Guidelines for the management of neonates and infants with hypoplastic left heart syndrome: the European Association for Cardio-Thoracic Surgery (EACTS) and the Association for European Paediatric and Congenital Cardiology (AEPC) Hypoplastic Left Heart Syndrome Guidelines Task Force

Alphonso, N.; Angelini, A.; Barron, D.J.; Bellsham-Revell, H.; Blom, N.A.; Brown, K.; ... ; Simpson, J.M.

European Journal of Cardio-Thoracic Surgery 58 (2020) 416–499
doi:10.1093/ejcts/ezaa188

GUIDELINES

Cite this article as: Alphonso N, Angelini A, Barron DJ, Bellsham-Revell H, Blom NA, Brown K *et al.* Guidelines for the management of neonates and infants with hypoplastic left heart syndrome: The European Association for Cardio-Thoracic Surgery (EACTS) and the Association for European Paediatric and Congenital Cardiology (AEPC) Hypoplastic Left Heart Syndrome Guidelines Task Force. Eur J Cardiothorac Surg 2020;58:416–99.

Guidelines for the management of neonates and infants with hypoplastic left heart syndrome: The European Association for Cardio-Thoracic Surgery (EACTS) and the Association for European Paediatric and Congenital Cardiology (AEPC) Hypoplastic Left Heart Syndrome Guidelines Task Force

Nelson Alphonso[a], Annalisa Angelini[b,‡], David J. Barron[c,†], Hannah Bellsham-Revell [d,‡], Nico A. Blom[e,‡], Katherine Brown[f], Deborah Davis [g,h], Daniel Duncan[h], Marny Fedrigo[i,‡], Lorenzo Galletti[j,†], David Hehir[k], Ulrike Herberg [l,‡], Jeffrey P. Jacobs[m,†], Katarzyna Januszewska[n,†], Tom R. Karl [o,*†] (Chaiman HLHS Guidelines Task Force), Edward Malec[n,†], Bohdan Maruszewski [p,†], James Montgomerie[q], Christian Pizzaro[h,r,†], Dietmar Schranz[s,‡], Amanda J. Shillingford [t] and John M. Simpson[u,‡]

[a] Queensland Pediatric Cardiac Service, Queensland Children's Hospital, University of Queensland, Brisbane, QLD, Australia
[b] Department of Cardiac, Thoracic Vascular Sciences and Public health, University of Padua Medical School, Padua, Italy
[c] Department of Cardiovascular Surgery, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada
[d] Department of Paediatric Cardiology, Evelina London Children's Hospital, London, UK
[e] Division of Pediatric Cardiology, Department of Pediatrics, Leiden University Medical Center, Leiden, Netherlands
[f] Paediatric Intensive Care, Heart and Lung Division, Great Ormond Street Hospital NHS Foundation Trust, London, UK
[g] Department of Anesthesiology, Thomas Jefferson University, Philadelphia, PA, USA
[h] Nemours Cardiac Center, A.I. Du Pont Hospital for Children, Wilmington, DE, USA
[i] Department of Cardiac, Thoracic Vascular Sciences and Public Health, University of Padua Medical School, Padua, Italy
[j] Unit of Pediatric Cardiac Surgery, Bambino Gesù Children's Hospital, Rome, Italy
[k] Division of Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
[l] Department of Pediatric Cardiology, University Hospital Bonn, Bonn, Germany
[m] Cardiology in the Young, St. Petersburg, FL, USA
[m] Division of Pediatric Cardiac Surgery, University Hospital Muenster, Westphalian-Wilhelm's-University, Muenster, Germany
[n] EACTS, Windsor, UK
[o] Department for Pediatric Cardiothoracic Surgery, Children's Memorial Health Institute, Warsaw, Poland
[p] Department of Anesthesia, Birmingham Children's Hospital, Birmingham, UK
[q] Department of Surgery, Thomas Jefferson University, Philadelphia, PA, USA
[r] Pediatric Heart Center, Justus-Liebig University, Giessen, Germany
[s] Division of Cardiology, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[t] Evelina London Children's Hospital, London, UK

* Corresponding author. 11260 Donner Pass Road C1 1017, Truckee, CA 96161, USA. Tel: +1-727-303 9511; e-mail: trkarl.aus@gmail.com (T.R. Karl).

† Representing the European Association for Cardio-Thoracic Surgery.
‡ Representing the Association for European Paediatric and Congenital Cardiology.

Document Reviewers: François Lacour-Gayet (Oman), René Prêtre (Switzerland), Matthias Siepe (Germany), Birgit Stiller (Germany) and one anonymous reviewer.

Disclaimer 2020: The EACTS/AEPC Guidelines represent the views of the EACTS and the AEPC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating. The EACTS and AEPC are not responsible in the event of any contradiction, discrepancy and/or ambiguity between the EACTS and AEPC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the EACTS and AEPC Guidelines fully into account when exercising their clinical judgement as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies; however, the EACTS and AEPC Guidelines do not, in any way whatsoever, override the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and, where appropriate and/or necessary, in consultation with that patient and the patient's care provider. Nor do the EACTS and AEPC Guidelines exempt health professionals from giving full and careful consideration to the relevant official, updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

2D	2-Dimensional
3D	3-Dimensional
AA	Aortic atresia
ABG	Arterial blood gas
ACE	Angiotensin-converting enzyme
Ao	Aorta
AoV	Aortic valve
AS	Aortic stenosis
Asc Ao	Ascending aorta
ASD	Atrial septal defect
AV	Atrioventricular
AVV	Atrioventricular valve
AVSD	Atrioventricular septal defect
BCPS	Bidirectional cavopulmonary shunt
BNP	Type B natriuretic peptide
BP	Blood pressure
b-PAB	Bilateral pulmonary artery banding
BW	Birth weight
CHD	Congenital heart disease
CO	Cardiac output
CoA	Coarctation of aorta
CPB	Cardiopulmonary bypass
c-S2P	Comprehensive S2P
CT	Computed tomography
DA	Ductus arteriosus
Desc Ao	Descending aorta
DHCA	Deep hypothermic circulatory arrest
DO_2	Oxygen delivery
ECG	Electrocardiogram

ECHSA	European Congenital Heart Surgeons Association
ECLS	Extracorporeal life support
ECMO	Extracorporeal membrane oxygenation
EFE	Endocardial fibroelastosis
FiO_2	Fraction of inspired oxygen
FO	Foramen ovale
Hb	Haemoglobin
Hct	Haematocrit
HLHC	Hypoplastic left heart complex
HLHS	Hypoplastic left heart syndrome
HR	Heart rate
h-S1P	Hybrid stage 1 palliation
IAA	Interrupted aortic arch
IAS	Intact atrial septum
ICU	Intensive care unit
IPCCC	International Paediatric and Congenital Cardiac Code
ISNPCHD	International Society for Nomenclature of Paediatric and Congenital Heart Disease
IS-1	Interstage 1
IS-2	Interstage 2
ISV	Infants with Single Ventricle
LA	Left atrium
LCOS	Low cardiac output syndrome
LPA	Left pulmonary artery
LV	Left ventricle
MA	Mitral atresia
MBTS	Modified Blalock–Taussig shunt
MPA	Main pulmonary artery
MRI	Magnetic resonance imaging
MS	Mitral stenosis
MV	Mitral valve
NEC	Necrotizing enterocolitis
NIRS	Near infrared spectroscopy
NPCQIC	National Paediatric Cardiology Quality Improvement Collaborative
PA	Pulmonary artery
PAB	Pulmonary artery banding
pCO_2	Partial pressure of carbon dioxide
PGE1	Prostaglandin E1
PHT	Pulmonary hypertension
PTFE	Polytetrafluoroethylene
PV	Pulmonary valve
PVR	Pulmonary vascular resistance
Qp	Pulmonary blood flow
Qs	Systemic blood flow
RA	Right atrium
RBCs	Red blood cells
RCP	Regional cerebral perfusion
RCT	Randomized controlled trial
r-FO	Restrictive foramen ovale
RPA	Right pulmonary artery
RR	Respiratory rate
RV	Right ventricle
S1P	Stage 1 palliation
S2P	Stage 2 palliation
SaO_2	Arterial oxygen saturation
SO_2	Oxygen saturation
STS CHSD	Society of Thoracic Surgeons Congenital Heart Surgery Database
SV	Single ventricle
SVC	Superior vena cava
SvO_2	Mixed venous SO_2
SVR	Systemic vascular resistance
SVRT	Single Ventricle Reconstruction Trial
TAPVD	Totally anomalous pulmonary venous drainage
TOE	Transoesophageal echocardiography
TR	Tricuspid regurgitation
TV	Tricuspid valve
VO2	Oxygen uptake
VSD	Ventricular septal defect

'The doer alone learneth'.

Friedrich Nietzsche

Also Sprach Zarathustra: Ein Buch für Alle und Keinen (1883)

1. INTRODUCTION AND METHODOLOGY

A widely cited description of hypoplastic left heart syndrome (HLHS) was provided by Lev in 1952, although references to this anatomical entity had appeared sporadically over the preceding 400 years. The syndrome was named in 1958 by Noonan and Nadas [1, 2]. Although specific figures for all of Europe are not readily available, the HLHS phenotype occurs in ∼0.016–0.036% of live births in Canada and the USA. Thus, each year ∼56–126 newborns in Canada and 640–1440 in the USA are affected [3–7]. Estimates for the incidence of HLHS (among all live births) in Germany, Croatia and Belgium are 0.016%, 0.017% and 0.009%, respectively [8]. The incidence is probably in transition to some extent, because accurate foetal diagnosis and termination of pregnancy have become increasingly prevalent in many countries. HLHS represents 2–9% of congenital heart disease (CHD) cases but accounts for 23% of neonatal deaths from congenital heart malformations [9–13]. Although it is not the most critical issue in child health worldwide, success with treatment of HLHS has become a new standard for assessment of the quality of care delivered by cardiac teams worldwide. Importantly, the technology and knowledge base developed for treatment of HLHS have had far reaching implications for dealing with other complex paediatric problems, both cardiac and non-cardiac.

Co-authors were primarily nominated, approved and invited by the European Association for Cardio-Thoracic Surgery (EACTS) Congenital Domain chairman and/or the Guidelines Task Force chairman, and the Association for European Paediatric and Congenital Cardiology (AEPC). The contributing authors represent primarily teams and institutions with a large and favourable clinical and/or research experience with HLHS. All surgical co-authors are EACTS members. To recapitulate contemporary clinical practice, we have tried to invite representatives from all medical and surgical specialties whose scope of interest includes infants with HLHS. In the creation of these guidelines, the authors have considered all relevant published literature and their considerable individual and collective experience with patients with HLHS. All recommendations made in the guidelines are qualified with appropriate weight of evidence statements [14]. These guidelines cover initial foetal diagnosis of HLHS [with brief reference to some non-HLHS variants and unbalanced

atrioventricular septal defect (AVSD) when appropriate] through to (but not including) stage 2 palliation (S2P). Class of recommendation and level of evidence are defined as in previous guidelines (Tables 1 and 2).

In **PICOT** format, the scope of the guidelines inquiry could be framed as follows:

Problem	**I**ntervention	**C**omparison	**O**utcome	**T**ime frame
HLHS (foetus, newborn, infant)	• Diagnosis • Resuscitation • Surgical and hybrid treatment • Intensive care (preoperative and postoperative) • Interstage 1 care	• Natural history • No active treatment • Palliative care	• Preoperative deaths • Operative deaths • Survival through interstage 1 to stage 2 palliation	• Foetus to stage 2 palliation • No time limitations on literature review

HLHS: hypoplastic left heart syndrome.

The specific primary questions addressed in the paper are as follows:

1. What are the relevant standard definitions and anatomical spectrum of HLHS?
2. How does HLHS physiology influence presentation and treatment?
3. How is HLHS best diagnosed prenatally and postnatally?
4. How does prenatal treatment influence the course of HLHS after birth?
5. What is the influence of prenatal diagnosis on delivery planning?
6. What are the postnatal treatment options for HLHS (prior to surgery) based on presentation?
7. What are the relevant current surgical options and technical strategies?
8. What is the role of hybrid stage 1 palliation (h-S1P), and which techniques are applicable?
9. How can patients with HLHS best be managed in the intensive care unit (ICU) after surgery?
10. How should patients be managed during interstage 1 (IS-1) following Norwood or h-S1P?
11. What are the outcome expectations in the current era, based on multi-institutional databases?

Literature searches were conducted primarily in PubMed and institutional collections. Initial searches in PubMed (using no time limits) for 'HLHS' returned 3711 publications. In the final version of the manuscript, 704 (19%) source references are cited. Articles were selected based on relevance and scientific merit, as determined by the co-author for each subheading relating to HLHS (see Table of Contents). No a priori inclusion or exclusion criteria were used. Priority was given to randomized controlled trials (RCTs) (of which there were 2) and to larger and/or multicentric studies. All co-authors had the opportunity to read and propose edits for all sections of the manuscript, irrespective of primary interest. It is well appreciated that RCTs are rare in the paediatric cardiac literature, especially relating to HLHS. Because there is little information in the literature from RCTs, this guidelines paper is (of necessity) weighted heavily towards observational studies and expert opinion, which form the basis for the great majority of papers reviewed. Guideline recommendations can be considered to be consensus statements from the co-authors based on personal experience and review of extant literature.

It is recognized by the authors that the surgical treatment of infants with HLHS has not been embraced by all practitioners, families and societies. In fact, in many parts of the world, active treatment may be impractical or even impossible, based on local resources. There are philosophical issues as well, which may take into account (among other things) the wisdom of treatment of critically ill neonates whose best outcome may still be compromised from both cardiac and neurodevelopmental points of view. It is widely accepted by practitioners and institutions that both termination of pregnancy and withholding definitive postnatal treatment for HLHS in favour of 'comfort care' (i.e. without any expectation of survival) remain ethically justified. The latter strategy is often termed 'compassionate care', although the term is not precise, and in no way implies that active treatment of HLHS is not compassionate. This is a complex area of discussion that is well beyond the scope of these guidelines, which are meant to help in applying definitive treatment strategies to newborns (and foetuses) whose families (after receiving the best available information in an impartial manner) desire that approach. In all cases, our role is to provide the best support possible.

Table 1: Classes of recommendations

Classes of recommendations	Definition
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases harmful.

Table 2: Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of experts and /or small studies, retrospective studies, registries.

The long-term outcome for HLHS survivors has become better defined over the past decade as we follow patients with HLHS into their young adult years. Many (but not all) patients with HLHS who have had a Fontan operation will require a heart transplant for some manifestation of Fontan failure. A heart transplant has been referred to as the 'fourth stage' in the surgical treatment of HLHS, although the time course varies considerably from case to case. Although maintenance of suitability for a heart transplant [especially pulmonary artery (PA) development and preservation] should be borne in mind as a tertiary goal in the treatment sequence, the issues relating to heart transplantation are beyond the scope of these guidelines. Heart transplantation as a primary treatment for infants with HLHS, although used more liberally in the 1980s and 1990s, is now reserved for exceptional cases who are not candidates for a Norwood or h-S1P strategy. This specific topic is also not dealt with in these guidelines.

2. ANATOMY AND NOMENCLATURE

2.1 Definitions

HLHS encompasses a heterogeneous group of congenital cardiac anomalies characterized by the presence of a hypoplastic or virtual left ventricle (LV), usually not forming the apex of the heart, with the aorta (Ao) and/or mitral hypoplasia or atresia. The term HLHS includes:

1. Mitral atresia (MA)/aortic atresia (AA)
2. Mitral stenosis (MS)/AA
3. MS/aortic stenosis (AS)
4. MA/AS + ventricular septal defect (VSD)
5. Hypoplastic left heart complex (HLHC) (hypoplastic Ao, LV is small or not able to support systemic circulation).

We do not include double outlet right ventricle (RV) with a small LV, congenitally corrected transposition of the great arteries with a large VSD and a small LV, an unbalanced AVSD with a small LV or long-segment subaortic AS with AS, VSD and Ao arch hypoplasia [15].

The common feature of HLHS is a functional single ventricle (SV) chamber in association with some degree of hypoplasia of the ascending (Asc) Ao or arch. The physiological consequence is that systemic blood flow (Qs) is provided (completely or partially) by the RV via a ductus arteriosus (DA). Thus, the DA and adequate mixing at the atrial level are essential for postnatal survival. A restrictive or closed foramen ovale (FO) may result in pulmonary oedema and hypoxia and fatal lung parenchymal disease [16, 17].

2.2 Hypoplastic left heart syndrome versus hypoplastic left heart complex

HLHS is synonymous with severe hypoplasia of the left heart structures, in which Qs cannot be guaranteed. It may be defined as a spectrum of cardiac malformations with normally aligned great arteries without a common atrioventricular valve (AVV), characterized by underdevelopment of the left heart, with significant hypoplasia of the LV [including atresia, stenosis or hypoplasia of the aortic or mitral valve (MV), or both valves], and hypoplasia of the ascending Ao (Asc Ao) and Ao arch. HLHC sits at the milder end of the spectrum of HLHS and is characterized by underdevelopment of the left heart with significant hypoplasia of the LV and hypoplasia of the Ao valve (AoV) or the MV, or both valves, in the absence of intrinsic valvar stenosis or atresia of the AoV or the MV, and with hypoplasia of the Asc Ao and Ao arch. The MV and AoV are minute, with or without dysplasia of the leaflets, or abnormalities of the tendinous cords or papillary muscles [18].

