year and older, yet in the Republic of Belarus using of ARNI in children is limited.

Beta blockers can be used in addition to ACEIs in all patients with stable mild, moderate, severe congestive HF, with reduced ejection fraction. In case of

tachycardia, negative chronotropic and inotropic effects have a beneficial effect on the myocardium reducing the need for oxygen. However, when initiating treatment the manifestations of HF may worsen due to a decrease in CO. Therefore, the initial dose should be low and increased gradually over 8 weeks or more to the target or maximum tolerated while monitoring HR, BP and ejection fraction of LV, diuresis and body weight. Beta blocker therapy is not started in decompensated HF. The preferred drug is *carvedilol* (for children 0–14 years old, the initial dose is 0.03 mg/kg/day in 2 divided doses (maximum dose 0.2 mg/kg/day), for adolescents the initial dose is 1.5 mg/day in 2 divided doses (maximum dose 18.75 mg/day)).

Diuretics are an integral part of the complex treatment of children with HF stages IIB and III. They can be prescribed for stage IIA in the presence of edema.

Aldosterone receptor antagonists (*spironolactone, eplerenone*) are often used in patients with HF, especially those with moderate to severe symptoms, including those taking ACEIs or ARBs, since aldosterone can be synthesized independently of the RAAS. The greatest effect is observed in patients with severe right ventricular HF and congestive changes in the liver, since in this case the metabolism of aldosterone decreases and its concentration in the blood increases significantly. Serum potassium and creatinine levels should be regularly monitored because of the risk of hyperkalemia and renal dysfunction which increases when used concomitantly with ACEIs or ARBs. In patients with HF, when ACEIs are insufficiently effective, it is preferable to use them in a combination with aldosterone receptor antagonists rather than with ARBs. Spironolactone is prescribed to adolescents at an initial dose of 25 mg once a day, max dose is 50 mg per day once. Contraindications to use include serum potassium level > 5.0 mmol/l, creatinine > 220 μmol/l, simultaneous administration of ACEIs and ARBs.

In the presence of volume overload, loop **diuretics** should initially be used (most often *furosemide* 1–3 mg/kg per day) due to their rapid effect (10–15 minutes after intravenous administration of furosemide). *Thiazide diuretics* can be prescribed to children with HF IIA when patients have mild fluid retention and no signs of pulmonary congestion (*hydrochlorothiazide* starting at a dose of 1 mg/kg/day, max 2.5 mg/kg/day, maintenance dose 12.5 mg per day once for school-age children). Patients with low BP and a tendency to collapse should not be prescribed thiazide diuretics since they have the most powerful hypotensive effect. With long-term use of loop diuretics, especially when combined with thiazide diuretics, hypokalemia and alkalosis, hyponatremia and hypomagnesemia, hypovolemia with arterial hypotension can occur. Therefore, as the patient's condition improves the dose of diuretics should be reduced to a minimum up to complete withdrawal if other drugs allow to control the symptoms of HF.

INOTROPIC DRUGS

This group includes *glycoside and non-glycoside drugs*. Non-glycoside inotropic agents include adrenergic (adrenaline, norepinephrine, dopamine, dobutamine) and non-adrenergic (milrinone, enoxymone — phosphodiesterase inhibitors) agents. Despite the improvement in myocardial contractility, non-glycoside drugs, when

used long-term in the treatment of chronic HF, lead to an increase in mortality. Currently recommended for use only in case of acute decompensation to stabilize the condition of the patient, including as a bridge to heart transplantation.

Dobutamine, a β1-adrenergic agonist, increases SV and CO, reduces both systemic and pulmonary perifferal vascular resistance if given at medium and high doses (7.5–10 mcg/kg/min), increases HR and systemic BP, reduces the filling pressure of the ventricles, at low doses (2–4 mcg/kg/min) increases renal and coronary blood flow, improves oxygen supply to the myocardium. **Dopamine** at a dose of 5 to 10 mcg/kg/min is used in the case of decompensated refractory HF to increase cardiac output, stabilize systemic BP and increase diuresis. The effect occurs within 5 minutes from the start of the infusion with peak effect after 5–7 minutes. It has a tachycardic and arrhythmogenic effect. **Milrinone** is used at a loading dose of 25–50 mcg/kg/min, maintenance dose of 0.25–1 mcg/kg/min. Milrinone should be used with caution in patients with hypotension because of the risk of peripheral vasodilation.

