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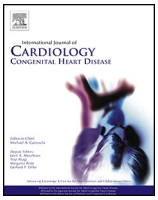

Hypoplastic left heart syndrome (HLHS) becomes of age: Assessing the young adult with HLHS including the neoaorta/aortic arch

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ABSTRACT

Hypoplastic left heart syndrome (HLHS) is one of the most complex congenital heart defects (CHD), characterized by a hypoplastic left ventricle (LV), dominant right ventricle (RV) and small left-sided heart structures. The introduction of the Norwood operation has significantly improved outcomes, with 5-year survival reported up to 65 %. Despite these advances, post-operative morbidity and mortality remain high, and the long-term complications in adult survivors represent a challenge. The number of HLHS patients with Fontan circulation is expected to double in the next 20 years, leading to a growing population requiring specialized care from adult congenital heart disease (ACHD) teams.

This article reviews current management strategies for HLHS, outlines potential long-term complications, and highlights existing knowledge gaps. Specific considerations in this population include the assessment of the neoaorta and aortic arch, and systemic RV dysfunction in the setting of a Fontan circulation. The proposed surveillance strategy emphasizes the need for vigilant monitoring and timely intervention to treat the complications unique to this population, ensuring better outcomes for HLHS patients reaching adulthood.

1. Introduction

Hypoplastic left heart syndrome (HLHS) is one of the most complex congenital heart defects (CHD), accounting for 2–3 % of all CHD [1].

Since the introduction of Norwood operation as part of the staged surgical management for children with HLHS approximately four decades ago, survival rates have improved significantly, with 5-year survival reported up to 65 %[2–4]. Despite the advances in surgical techniques and medical management leading to improved survival, the post-operative morbidity and mortality remain considerable. Adults who were born with HLHS still form a small group and the management of their long-term complications remains a challenge. Importantly, the number of survivors with Fontan circulation, including those with HLHS, is expected to double over the next 20 years. Therefore, adult congenital heart disease (ACHD) multidisciplinary teams will soon face a remarkable increase in the number of these patients in their everyday clinical practice.

In this article, we review current management strategies for HLHS patients, outline potential long-term complications, and highlight knowledge gaps. Furthermore, we propose a comprehensive surveillance strategy for these patients in adulthood.

2. HLHS definition and morphologic subtypes

HLHS is defined as a spectrum of cardiac malformations that include normally related great arteries in the presence of significant left ventricular (LV) inflow or outflow obstruction and LV hypoplasia, and hypoplasia of the ascending aorta and aortic arch [5]. While intact

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ventricular septum is not part of the definition of HLHS, recent reports support its inclusion in the diagnostic criteria [6]. Based on the extent of LV inflow and outflow obstruction, the following three morphologic subtypes are possible: mitral valve (MV) stenosis with aortic valve (AV) stenosis, MV stenosis with AV atresia, and MV atresia with AV atresia. All three morphologic subtypes share the common feature of the LV being inadequate to support the systemic circulation. Foetal survival depends on the patency of the ductus arteriosus, which supplies the systemic circulation from the right ventricle (RV) into the descending aorta. Due to inconclusive results of various studies, the association between morphologic ventricular subtype and survival in the first year of life remains unknown [7–9]. Nevertheless, a recent study reported that the presence of AV atresia in HLHS patients was independently associated with adverse outcomes at a mean follow-up of 6.4 ± 4.7 years after Fontan operation [10].

The exact aetiology of HLHS is not yet fully understood, but 5–10 % of HLHS patients have an identifiable syndrome or chromosomal abnormality and an association with genetic syndromes has been described, most commonly Turner syndrome, which was associated with a significant impact on mortality of HLHS patients [11,12].

3. Surgical management of HLHS

Since its introduction approximately 40 years ago, the staged surgical approach, culminating in the Fontan circulation, has remained the mainstay for the management strategy for patients with HLHS [13].