The terms AS and MS imply that there is fusion at the level of the valvar leaflets and maldevelopment of the valve apparatus (hence true valvar stenosis). In contrast, hypoplasia of the AoV, MV and LV indicates that the valves are small but not intrinsically stenotic [16, 17].

2.3 Morphological approach to hypoplastic left heart syndrome

Four patterns of left ventricular morphology are recognized [19–21]:

1. A 'slit-like ventricle' characterized by a flattened, virtual LV within the left posterior aspect of the ventricular mass, which can be identified indirectly by the coronary vessels on the epicardial surface encircling the LV as happens in the normal heart. This form is associated with MA and AA. No valve tissue or endocardial fibroelastosis (EFE) is detected. The atrioventricular (AV) junction is muscular.
2. A 'miniature LV' with a nearly normal size and parietal thickness but not forming the cardiac apex, associated with normal Ao and MV (i.e. small but not stenotic). In MS and AS, the LV can be nearly normal in size and parietal thickness but does not form the cardiac apex. The Ao and MV are anatomically normal.
3. A 'small LV cavity with a thick parietal wall', associated with a wide range of AoV malformations, either stenotic or atretic, and MS. EFE is usually recognizable as a firm, whitish layer on the LV endothelial surface that, besides the thick parietal wall, further contributes to the stiffness of the LV. It can be focal, involving the papillary muscles or septum, or diffuse, covering all the ventricular cavity with severe thickening due to deposition of EFE. There is no association between the severity of the EFE and the size of the AoV.
4. LV 'dilation' associated with mitral regurgitation, with leaflet redundancy, thin LV parietal wall and giant left atrium (LA), which can produce right chamber compression.

2.4 Aortic valve and mitral valve

AA or AS is often characterized by restricted cusp excursion and post-stenotic dilation of the Asc Ao. In AA, an imperforate membrane guards the hypoplastic annulus and Asc Ao; 3 well-formed commissures can still be identified.

Congenital AS includes a wide range of morphological features, from tricuspid AoV valve dysplasia or asymptomatic bicuspid AoV, to a unicuspid, severely stenotic valve and annular hypoplasia. They can be dysplastic with nodular degeneration and thickening. The normal structure of the leaflets comprises a fibrosa covered by the ventricularis and the arterialis and by the

spongiosa located on the ventricular side between the fibrosa and the ventricularis. In the setting of dysplasia, the structure is altered, with a loss of fibrosa integrity, mucoid degeneration and nodular thickening. The dysplastic leaflets are usually thicker and more rigid than normal ones.

HLHS with MS/AS manifests with severe AS and LV remodelling to variable degrees. There may be hypoplasia or dilation, if the latter is associated with mitral regurgitation. HLHS can occur with a borderline LV or even a relatively normal LV. Valve stenosis is due, in most cases, not only to the fusion of the leaflet with the rudimentary commissures but also (sometimes mainly) to irregular cusp thickening. In the setting of a unicuspid valve, there is 1 commissure, with an eccentric intrinsically stenotic commissural orifice, 1 well-formed interleaflet triangle and a small Ao annulus and dysplastic leaflet with myxoid nodular excrescences (usually located on the LV aspect of the valve). Two raphes can be identified as remnants of the commissures, indicating a lack of leaflet separation or fusion. Bicuspid AoV are non-stenotic, but stenosis is often present when there is associated dysplasia of the leaflets. Two well-formed commissures and interleaflet triangles and 1 aborted triangle relating to the raphe can be identified. Even a tricuspid valve (TV) can be stenotic due to leaflet dysplasia. With dysplasia there is irregular cusp thickening with nodular excrescences protruding into the AoV orifice, hampering its opening.

The MV can be recognized as a nodule of white tissue in the MA with a slit-shaped LV. In a miniature LV, the MV leaflets are thin, with well-separated fine chordae and papillary muscles. In a small LV with a thick parietal wall, usually associated with MS/AA, the MV can have thick leaflets, short thick (but separate) chordae and small papillary muscles coated with EFE. Dysplasia of the leaflets is a common feature.

The Asc Ao and Ao arch can be hypoplastic to different extents, reflecting the amount of blood flowing through the ventricles into the Ao. In all subtypes, it is narrower than the pulmonary trunk. In MA/AA, the Asc Ao and aortic arch are the narrowest; in miniaturized ventricles with well-formed valves, the Asc Ao is largest. In cases with small LV and a thick parietal wall, the Ao is of an intermediate dimension. In some cases, there is paraductal coarctation due to exuberant DA tissue.

2.5 Atrial septum

The morphology of the atrial septum at birth influences the pathophysiology and haemodynamic state of the neonate. In the setting of HLHS, a restrictive FO (r-FO) is reported in 25% of cases and intact interatrial septum in 1% of pathological series and 6% of clinical series. The closed or r-FO produces foetal hydrops and LA hypertension. Abnormal lung development occurs, characterized by pulmonary cystic lymphangiectasia and pulmonary vein muscularization, which persists postnatally, with an impact on survival both at birth and later when bidirectional cavopulmonary shunt (BCPS) is attempted. The lack of communication between the atria prevents systemic oxygenated placental blood from reaching the left heart, the Asc Ao and the systemic circulation. The premature closure or restriction of the FO results in the diversion of blood flow from the LA and cardiac chamber remodelling. The RV and TV are well developed because they handle the entire Qs, which reaches the right atrium (RA). The TV can show some degree of leaflet dysplasia and abnormalities of the subvalvular apparatus. The pulmonary trunk is dilated, and the DA is prominent because it carries the entire systemic circulation. The LV is usually small with hypoplasia and dysplasia of the MV apparatus, often associated with EFE. The Ao is hypoplastic with normal origin of the coronary arteries. The AoV is hypoplastic, with the entire leaflet spectrum, from imperforate to unicuspid, bicuspid or tricuspid.

Three different patterns of the atrial cavity and atrial septum can be recognized in HLHS with intact or r-FO [18, 22, 23]:

- Type A: A relatively large LA with a thick septum secundum and a thin septum primum adherent to each other, often associated with a leftward and posteriorly deviated septum primum, and massively dilated pulmonary veins. The decompression pathway from the LA can be to the innominate vein, the right superior vena cava (SVC) and the RA. This pathway is unobstructed.
- Type B: A small, muscular LA with circumferential thickening of the atrial walls and a thick 'spongy' muscular atrial septum without distinction between the septum primum and septum secundum. The LA appears muscular and the pulmonary veins are usually small.
- Type C: A giant LA with a thin, rightwards bulging septum and identifiable septum primum and secundum, in the setting of severe mitral regurgitation. The pulmonary veins are usually large.

2.6 Pathophysiology

In the setting of AA/MA or AA/MS, which represents the most severe form of HLHS, the systemic circulation is supported by the RV with flow in the Ao arch and the Asc Ao retrogradely through the DA. In some patients with a mild form of HLHS, those with AS/MS, those with AS and LV hypoplasia or those with HLHC, the systemic circulation may depend only partially on the RV and DA, because flow to the Asc Ao and to various portions of the aortic arch and branches is supplied by antegrade flow from the LV. In rare cases of hypoplastic left heart structures without intrinsic valve stenosis or atresia, the systemic circulation may be entirely dependent on the LV, although such patients are usually in severe congestive cardiac failure and require surgical intervention.

2.7 Epidemiology

HLHS represents 8–12% of heart defects of infants with critical heart disease [24]. Untreated, it is universally fatal and accounts for 25% of deaths in the first few weeks of life [25]. There is a tendency towards a lower prevalence over the last decade [26]. The majority of such children have situs solitus and concordant AV and ventriculo-arterial connections. The RA, RV, TV and PAs are normal in size and character. An atrial septal defect (ASD) allows mixing of LA and RA atrial blood. The pulmonary veins may be dilated, particularly in the presence of a highly restrictive intra-atrial communication. Coarctation of the Ao (CoA) coexists in at least 80% of affected infants, although the severity is variable. The coronary arteries are usually normal. However, in the presence of MS, the vessel walls may be thicker, with multiple coronary artery connections to the LV.

2.8 Associated heart anomalies

Associated anomalies of HLHS include totally anomalous pulmonary venous drainage (TAPVD), TV and pulmonary valve (PV), coronary arterial anomalies, interrupted aortic arch (IAA), VSD and abnormalities of the systemic veins. Structural anomalies of the PV are rare. A bicuspid PV has been reported in 4% of cases. The presence of associated heart anomalies is important in determining the surgical approach [26, 27].

2.9 Associated syndromes

Genetic syndromes are present in ~10–25% of patients with HLHS, including Turner and Noonan syndrome, trisomy anomalies, Holt–Oram syndrome, CHARGE association and Jacobsen syndrome [28–30]. However, studies involving non-syndromic family members have suggested that heritability is complex [31]. No single disease-causing pathway has yet been identified.

2.10 Histomorphological substrates and vascular abnormalities

Cases of HLHS with AA/MA or with MA + VSD + and a patent AoV may have normal myocardial architecture at birth and normal coronary vasculature. Subtypes of HLHS with patent inflow and obstructed outflow present with disarray of the myocyte architecture and thick myocardium. Such hearts are prone to vascular abnormalities, such as coronary artery fistulas or sinusoids.

Microscopic evaluation of HLHS specimens with ventriculo-coronary connections demonstrate that sinusoids from the endocardial surface may extend into the myocardium [31]. The sinusoids frequently exist with EFE of the LV. The luminal diameters of the coronary arteries and ostia in HLHS are not different from those of control specimens.

Focusing on the microvasculature, Salih *et al.* [32] described an interesting finding that unoperated hearts with HLHS have a higher mean and maximal diffusion distance from any arbitrary point to the nearest capillary than do normal age-matched control hearts.

3. IMAGING

During infancy, the dominant imaging modality for HLHS is echocardiography because of its non-invasive nature, availability and portability in all clinical settings from the ICU to the outpatient clinic. The complementary use of magnetic resonance imaging (MRI), computed tomography (CT) and angiography before and after different surgical stages is also of value (Tables 3 and 4 and Fig. 1).

Finally, through all surgical approaches, assessment of RV and TV function (reviewed in a separate section) is vital. There will be a high degree of institutional variability as to the exact approach taken, based on modality availability, local expertise and preference. Thus, the aim will not be to strictly define a 'right' or 'wrong' approach but to critically examine all approaches.

3.1 Haemodynamic changes after birth

The postnatal assessment of HLHS should take into account the prenatal findings. The changes in loading conditions and the potential closure of foetal shunts in the transition from the prenatal to the postnatal circulation affect the interpretation of the images. There is an increase in systemic vascular resistance (SVR) due to the loss of the placental circulation after birth, coupled with hormonal changes such as an increase in corticosteroids and vasopressin. Pulmonary vascular resistance (PVR) falls dramatically, due largely to inflation of the lungs and release of pulmonary vasodilators such as endogenous nitric oxide [33]. The resulting increase in pulmonary blood flow (Qp) means that pulmonary venous return increases, increasing the LA pressure. Without administration of prostaglandin E1 (PGE1), the DA will constrict and close, with implications for maintenance of systemic arterial blood flow. The ductus venosus will also close following the loss of the placental circulation at birth.

These changes may be highly relevant for clinical decision-making after birth. For example, an LV that appears severely hypoplastic in the context of HLHC may appear larger following increased pulmonary venous return to the LA after birth. In classical HLHS, the longer-term outcome will inevitably be a functionally SV circulation. The imaging specialist needs to be aware of the requirements for effective haemodynamics, including adequate RV function, minimal TV and PV regurgitation, unobstructed systemic arterial pathways and low PVR.

With these features in mind, prenatal findings that raise specific concerns for postnatal management include the following:

- Significant tricuspid regurgitation (TR): This condition can be anticipated to worsen postnatally with increased systemic arterial pressure and vascular resistance.
- Impaired RV function: Higher systemic pressures and SVR will be expected to affect RV function adversely.
- Intact atrial septum (IAS) or r-FO: This situation has adverse effects on pulmonary vascular development, leading to pulmonary hypertensive changes and pulmonary lymphangiectasia. Pulmonary vein Doppler assessment has been used to predict severe restriction, and foetal cardiac MRI is being increasingly used to identify abnormal lung development (nutmeg lung) [33]. This modality has been helpful in identifying cases at particularly high risk after birth or potential candidates for septal perforation.

Birth weight (BW), gestational age at delivery and extracardiac anomalies (e.g. diaphragmatic hernia) may have a major impact on the initial therapeutic approach and prognosis [34, 35].

3.2 Preoperative imaging in classical hypoplastic left heart syndrome

The dominant initial modality for preoperative imaging in classical HLHS is transthoracic echocardiography (Fig. 2). Other imaging modalities (CT/MRI/angiography) should be used when relevant questions remain following echocardiographic assessment. A full sequential segmental echocardiographic examination should be performed [36, 37]. Patency of the MV and AoV should be documented, along with the morphology of the LV (slit-

Table 3: Advantages and disadvantages of different supplementary imaging modalities

Echocardiography	Magnetic resonance imaging	Computed tomography	Angiography
No radiation	No radiation	Radiation	Radiation
Moderate time use	Time-consuming	Rapid acquisition	Time-consuming
No anaesthetic	May require anaesthetic (centre dependent)	Can be done 'awake' in some cases	May require anaesthetic (centre dependent)
Non-invasive, no contrast	Non-invasive, can be done without contrast	Non-invasive, contrast required	Invasive and contrast required
No robust flow assessment, some volume assessment	Quantitative assessment of volumes and flow	Cannot assess volumes and flow	Surrogate measures of flow only
Cannot calculate PVR	When combined with catheter can calculate PVR	Cannot assess PVR	Can calculate PVR with flow assumptions
Cannot proceed to intervention if required	Cannot proceed to intervention if required	Cannot proceed to intervention if required	Can proceed to intervention if required

PVR: pulmonary vascular resistance.

Table 4: Comparison of various non-invasive imaging modalities for different anatomical areas

Area	Echocardiography	Magnetic resonance imaging	Computed tomography
Pulmonary veins	++	+++	+++
Systemic veins	++	+++	+++
Atrial septum	+++	+	+
Tricuspid valve	+++	++	-
Right ventricular function	++	+++	-
Right ventricular volume	+	+++	+
Coronaries	++	+++	+++
Aortic arch	++	+++	+++
Branch pulmonary arteries	+	+++	+++
Shunt/conduit	+	++	+++
Stents	+	+	+++
Major airways	-	+	+++
Lung parenchyma	-	+	+++

Foetal assessment	1. Echocardiogram 2. Foetal MRI for selected cases (e.g. arch or pulmonary vein anomalies)
Initial assessment	1. Clinical parameters 2. Echocardiogram 3. MRI/CT/catheterization for selected cases (e.g. arch or pulmonary vein anomalies)
Intraoperative assessment	1. Clinical parameters 2. Epicardial or transoesophageal echocardiogram 3. CT/angiography if concerns not addressed by echocardiography (e.g. shunt, PAs, arch, Ao-PA connection)
Post-Norwood assessment	1. Transthoracic echocardiography +/- transoesophageal echocardiography if concerns 2. CT/angiography if concerns not addressed by echocardiography (e.g. shunt, PAs, arch, Ao-PA connection)
Pre-BCPS assessment	1. Transthoracic echocardiography +/- transoesophageal echocardiography if uncertainty remains. 2. MRI/CT with angiography if intervention anticipated

Figure 1: Multimodality imaging pathway for hypoplastic left heart syndrome. Ao: aorta; BCPS: bidirectional cavopulmonary shunt; CT: computed tomography; MRI: magnetic resonance imaging; PA: pulmonary artery.

shaped, dilated/globular, hypoplastic). Features of particular importance may be considered systematically as follows:

1. Life-maintaining structures:
   a. Atrial septum: The atrial septum can be assessed with echocardiography, but the clinical picture is essential [7]. As Qp increases, the transatrial Doppler gradient increases. The judgement of severe restriction at the FO is better based on poor systemic arterial SO_2 (SaO_2) (reflecting reduced pulmonary venous return to the systemic circulation) and pulmonary vein Doppler interrogation, particularly significant 'a' wave reversal, i.e. flow from the atrium into the pulmonary veins during atrial contraction (Fig. 3).
   b. Ductus arteriosus: DA patency is essential to support Qs. In classical HLHS, the DA is usually large and straight, arising in the usual position, with predominantly right-to-left flow of low velocity (<2 m/s). Higher velocity right-to-left flow indicates DA restriction.
2. Prognostic features:
   a. Ventricular function: Poor RV function is a predictor of mortality throughout surgical palliation (see later detailed section on assessment of RV function) (Fig. 4).
   b. Tricuspid valve function: Significant TR is a poor prognostic factor in HLHS, especially if noted prenatally (with low SVR and pressure). Conversely, TR that was not present at birth may reflect volume loading due to high, uncontrolled Qp, which may improve when addressed during the operation (see later detailed section on assessment of TV).
   c. Pulmonary valve function: The PV (neo-AoV post-S1P) should be competent and non-stenotic. Significant stenosis and/or regurgitation (but not a bicuspid PV alone) may preclude a Norwood operation. When the neo-Ao is constructed, there is potential for further distortion of the PV; thus function should be assessed both preoperatively and intraoperatively. The PV can be imaged using 2-dimensional (2D) echocardiographic imaging and colour Doppler, and the number of cusps can be assessed using a high parasternal short-axis view.
   d. Branch pulmonary arteries: Well-developed PAs, free of obstruction, are essential for an effective SV circulation [38]. They may become distorted through staged surgical palliation, but intrinsic

