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TREATMENT OF PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL HEART DEFECTS

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Abstract. Patients with pulmonary arterial hypertension, associated with congenital heart disease (PAH-CHD) are a heterogeneous population with a varied course of PH. Improvements in pediatric cardiac surgery have changed the epidemiology and survival rate of patients with CHD, of which 90% reach adulthood. Progress in terms of prognosis has also been observed among patients with PAH-CHD. Better survival was observed in ES compared with PAH after defect correction. Advances in surgical treatment of CHD and an increase in life expectancy have led to the study of PAH-CHD and the need to create recommendations for drug treatment of this category of patients. In most of studies, the evaluation of drug treatment of group 1 PAH was carried out without identifying its subgroups. And thus, according to existing recommendations, treatment algorhithms for patients with PAH-CHD are similar to approaches to other forms of PAH. However, various clinical, functional, physical and hemodynamic characteristics of patients with PAH-CHD call into question of correct risk stratification approaches development. Multicenter randomized clinical trials included predominantly a small number of patients with corrected defects, which does not allow the results to be interpreted for the entire population of patients with PAH-CHD. Data from single-center observational studies, expert opinion, and several randomized trials primarily involving patients with Eisenmenger syndrome (ES) indicate the effectiveness and safety of PAH-specific therapy in patients with PAH-CHD. In this literature review, we examined and showed the results of studies involving patients with PAH-CHD and their response to specific therapy. The results obtained significantly expanded the possibilities of using bosentan, sildenafil, epoprostenol, riociguat, ralinepag, sotatercept as they lead to improvement of functional capacity and hemodynamic parameters in patients with PAH-CHD, and only epoprostenol demonstrated an effect on prognosis. Combination PAH-specific therapy, initial or sequential administration of two or more drugs with different mechanisms of action, is an important treatment strategy for patients with PAH. The role of such therapy has increased in recent years. Based on the results of the AMBITION, SERAPHIN, GRIPHON, COMPASS-2 studies, initial or sequential oral combination PAH-specific therapy is recommended for patients with WHO FC II or III. At the same time, there is little evidence to support the effectiveness of this approach in ES patients. The use of anticoagulants in PAH-CHD remains controversial. Low-flow oxygen therapy should be considered individually and continued when there is a significant predominance of subjective or objective benefit. Iron deficiency is associated with poor survival in ES. It is important to note that microcytosis is rare in patients with iron deficiency cyanosis and a normal mean red cell volume does not indicate the absence of anemia. In cases of intolerance to oral iron, intravenous drugs should be used.

Currently, based on existing guidelines, most centers follow a consistent symptom-based approach in the treatment of patients with PAH-CHD. Therapy begins with oral ERAs or PDE-5 inhibitors and is escalated if symptoms persist or clinical worsening occurs. If there is no effect of oral PAH-specific therapy, it is recommended to consider parenteral drugs.

Keywords: pulmonary arterial hypertension, congenital heart disease, right heart catheterization, mean pulmonary artery pressure, Eisenmenger syndrome, PAH-specific therapy.

Introduction. Pulmonary hypertension (PH) is defined as a condition in which the mean pulmonary artery pressure (mPAP) is > 20 mmHg. Pulmonary arterial hypertension (PAH), associated with congenital heart defects (CHD), belongs to the first group of the PH classification and represents subgroup of PH, which is hemodynamically characterized by the presence of precapillary PH with pulmonary capillary wedge pressure ≤ 15 mmHg and pulmonary vascular resistance (PVR) ≥ 2 Wood units. In table 1 clinical classification of congenital systemic-to-pulmonary shunts associated with PAH is presented [1, 2].

Improvements in pediatric cardiac surgery have changed the epidemiology of PAH-CHD and improved the survival rate of patients with CHD, of which 90% reach adulthood [3]. According to Mazor D.E. et al. the incidence of PAH-CHD in newborns is 8.23 per 1000 people, in children – 13.11 per 1000 people, in adults– 6.12 per 1000 people and in the elderly – 3.80 per 1000 people [4].

Survival of PAH has been studied in the large national registries REVEAL, French, Chinese, UK and Ireland. After the development and implementation of specific drug therapy into clinical practice, patient survival has significantly improved and by the 5th year of observation it is now 35 - 65% [6]. Progress in terms of prognosis has also been observed among patients with PAH-CHD, with better survival rates than in idiopathic pulmonary arterial hypertension (IPAH) or hereditary forms of PAH [7, 8]. Recent studies indicate an improvement in 5-year survival for Eisenmenger syndrome (ES) from 91 to 95% [9].