The Stage 1 procedure of the Norwood protocol (Fig. 1) aims to restore reliable systemic and pulmonary blood flow, while protecting the pulmonary vascular bed from pulmonary hypertension. It is performed in the first week of life and involves reconstruction of the neo-aorta by dividing the main pulmonary artery and anastomosing it to the ascending aorta with a Damus-Kaye-Stansel (DKS) connection. The pulmonary blood supply is delivered via a modified Blalock-Taussig shunt or an RV-to-pulmonary artery conduit [14,15]. An atrial septectomy is also performed to ensure unrestricted free filling of the RV, which in turn is connected to the neo-aorta.

An alternative to the Norwood Stage 1 procedure is a hybrid approach, which may be beneficial in very high-risk patients, including those with significant extracardiac anomalies and those born prematurely or with low birth weights [16,17]. This approach combines interventional cardiac catheterization and off-pump surgery. It includes bilateral pulmonary artery banding with stenting of the ductus arteriosus and atrial septectomy or percutaneous balloon atrial septostomy. The main difference between the two approaches is the way in which the coronary and cerebral circulations are perfused. In the latter the coronary and cerebral blood flow is provided in a retrograde manner via stented ductus arteriosus. Therefore, retrograde aortic arch obstruction may occur due to stenosis at the site of ductus arteriosus connecting to the native aorta, thus close monitoring is paramount [18].

Stage 2 of the Norwood protocol involves a bidirectional Glenn, which is most commonly performed at the age of 4–6 months. During this procedure, the superior vena cava is anastomosed to the pulmonary artery, which provides more reliable pulmonary blood flow and reduces the volume load on the systemic RV.

Stage 3 is the last stage of the Norwood protocol and involves the Fontan procedure, during which the pulmonary circulation is completely separated from systemic by connecting the inferior vena cava directly to the pulmonary artery via either an intracardiac or extracardiac conduit. It is usually performed at the age of 2–3 years.

Despite advances in surgical techniques and medical management, the morbidity and mortality of this palliative staged approach remains high. Hospital mortality during the Norwood protocol ranges from 16 % to 21 % and the overall transplant-free survival after the Norwood operation is reported to be 60–65 % at 5 years of follow-up [2,4,12,19]. Of note, the period between successfully completed Stage 1 procedure and Stage 2 procedure, commonly referred to as an interstage period, is a particularly fragile period as the risk of mortality during this period is up to 15 % [7,20,21]. Completion of Fontan palliation may be contraindicated in some cases and these patients may survive into adulthood, albeit with a high mortality and a significant burden of heart failure and arrhythmias [22,23].

4. Late outcomes after the fontan palliation

Patients with a Fontan circulation lack a subpulmonary ventricle and compared to normal subjects have chronically elevated systemic venous pressure, abnormal pulmonary perfusion, and reduced ventricular preload, which results in decreased cardiac output making the Fontan circulation both fragile and delicate [24]. Despite the increased survival rates in patients with a Fontan circulation observed over the last two decades, late morbidity and mortality remain considerable [25,26]. The effect of ventricular morphology on long-term survival of these patients has yet to be fully elucidated as meta-analyses show conflicting results. Some studies report no association between ventricular morphology and