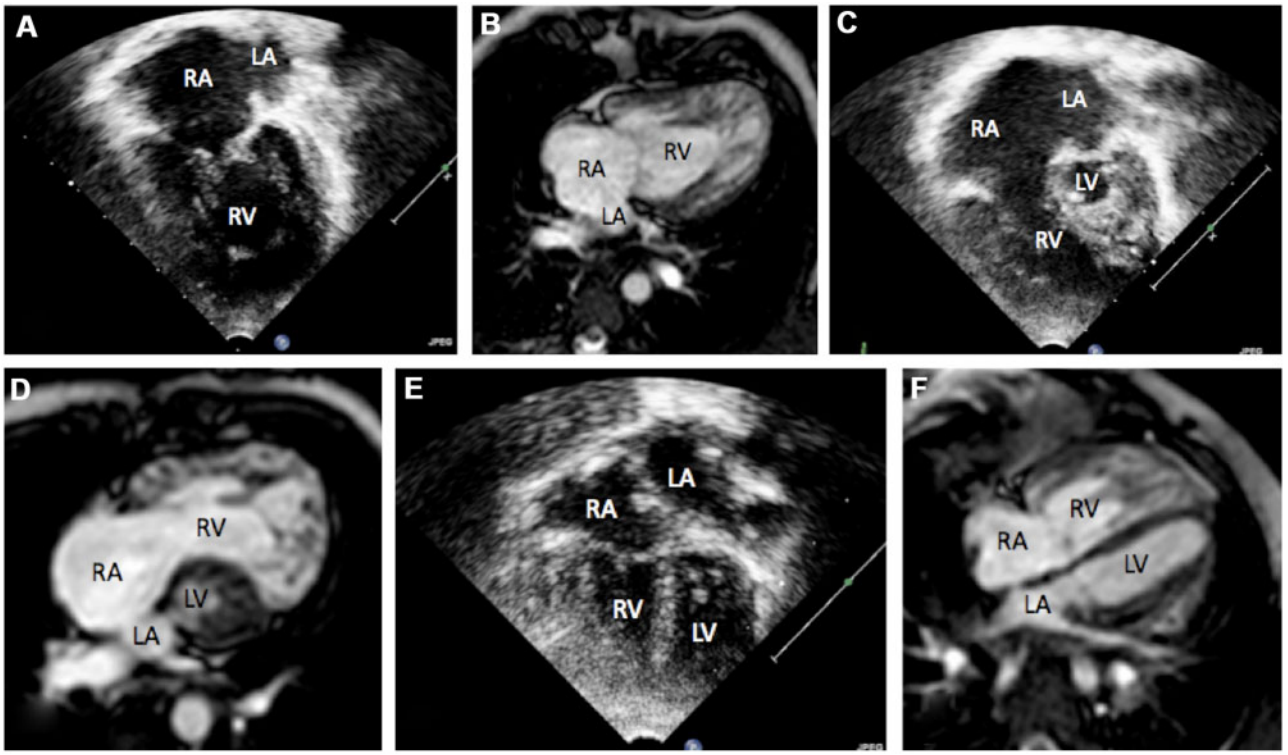

Figure 2: Morphological characteristics in case of classical hypoplastic left heart syndrome on echocardiogram and magnetic resonance scan. (**A** and **B**) Mitral atresia and aortic atresia; (**C** and **D**) mitral stenosis and aortic atresia; (**E** and **F**) mitral stenosis and aortic stenosis. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

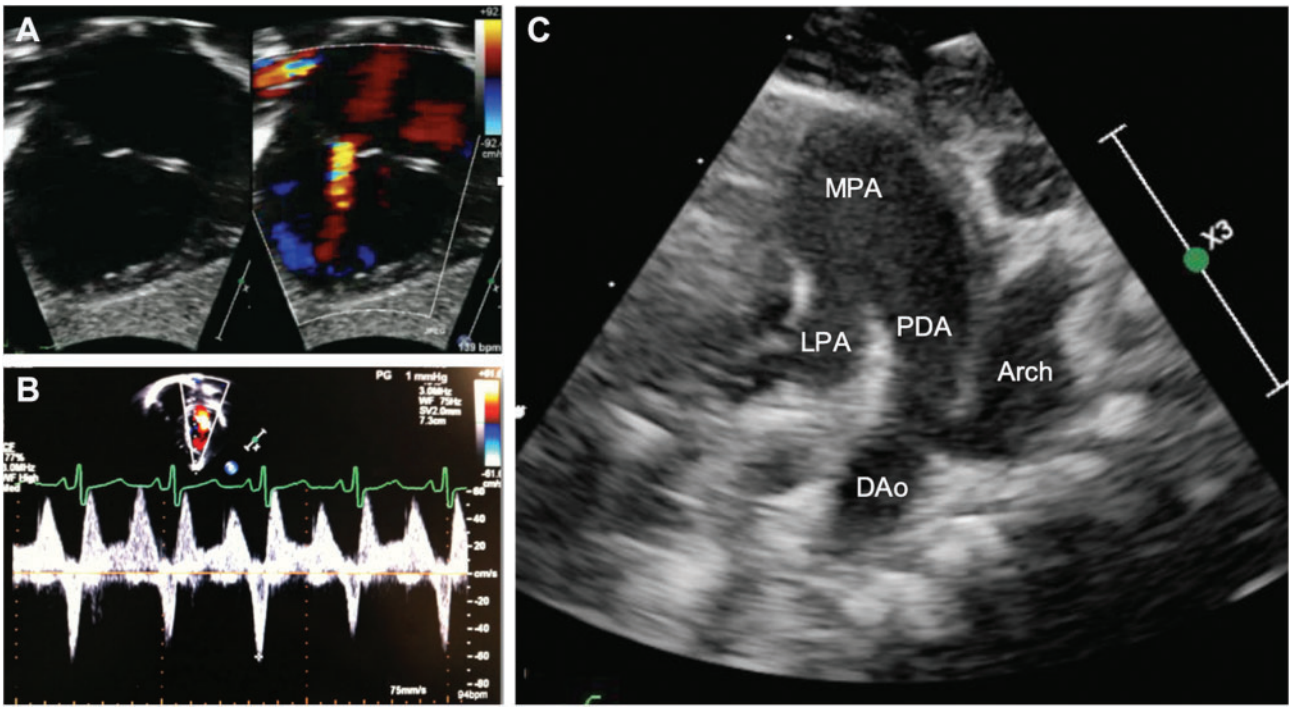

Figure 3: Life-maintaining structures. Small restrictive foramen ovale (**A**) with significant A-wave reversal on pulmonary vein Doppler scan (**B**). Large DA with coarctation of the aorta (**C**). DA: ductus arteriosus; DAo: descending aorta; LPA: left pulmonary artery; MPA: main pulmonary artery; PDA: patent DA.

hypoplasia is very important. Branch PAs are often well seen with echocardiography, but if there are significant concerns, CT or MRI can provide further information. Spiral origin of the branch PAs may be observed, usually in the context of non-classical HLHS, and may be important for the surgeon.

e. Ascending aorta: The perceived significance of Asc Ao size as a surgical risk factor varies [39, 40]. Size is of theoretical importance due to the retrograde nature of coronary perfusion after before and after S1P. The measurement is usually made in the mid Asc Ao, which in patients with MA/AA is often <2 mm in diameter.

f. Coronary arteries: Coronary arterial origins in HLHS are typically normal [41]. Coronary artery (to ventricular cavity) fistulae may be observed, particularly in the MS/AA type of classical HLHS, wherein the LV is typically globular in shape. Reports of the significance of such findings vary from a definite impact on prognosis to little or no impact [40, 41]. Coronary artery fistulae are best seen by highlighting the LV in the colour box and reducing the scale. Sometimes they can be traced to coronary arteries; other times they are just seen as 'flickers' of flow.

3. Surgical relevance:

a. Arch position and branching: In classical HLHS the Ao arch is usually left-sided, but a right arch, as well as abnormalities of branching, can occur [42]. The morphology of the arch has implications for surgical reconstruction, and an aberrant right subclavian has implications for arterial shunt placement [43, 44]. The latter also has implications for placement of a radial artery pressure monitoring line, because the aberrant right subclavian may be sacrificed at the time of reconstructing the arch. Arch sidedness and branching are often seen clearly on foetal imaging, but if there is doubt, CT or MRI can be used (Fig. 5).

b. Systemic venous anatomy: The number of superior caval veins is important for later BCPS. Interruption of the interior vena cava with azygous continuation is also essential to note, as BCPS will complete the total cavopulmonary connection (except for hepatic venous drainage).

c. Pulmonary venous drainage: The drainage of the pulmonary veins to the LA should be established using a combination of echocardiographic views including the superior 'crab' view, which can show the drainage of most or all veins. Superiorly directed flow from the LA through a persisting levoatrial cardinal vein should be sought. TAPVD is suspected when there is a pulmonary venous confluence separate from the LA. This is particularly relevant with obstruction to pulmonary venous drainage, because there may have been long-standing pulmonary venous hypertension during foetal life with implications for growth and development of the pulmonary circulation. This situation can translate into an unacceptably high PVR to achieve an effective SV circulation. Non-obstructed TAPVD does not preclude S1P but has prognostic importance for PVR. Suspected abnormalities of the pulmonary venous drainage can be confirmed on CT, MRI or angiography. Postoperative review of repaired TAPVD using the same modalities is also indicated. Partially anomalous pulmonary venous drainage to the caval veins is not important for S1P but is relevant at later stages.

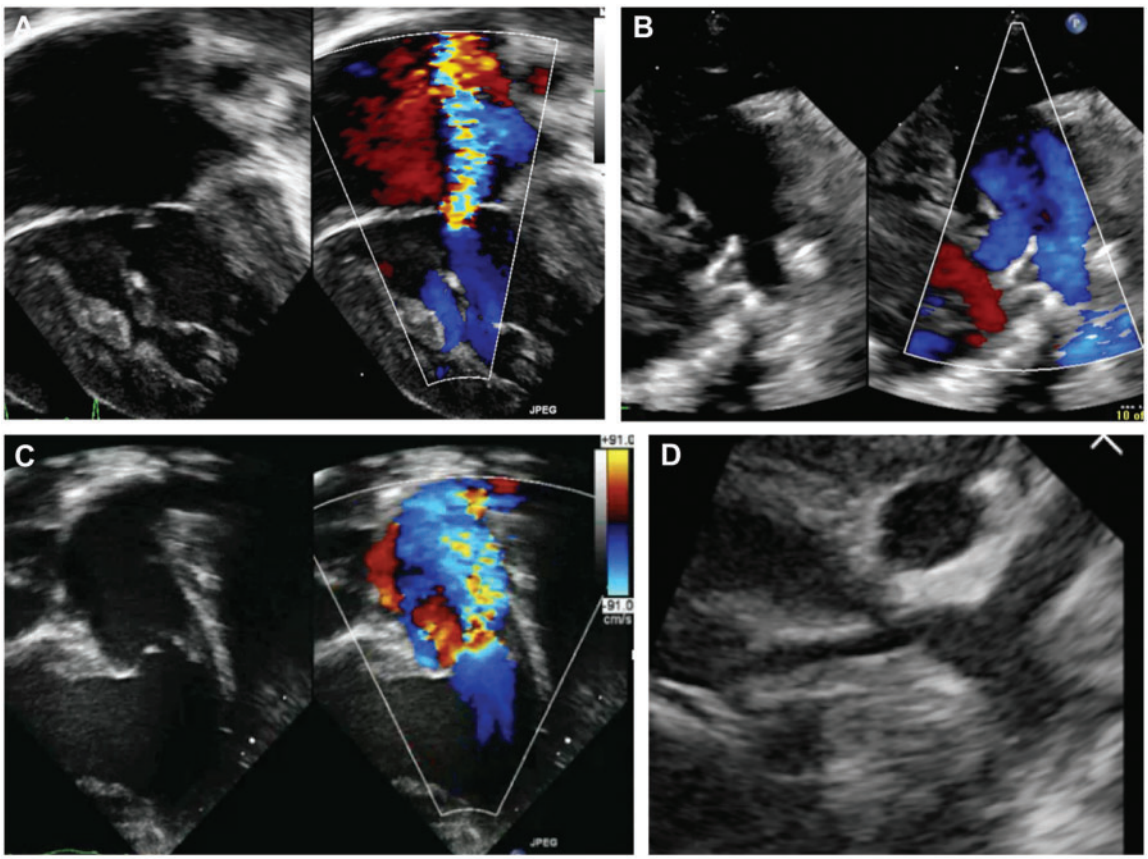

Figure 4: Prognostic factors. Tricuspid regurgitation (**A**); branch pulmonary arteries (**B**); stenotic pulmonary valve (**C**); and small ascending aorta (**D**).

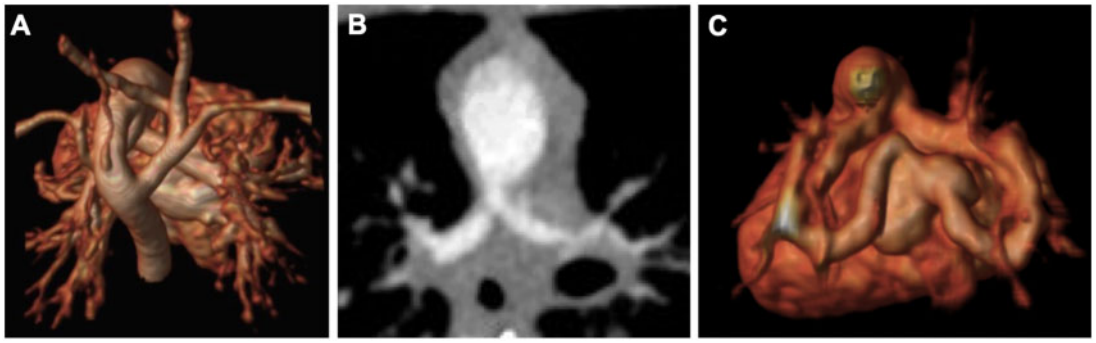

Figure 5: Further preoperative computed tomographic images. Right aortic arch with aberrant right subclavian artery (**A**), hypoplastic branch pulmonary arteries (**B**) and abnormal morphology of the pulmonary veins (**C**).

3.3 Preoperative imaging in hypoplastic left heart syndrome variants

Individual cardiac anatomy and loading conditions must be considered. For example, an ASD may direct blood flow left to right or render assessment of MS difficult. Ventricular volumes can be assessed quantitatively by MRI but only form part of the picture, because patients may have an adequate ventricular size with inadequate valves, or an apparently 'small' ventricle may be discounted in the presence of a large left-to-right atrial shunt [45].

3.3.1 Critical aortic stenosis. The morphology of the AoV should be assessed in terms of numbers of cusps and leaflet fusion. Measurements of the left heart structures should be made and *z*-scores calculated. Assessment of the MV size, stenosis and regurgitation is important to guide the initial approach. EFE is often seen in AS as a white layer on the endocardium, often affecting the papillary muscles and affecting MV function. Identification of EFE is subject to observer error on echocardiography. Late gadolinium enhancement on MRI may assist in assessing the severity and distribution of EFE but may be technically difficult in early infancy [46]. Different scores have been proposed to predict the likelihood of successful biventricular repair in the short term [47–49]. However, some patients will develop pulmonary hypertension (PHT) due to LV diastolic dysfunction. In others, further procedures for MS, EFE or even Ross/Konno surgery may be necessary to optimize borderline bi-V physiology. The h-S1P can be used to delay decisions concerning risk stratification and SV or bi-V repair beyond the neonatal period.

3.3.2 Hypoplastic left heart complex. Loading conditions in severe CoA can make assessment of the left heart difficult. In patients with this condition, it is best to allow the PVR to fall to allow the left heart to be 'challenged' prior to making a decision. *z*-Scores can be used to assess the relative sizes of the structures, but many of the available algorithms are designed for critical AS and may not be applicable in HLHC.

3.3.3 Unbalanced atrioventricular septal defect. Assessment should be made of associated features, e.g. AoV issues and CoA. The size of the ventricular and atrial components should be noted. Malalignment of the atrial and ventricular septa predicts difficulty in septation. Assessment of the AV valve itself and the size of each component can provide additional information. Scores are available to assess different areas, e.g. ratio of left AV valve area to total AV valve area and inflow angle [50–52].