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Table 1

Nice 2013 world symposium on pulmonary hypertension's clinical classification of congenital systemic-to-pulmonary shunts associated with PAH.

Eisenmenger syndrome	All large intracardiac and extracardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple-organ involvement are usually present.
Left-to-right shunts	Correctable Non-correctable Include moderate-to-large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature.
PAH with coincidental CHD	Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects is contraindicated.
Postoperative PAH	CHD is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative haemodynamic lesions. The clinical phenotype is often aggressive.

However, in a study by Marnes et al. [8] in patients with ES, arteriovenous shunts and PAH after correction of the defect the 20-year survival rate was 87%, 86% and 36%, respectively. At the same time, the 15-year survival rate in patients with a small defect was worse (66%), which was explained by the possible combination of IPAH and CHD. In Ukraine, life expectancy in 45 patients after the diagnosis of PAH, among whom 50% were patients with PAH-CHD, averaged 12.14±6.38 months, and overall mortality within 14 months was 10.94% [10].

In ES, the localization of the defect can influence the evolution of PAH, and Ramjung S. et al. were the first who showed the relationship between survival and the anatomical and pathophysiological classification of PAH-CHD [11]. In a study by Kempny A. et al. [10] in a large cohort of patients they showed that 5-year survival rate for pre-tricuspid defects was significantly lower (55%) compared with post-tricuspid (76.6%, $p < 0.001$) and complex defects (71.4 %, $p = 0.011$).

Advances in surgical treatment of CHD and an increase in life expectancy have led to the study of PAH-CHD and the need to create recommendations for drug treatment of this category of patients [12]. In most large studies, the evaluation of drug treatment of group 1 PAH was carried out without identifying its subgroups. However, the features of structural changes in the myocardium and cardiac hemodynamics in CHD determine differences in both pathogenesis and response to therapy in comparison with PAH. For example, a positive reversible pharmacological test cannot be an indication for calcium antagonist therapy in PAH-CHD, since peripheral dilation and negative inotropic effect increase the degree of right-to-left shunt [13]. Multicenter randomized clinical trials included predominantly a small number of patients with corrected defects, which does not allow the results to be interpreted for the entire population of patients with PAH-CHD. Data from single-center observational studies, expert opinion, and several randomized trials primarily involving patients with ES indicate the effectiveness and safety of PAH-specific therapy in patients with PAH-CHD [12, 13].

The randomized, placebo-controlled BREATHE-5 trial [14] examined the effectiveness of bosentan therapy in 54 patients with PAH-CHD. After 16 weeks of therapy, in the bosentan group there was an increase in the 6-minute walk test (6MWT) distance by 12.08%, in the placebo group just by 2.74%. Improvement in FC WHO was observed in 35% of patients in the bosentan group and 13% of patients in the placebo group. A common side effect in the bosentan group was peripheral edema (19% of patients). Two patients in each group discontinued treatment due to angina, elevated liver transaminases in the bosentan group, and fatigue and progression of PAH in the placebo group. In the open-label phase of the BREATHE-5 study [15] with a follow-up duration of 40 weeks, patients in the bosentan group maintained their improvement in 6MWT, while those in the placebo group had an 8.30% improvement.

In studies with bosentan therapy lasting more than a year, beneficial effects were not always observed. In four studies, improvements in 6MWT were observed in the first 4–12 months, after which values returned to baseline [16]. At the same time, the improvement in FC WHO remained throughout the entire follow-up period. During the study, three patients died as a result of arrhythmia and one - due to brain abscess, bosentan was discontinued in two patients (nasopharyngitis and no improvement), hemoptysis occurred in one patient, and four patients required escalation of PAH therapy. In a study by van Loon R.L. et al. [17], an improvement in 6MWT during 4 months was observed in 20 adults and 10 children with more severe PAH symptoms. However, after 2 years and 7 months of follow-up the values remained unchanged in adults and worsened in children, which allowed the researchers to speculate about the possibility of long-term deterioration of 6MWT in severe patients with PAH-CHD. In a study by Duffels M.G. et al. [16] the beneficial effect of bosentan persisted after 2 years of follow-up only in a subgroup of patients with ES.

Common adverse events in the studies were peripheral edema and elevated liver enzymes. There was no decrease in saturation in any study. During therapy with endothelin receptor antagonists (ERA), control of saturation is extremely important, because its decrease in this population of patients indicates the predominance of side peripheral vasodilatation over pulmonary vasodilatation.