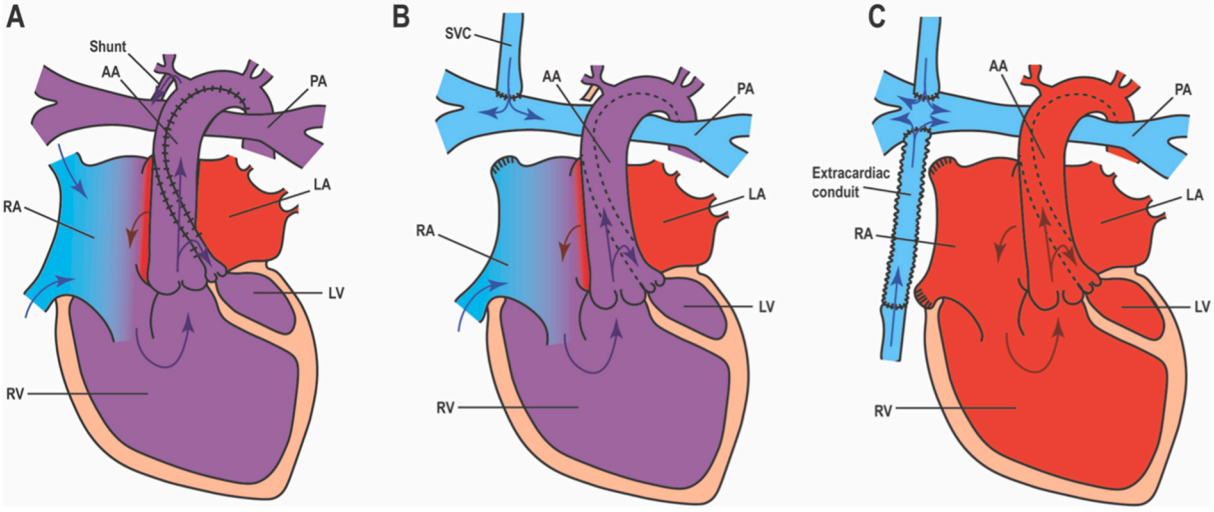

Fig. 1. Surgical management of HLHS. Panel A. The Norwood procedure (Stage 1). **Panel B.** Bidirectional Glenn procedure (Stage 2). **Panel C.** Total Cavopulmonary Connection (Stage 3).
Abbreviations: RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; AA, ascending aorta; SVC, superior vena cava.

survival, whereas others report a dominant RV to be a risk factor for mortality [27,28]. Although patients with HLHS after the Fontan completion do not seem to have worse survival compared to other Fontan patients, some studies suggest that HLHS may be predictive of early Fontan failure, prolonged hospitalization, and adverse events, including reoperations, percutaneous interventions, pacemaker implantations, thromboembolic events, and arrhythmias[10,29–31].

As more patients with Fontan circulation survive into adulthood, ACHD cardiologists are becoming increasingly aware of their mid- and long-term complications. Still, much remains unknown. A recent American Heart Association Statement paper proposed surveillance strategies for the long-term follow-up of Fontan patients that can also be applied to patients with HLHS [32]. However, more than 20 % of HLHS patients will experience Fontan failure within 10 years and more than two-thirds will suffer a serious adverse event by 15 years after their Fontan completion, making them a particularly vulnerable group [10]. Furthermore, the need for ascending aorta and aortic arch reconstruction exposes them to potential complications that merit special attention. Therefore, greater vigilance in detecting potential long-term sequelae and consideration of complications specific to this unique population is necessary. Several predictors of late mortality in Fontan patients have been identified, including the development of protein-losing enteropathy (PLE), lower serum albumin levels, baseline B-type natriuretic peptide (BNP) and temporal BNP changes, an increase in end-diastolic ventricular volumes, pacemaker implantation, and atrial tachycardia or flutter [25,33,34]. The improvement of morbidity and mortality in these patients is therefore highly dependent on the timely detection and proper management of the aforementioned potential complications [32]. Based on these data and our own early experience with HLHS patients transitioned to ACHD care, we hereby propose an HLHS-specific surveillance strategy for this growing number of patients (Table 1).

Table 1
Surveillance strategy for the adult with HLHS.