3.4 Intraoperative imaging for Norwood stage 1 palliation

Imaging modalities in the operating room comprise clinical assessment using invasive methods as well as echocardiography (Fig. 6). There are a number of potential approaches to intraoperative imaging of the initial operation. Epicardial echocardiography can be extremely useful but is very operator dependent, and good communication between the surgeon and imaging specialist is essential. Not all views are possible, because fragile patients will not tolerate prolonged attempts. Transoesophageal echocardiography (TOE) can be performed using a size-appropriate probe but can also compromise ventilation and haemodynamics. TOE has been facilitated by the development of 'micro' TOE probes suitable for the smallest infants, now extending to weights <2 kg [53, 54]. Transoesophageal intravascular ultrasound catheters have been employed (off label) in selected cases [55, 56]. Advantages of TOE include multiplane images that can be generated while the surgeon operates. The epicardial approach has the advantage that components of the S1P can be readily imaged, including the shunts and the reconstructed Ao arch, which may be more technically difficult with TOE. Intravascular probes have limited imaging planes, are expensive and are designated as single use. There are few comparative studies of the different modalities, and the choice is institution-dependent. A summary of the TOE/epicardial views is shown in Tables 5 and 6.

Following the operation, the imaging specialist needs to consider the haemodynamic picture and address surgical concerns (Fig. 6). If there is concern over any surgical technical issue, then additional imaging modalities may be required. This applies particularly to areas of the repair that are difficult to assess by echocardiography, for example, shunts and branch PAs. Some centres may have the ability to perform exit angiography with a portable

C-arm or in a hybrid operating room, but moving to a catheter laboratory or CT may take time and increase clinical risk. For cases requiring extracorporeal membrane oxygenation (ECMO), it may be better to perform further investigations after stable extracorporeal support has been established.

Structured echocardiographic operative reporting systems such as the Technical Performance Score may provide a useful metric for HLHS surgery but should always be considered in the context of the clinical picture [58, 59]. Thus, due to the limitations of echocardiographic assessment alone outlined above, an 'optimal' score based on echocardiographic imaging should not preclude further investigation if there are clinical concerns.

Imaging of the RV–PA conduit can be challenging because any pressure from a probe placed directly on the shunt or conduit can cause haemodynamic compromise. The RV–PA conduit is anterior and more accessible than a modified Blalock–Taussig shunt (MBTS). If the shunt or conduit is seen, attention should be paid to both proximal and distal anastomoses and the lie of the tube graft, which should not be kinked. Flow in an MBTS can be affected by the size of the innominate artery, and significant flow acceleration in this area should be noted. In RV–PA conduits, proximal obstruction from ventricular muscle is possible. If the shunt or conduit cannot be seen, then flow in the branch PAs and haemodynamics may help assess the Qp.

3.4.1 Echocardiographic views. Parasternal short- and long-axis views are similar to those obtained with transthoracic echocardiography. Tilting the echo probe anteriorly will bring in the neo-Ao and Ao-PA connection. Directing the echo-beam inferiorly will bring in the TV. A four-chamber type view can be obtained by moving the probe towards the apex of the heart. A high long axis may be possible by placing the probe over the neo-Ao or shunt. This view can also interrogate the reconstructed Ao arch.

3.5 Imaging after Norwood stage 1 palliation atrial communication

Resection of the entire atrial septum is generally not advisable or possible, particularly in cases with a small LA, so in most newborns residual tissue will be seen. Assessment is, as

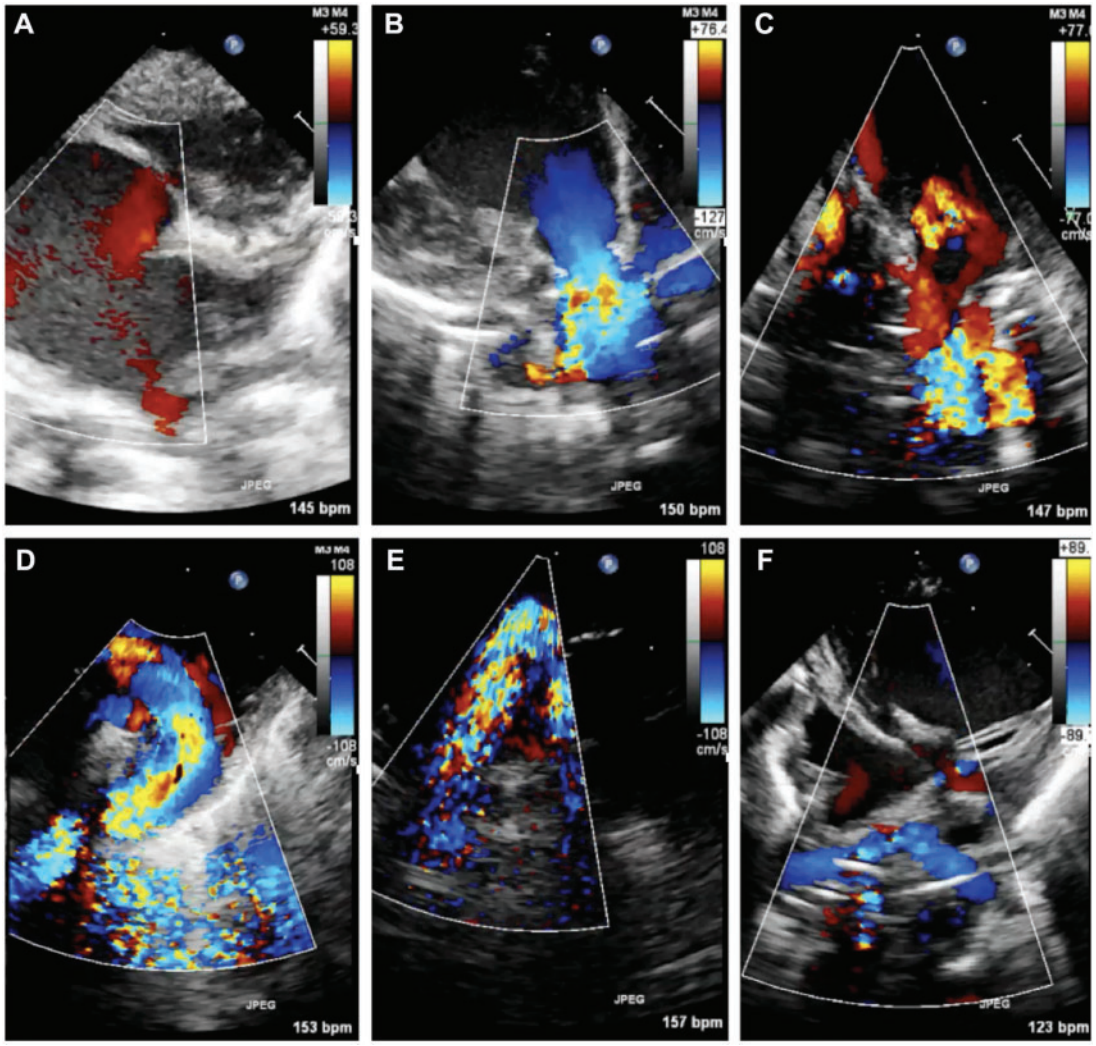

Figure 6: Intraoperative assessment of the Norwood procedure. Unrestrictive foramen ovale (**A**); unobstructed neoaorta (**B**); flow in the proximal aortopulmonary connection (**C**); unobstructed aortic arch (**D**); flow in the shunt (**E**); and flow in both undistorted branch pulmonary arteries (**F**).

preoperatively, based on a combination of echocardiographic parameters and the clinical status of the baby, including evidence of congestion on the chest X-ray. Due to high Qp, the transatrial gradient should not be used alone (Fig. 7).

1. Neoaortic valve: It is essential to assess for stenosis or regurgitation, either intrinsic to the valve or caused by distortion following S1P. Assessment includes 2D, colour and Doppler echocardiography. Pulsed-wave Doppler permits localization of the level of stenosis.
2. Aorta-pulmonary artery connection and coronary flow: The connection can be challenging to image, and in the presence of ventricular dysfunction or changes on the electrocardiogram (ECG), further imaging modalities may be required. Torsion of the native Asc Ao and anastomotic narrowing are the key issues.
3. Aortic arch: All components should be assessed, from the Asc Ao to the distal arch. Pulsed-wave Doppler can be useful to assess the exact level of obstruction. Obstruction can arise from torsion of the arch, anastomotic suture lines, residual ductal tissue or degenerative changes in the patch material employed. It is useful to know the exact reconstructive technique employed. Arch obstruction can usually be seen clearly on echocardiographic scans, but CT and MRI can give more precise information [60].
4. Pulmonary blood flow: Assessment consists of review of the branch PAs and the mode of Qp. Branch PAs can thrombose, have anastomotic narrowing or become twisted, rotated or stretched. The MBTS can usually be seen clearly on echocardiographic scans but viewing the more anterior RV–PA conduit can be more difficult. With both the MBTS and the RV–PA conduit, both ends of the shunt as well as the calibre must be reviewed. The type of RV–PA conduit (ringed or not) should be noted before the assessment, along with the insertion technique (trans-myocardial, 'dunk' technique). The RV–PA conduit can lie either to the left or to the right of the neo-Ao, and this information should be known prior to assessment.

If SaO_2 remains low despite what appears to be adequate patency on echocardiographic scans, or if there seems to be PA distortion, then consideration should be given to another imaging modality. Angiography allows intervention if required, but CT and MRI are less invasive [61, 62]. After S1P, CT provides better resolution and is quicker than MRI and therefore might be better tolerated by a non-anaesthetized patient. Doppler flow patterns differ between the MBTS and RV–PA conduit, the latter having more pulsatility. Pulsed Doppler interrogation at different points may highlight a significant step-up in velocity, indicating a stenosis. Additionally, if flow velocity through the shunt is low, the shunt may be large or the PVR still elevated.

3.6 Imaging after hybrid stage 1 palliation (see also Hybrid section)

Assessment after h-S1P involves the specific anatomical interventions plus continued review of RV and TV function (see later specific sections on RV and TV) (Fig. 8). Specific areas of concern include:

1. Atrial communication: An atrial septostomy may be performed at the same time as h-S1P. Even after an atrial intervention, r-FO can recur. A transatrial gradient alone is not sufficient to assess the FO, because the derived gradient is dependent both on pulmonary venous return and the size of the FO. Pulmonary venous flow patterns should be assessed as well as the transatrial gradient. Bilateral

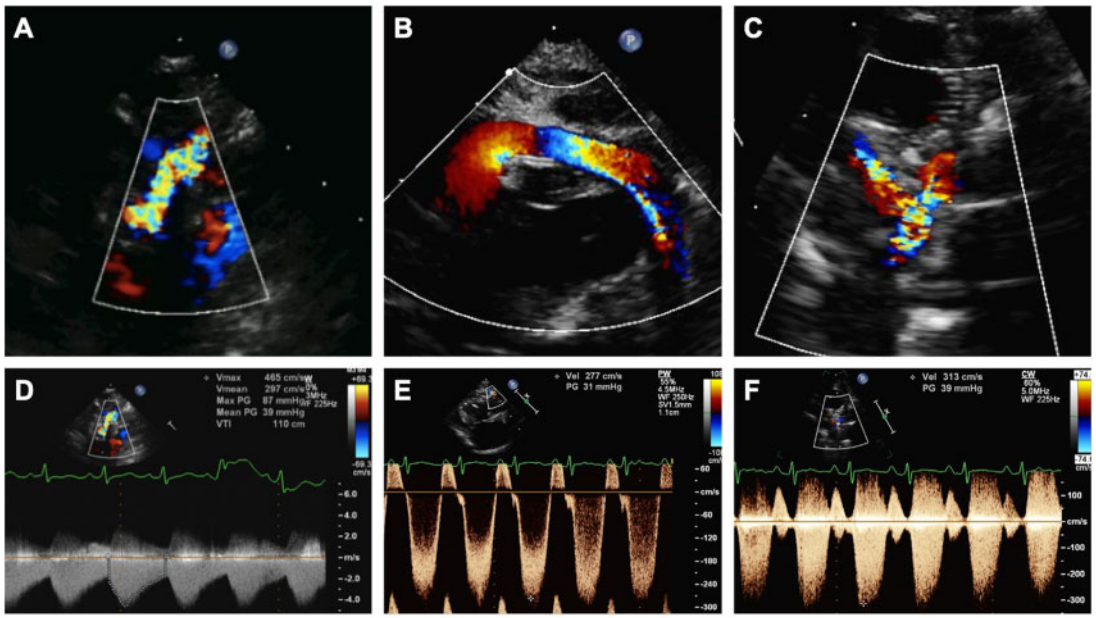

Figure 7: Post-Norwood echocardiography (**A–F**). Modified Blalock–Taussig shunt flow (**A**) and Doppler scan (**D**); proximal right ventricle–pulmonary artery conduit (**B**) and Doppler scan (**E**); distal right ventricle–pulmonary artery conduit and branch pulmonary arteries (**C**) and Doppler scan (**F**).

pulmonary artery banding (b-PAB) Doppler interrogation shows changes with an increasingly r-FO. The wave form shifts from sawtooth to pulsatile, with a lower diastolic velocity. This pattern can 'normalize' after a successful atrial intervention.

2. Pulmonary artery banding: The usual pattern for pulmonary artery banding (PAB) is sawtooth. As stated previously, a loss of this pattern in combination with clinical and echocardiographic evidence of r-FO can be helpful. If the sawtooth pattern is not present without evidence of r-FO, the cause could be increased PVR or a loose band. A chest X-ray may differentiate between the 2 potential causes. Each b-PAB should be assessed separately, and the best position for Doppler interrogation is the high parasternal short axis.
3. Ductus arteriosus stent: Velocity through the DA stent trends upwards with time. Early high velocity (>2 m/s) or a significant upward trend may suggest stent obstruction due to stent neo-intimal proliferation or DA constriction if the stent has not completely covered the DA tissue. Pulsed Doppler interrogation should be performed:
   a. Prior to stent placement
   b. Proximal, mid and distal stent (intraoperatively)
   c. Beyond the stent
4. Retrograde arch flow: In the absence of antegrade Ao arch flow, obstruction of retrograde flow into the native arch may occur due to arch hypoplasia/CoA or the ductal stent. This can compromise coronary blood flow, leading to myocardial ischaemia with reduced cardiac function and/or ischaemic ECG changes. An increased retrograde systolic velocity into the transverse arch may be seen but is often underestimated with echocardiography. If obstruction is suspected, then CT or angiography should be considered.
5. Reassessment of the left heart: If the hybrid procedure has been performed to allow further growth and assessment of left heart structures, it is important that a full left heart assessment, as described previously, be performed.

3.7 Assessment prior to bidirectional cavopulmonary shunt

Timing of the BCPS is optimal at ∼3–6 months of age [63]. The Single Ventricle Reconstruction Trial (SVRT) did not show any difference in cardiac size or function between S1P with MBTS and S1P with RV–PA conduits when studied with echocardiography [64, 65]. However, adverse remodelling was noted in the latter group when assessed with computational haemodynamic models [64] (Fig. 9).

A successful BCPS requires adequate branch PAs and normal downstream resistance. A recent review of practice confirmed that most children undergo cardiac catheterization prior to BCPS [65] to assess suitability. However, in most children there are no concerns about the distal resistance; therefore, non-invasive assessment with echocardiography and MRI/CT is sufficient, yielding comparable results compared to angiography [61, 66, 67]. If there are concerns about the PVR, or if intervention is being considered for either a shunt or branch PAs, then a cardiac catheter study should be performed. In addition to assessing the branch PAs and the number, size and position of the SVC, operated areas should be reviewed as described previously, with further assessment of the RV and TV function. At this assessment, it is important to confirm the pulmonary venous drainage, because anomalous veins draining to the SVC will need to be dealt with during the BCPS operation.

Cardiac CT has emerged as another modality to reduce the risk of the anaesthetic required (in some centres) for catheterization. MRI and CT can show changes in structure and function as well as assist with surgical planning in cases with complex arch obstruction [68, 69]. Volume loading of the RV is often seen after S1P, with reduced function and TR, the latter attributed to annular dilation and distraction of papillary muscles [70]. After BCPS (with cavitary volume reduction) the function often improves

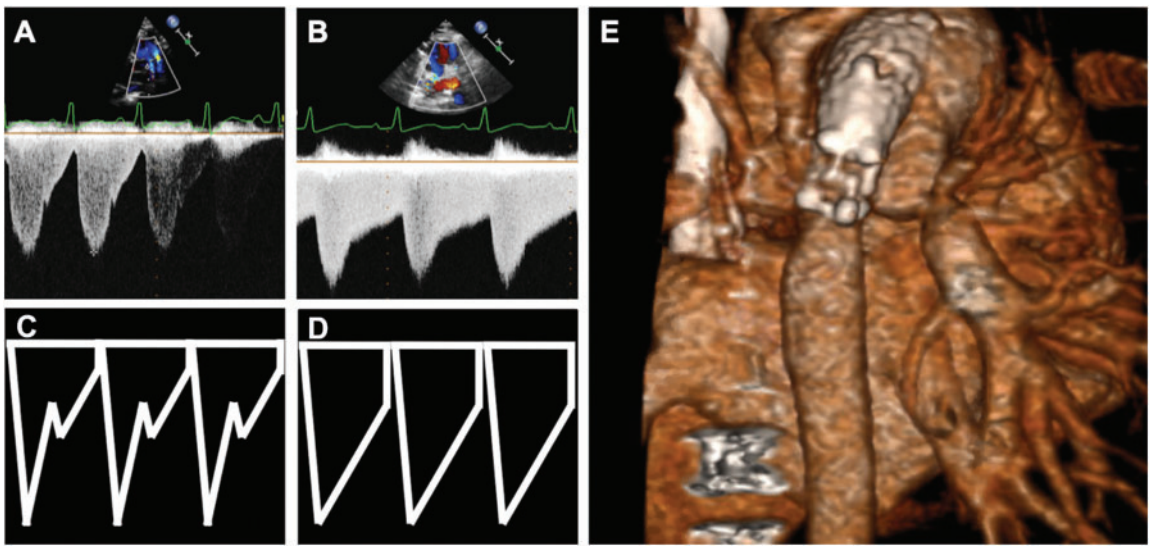

Figure 8: (**A–E**) Echocardiography after hybrid stage 1 palliation. Left pulmonary Doppler scan in the presence of restrictive foramen ovale (note trace is more 'pulsatile' than 'sawtooth') (**A** and **C**); left pulmonary artery Doppler scan after septostomy (note trace has regained 'sawtooth' pattern); (**B** and **D**) distal stent obstruction on computed tomography (**E**).