Cardiac glycosides are used in patients with systolic HF when ACEIs and diuretics do not allow to control symptoms. Currently, low doses of digoxin are recommended for treatment of HF in children (weighing more than 55 kg up to 0.25 mg/day, weighing less than 55 kg up to 0.125 mg/day). At such a dose extracardiac neuromodulatory effect of glycosides is fully manifested but no proarrhythmic effect is present. In HF due to CHD the saturation dose is administered first (40–50 mcg/kg in infants, 30–40 mcg/kg in children greater than one year, administered over 2–3 days three times per day). In case of DCMP a maintenance dose of digoxin is given without saturation (infants — 10–12 mcg/kg/day; older than one year — 8–10 mcg/kg/day).

TREATMENT OF CARDIAC ARRHYTHMIAS

As most antiarrhythmic drugs decrease myocardial contractility the potential risks and benefits of their use should be considered before initiation of treatment. Antiarrhythmic therapy is prescribed to selected patients with arrhythmias that persist after correction of conditions that could contribute to their occurrence (electrolyte or metabolic disorders, hypoxia), subject to poor tolerance.

Class III antiarrhythmic drugs (amiodarone, sotalol) are preferred. **Amiodarone** (10 mg/kg/day for 10 days followed by 5 mg/kg/day 5 days a week), which is effective against both supraventricular and ventricular arrhythmias, does not affect myocardial contractility and has a mild peripheral vasodilator action. It is possible to use **sotalol** starting with minimal doses (initial dose 0.3 mg/kg/day 2 times a day to 2 mg/kg/day in 2–3 doses), given its pronounced beta-blocking properties.

TREATMENT AND PROPHYLAXIS OF THROMBOEMBOLISM

Routine administration of antiplatelet agents is not recommended for children with chronic HF. Indications for anticoagulants use in children with HF include:

– artificial mechanical heart valves;

– primary pulmonary hypertension (PH) or stage 4 secondary PH in heart disease;

– significant dilatation of the heart chambers, abrupt decrease in myocardial contractility;

– atrial fibrillation;

– history of thromboembolism with EF less than 25 % (shortening fraction less than 15 %);

– signs of blood clots in the cavities of the heart according to ECHO-CG;

– infective endocarditis.

Heparin is used at a dose of 100–150 units/kg/day subcutaneously every 12 hours, from 1.5 to 4 weeks, under the control of activated partial thromboplastin time (with an extension of 1.5 times compared to the original).

Warfarin is given at initial dose 0.1–0.2 mg/kg/day, followed by INR control on days 2–4 and dose adjustment to maintain the target INR value of 2.0–3.0. Before initiation of treatment conditions associated with a high risk of bleeding (coagulopathies, ulcerative lesions of the gastrointestinal tract, etc.) should be ruled out. When a maintenance dose is determined continuous use of **warfarin** with regular monitoring of INR every 10–14 days is recommended. Typically the maintenance dose is 0.09–0.33 mg/kg/day.

Low molecular weight heparins can also be used.

TREATMENT OF ANEMIA

When diagnosing HF and during subsequent follow-up, evaluation for anemia is recommended (hemoglobin, hematocrit, serum iron, ferritin, transferrin). If anemia is detected, iron supplements can be prescribed; if there is a significant deficiency, iron supplements are administered intravenously. If anemia persists after replenishing iron depot, erythropoietin medications are recommended.

Main groups of drugs for the treatment of chronic HF with reduced and normal ejection fraction in children showed in Table 3.