Test	Comment
Outpatient visit - History and medication review, - clinical examination (including radio-femoral delay)	At least every 12 months (more frequent if clinically indicated)
12-lead ECG	At every outpatient visit
CXR	At transition to ACHD and when indicated
Blood tests	Every 12 months (more frequent if clinically indicated): FBC, renal and liver function, serum protein and albumin level, BNP or NT-proBNP, iron studies (including transferrin saturation), thyroid function, vitamin D level. Specific liver tests as clinically indicated. At transition to ACHD care and re-test during pre-transplant work-up: HLA testing
Echocardiography	Every 12 months
ECG Holter monitor	Every 12–24 months
CPET	At transition to ACHD and when clinically indicated
CMR	At transition to ACHD, then every 3–5 years
CT angiography of aorta	At transition to ACHD when CMR contraindicated as baseline or when indicated[a]
Cardiac catheterization	As clinically indicated[b] Consider baseline catheterization – MRI-guided if feasible – at transition to ACHD care.
Liver US	Every 1–2 years once under ACHD care.
"Family planning"	Once ACHD care is established[c]
Other	Sleep study; consider for all overweight patients

Abbreviations: ECG, electrocardiogram; FBC, full blood count; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ACHD, adult congenital heart disease; HLA, human leukocyte antigen; CPET, cardiopulmonary exercise test; CMR, cardiac magnetic resonance; CT, computed tomography; US, ultrasound.

[a] When suspicion of significant stenosis of neo-aorta/aortic arch based on clinical findings, findings on cross-sectional imaging or for further evaluation due to suboptimal imaging quality.

[b] Both right- and left-heart catheterization should be performed. Consider baseline catheterization – MRI-guided if feasible [107] – in selected cases after clinical review, cross-sectional imaging, and discussion with the patients.

[c] Comprehensive discussion of pregnancy and family planning should be considered at transition to ACHD care or when required based on patients wishes. A question regarding family planning and contraception should be asked during every outpatient visit.

5. Specific considerations for HLHS population

5.1. Assessment of the neo-aorta/aortic arch

Hypoplasia of the ascending aorta and aortic arch is by definition one of the major constituents of the HLHS. As previously discussed, the neo-aorta is constructed during stage 1 of the Norwood procedure by connecting the hypoplastic aortic arch and the main pulmonary artery using the pulmonary valve in the systemic circulation, creating the so-called neo-aortic valve. There is emerging evidence indicating morphologic and physiologic abnormalities (Fig. 2) of the reconstructed neo-aorta that may contribute to ventricular dysfunction[35–40].

In paediatric patients, re-coarctation (re-CoA) of the aorta occurs in up to 37 % of cases after the Norwood procedure. It is one of the most severe complications, contributing significantly to high morbidity and mortality in the interstage period[41–46]. It can lead to ventricular dysfunction, atrioventricular valve (AVV) regurgitation, and hemodynamic collapse. Intervention for re-CoA is suggested when peak-to-peak gradient exceeds 10 mmHg [41,47]. Percutaneous intervention with transcatheter balloon angioplasty has been shown to be effective in reducing the gradients and normalizing the vessel diameter [43,47]. Furthermore, the use of stents for managing re-CoA or aortic arch stenosis is steadily growing with good results [48,49]. Although the association between re-CoA and mortality in the adult HLHS population has not been investigated, based on data from adults with isolated aortic coarctation (CoA), one might be concerned that these patients not only have increased arterial stiffness but also impaired baroreceptor sensitivity. This may have a causative role in the later development of systemic hypertension, suggesting that similar pathophysiologic mechanisms may be initiated in HLHS patients, making them susceptible to ventricular dysfunction [50]. As interstage monitoring programs have improved outcomes during this fragile period in paediatric patients, the importance of close monitoring of the neo-aortic valve and aortic arch in adulthood cannot be overemphasized[51–53]. Therefore, regular assessment of the neo-aorta and aortic arch using cross-sectional imaging with a low threshold for invasive haemodynamic assessment with or without intervention is clearly warranted. This is particularly important in cases of poorly controlled arterial hypertension, as this may be a sign of underlying re-CoA. Although the current guidelines recommend repair of CoA or re-CoA in patients with isolated CoA when the peak-to-peak gradient is $\geq$ 20 mmHg, this cut-off should not be applied to HLHS patients with Fontan circulation and a systemic RV, in whom even the smallest pressure gradient can lead to early Fontan failure. Catheter intervention may be considered when the peak-to-peak gradient is $\geq$ 10 mmHg, provided the procedure is technically feasible and carries an acceptable risk.