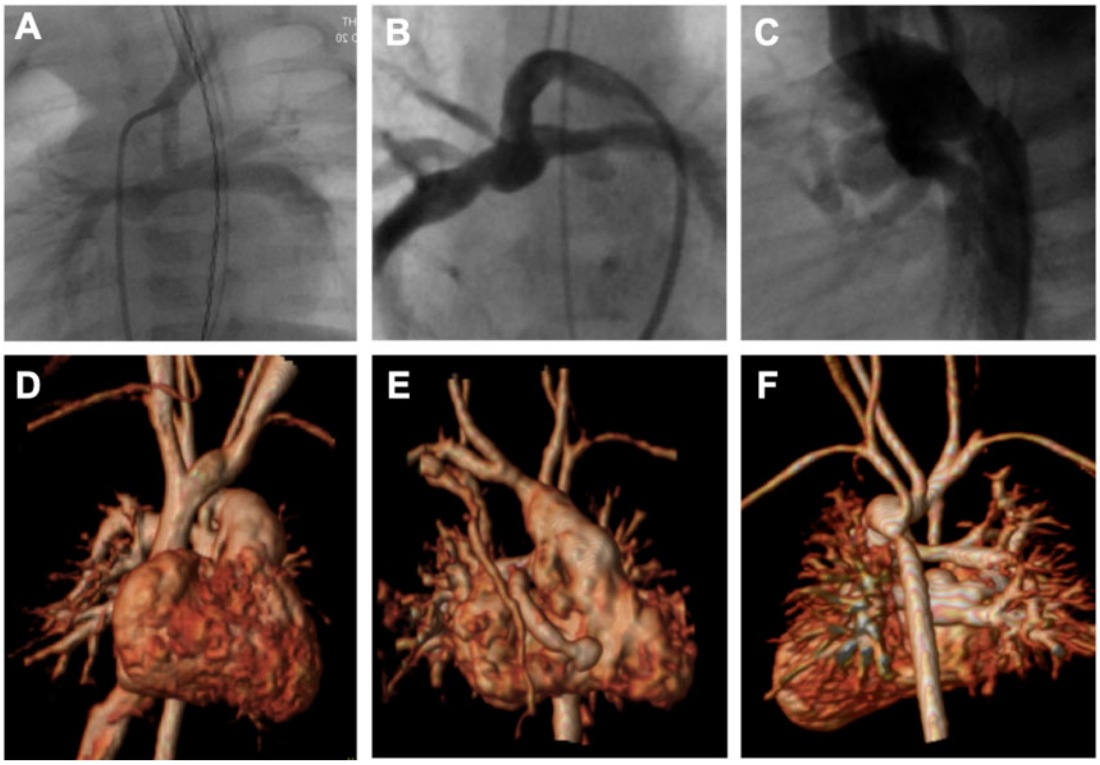

Figure 9: (**A–F**) Assessment prior to bidirectional cavopulmonary shunt. Classical Norwood procedure: angiogram of modified Blalock–Taussig shunt and branch pulmonary arteries (**A**) and magnetic resonance imaging 3-dimensional reconstruction (**D**); Norwood procedure with right ventricle–pulmonary artery conduit: angiogram of polytetrafluoroethylene tube with some proximal narrowing (**B**) and magnetic resonance imaging 3-dimensional reconstruction (**E**) with some proximal narrowing; arch reconstruction with some distal narrowing on the angiogram (**C**) and the magnetic resonance imaging (**F**).

[71]. For that reason, impaired contractility *per se* is not a contraindication to BCPS but potentially an indication for earlier S2P. In contrast, improvement in moderate or severe TR is seldom seen after BCPS, possibly due to significant TR being caused by an intrinsic abnormality in the TV rather than volume loading alone.

3.8 Right ventricular volume and function

In order to interpret functional metrics in HLHS, changes in RV preload must be understood. When PVR falls postnatally, assuming that there is unobstructed flow across the FO, preload increases. An S1P aims to regulate Qp through a restrictive shunt (or b-PAB). As a child grows, the diameters of systemic-to-pulmonary shunts, RV to PA conduits and PABs remain relatively constant, possibly leading to a gradual fall in effective RV preload. Likewise, after BCPS, only blood from the SVC will reach the pulmonary circulation, with a fall in Qp/Qs, leading to a significant fall in preload [72] (Fig. 10).

The current standard for measuring RV volume, flow and RV ejection fraction is cardiac MRI, although CT is emerging as a comparable modality [69]. MRI has the additional benefits of quantifying TR and providing anatomical information required for BCPS, including the size of the branch PAs, shunt imaging and adequacy of Ao arch reconstruction. For volume assessment, 3-dimensional (3D) echocardiography and cardiac MRI correlate well in adults and older children [73, 74], but there is a bias for the former to produce lower volume measurements than cardiac MRI, which appears most marked in smaller patients [73–75].

Assessing RV systolic function in HLHS is problematic, given the changes in volume loading summarized above. Virtually all metrics of cardiac function are load dependent, so caution should be observed in the interpretation of results. Most studies have addressed the impact of systolic ventricular function on outcome, but diastolic function is also extremely important, particularly when the ventricle becomes 'preload deprived' following the BCPS.

Favourable RV systolic function predicts early survival after S1P [76, 77]. However, subjective assessment of RV function in HLHS by echocardiography is challenging, with poor agreement with MRI, even in experienced hands [78]. Objective echocardiographic assessment of RV systolic function in HLHS is particularly difficult given the complex morphology, anteriorly located RV and coarse trabeculations. In clinical practice, a number of different parameters have been applied, most of which have simply been extrapolated from assessment of the bi-V circulation. There are few studies of 'normal' ranges in HLHS, and often RV values from patients with a structurally normal heart are used for comparison. Recent studies have compared functional data from normal hearts to HLHS with preserved or reduced systolic function to guide expectations [79]. Furthermore, recent data have shown the impact of LV morphology on myocardial deformation. There is reduced septal deformation in cases with larger LVs [80]. The presence of RV apical bulging, related to a larger LV, also has a negative impact on global RV deformation, with an impact on clinical outcome [81]. Serial measurement of RV deformation using speckle tracking has been shown to affect surgical outcome when assessed post-S1P or pre-BCPS, so this means of analysis may be useful prognostically but must take into account the morphological differences within the HLHS group [82–84]. In practice, these measures may be more useful in tracking patients

Table 5: Suggested structure for intraoperative assessment based on echocardiographic and clinical factors

Area of interest	Suggested echocardiographic views	Echocardiographic findings	Other evidence
Atrial septum and foramen ovale	Epicardial parasternal short axis Epicardial and TOE four-chamber TOE 0°, 45°, 90°	Optimal: Mean gradient <2 mmHg[a] Adequate: Mean gradient 2–4 mmHg Inadequate: Mean gradient >4 mmHg	Pulmonary haemorrhage may suggest LA hypertension
Proximal arch	Epicardial parasternal long axis TOE 60°	Optimal: Peak gradient <20 mmHg Adequate: Peak gradient 20–40 mmHg or <30% discrete narrowing on 2D or colour Inadequate: Peak gradient >40 mmHg or >30% discrete narrowing on 2D or colour	Gradient between the upper and lower limb arterial lines >20 mmHg
Distal arch	Epicardial parasternal long axis Epicardial high long axis High mid-oesophageal TOE views	Optimal: Peak gradient <20 mmHg Adequate: Peak gradient 20–40 mmHg or <30% discrete narrowing on 2D or colour Inadequate: Peak gradient >40 mmHg or >30% discrete narrowing on 2D or colour	Gradient between the upper and lower limb arterial lines >20 mmHg
Ao-PA connection and coronary flow	Epicardial high parasternal long axis (anterior tilt) Epicardial high parasternal short axis TOE 60° view	Concern on echo 2D and/or colour Poor RV function	Ischaemic features on ECG
Qp	Epicardial parasternal short axis Epicardial parasternal long axis Epicardial high long axis	Good flow in shunt/conduit and both branch PAs without distortion	SO_2 Arterial pulse pressure
TV	Epicardial parasternal long axis Epicardial four-chamber TOE 0° four-chamber view, 60°, 90° and 120° TOE transgastric	Grade of TR Flail chords	CVP trace may be pulsatile in severe TR

[a]Optimal: accept. Adequate: team discussion about accepting. Inadequate: operative revision indicated. NB: Where numbers are quoted, this was designed on postoperative echocardiograms.
CVP: central venous pressure; 2D: 2-dimensional; ECG: electrocardiogram; LA: left atrium; PA: pulmonary artery; Qp: pulmonary blood flow; RV: right ventricle; SO_2: oxygen saturation; TOE: transoesophageal echocardiogram: TR: tricuspid regurgitation; TV: tricuspid valve.

Table 6: Summary of evidence for imaging at each stage

Stage	Imaging modality	Evidence
Foetal	Echocardiography Foetal MRI	Echocardiography is the standard method used in all institutions Foetal MRI may be considered if available to look at lung parenchyma or complex arch anatomy [2, 57]
Preoperative	Echocardiography Cardiac MRI Cardiac CT Angiography	Echocardiography is the standard method used in all institutions Cardiac MRI or CT may be used if available to clarify complex anatomy Angiography in selected cases
Intraoperative	Epicardial echocardiography Transoesophageal echocardiography Exit angiography	Echocardiography is the standard method for assessment but is not uniformly performed. Epicardial echocardiography or TOE depends on unit preference and facilities Some institutions use exit angiography for unexplained desaturation or suspicion of arch obstruction
After SP1	Echocardiography Cardiac MRI Cardiac CT Angiography	Echocardiography is the primary method of monitoring, with use of CT, MRI or angiography if there are concerns. This will be unit dependent and based on available facilities. Angiography is often considered the best modality if an intervention is felt likely
Pre-BCPS assessment	Echocardiography Cardiac MRI Cardiac CT Angiography	Transthoracic echocardiography with 3D and TOE added for concerns over the AVV is standard. For assessment of BCPS there is no difference in MRI alone versus angiography [31, 32]. Some centres use CT rather than MRI

AVV: atrioventricular valve; BCPS: bidirectional cavopulmonary shunt; CT: computed tomography; 3D: 3-dimensional; MRI: magnetic resonance imaging; SP1: stage 1 palliation; TOE: transoesophageal echocardiogram.

Table 7: Summary of range of right ventricular function techniques that are applied in clinical practice and some of their limitations

Method	Advantages	Disadvantages
TAPSE	Simple and rapid	• No HLHS normal ranges • Longitudinal function only • Translational motion
RV FAC	Moderately easy to perform Good correlation with MRI EF	• Automated FAC more repeatable than manual • No HLHS 'normal' ranges
TR dP/dT	Simple and rapid	• No HLHS 'normal' ranges • Only applies if TR is present
Pulsed tissue Doppler of TV annulus	Simple and rapid	• No HLHS 'normal' ranges • Longitudinal function only
MPI	Easy to calculate using TDI Pulsed Doppler scan of blood flow requires inflow and outflow views	No correlation with MRI
S:D ratio	TR necessary to calculate Prognostic value in adults	Impact of heart rate on values
3D echo	Aims to measure true RV volumes and EF	Variable correlation with MRI EF
2D strain	Measures deformation of myocardium Automated/highly repeatable Correlates with MRI EF	• No HLHS normal ranges • Impact of different morphology • Impact of different vendor software

2D: 2-dimensional; 3D: 3-dimensional; dP/dT: change in pressure/change in time; EF: ejection fraction; FAC: fractional area change; HLHS: hypoplastic left heart syndrome; MPI: myocardial performance index; MRI: magnetic resonance imaging; RV: right ventricle; S:D: systolic:diastolic; TAPSE: tricuspid annular plane systolic excursion; TDI: tissue Doppler imaging; TR: tricuspid regurgitation; TV: tricuspid valve.

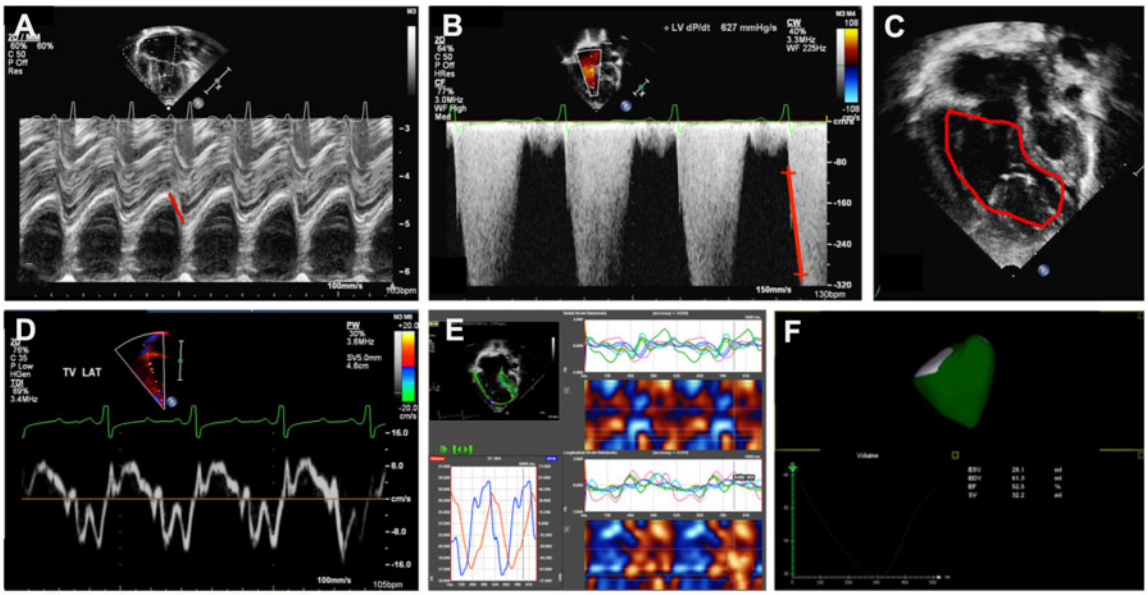

Figure 10: Echocardiographic assessment of right ventricular function. (**A**) Tricuspid annular plane systolic excursion; (**B**) right ventricle; (**C**) dP/dT fractional change area; (**D**) tissue Doppler imaging; (**E**) speckle tracking; 3-dimensional right ventricular volume and (**F**) functional analysis. dP/dT: change in pressure/change in time; LV: left ventricle; TV: tricuspid valve.

over time than as absolute values, but even this may be difficult in patients undergoing different procedures that have an impact on loading conditions. Furthermore, the presence of significant TR permits the RV to decompress into the RA, with further impact on reliable assessment of RV contractility function. Table 7 summarizes the techniques applied in clinical practice and some of their limitations [80–83, 85].