Table 3

Main groups of drugs for the treatment of CHF with reduced and normal ejection fraction in children

Drug family	HF with reduced EF	HF with preserved or mildly decreased EF
Diuretics	Recommended for all patients with stages IIB–III HF, in case of congestion	Can be used for normalization of volemic status (under the close monitoring of kidney function and BP). As antihypertensives

End of the Table 3

Drug family	HF with reduced EF	HF with preserved or mildly decreased EF
ACEIs	Indicated for all patients with grade IIa or higher chronic HF in the	Routinely not indicated.

	absence of specific contraindications	Used in patients with hypertension (under the close monitoring of kidney function and BP) (risk of hypotension, renal dysfunction)
β-adrenergic agonist	Indicated for all patients with symptomatic and asymptomatic HF with LV systolic dysfunction in combination with ACEIs in the absence of specific contraindications	Routinely not indicated. Can be prescribed if necessary to control the ventricular rhythm in atrial fibrillation
Mineralocorticoid receptor antagonists	Indicated for systemic LV dysfunction	Not indicated
ARBs	In case of ACEIs intolerance	Can be used in patients in which ACEIs indicated but poorly tolerated
Digoxin	In patients with congestive HF (IIB and higher), stage HF IIA with persistence of symptoms despite sufficient pharmacotherapy	Not recommended if not otherwise specifically indicated (arrhythmias, which need to control the atrial rhythm)
Non-glycoside inotropic agents	Can be used as palliative treatment to relieve symptoms in patients with advanced HF, if transplantation not possible or as a bridge to transplantation	Not indicated. Phosphodiesterase inhibitors (milrinone) can be used if specific indications are present (pulmonary hypertension)

SURGICAL TREATMENT

1. Artificial pacemaker implantation — in 2nd or 3rd grade AV block associated with ventricular dysfunction.

2. Cardiac resynchronization therapy:

– In patients with EF < 35 %, complete left bundle branch block, in QRS > normal upper range, medication-resistent HF grades IIA and higher.

– Systemic right ventricle with EF < 35 %, complete right bundle branch block, in QRS > normal upper range, medication-resistent HF grades IIA and higher.

3. Implantable cardioverter/defibrillator:

– Children with HF who had cardiac arrest if the potentially correctable cause has not been identified.

– Children with DCMP and unexplained syncope and at least moderate LV dysfunction, EF < 35 %.

– Adolescents with hypertrophic cardiomyopathy, arithmogenic cardiomyopathy, familial cardiomyopathy, associated with sudden cardiac death (SCD), in presence of at least one factor of SCD. At younger ages — benefits and risks are assessed because of technical difficulties of the surgery.

– In case of congenital heart disease and LV disfunction.

– Non-compact myocardium and moderately decreased LVEF.

– Patients with tachycardia and Left Ventricular Assist Device.

4. Catheter ablation:

– In case of tachycardia-induced cardiomyopathy, if medicamental treatment is ineffective (in adolescence is the second-choice therapy).

– Frequent ventricular extrasistoles, cardiomyopathies of unknown origin if medicamental treatment is ineffective;

5. Ventricular Assist Device:

– As a bridge to transplantation in children who permanently need inotropic agents, with evidence of early reversable dysfunction of at least one system of organs other than the heart.

– In children who are not eligible for transplantation — as long-term maintenance therapy.

HEART TRANSPLANTATION

Indications:

– Advanced HF NYHA (Ross) IV class (III stage);

– Severe concomittant arrhythmia and thromboembolism;

– Lack of effect from correct and long-term adequate drug therapy for HF;

– Unfavourable prognosis for the next year of life.

In developed countries of Europe and the USA more than 500 heart transplantations are performed per year in patients under 17 years of age, of which about one fifth are performed in children under the age of one year. Survival rate in the first year after transplantation is 90 %. Five-year survival rate — 75 %.

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Учебное издание

Крылова-Олефиренко Анна Викторовна
Козыро Инна Александровна
Белькевич Анна Геннадьевна
Чичко Алексей Михайлович

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На английском языке

Ответственная за выпуск Е. К. Филипович
Переводчик А. В. Крылова-Олефиренко
Компьютерная вёрстка Н. М. Федорцовой

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