In addition to re-CoA, these patients may also develop neo-aortic dilatation, which may lead to progressive regurgitation of the neo-aortic valve [39]. The underlying mechanism of the dilatation is unknown; however, it is probably multifactorial and includes anatomical, genetic, and hemodynamic factors[54–56]. Due to data limited to case reports, the exact thresholds for intervention are unknown. The timing of surgical management is usually based on early symptoms, progression of neo-aortic valve regurgitation, and/or compression of the left pulmonary artery by the neo-aortic aneurysm, which increases the risk of Fontan failure. As cases of neo-aortic dissection have been reported in the literature [57,58], close monitoring is warranted. Valve-sparing neo-aortic root replacement appears to be feasible option in these

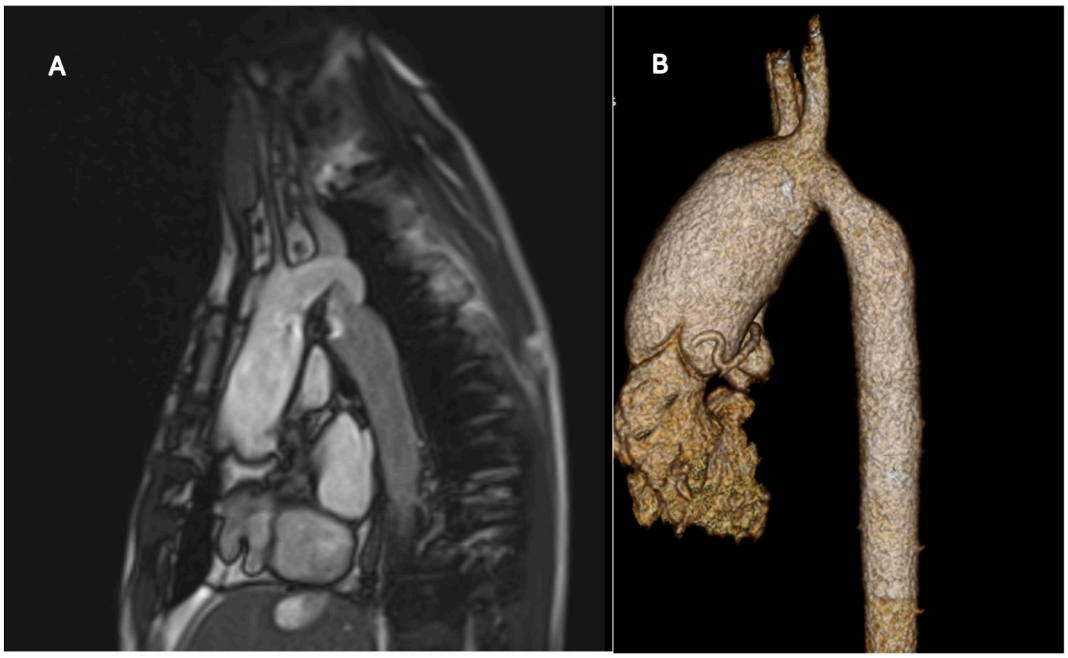

Fig. 2. Panel A. CMR of aorta in adult patient with HLHS shows mildly dilated aortic root and mildly hypoplastic left-sided aortic arch with tortuosity of the proximal descending aorta. **Panel B.** CT angiography of aorta, 3D reconstruction in adult patient with HLHS. Abnormal neo-aortic anatomy with dilated neo-aortic root and narrowed site of previous coarctation can be seen.
Abbreviations: CMR, cardiac magnetic resonance; HLHS, hypoplastic left heart syndrome; CT, computed tomography.

patients. In cases of severe neo-aortic regurgitation or heavily dysplastic neo-aortic valve valve-sparing procedure may not be possible and therefore the neo-aortic valve and root replacement may be required [59–62].