1. Tricuspid annular plane systolic excursion [57, 86]
   - Quick and easy to perform
   - Correlates with exercise capacity after Fontan [87]
2. Fractional area change [88, 89]
   - Better correlation when automated method is used
3. Pressure change with time [90]
   - Reliant on TR and loading conditions

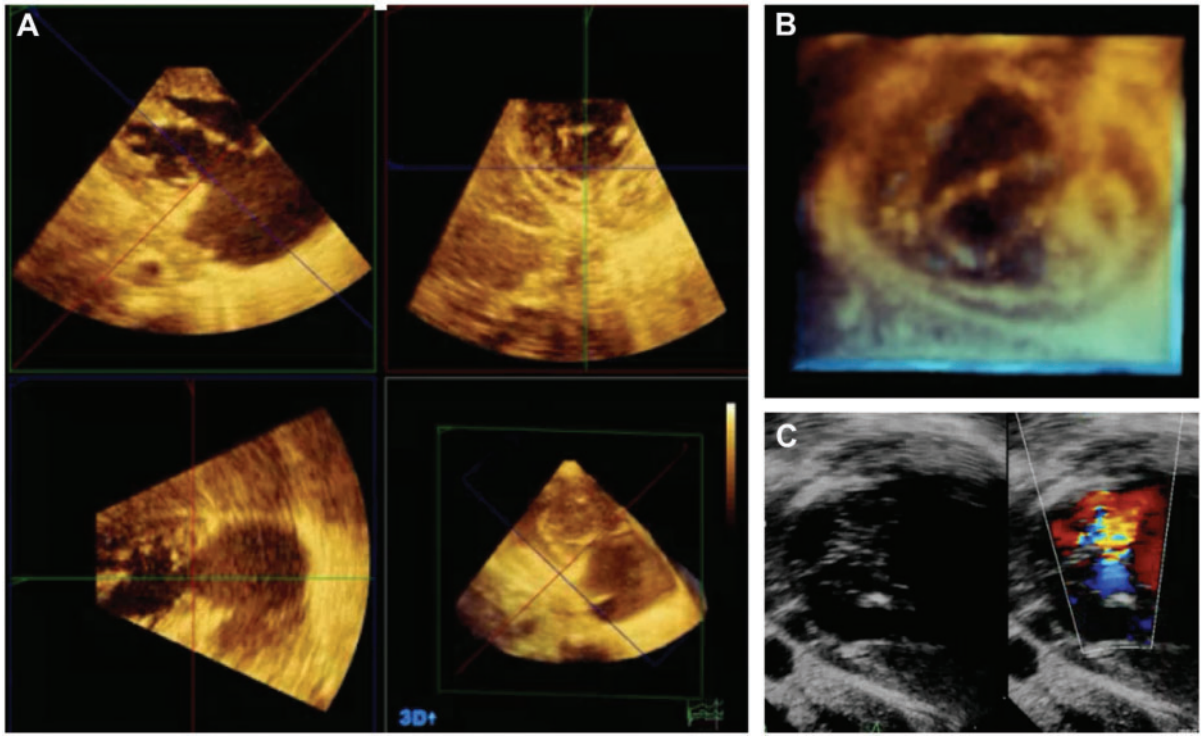

Figure 11: Assessment of the tricuspid valve. 3-Dimensional multiplanar reformat (**A**), 3-dimensional rendering (**B**) and 2-dimensional rendering with colour (**C**).

4. Tissue Doppler [91, 92], myocardial performance index [93–95], systolic-to-diastolic time ratio [96]
5. Important to correct for age and heart rate (HR)
6. For non-tissue Doppler methods, TR must be present
   - 3D Echocardiography [75, 97]
   - Less accurate in smaller children
   - Useful for assessment of TV
   - No difference in 3D volume and function between different shunt-conduit types [73]
7. Speckle and strain [70, 86, 98, 99]
   - Investigation of synchrony
   - Can be used to improve previously manual measures: FAC, tricuspid annular plane systolic excursion
   - Has been studied in relation to Qp source. Abnormal circumferential deformation in RV–PA conduit cases [100]
8. Diastology [101, 102]
   - Due to differences in SV preload, standard measures cannot be interpreted in the same way

3.9 Tricuspid valve assessment

In HLHS, 12% of right AVVs are bicuspid, and a further third are moderately or severely dysplastic [103] (Fig. 11). 2D echocardiography has significant limitations in defining TV anatomy and regions of regurgitation, and a systematic correlation with surgical findings has shown relatively poor agreement [104].

The investigation of the mechanism of TR is particularly important because of the need for TV repair during staged surgical procedures in about a third of patients. Structural abnormalities include dysplasia, apical displacement of leaflets (as in Ebstein anomaly), bi-, tri- or quadrileaflet morphology, leaflet tethering and/or prolapse and accessory orifices. Superimposed on the morphological abnormalities are functional components, including RV dysfunction, RV dys-synchrony and TV annular dilation.

The introduction of real-time 3D echocardiography has facilitated assessment by permitting projection of rendered en face views of the TV as well as systematic 'dissection' of the TV using multiplanar reformatting techniques [105]. These techniques, when combined with 3D colour flow and Doppler, permit mapping of regions of TR as well as identification of leaflet number, clefts and failures of coaptation. The size of the TV annulus can also be accurately measured in all planes. Most software permits the above interrogation of the valvar structure and gives a semi-quantitative guide to severity of TR.

In a research setting, a 3D echocardiographic approach can be quantified to compute a TV tethering volume, which correlates with the indexed RV volume, severity of TR and outcome [106]. Recent work following patients pre-S1P through to BCPS has shown that TR is associated with greater leaflet size and prolapse rather than failure of coaptation [107]. Aside from morphological considerations, there appears to be a relationship between myocardial contraction patterns and severity of TR in HLHS. In a 2D strain study, patients with a large difference between the RV free well and septal peak systolic strain had worse TR than those with a smaller difference. Similarly, a high dispersion of time to peak systolic strain was associated with more severe TR. Thus, the competence of the TV needs to be considered in the context of RV function [108].

Imaging for hypoplastic left heart syndrome at various time points

Preoperative assessment of classical hypoplastic left heart syndrome		
Recommendations	**Class**[a]	**Level**[b]
Transthoracic echocardiography is sufficient to plan initial surgery in most cases	I	C
CT or MRI should be performed because of anatomical concerns (e.g. pulmonary venous drainage path)	I	C
Chest CT for clinical suspicion of lung disease such as pulmonary lymphangiectasia	I	C
Angiography should principally be used when catheter intervention is being considered	I	C
3D echocardiography may assist in imaging the tricuspid valve to assess morphology and regurgitation	I	C
Additional features in the preoperative assessment of hypoplastic left heart complex		
The size of the left heart structures should be measured and the *z*-scores, calculated	I	C
Cardiac MRI may be used to define the extent of EFE	IIb	C
Predictive scores can be used to aid decision-making for SV versus bi-V circulation in critical AS	IIa	C
Predictive scores can be used to aid decision-making for SV versus bi-V circulation in unbalanced AVSD	IIa	C
Intraoperative assessment of the Norwood procedure		
Intraoperative transoesophageal or epicardial echocardiography should be used in conjunction with haemodynamic assessment	I	C
Exit angiography or CT should be considered for clinical concerns, particularly for anatomy less accessible to echocardiography	I	C
Postoperative assessment of the Norwood procedure		
Transthoracic echocardiography should be the initial imaging modality, to include all operated regions: atrial communication, neo aortic valve, aortic-pulmonary artery connection, coronary flow, arch reconstruction, source of Qp and branch pulmonary arteries	I	C
Angiography or CT should be considered for clinical concerns unanswered by echocardiography	I	C
Postoperative assessment of the hybrid procedure		
Transthoracic echocardiography should be the initial imaging modality for postoperative assessment to include all operated regions: atrial communication, DA stent, aortic arch flow, bilateral pulmonary artery banding	I	C
Angiography or CT should be considered if clinical concerns are unanswered by echocardiography	I	C
Pre-bidirectional cavopulmonary shunt assessment		
Initial imaging modality for pre-bidirectional cavopulmonary shunt assessment is transthoracic echocardiography	I	C
Cardiac MRI or CT can be used instead of angiography prior to bidirectional cavopulmonary shunt	IIa	B
Cardiac catheterization, if there are indications for PVR measurement or intervention	I	C
Right ventricular function assessment		
Objective echocardiographic measures of RV function should be used where possible. Subjective assessment is unreliable	IIa	C
3D echocardiography for functional assessment of the RV, but agreement with MRI is suboptimal	IIa	B
Cardiac MRI is the standard for measurement of RV volume and function	I	B
TV assessment		
2D echocardiography has limitations in defining anatomy with poor agreement with surgical findings	IIa	C
3D echocardiography should be considered when there is significant TR to image TV morphology and regions of regurgitation	I	C

[a]Class of recommendation.
[b]Level of evidence.
AS: atrial stenosis; AVSD: atrioventricular septal defect; bi-V: biventricular; 3D: 3-dimensional; EFE: endocardial fibroelastosis; CT: computed tomography; DA: ductus arteriosus; MRI: magnetic resonance imaging; PVR: pulmonary vascular resistance; Qp: pulmonary blood flow; RV: right ventricular; SV: single ventricle; TV: tricuspid valve; TR: tricuspid regurgitation.

4. PRENATAL DIAGNOSIS AND ASSESSMENT

Prenatal detection of CHD, including HLHS, has increased over the past several decades [109–111]. Although prenatal diagnosis of CHD has not consistently correlated with lower mortality, the ability to optimize perinatal care (i.e. preventing DA closure with PGE1 early after birth) may alter the natural history by improving the preoperative haemodynamic status, with reduction of acidosis and end organ injury [112–117]. It is well known that HLHS survivors have a high incidence of neurodevelopmental and psychological impairment, influenced by multifactorial and cumulative risk factors along the continuum of care [118]. There is a growing body of literature revealing characteristic developmental brain abnormalities and altered cerebral blood flow patterns present in the foetus and neonate with HLHS [118–120]. Prenatal diagnosis may have implications for guiding *in utero* therapies designed to improve cerebral blood flow and oxygen delivery (DO_2) to the developing foetal brain and will be an important area of investigation to identify modifiable variables that ultimately improve longer-term outcomes for patients with HLHS. Finally, early diagnosis of HLHS enables time for detailed counselling regarding the diagnosis and implications as well as opportunities to provide support for families making decisions about the pregnancy and the care of the foetus.

4.1 Timing of prenatal detection

HLHS and its variants can be accurately diagnosed with foetal echocardiography. Classical forms with a severely hypoplastic LV can be detected at 11–14 weeks but more commonly in mid-gestation at 18–22 weeks during the standard foetal anatomy screening ultrasound [121–123].

4.2 Guidelines for foetal diagnosis of hypoplastic left heart syndrome

Guidelines for cardiac screening in the foetus have been developed by several professional organizations [123–125]. Standard four-chamber views demonstrate size discrepancy between chamber sizes (Fig. 12). However, variants of HLHS such as an unbalanced AVD with severe asymmetry or borderline LV in complex CoA or critical AS with evolving HLHS may be not detected in early gestation due to the subtlety of LV hypoplasia or structural abnormalities of the MV or AoV. Incorporation of outflow tract views and the three-vessel tracheal view allows for comparison of PA, ductal arch and Ao arch sizes in order to identify size discrepancies that may be early markers of evolving HLHS and warrant serial prenatal evaluations (Fig. 12 and Table 8).

These views are particularly effective in early gestation [121, 122]. Abnormal cardiac screening views should be reviewed by a foetal cardiologist for more comprehensive anatomical and physiological evaluation and family counselling.

4.3 Critical components of prenatal detection

Once a diagnosis of HLHS is suspected or confirmed, serial anatomical and physiological assessments are necessary (Table 8). The typical prenatal haemodynamics in HLHS are illustrated in Fig. 13. In addition to the recommended imaging and Doppler components of the standard foetal echocardiogram, imaging components include evaluation of the systemic and pulmonary venous connections, size of the atrial communication, the presence and degree of TR, ventricular function and HR [123]. Flow

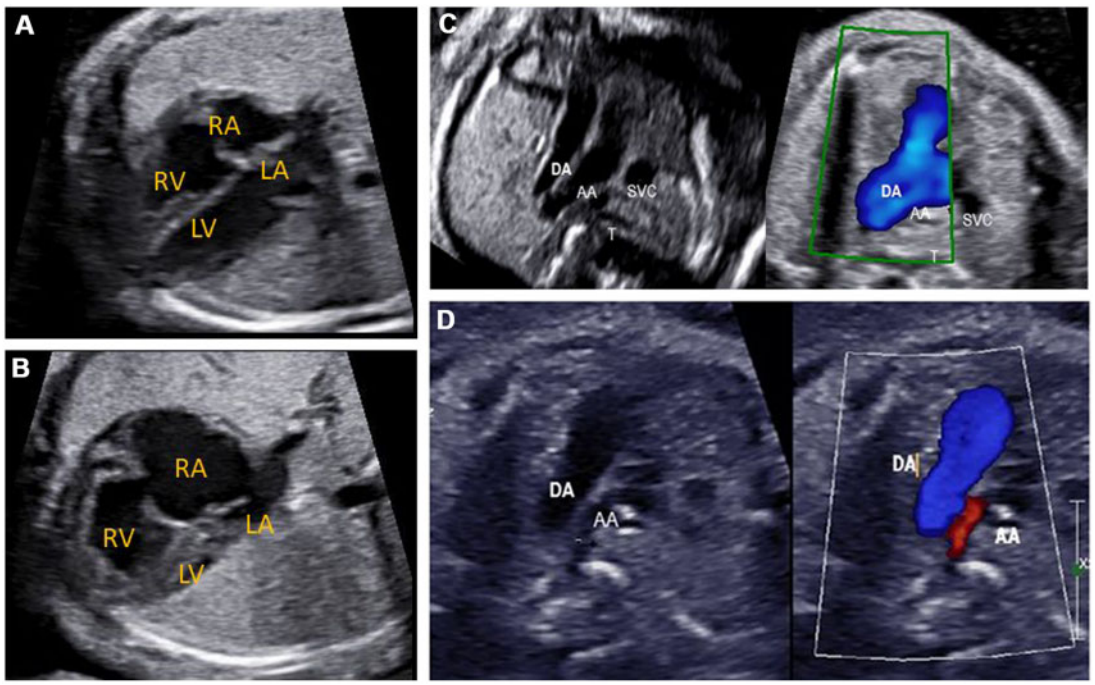

Figure 12: Important foetal echocardiographic views demonstrating differences between a normal heart and hypoplastic left heart syndrome. (**A**) Four-chamber view of a normal heart; (**B**) four-chamber view of hypoplastic left heart syndrome; (**C**) three-vessel tracheal view of normal heart; (**D**) three-vessel tracheal view of hypoplastic left heart syndrome showing smaller AA with flow reversal. AA: aortic atresia; DA: ductus arteriosus; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle; SVC: superior vena cava; T: trachea.

Table 8: Key imaging components for hypoplastic left heart syndrome foetal echocardiogram

Component	Imaging aim
Cardiac	
Situs	Assess for features of heterotaxy
Foetal heart rate	Rate, rhythm
Pulmonary veins	Delineate anatomy, assess for decompressing vein Doppler assessment: measure VTI of forward to reverse flow
Interatrial communication	Size and Doppler velocity
Tricuspid regurgitation	Qualitative assessment
Venous duct	Doppler assessment of flow pattern
Right ventricular function	Qualitative assessment
Ductus arteriosus	Doppler to confirm unrestrictive flow
Ascending aorta	Size and direction of flow
Aortic isthmus	Size and Doppler assessment of flow pattern
Extracardiac	
Middle cerebral artery	Doppler
Placental function	Umbilical artery Doppler Uterine artery Doppler
Effusion/hydrops	
Foetal somatic growth	
Extracardiac structural defects	

VTI: velocity time integral.

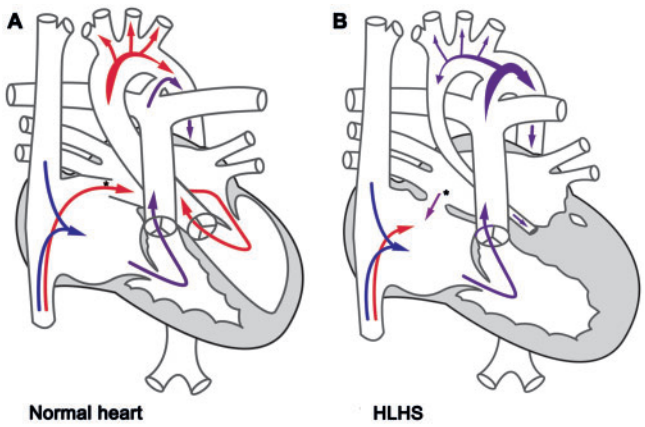

Figure 13: Prenatal blood flow patterns in the (**A**) foetus with normal heart and (**B**) foetus with HLHS. Flow across the atrial septum (*) is right to left in the normal heart and left to right in the foetus with HLHS. The foetus with HLHS relies on left-to-right shunting across the atrial septum. Retrograde flow is also demonstrated in the transverse and ascending aorta. Red arrows: oxygenated blood, blue arrows: deoxygenated blood and purple arrows: mixed blood. (Modified with permission from Herberg U, Hövels-Gürich H. Neurological and psychomotor development of foetuses and children with congenital heart disease—causes and prevalence of disorders and long-term prognosis. Z Geburtshilfe Neonatol 2012;216:132–40.). HLHS: hypoplastic left heart syndrome.

restriction across the atrial septum may not be recognized until the third trimester concomitant with increasing foetal Qp.

Evaluation for extracardiac abnormalities, including chromosome abnormalities and growth impairment, should also be incorporated because these comorbidities can adversely impact outcomes [30, 126, 127]. The foetus with HLHS tends to be smaller than normal, with declining growth rates particularly in late gestation (Table 8) [128, 129]. Changes in cerebral and placental blood flow and progressive impairment of brain development have been demonstrated in late gestation. We recommend serial evaluations of the foetus with HLHS to include not only assessment of the cardiovascular physiology but also biometric and Doppler assessments of placental and cerebral blood flow into the third trimester.

Several anatomical and physiological risk factors have been identified in the foetus with HLHS (Table 9) [34, 130–133].

Serial follow-up with foetal echocardiography and consultation with a foetal cardiologist is recommended throughout gestation. Four- to 6-week intervals are generally considered appropriate. Evaluation in late gestation ≥36 weeks is beneficial to identify risk factors that may impact the stability of the foetus at delivery (i.e. r-FO, changes in ventricular function, growth restriction).