Evidence for the use of ambrisentan in PAH-CHD is limited to a single-center study of 17 patients with ES [18], in which an improvement in 6MWT was observed during 160 days (389 ± 74 vs. 417 ± 77 meters, $p = 0.03$),

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FC WHO in 2 patients. During long-term follow-up for 2.5 years, 6MWT, FC and hemoglobin levels were maintained.

The effectiveness of treatment with macitentan was proven in the SERAPHIN study involving 62 patients with PAH after correction of defects (8% of the study population), the results of which indicate a decrease in morbidity and mortality with macitentan treatment, regardless of the specific therapy performed at inclusion [19]. In the MAESTRO trial [20], which included 220 patients with ES, 135 of whom had FC II WHO, macitentan was not superior to placebo as to 6MWT in duration of 16 weeks' treatment. The mean change in 6MWT was 18.3 meters and 19.7 meters in the macitentan and placebo groups. At the same time a 20% decrease in NT-proBNP was observed in the macitentan group. Among patients who participated in the hemodynamic sub-analysis, PVR decreased on average by 409.8 dynes/sec/cm^{-5} in the macitentan group and increased by 79.4 dynes/sec/cm^{-5} in the placebo group. Also 6MWT improved by 34.1 meters in the macitentan group and by 3.5 meters in the placebo group. An explanation for these results may be the inclusion of patients with Down syndrome and previous therapy with phosphodiesterase type 5 inhibitors (PDE-5I) (27%), which may have led to an improvement in 6MWT before initiation of macitentan therapy.

Clinical trials comparing ERAs with each other were not carried out. In a study by Tay E.L. et al. involving 40 patients with PAH-CHD, switching from bosentanan to macitentan improved FC WHO, decreased NT-proBNP levels, and improved RV function by echocardiography without significant differences in the number of hospitalizations due to HF [21].

In the SUPER-1 study involving 18 patients with PAH after defect correction (6% of the general population) treatment with sildenafil for 12 weeks lead to improvements in 6MWT and FC WHO [22]. In a study by D'Alto M. et al. [23] in 32 patients with PAH-CHD, adding sildenafil to initially ineffective bosentan therapy after 16 weeks led to an improvement in 6MWT by 22.87%, a decrease in PVR by 20.84%, an improvement in FC WHO from III to II, and a decrease in NT-proBNP levels by 60.14%. No significant changes in mPAP were observed.

Arterial hypotension as an unfavorable effect of sildenafil was observed by Chau E.M.C. et al. [24] only in the group of PAH-CHD.

The PATENT-1 and PATENT-2 studies examined the effectiveness of riociguat in 35 patients with PAH after defect correction (8% of the study population) [25]. By the end of the 12-th week in both groups 2,5 mg and 1,5 ng there was improvement of 6MWT distance by 10% and decrease in PVR, NT-proBNP and WHO FC. Syncope occurred in 1% of patients in the placebo group and in 4% of patients in the riociguat group (dose 2.5 mg). In PATENT-2 study with 2 years observation period 33 patients with PAH-CHD from PATENT-1 were included. There was improvement in 6MWD by 18%; 32% of patients improved to a better WHO FC, 60% remained stable at the same class.

Since the 90s of the twentieth century, prostaglandins and prostacyclin analogs have become the most important components of specific therapy of patients with PAH-CHD. In several small studies, intravenous epoprostenol had beneficial effects on hemodynamics, FC WHO, and functional capacity in patients with PAH-CHD. In a study by Fernandes S.M. et al. [26] epoprostenol therapy for 3 months resulted in a 78% increase in 6MWT in eight patients with PAH-CHD. However, the sample size was small and 6MWT averaged 44 meters at inclusion. In a larger study of Rosencveig E.B. et al. 20 patients with PAH-CHD who had failed previous HF therapy (oxygen, anticoagulants, digoxin, and diuretics) did not respond to epoprostenol therapy during short-term follow-up [27]. However, epoprostenol therapy for 1year improved FC WHO in 70% of patients, increased 6MWT from 408±149 meters to 460±99 meters ($p = 0.13$), and also decreased PVR from 25±13 to 12±7 Wood Unit ($p<0.01$) and mPAP from 77±20 to 61±15 mmHg ($p<0.01$). Poor adherence to therapy and risk of complications in this study were associated with the need for a central venous catheter [28]. In a more recent study by D'Alto M. et al. the addition of a parenteral prostanoid in patients with ES receiving dual oral combination therapy resulted in significant improvements in clinical and hemodynamic parameters with no need to interrupt therapy due to side effects during 2 years of follow-up [29].