Another reported complication is native aortic root thrombosis (NART) [63]. Although rare, it is a life-threatening complication, which should be excluded in cases of new ventricular arrhythmias or signs of ischemia, such as chest pain, ST changes, and unexplained reduced ventricular function [64]. It is most common in young children, but it can also occur in older children and adults. As transthoracic echocardiography can be false-negative, transoesophageal echocardiography, computed tomography (CT) coronary angiography or cardiac catheterization should be performed in high clinical suspicion for NART. Current treatment strategies include anticoagulation, systemic thrombolysis, catheter-directed thrombolysis, or surgical thrombectomy. Patients should be screened for underlying hypercoagulability and long-term anticoagulation should be tailored according to the risk factors.

Coronary supply in patients with HLHS after Norwood procedure relies on retrograde flow via a DKS anastomosis (blood leaves the heart via the neo-aortic valve into the neo-aorta with some of the blood flowing retrogradely in the diminutive native aorta and into the coronary arteries). Therefore, in patients with ischemic ECG changes, RV dysfunction, or systemic AVV regurgitation, a possible stenosis of this connection should also be considered. In case of obstruction, turbulent flow through the DKS can be seen on transthoracic echocardiography and can be further evaluated with CT, cardiac magnetic resonance (CMR), and/or cardiac catheterization [65].

5.2. Right ventricular dysfunction

The RV in patients with HLHS is the sole functional ventricle and acts differently at the molecular level than a normal LV or RV [66]. It is subject to abnormal hemodynamic demands that predispose the systemic RV to both systolic and diastolic dysfunction.

RV dysfunction leads to poor growth, fluid retention, exercise intolerance, and general fatigue. Several studies have demonstrated that the development of RV dysfunction at any stage is one of the critical determinants of poor clinical outcome in patients with HLHS[67–69]. As there are no uniformly agreed normal values of functional indexes for systemic RV, serial monitoring of these patients with echocardiography and other imaging modalities such as CMR is crucial for the timely diagnosis of RV dysfunction and identification of underlying causes [70–74]. Despite the limitations of echocardiography in evaluating morphologically abnormal ventricles, a fair correlation between 3D echocardiographic and CMR-derived ejection fraction has been shown [75]. A recent meta-analysis including 33 % of patients with a dominant RV identified increased end-diastolic ventricular volumes, a marker of systolic ventricular dysfunction, as one of the predictors of late death after the Fontan completion [33].

Neo-aortic arch stenosis should be excluded in these patients as its timely intervention could lead to an improvement in RV function. Systemic AVV regurgitation is another important cause of RV dysfunction [76]. Its mechanism is usually multifactorial and includers structural abnormalities of the systemic AVV and functional causes such as RV dilatation and dysfunction, leading to annular dilatation and failure of leaflet coaptation [77–81].

To date, there is no evidence that medical therapy may have a positive effect on long-term survival in adult patients [82–88]. Albeit empiric afterload reduction has been employed in some patients. A single report suggested that the use of digoxin in the interstage period in patients with HLHS may have contributed to the preservation of RV volumes and tricuspid valve indices and thus to less adverse single ventricle remodelling [89].

Hemodynamic monitoring of patients with heart failure (HF) using implantable devices has recently attracted considerable interest. According to 2022 AHA HF guidelines, it should be considered for symptomatic patients on maximal medical therapy with history of previous HF hospitalizations [90]. One of these devices can be implanted in the pulmonary artery to monitor pressures wirelessly and its use showed a reduction in the risk of recurrent HF hospitalizations [91]. Based on these results and the increasing burden of HF in the CHD population, this technology is gaining more interest, especially in patients with a Fontan

circulation who have chronically elevated systemic venous pressures and who may require multiple cardiac catheterizations throughout their lives to evaluate the Fontan circuit. The advantage of implantable hemodynamic monitoring is that it allows serial measurements under real-life conditions, without the need for sedation and fasting as with cardiac catheterization. Implantable hemodynamic monitoring in HLHS patients may help titrate medical therapy, prevent HF hospitalizations, and optimize timing of heart transplantation [92]. Albeit data is currently lacking. Similarly, elective drug therapy in this vulnerable group of patients may have a role, thus further investment in multicentre, prospective, controlled studies is clearly warranted.