4.4 Delivery planning

Delivery planning for a foetus with HLHS should involve communication and coordination with a multidisciplinary team that includes at minimum the obstetrical team, maternal-foetal specialist, paediatric cardiologist and neonatologist and/or cardiac intensivist. Delivery should occur in a hospital with access to on-site neonatology or cardiology care, which can facilitate the initial evaluation/stabilization of the newborn, securing of intravenous access and initiation of a PGE1 infusion (Table 9). Due to the need for cardiovascular resources, delivery should occur in a hospital setting that is close to a specialized cardiac centre [134]. In the absence of risk factors, there are no data to support elective caesarean or preterm delivery [135]. Spontaneous delivery is encouraged up to 40 weeks, and elective deliveries should be no earlier than 39 weeks, because adverse neonatal outcomes have been associated with elective delivery even at 37–39 weeks [123, 136, 137]. The overall goal is to optimize a baby's maturity at delivery, improve perinatal health and thereby increase the postnatal treatment options.

4.5 'High risk' hypoplastic left heart syndrome: restrictive foramen ovale or intact atrial septum

An r-FO occurs in 6–20% of foetuses with HLHS [22, 123, 138]. Because the total Qp demand *in utero* is low, the foetus with an r-FO may have minimal alterations detected by ultrasound. However, upon separation from the maternal circulation, the Qp increases five-fold, and the baby can develop severe hypoxaemia, ultimately with significant morbidity and mortality [33, 131, 139–147] (Fig. 14).

Significantly restrictive left-to-right shunting leads to LA and pulmonary venous hypertension as well as abnormal pulmonary vascular and parenchymal development (e.g. arterialization of the pulmonary venous vasculature, pulmonary lymphangiectasia and PHT) [22, 33, 34, 131, 138–140, 144, 146, 148]. With foetal cardiac MRI, the appearance of a 'nutmeg lung' indicates pulmonary lymphangiectasia secondary to pulmonary venous obstruction [33, 149–152].

4.6 Foetal echocardiographic evaluation in hypoplastic left heart syndrome with restrictive foramen ovale/intact atrial septum

Direct imaging of the size of the atrial communication can be challenging, although the presence of a high velocity Doppler

Table 9: Diagnostic 'red flags' for hypoplastic left heart syndrome

Anatomical risk factors	Anatomical findings	Physiological findings	Intervention/implication
r-FO, IAS	FO size Atrial septum bowing to right atrium, left atrial dilation Pulmonary vein distension, decompressing vein	Pulmonary vein Doppler: VTIf/VTIr <3 increases risk for immediate postnatal intervention	Maternal hyperoxygenation to assess pulmonary vasoreactivity Foetal intervention to decompress left atrium Delivery in specialized cardiac centre
Ventriculocoronary communications (associated with Ms/AA)	Multiple colour Doppler signals in right ventricle and/or left ventricular myocardium		
Right ventricle dysfunction	Tricuspid regurgitation Effusion Hydrops	Qualitative assessment Shortening fraction Ejection fraction	
Variants of HLHS			
HLHS with TAPVD	Obstructed TAPVD	Flow obstruction in connecting vein	Increased risk of death Delivery in a specialized surgical centre
Critical atrial stenosis, evolving HLHS	Dilated left ventricle, EFE		Foetal balloon valvuloplasty
HLHS with heterotaxy	Situs, venous anomalies	Foetal bradycardia or heart block	
Extracardiac disease			
	Extracardiac anomalies Chromosomal disease Growth restriction		

AA: aortic atresia; EFE: endocardial fibroelastosis; HLHS: hypoplastic left heart syndrome; IAS: intact atrial septum; MS: mitral stenosis; r-FO: restrictive foramen ovale; TAPVD: totally anomalous pulmonary venous drainage; VTIf/VTIr: velocity time integrals for forwards and reverse pulmonary valve flow on pulmonary venous Doppler.

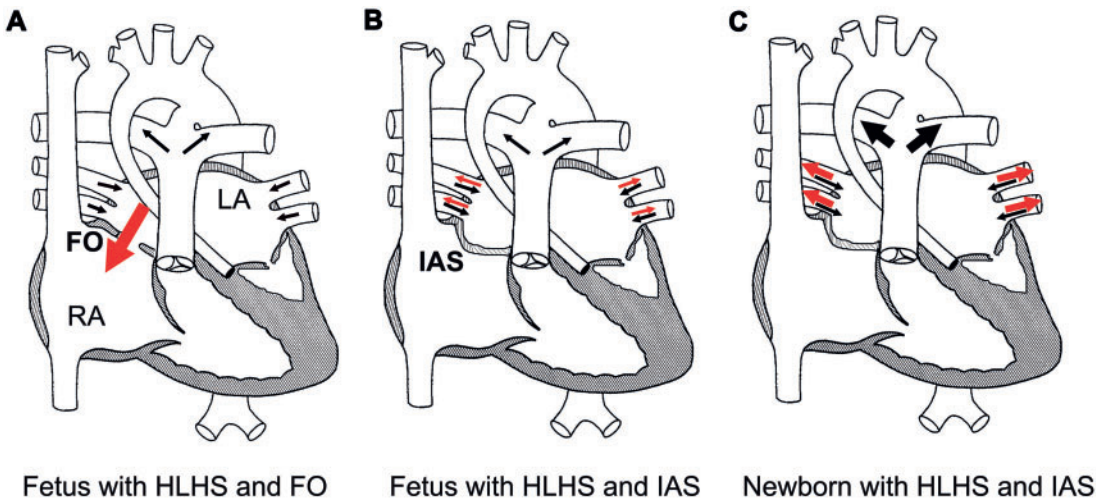

Figure 14: Foetal and neonatal circulation in HLHS. (**A**) In the foetus with unrestrictive foramen ovale, pulmonary venous blood shunts into the RA; (**B**) in the foetus with a restrictive foramen ovale, obstruction to LA egress leads to LA and pulmonary congestion and intrauterine pulmonary hypertension; (**C**) After birth, the lungs expand with an increased pulmonary blood flow and worsening left atrium and pulmonary hypertension. Insufficient interatrial mixing results in marked hypoxaemia). (Modified with permission from Herberg U, Berg C, Geipel A, Gembruch U, Breuer J. Foetal therapy: what works? Closed interatrial septum. Cardiol Young 2014;24 Suppl 2:47–54). FO: foramen ovale; HLHS: hypoplastic left heart syndrome; IAS: intact atrial septum; LA: left atrium; RA: right atrium.

gradient (>0.6 m/s) is concerning (Fig. 15). Traditional 2D echocardiographic measurement of the FO diameter is not necessarily predictive of postnatal status [147]. Doppler assessment of the pulmonary venous flow in the third trimester is a reliable and reproducible tool for evaluating the integrity of the atrial septum. In a foetus with a normal heart, the pulmonary vein flow should be antegrade into the LA with biphasic systolic and diastolic peaks, with low velocity (or absent) flow during atrial contraction. In the setting of HLHS with a wide-open or only mildly r-FO, antegrade flow will occur with systolic and diastolic peaks and with a low velocity, retrograde peak during atrial contraction [130, 144, 152, 153] (Fig. 16A–D). With greater degrees of flow restriction, retrograde flow increases. A velocity time integral of the antegrade and retrograde flow into the LA is a marker for the degree of atrial restriction (Fig. 16D). It is vital that pulmonary venous Doppler assessments be incorporated as a routine

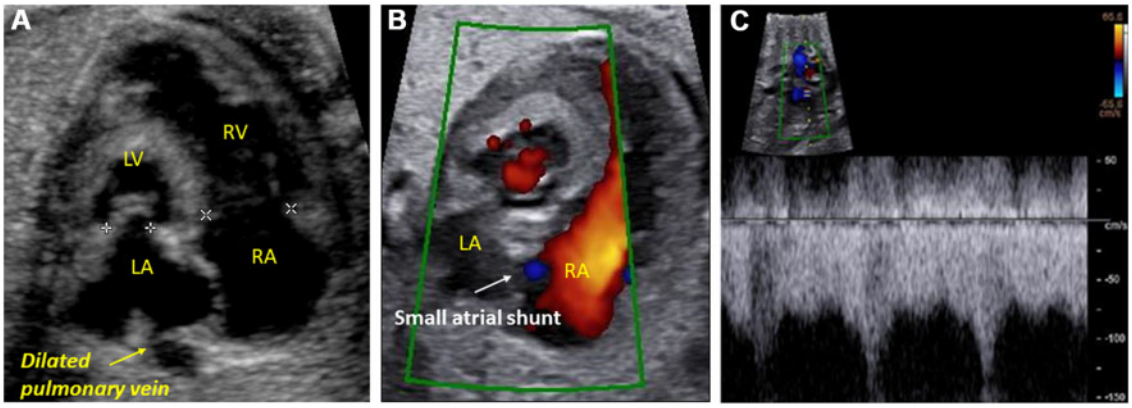

Figure 15: Key echo findings of hypoplastic left heart syndrome with restrictive foramen ovale. (**A**) Four-chamber hypoplastic left heart syndrome view showing dilated left atrium and pulmonary veins, left-to-right bowing of atrial septum; (**B**) colour Doppler scan revealing small atrial shunt; (**C**) spectral Doppler scan of restrictive atrial shunt showing high velocity shunting. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

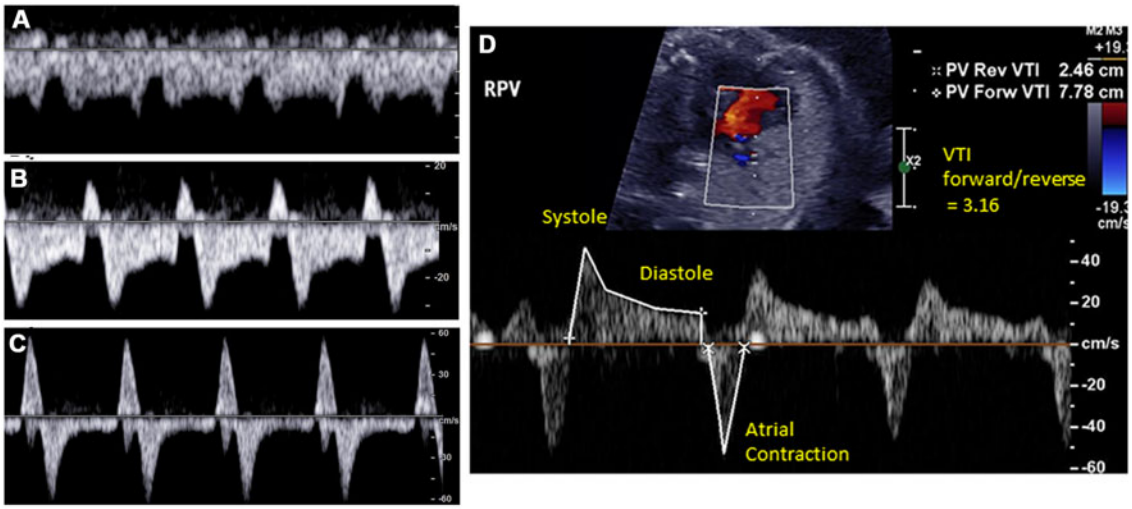

Figure 16: Representative spectral Doppler sample in pulmonary veins from (**A**) normal foetal heart demonstrating antegrade flow throughout cardiac cycle; (**B**) hypoplastic left heart syndrome foetal heart with small degree of flow reversal with atrial contraction; (**C**) hypoplastic left heart syndrome foetal heart with significant flow reversal representing severe atrial restriction; and (**D**) sample measurement of VTI Doppler scan. PV: pulmonary valve; RPV: right pulmonary valve; VTI: velocity time integral.

component of the foetal echocardiographic assessment in HLHS, and repeated with serial examinations into the third trimester.

To predict the severity of atrial flow restriction and need for urgent intervention on the atrial septum at birth, a classification algorithm based on flow patterns in the pulmonary veins has been developed: 'low risk' for foetuses with velocity time integrals for forwards and reverse PV flow >5 (unobstructed FO), 'medium risk' with a pulmonary velocity time integrals for forwards and reverse PV flow between 3 and 5 (mildly r-FO) and 'high risk' with a pulmonary velocity time integrals for forwards and reverse PV flow <3 [123, 153] (Fig. 16D). In addition, pulmonary venous A-wave duration ≥90 ms has been used as the threshold for atrial decompression [154]. Testing for foetal pulmonary vasoreactivity with maternal hyperoxygenation is a supplemental diagnostic tool and a helpful adjunct for risk stratification. Oxygen is a PA vasodilator and should lead to augmented Qp in the setting of normal pulmonary vasculature. Oxygen provided to the mother via face mask is transmitted into the foetal circulation and pulmonary vasculature. The degree of pulmonary vasoreactivity can be assessed by changes in PA Doppler flow patterns before and after maternal hyperoxygenation. The absence of a normal vasodilatory response in the foetus with HLHS is a poor prognostic marker suggestive of abnormal pulmonary vasculature [155–157].

HLHS with severely r-FO or IAS is associated with high perinatal and perioperative mortality, with an odds ratio of 4.0 (confidence interval 1.3–12.3) for preoperative death [27]. The 1-month survival rate ranges from 30% to 50% [22, 34, 131, 142, 146, 158]. The overall survival rate to S2P or to a heart transplant ranges from 0% to 42% [140, 146]. Patients with a prenatal diagnosis of IAS who had immediate transcatheter intervention had a highly significant survival benefit compared to those who were not diagnosed prenatally and therefore underwent either delayed intervention or no intervention ($P < 0.001$) [140]. Still, the mortality probability for babies with HLHS and r-FO/IAS after successful

neonatal septostomy remains significantly higher compared to that of those without atrial obstruction ($P < 0.03$).

4.7 Foetal intervention in hypoplastic left heart syndrome with restrictive foramen ovale/intact atrial septum

Foetal intervention can be offered to foetuses with HLHS with r-FO or IAS; criteria for consideration of a foetal intervention are shown in Table 10 (Fig. 17).

Early decompression of the LA may prevent ongoing pulmonary vascular changes [148], decrease the need for immediate perinatal interventions (caesarean delivery, immediate postnatal access to cardiac therapy procedures and neonatal resuscitation) and may result in better S1P survival [143, 159]. Early gestational age, the need for large needles and the risk of spontaneous closure of the created atrial communication must be considered, and optimal timing is yet to be defined. In foetuses undergoing atrial septoplasty, an atrial communication ≥3 mm was associated with a decreased need for emergency postnatal atrial septoplasty and better S1P survival [159]. A limitation of foetal balloon-septoplasty is that the FO can again become restrictive or close as gestation progresses. Atrial stents may perform better, with a trend towards improved discharge survival [143, 154, 159].

Foetal death related to the septostomy procedure was reported in up to 13% of cases, and despite successful decompression, the long-term outcome remains poor compared to standard-risk HLHS (44–58% survival after successful foetal intervention) [143, 154, 159]. This outcome may be related to irreversible pulmonary vascular changes. Studies are needed to develop comprehensive criteria that identify foetuses with reversible PHT, incorporating foetal echocardiography, cardiac MRI and maternal hyperoxygenation.

4.8 Delivery of foetuses with hypoplastic left heart syndrome and restrictive foramen ovale/intact atria septum

Delivery of a foetus with HLHS and severely r-FO or IAS should occur in a specialized cardiac centre where resources are available for emergency intervention to decompress the LA (catheterization with ballooning or stent, surgery, ECMO). In this scenario, a planned caesarean delivery may be necessary to ensure that all personnel are available for the necessary coordination of multidisciplinary care [123, 160].

4.9 Other 'high risk' hypoplastic left heart syndrome features

HLHS in the setting of TAPVD, especially with *in utero* flow obstruction, has a bad prognosis (3-year mortality rate is 27% without obstruction vs 73% with obstruction) [161]. As in HLHS with r-FO/IAS, egress from the pulmonary veins is obstructed,

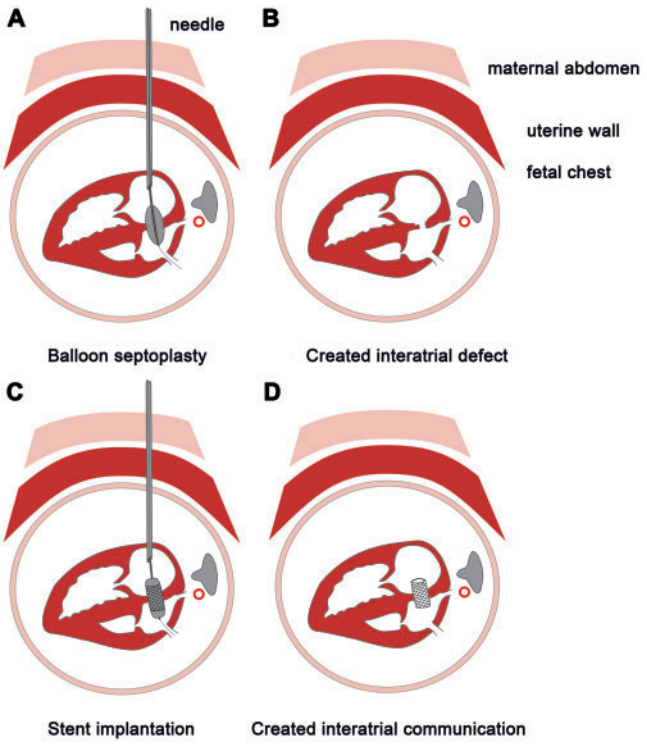

Figure 17: *In utero* intervention in a foetus with hypoplastic left heart syndrome and restrictive foramen ovale or intact atrial septum. The catheter is advanced transabdominally into the uterine wall and through the foetal chest, aimed at the atrial septum. The balloon is inflated (**A**) and a defect is created (**B**). A coronary stent mounted on a balloon is deployed at the atrial septum (**C**) to create a permanent interatrial communication (**D**). (Modified with permission from Herberg U, Berg C, Geipel A, Gembruch U, Breuer J. Foetal therapy: what works? Closed interatrial septum. Cardiol Young 2014;24 Suppl 2:47–54).