A randomized trial of subcutaneous treprostenil [30] included 109 patients with PAH after defect correction or ES (23% of the total population). 6MWT improved by an average of 16 meters in all patients in the treprostenil group and was not significantly different in patients with PAH-CHD and idiopathic PAH.

In a prospective study of 13 patients with ES [31] treatment with inhaled iloprost for 24 weeks led to improvements in physical activity and quality of life in the absence of hemodynamic changes. However, in a pilot study by Nashat H. et al. adding of inhaled iloprost to existing first-line PAH-specific therapy did not improve 6MWT in patients with ES [32].

The 12-week randomized, placebo-controlled ALPHABET trial [33] examined the effectiveness of oral beraprost sodium in patients with PAH. The study results indicate a significant improvement in 6MWT in patients with IPAH and statistically insignificant changes in the PAH-CHD group. In this study the sample size and follow-up duration were small, the dose of beraprost was lower in the PAH-CHD group (62 ± 36 mcg four times daily vs. 96 ± 35 mcg four times daily, respectively).

The effectiveness of prostacyclin receptor agonist therapy selexipag was studied in the randomized GRIPHON trial involving 1156 patients (110 patients had PAH after defect correction) and the risk of death or PAH-related complications were significantly lower in selexipag group. The drug showed similar efficacy in different dosage groups. In the group of patients with PAH-CHD, a slight improvement in 6MWT (12 meters) was observed, which was explained by treatment with ERA or PDE5 inhibitors before inclusion in the study. Separate patient subgroup analyzes have not been performed and data regarding the effects of selexipag in patients with PAH-CHD are not available.

In a study by van Dissel A.C. et al. involving 34 patients, including 21 with ES, 2 - with systemic-pulmonary shunts, and 11 - with PAH after defect correction, the tolerability of selexipag was low, especially in patients with ES. A significant improvement in prognosis was

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observed only in the group of patients with PAH after defect correction [34].

The efficacy and safety of new prostacyclin receptor agonist ralinepag, which mechanism of action is associated with increased levels of cyclic adenosine monophosphate and leads to vasodilation and inhibition of smooth muscle cell proliferation, is studied in a phase III open-label extension study ROR-PH-303. At the moment of publication it included 107 participants, among them 4 (3,7%) had PAH-CHD at least one year after defect repair. Median treatment duration was 51,9 weeks. Results of the study showed significant improvement from baseline in 6MWT (mean raise on 50 meters), NT-proBNP levels (mean decrease on 80 pg/ml), WHO FC and risk scores to week 28 and 52 [35].

Sotatercept is the new drug with evidence to restore the balance between anti-proliferative (BMPR-II-mediated) and pro-proliferative (ActRIIA-mediated) effects. In phase-II PULSAR study the safety and efficacy of sotatercept on top of background PAH therapy in 104 PAH patients, including those with simple corrected CHD, comprised of a 24-week placebo-controlled treatment period followed by an open-label extension period was demonstrated [36]. Continuing phase- 3 STELLAR study with 323 participants, including 5.0% of patients with corrected PAH-CHD, showed mean change from baseline at week 24 in 6MWT on 34.4 meters in sotatercept group and on 1.0 meter in placebo group, decrease of NTproBNP levels on 230.3 pg/ml in sotatercept group and on 58.6 pg/ml in placebo group, improvement of WHO FC was observed in 29.4% and 13.8% of patients, respectively. There was also a significant difference in the distribution of time to first occurrence of death or nonfatal clinical worsening event in the sotatercept and placebo groups ($p<0.001$) [37]. In ongoing phase 3 ZENITH study sotatercept is studied in combination with maximum standard therapy in PAH patients, including patients with corrected congenital shunts [38].