5.3. Optimal physical conditioning

Exercise intolerance in patients with Fontan circulation remains one of the most important factors contributing to impaired functional status and reduced quality of life. Their aerobic exercise capacity, as measured by peak oxygen uptake (VO2), is reduced with an average predicted peak VO_2 of up to 61 % [93]. However, a proportion of these patients can achieve normal exercise and work capacity (peak $VO_2 \geq 80$ %), which conveys a better prognosis [94,95]. An optimal body mass index (BMI) and regular physical exercise are variables that have been positively associated with peak VO_2 in several studies[94–96] and are to be encouraged.

The benefits and safety of exercise in patients with CHD, including those with a Fontan circulation, are well established[97–100]. Both moderate aerobic exercise and resistance training, which primarily target lower limb muscles development, are considered safe and beneficial in most cases[101–103]. A recent multicentre randomized controlled trial has demonstrated that a 12-week centre- and home-based cardiac rehabilitation intervention improved the health-related quality of life of adolescents and young adults with CHD and improved BMI, blood pressure, disease knowledge, and levels of physical activity [104]. Therefore, timely implementation of prevention programmes in the regular care of patients with CHD, including HLHS, should be standard practice to promote a healthy lifestyle, including healthy diet, optimal weight and daily physical activity.

5.4. Other considerations

As more female patients with HLHS are now reaching childbearing age, counselling about pregnancy and contraception is an essential part of continuous healthcare and should begin early to ensure safe and informed decisions. Issues such as safety and efficacy of contraception and the risks of pregnancy should be discussed. In terms of contraception, progesterone-only contraceptives are preferred, intradermal devices are safe and optimal. Intrauterine devices are also advised, although for safety reasons they should be implanted by experienced gynaecologist [105]. Patients need to understand both the short and long-term issues related to pregnancy, such as thrombosis, heart failure, death, their lifespan prospects, and CHD recurrence risk. The assessment and discussion with a multidisciplinary ACHD team is needed. If the patients decide to become pregnant, they should be followed-up in a tertiary multidisciplinary centre to minimize the risk for complications during pregnancy.

Heart transplantation is currently the only therapeutic option that provides long-term survival and a good quality of life in HLHS patients with end-stage heart failure. Although it is connected with numerous challenges and high post-operative mortality, it can be successfully performed in selected cases [106]. Human leukocyte antigen (HLA) sensitization due to previous surgeries is one of the many challenges of transplantation in these complex patients. Multi-organ failure, including the liver, is part of the natural history of HLHS patients. Close monitoring of the liver function may help determine the optimal timing for transplantation. The need for and timing of a comprehensive pre-transplantation assessment should be discussed with the patient well in advance of a formal referral to the heart failure and transplant team.

6. Conclusion

As more patients with HLHS survive into adulthood, ACHD cardiologists are increasingly confronted with their unique mid- and long-term care needs. We hereby present a tailored surveillance approach for this group of patients with the most extreme form of CHD, highlighting the multiple challenges but also the opportunities for optimal outcomes. Future research is essential to improve therapeutic strategies for preserving RV function and delaying Fontan failure, enabling this growing cohort of CHD patients to reach their full life potential.

CRediT authorship contribution statement

Polona Kačar: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Pietro Paolo Tamborrino:** Conceptualization, Writing – review & editing. **Giulia Iannaccone:** Conceptualization, Visualization, Writing – review & editing. **Gianfranco Butera:** Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing. **Margarita Brida:** Supervision, Validation, Writing – review & editing. **Katja Prokšelj:** Supervision, Writing – review & editing. **Michael A. Gatzoulis:** Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. **Claudia Montanaro:** Conceptualization, Data curation, Supervision, Validation, Visualization, Writing – review & editing.

Disclaimer

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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