Combination PAH-specific therapy, initial or sequential administration of two or more drugs with different mechanisms of action, is an important treatment strategy for patients with PAH. The role of such therapy has increased in recent years. Based on the results of the AMBITION, SERAPHIN, GRIPHON, COMPASS-2 studies, initial or sequential oral combination PAH-specific therapy is recommended for patients with WHO FC II or III [1]. At the same time, there is little evidence to support the effectiveness of this approach in ES patients. In a study by Iversen K. et al. 21 patients with ES received sildenafil or placebo in addition to bosentan therapy [39]. Patients did not improve 6MWT distance (21 meters vs. 8 meters, $p = 0.48$) and resting saturation increased significantly (+2.9% vs. -1.8%, $p < 0.01$). In contrast, in the study by D'Alto M. et al. [40] in 32 patients with ES and bosentan therapy, additional administration of sildenafil led to a significant improvement in FC WHO (2.1 ± 0.4 vs. 2.9 ± 0.3; $p = 0.042$) and 6MWT (360 ± 51 meters vs. 293 ± 68 meters; $p=0.005$), to decrease in NT-proBNP (303 ± 366 pg/ml vs. 760 ± 943 pg/ml; $p=0.008$) and PVR index (19 ± 9 Wood Units vs. 24 ± 16 Wood Units, $p=0.003$). In a study by Diller G.P. et al. in 153 patients with ES [41], 17.6% of whom received combination of bosentan and sildenafil, 1-, 5-, and 10-year mortality rates were 92%, 75%, and 57%, combined therapy was associated with better survival (OR 0.42, $p=0.015$).

In the COMPERA registry, among 680 patients with PAH-CHD at the time of inclusion [42], 70% of patients received PAH-specific monotherapy and 30% of patients received combination therapy. During 2 years of observation the number of patients receiving combination therapy increased to 50%. A 5-year survival for PAH-CHD was significantly better compared with idiopathic PAH (76% vs. 54%; $p<0.001$) and differed depending on diagnosis and therapy. However, overall survival in PAH-CHD was significantly lower compared with CHD without PAH, despite an increase in the number of patients receiving combination therapy.

The use of anticoagulants in PAH-CHD is controversial: on the one hand, microthrombosis can aggravate pulmonary vascular disease, on the other hand, hemoptysis often complicates the clinical course of PAH. There are no randomized studies on this issue. According to expert opinion, in the absence of significant hemoptysis, treatment with oral anticoagulants may be considered in patients with pulmonary artery thrombosis or symptoms of HF [43].

Hypoxia in patients with ES is not caused by alveolar hypoxia, but by right-to-left shunt of blood, resulting in deoxygenated blood from the right side bypassing alveolar-capillary gas exchange. In early studies of oxygen use in patients with ES, no reduction in PVR was observed, but there was a marked improvement in 6MWT, dyspnea, and lower limb weakness [44]. In a prospective study by Sandoval J. et al. in 23 patients with ES after two years of using low-flow oxygen at night, no improvement in quality of life, exercise capacity, erythrocytosis, or mortality was observed [45]. Thus, low-flow oxygen therapy should be considered individually and continued when there is a significant predominance of subjective or objective benefit.

The percentage of inspired oxygen on most airlines during flight is 15%, compared to 21% at sea level. Hypoxia can cause pulmonary vasoconstriction, and thus the use of supplemental oxygen is recommended in patients with PH and class III or IV or arterial blood oxygen pressure being <8 kPa [1]. Broberg C.S. et al. studied the 10-year flight history of 53 patients with ES [46]. Most flights were performed without supplemental oxygen and no significant adverse events were observed. Thus, stable patients with ES are recommended to fly without the use of oxygen with mandatory prevention of thromboembolic complications and air humidification.

Chronic hypoxia in patients with PAH-CHD causes compensatory erythrocytosis. A weak inverse relationship between SpO_2 and hemoglobin levels during iron deficiency in the blood was found in the Diller G.P. study involving 171 patients with ES [41]. Broberg C.S. et al. studied 65 patients with ES and derived an equation for predicting hemoglobin levels at a given SaO_2 and the absence of iron, vitamin B12 or folate deficiency [47]. Predicted hemoglobin Hg = 61- (SpO_2 / 2)

In clinical practice, transferrin saturation and serum ferritin are used to assess iron levels. It is important to note that microcytosis is rare in patients with iron deficiency cyanosis and a normal mean red cell volume does not indicate the absence of anemia. Iron deficiency is associated with poor survival in ES [48]. Three months of

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oral iron therapy (ferrous sulfate 200 mg three times daily) in 25 patients with PAH-CHD and cyanosis resulted in improvements in 6MWT and quality of life. In cases of intolerance to oral iron, intravenous drugs should be used [49]. Previously, venesections were used to prevent thrombotic complications. However, iron deficiency and venesection are associated with an increased risk of cerebrovascular events [50] and currently venesection can only be performed in patients with high iron content, a hematocrit greater than 0.65, and hyperviscosity syndrome in the absence of dehydration.

Currently, based on existing guidelines, most centers follow a consistent symptom-based approach in the treatment of patients with PAH-CHD. Therapy is started with oral ERAs or PDE-5 inhibitors and is escalated if symptoms persist or clinical worsening occurs. If there is no effect of oral PAH-specific therapy, it is recommended to consider parenteral drugs.

Conclusions. Patients with PAH-CHD are a heterogeneous population with a varied course of PH. Over the past two decades, due to the evolution of surgical treatment methods, the development and implementation of PAH-specific therapy, and the organization of specialized expert centers with a multidisciplinary approach, the results of managing such patients have significantly improved. According to existing recommendations, treatment algorhithms for patients with PAH-CHD are similar to approaches to other forms of PAH. However, various clinical, functional, physical and hemodynamic characteristics of patients with PAH-CHD call into question of correct risk stratification approaches development. Accordingly, choosing the optimal treatment for this population requires a careful and expert approach. Large clinical studies did not include patients with ES, and a small number of study participants were patients with PAH after defect correction. In this literature review, we examined and showed the results of studies involving patients with PAH-CHD and their response to specific therapy. Bosentan, sildenafil, epoprostenol and riociguat improve functional capacity and hemodynamic parameters in patients with PAH-CHD, and only epoprostenol demonstrated an effect on prognosis. According to the assessment of saturation during therapy, these drugs did not lead to an increase in pulmonary-systemic shunting, which was a significant expected side effect. The results obtained significantly expanded the possibilities of using these drugs. Thus, relevant and promising directions at the moment are the development of stratification scales using existing prognostic markers and the conduct of large randomized double-blind clinical trials to evaluate the benefits of PAH-specific drugs, their comparison with each other, as well as the effectiveness of the initial and sequential combination, which will make it possible to develop future treatment algorithms for a heterogeneous group of patients with PAH-CHD.

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ЛІКУВАННЯ ЛЕГЕНЕВОЇ АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ, АСОЦІЙОВАНОЇ ІЗ ВРОДЖЕНИМИ ВАДАМИ СЕРЦЯ

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Резюме. Удосконалення дитячої кардіохірургії змінило епідеміологію легеневої артеріальної гіпертензії, асоційованої із вродженими вадами серця (ЛАГ-ВВС) та покращило показники виживання пацієнтів, серед яких 90% досягають повноліття. Після розробки та впровадження у клінічну практику ЛАГ-специфічної медикаментозної терапії суттєво покращилось виживання хворих і до 5-го року спостереження зараз становить 35 – 65%. Успіхи хірургічного лікування ВВС та збільшення тривалості життя призвели до вивчення ЛАГ-ВВС та необхідності створення рекомендацій щодо медикаментозного лікування цієї категорії хворих. У більшості досліджень оцінки медикаментозного лікування ЛАГ 1-ї групи проводилися без виділення окремих її форм. Таким чином, згідно з існуючими рекомендаціями алгоритми лікування пацієнтів з ЛАГ-ВВС ідентичні до підходів щодо інших форм ЛГ, які належать до 1-ї клінічної групи. Однак, особливості структурних змін міокарда та серцевої гемодинаміки при ВВС обумовлюють відмінності як патогенезу, так і відповіді на терапію, порівняно з ЛАГ. Багатоцентрові рандомізовані клінічні дослідження включали переважно невелику кількість пацієнтів з коригованими дефектами, що не дозволяє інтерпретувати отримані результати на всю популяцію пацієнтів з ЛАГ-ВПС. В даному огляді літератури ми вивчили та показали результати як багатоцентрових, так й одноцентрових досліджень за участю пацієнтів із ЛАГ-ВВС та їх відповідь на специфічну терапію. Бозентан, силденафіл, епопростенол, ріоцигуат, ралінепаг та сотатерцепт покращують функціональні можливості та параметри гемодинаміки у пацієнтів з ЛАГ-ВВС і лише епопростенол продемонстрував вплив на прогноз.

На цей момент, керуючись існуючими рекомендаціями, більшість центрів дотримуються послідовного симптом-орієнтовного підходу в лікуванні пацієнтів з ЛАГ-ВВС. Терапію починають із перорального прийому антагоністів рецепторів ендотеліну або інгібіторів ФДЕ-5 та проводять ескалацію терапії при збереженні симптомів або у разі клінічного погіршення. За відсутності ефекту від пероральної ЛАГ-специфічної терапії рекомендовано розглянути парентеральні препарати.

Ключові слова: легенева артеріальна гіпертензія, вроджена вада серця, катетеризація правих відділів серця, середній тиск у легеневій артерії, синдром Ейзенменгера, ЛАГ-специфічна терапія.

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