Table 10: Criteria for foetal atrial septostomy/stent implantation in hypoplastic left heart syndrome with restrictive foramen ovale/intact atrial septum

1. Severe restriction on echocardiography
• Foramen ovale diameter ≤1 mm on colour Doppler scan or closed or a decompressing vein from left atrium with flow obstruction
• Pulmonary venous Doppler scan consistent with high atrial pressure (to-and-fro flow, forward/reverse velocity time integral <3)
• Pulmonary venous A-wave duration ≥90 ms
2. Anatomical subtype
• Left atrium large enough to allow perforation of the atrial septum and insertion of a balloon or stent
3. Timing
• At any time in the setting of foetal hydrops (salvage procedure)
• Consider risk factors for procedure-related losses: early gestational age, large-sized needle and restriction or spontaneous closure of created defects
4. Perinatal management: see Table 9

which ultimately leads to pulmonary vascular obstructive disease and severe hypoxia at birth. TAPVD is commonly seen in the setting of heterotaxy, which is associated with multiple extracardiac conditions that can adversely affect prognosis. Due to limited Qp in the foetus, the degree of obstruction cannot be accurately graded. Therefore, delivery of any foetus with TAPVD should occur in a specialized centre with immediate access to emergency cardiovascular services such as ECMO or surgical and catheter-based interventions.

Other high-risk features identified in a foetus with HLHS, which may be associated with neonatal cardiovascular instability and poor longer-term outcomes, include severe TR, RV dysfunction and congenital heart block. Ventriculocoronary artery fistulas, typically associated with the MS/AA, have been associated with worse outcomes, although conflicting data have been presented in the literature [162–164]. No specific *in utero* interventions are available to address these high-risk lesions.

4.10 Emerging hypoplastic left heart syndrome in critical aortic stenosis with uncertain prognosis: indications for foetal intervention

Natural history studies have demonstrated that in foetuses with severe AoV stenosis and normally sized or dilated LV, left heart growth arrest can occur at mid-gestation, leading to an univentricular circulation at birth [165, 166]. The goal of foetal Ao valvuloplasty is to interrupt the sequence/trigger responsible for LV arrest by decompression of the LV and augmentation of flow across all left-sided structures. Intrauterine foetal Ao valvuloplasty promotes growth and function of LV structures [167–169] and may improve the likelihood of bi-V circulation at birth [170–172]. To identify foetuses at high risk of UV circulation at birth (critical AS with emerging HLHS), echocardiographic criteria have been developed from retrospective studies (Table 11) [173, 174].

In cases with poor LV function, severe EFE and severe MS, foetal intervention cannot restore left ventricular function. Selection criteria for foetal Ao valvuloplasty must identify foetuses at high risk to develop HLHS but with the capability to improve LV function and growth after foetal intervention. Current criteria are given in Table 11 [175]. Appropriate echocardiographic assessment, patient selection for intervention and counselling are critical, because there is a risk of procedure-related foetal demise (currently 11%, range 8.8–25%). Postnatal outcome depends not only on a successful prenatal intervention but also on postnatal treatment strategies requiring multiple interventional as well as operative procedures. Of live-born babies, survival with a bi-V outcome ranged from 38% to 68.6% [176, 177]. It should be emphasized that the strategy is evolving rapidly, and results are likely to improve.

Table 11: Predictors of the development of hypoplastic left heart syndrome in critical aortic stenosis

Foetal echocardiographic variables	Selection criteria for foetal aortic valvuloplasty
Aortic stenosis	Aortic valvar stenosis
Retrograde flow in the transverse aortic arch	Aortic annulus *z*-score >-3.5
LV dysfunction	MV annulus diameter *z*-score ≥-2
Monophasic mitral inflow	LV long-axis *z*-score >0
Left-to-right atrial shunting	MR or aortic stenosis Doppler gradient ≥20 mmHg

LV: left ventricle; MR: mitral regurgitation; MV: mitral valve.

4.11 Prenatal counselling

Prenatal counselling for CHD is an important element in the care of the foetus and the parents. There are many issues to discuss, but cerebral development is of major concern, especially when only retrograde perfusion of the foetal Ao arch (as in AA) is involved. Multiple neurodevelopmental abnormalities have been identified in survivors, but the findings are variable and not seen in every patient. There are multiple factors to consider in any prediction model, most of them not under the control of the treating team. Comprehensive details of neurodevelopmental outcome in HLHS are beyond the scope of these Guidelines (although volumes have been written on this topic in the past 20 years).

Counselling involves at minimum:

1. Description of the anatomical features of the diagnosis
2. Anticipated prenatal management
3. Anticipated perinatal course and management options
4. Description of data regarding longer-term outcomes
5. Inclusion of limitations of prenatal diagnosis to accurately predict longer-term outcomes.

Referral to a foetal cardiologist is recommended so that parents can receive the most reliable information regarding diagnostic findings, natural history, contemporary management practices and outcome data. The literature clearly demonstrates high rates of stress, anxiety and depression in parents receiving a diagnosis of CHD [178, 179]. Counselling is often offered in conjunction with a foetal cardiology nurse specialist and/or social worker. Multiple counselling sessions may be necessary, and inclusion of a consultation with a cardiothoracic surgeon, intensivist or other support personal such as a psychologist may also be beneficial. Key themes that arise for prenatal counselling include timely access to consultation, information regarding expectations and outcomes, providing written material and/or references regarding the diagnosis, reassurance that parents are not at fault for the diagnosis and access to peer support [180].

Importantly, parents should be provided with all potential management options for the pregnancy and postnatal care, which may include timely pregnancy termination, comfort care or surgical intervention. Providers are obliged to provide realistic expectations and remain neutral with regards to parental decision-making. Discussions should also include recommendations for delivery based on the anticipated needs of the baby at the time of birth. If present, risk factors should be reviewed with parents. Moreover, prenatal intervention options should be reviewed, if appropriate, and include any contemporary outcomes regarding risks and benefits to both foetus and the mother.

Foetal diagnosis of hypoplastic left heart syndrome

Recommendations	Class[a]	Level[b]
An obstetrical foetal anomaly scan should be performed at 18–22 weeks of gestation	I	C
During the obstetrical foetal anomaly scan, cardiac imaging should include, at minimum, a four-chamber view, outflow tract views and three-vessel tracheal view	I	C
It is recommended that a foetal cardiologist confirm the diagnosis of HLHS and provide counselling in conjunction with a multidisciplinary team that may include a maternal–foetal medicine specialist, obstetrician, neonatologist, paediatric cardiac surgeon, nurse specialist, psychologist and/or social worker	I	C
Foetal echocardiographic evaluation of HLHS should include detailed evaluation of the atrial septum, pulmonary veins (anatomy and Doppler flow patterns), ventricular function and TV (for regurgitation)	I	C
Foetal karyotyping should be offered following prenatal diagnosis of HLHS, particularly in the presence of extracardiac anomalies, to provide information regarding delivery management and prognosis	I	C
After a foetal diagnosis of HLHS and initial consultation, serial foetal echocardiographic follow-up is recommended at 4- to 6-week intervals, and at ≥36 weeks in order to assess for the evolution of high-risk features (such as flow restriction across the atrial septal communication), which may affect delivery management	I	C
In the foetus with HLHS and concern for a restrictive atrial septal communication (r-FO), maternal hyperoxygenation may be considered to test pulmonary vasoreactivity for prognostic purposes	IIb	C
In the foetus with an r-FO, foetal intervention to augment the size of the atrial septal communication may be considered to improve perinatal and longer-term outcomes	IIb	C
In foetuses with critical AS and features of emerging HLHS, foetal intervention may be considered to improve antegrade flow across the AoV in an effort to achieve a biventricular outcome	IIb	C
In the absence of risk factors, it is recommended that delivery of a foetus with HLHS occur spontaneously up to 40 weeks. Elective delivery planning (induction of labour or caesarean delivery) is recommended no earlier than 39 weeks as long as there are no obstetrical risk factors	I	B
It is recommended that a foetus with HLHS be delivered at a hospital with availability of immediate on-site neonatal care, intravenous prostaglandin E1 therapy, cardiac consultation and capability for timely transfer to a specialized facility for surgical intervention	IIa	B
For the high risk HLHS foetus with r-FO or IAS, delivery is recommended in a specialized cardiac centre with immediate access to specialists who can perform emergency interventions (cardiac catheterization, cardiac surgery, extracorporeal membrane oxygenation)	IIa	B

[a]Class of recommendation.
[b]Level of evidence.
AoV: aortic valve; AS: aortic stenosis; HLHS: hypoplastic left heart syndrome; IAS: intact atrial septum; r-FO: restrictive foramen ovale; TV: tricuspid valve.

5. DIAGNOSIS AND MANAGEMENT OF HYPOPLASTIC LEFT HEART SYNDROME IN THE NEWBORN

The clinical condition of a newborn with HLHS relates to the cardiac morphology and its consecutive pathophysiology, in particular DA patency, the quality of the pulmonary vein drainage to the TV pathway, coronary and cerebral perfusion and the function of the RV and TV [2, 76, 181–186]. The majority of neonates with HLHS born in high resource settings are diagnosed antenatally and managed prospectively from delivery. Universal screening by SaO_2 (pulse oximetry) is effective in postnatal detection of CHD and may enable early detection of HLHS if has been missed *in utero*. Typically, the neonate is tachypnoeic and the pre- and/or post-ductal values are <93% in HLHS, but SaO_2 >93% does not exclude neonatal HLHS. If HLHS is not detected early after birth, then over the first days of life, with the fall in PVR or constriction of DA that naturally occurs, the imbalance of PVR to SVR leads to a pulmonary run-off with low Qs. DA constriction is associated with a pale, poorly perfused newborn, with high HR and low-volume pulses. A medium-frequency murmur together with a hyperactive precordium can occur with heart failure-related TR [187–189]. During the assessment, the SaO_2 values should be interpreted in the context of the respiratory rate (RR). Tachypnoea in the context of high SaO_2 (>93%) represents a leading clinical sign of severe heart failure (Ross III or IV) [8]. Tachypnoea together with severe hypoxaemia might be associated with a significant pulmonary congestion. Rarely, the presence of highly r-FO or IAS, or obstructed TAPVD with pulmonary congestion, may lead to immediate postnatal deep cyanosis and respiratory distress requiring urgent intubation and resuscitation followed by consideration of a catheter-based or surgical intervention [22]. Such neonates have parenchymal lung disease (lymphangiectasia), and the presence of tissue hypoxia may lead to impaired ventricular function and even multiple organ failure.

5.1 Further diagnostic steps

Once HLHS is suspected, transthoracic echocardiography should immediately be performed. Of note, echocardiography is indicated in any newborn with persistent tachypnoea to exclude HLHS or to initiate sufficient treatment (class IIa, level C). The differential

diagnosis is sepsis, which is often considered the primary diagnosis. Therefore, a chest X-ray is indicated for analysing consecutive or concomitant lung parenchymal disease (class IIa, level C). The chest X-ray of HLHS neonates may show signs of congestion, or a 'white' lung. Mild cardiomegaly, an eight-shaped heart silhouette and uni- or bilateral prominence of pulmonary vascular markings might suggest obstructed TAPVD [190, 191]. The ECG may be normal, with the typical neonatal findings of right-axis deviation and right ventricular hypertrophy, but in some cases T-wave inversion appears across all precordial leads [192].

Echocardiography is the modality of choice for a definitive diagnosis [193, 194]. The left heart structures need to be carefully analysed to detect the subtypes of HLHS or differential diagnoses such as discordant transposition of the great arteries with hypoplastic sub-Ao right heart structures, unbalanced AVSD or double outlet RV with a small LV. Ventricular function is additionally influenced by the persistence of coronary obstructions and fistulae [78, 195, 196]. Cerebral blood flow assessment with the Doppler technique (especially right cerebral arteries) and assessment of the coeliac trunk are useful for interpreting the haemodynamic stability of a newborn with HLHS. Echocardiography facilitates decision-making for immediate cardiac interventions [197, 198]. Preoperative diagnostic cardiac catheterization should be reserved for diagnosis of complex additional lesions. Additional preoperative imaging such as cardiac MRI is useful in experienced centres as a non-invasive strategy (preferably without the need for intubation for anaesthesia).

Considering that the natural course of untreated HLHS is fatal, the goal of postnatal care is to allow reconstructive surgery (Norwood or h-S1P) under stable haemodynamic conditions [6, 134, 199].

A neonatal heart transplant is reserved for babies in which reconstructive surgery is not opportune [200–202]. Significant institutional differences in organization and postnatal care of newborns with HLHS still exist. In most instances, especially in the absence of a prenatal diagnosis, the newborn with HLHS must be stabilized in a neonatal ICU and transported to a centre in which definitive surgical care is available. A stable newborn with diagnosed or suspected HLHS should be placed on a low-dose infusion of PGE1 (5–10 ng/kg/min) to hold open the DA and avoid side effects (apnoea, early drop of PVR). Administration of oxygen and intubation/ventilation should be avoided (class IIa, evidence level B). These measures favour high Qp/Qs and have been linked to a higher incidence of complications [200, 202]. Depending on the institutional strategy, umbilical venous and arterial lines should be considered for immediate care to facilitate safe administration of medications (PGE1).

5.2 Monitoring and ongoing care

The clinical status of a newborn with HLHS will dictate the care strategy used prior to definitive intervention [203, 204].

Postnatal management of patients with hypoplastic left heart syndrome

Recommendations for initial assessment	Class[a]	Level[b]
Undiagnosed neonates with persistent tachypnoea or desaturation require transthoracic echocardiogram to rule out congenital heart disease, including HLHS	IIa	C
Cardiac imaging should include global cardiac function, structures by four-chamber view, outflow tract views, aortic arch, coeliac trunk and cerebral blood flow	I	C
A paediatric cardiologist should confirm the diagnosis of HLHS and provide counselling to the parents in conjunction with a paediatric cardiac surgeon	I	C
Echocardiographic evaluation of HLHS should define the HLHS type, including the situs, cardiac variants and detailed evaluation of the left ventricle and function, ventricular septal defect, atrial septum, pulmonary veins (anatomy and Doppler flow patterns), aortic arch including flow patterns (antegrade, retrograde) right ventricular function and tricuspid valve (see Table 9 for more information about 'foetal red flags')	I	B
If extracardiac abnormalities are detected, testing for chromosomal abnormalities is indicated to provide additional information for postnatal counselling and prognosis	I	C
Newborns with HLHS and restrictive DA, r-FO, TAPVD, PV stenosis or non-restrictive FO with high Qp should be considered for immediate transcatheter or surgical intervention	IIa	B
X-ray radiography to be undertaken by clinical indication only	IIb	C
ECG should be performed to exclude arrhythmias	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
DA: ductus arteriosus; ECG: electrocardiogram; HLHS: hypoplastic left heart syndrome; PV: pulmonary valve; Qp: pulmonary blood flow; r-FO: restrictive foramen ovale; TAPVD: totally anomalous pulmonary venous drainage.

Recommendations for initial treatment

Intervention	Class[a]	Level[b]
Prostaglandin E1 (low dose) should be administered	I	B
Oxygen should be administered only by strict indication	IIa	B
Intubation and ventilation should be used only by strict indication	IIa	B
Stable neonate: Minimal handling in a tranquil environment, with heart rate, respiratory rate, SaO_2 + blood pressure monitoring	I	B
Unstable neonate: Resuscitation, including intubation and ventilation and placement of central and invasive monitoring lines	I	B

[a]Class of recommendation.
[b]Level of evidence.
SaO_2: arterial oxygen saturation.

5.2.1 The stable newborn with hypoplastic left heart syndrome. The primary goal of care in a stable neonate with HLHS awaiting an intervention is minimal handling in a tranquil environment, with a PGE1 infusion at 5–10 ng/kg/min to preserve patency of the DA. Preoperative monitoring of patients with HLHS in the ICU includes RR and pattern, pre- and post-ductal pulse oximetry, continuous ECG and intermittent non-invasive systolic and diastolic blood pressure (BP) in the right arm (if an anomalous right subclavian artery is excluded). To detect a BP gradient between the right and left arm, an additional systolic and diastolic BP measurement should be performed in all extremities. Usually, fluids should be administered without restriction, according to standard neonatal recommendations. Fluid balance should be carefully monitored; however, insertion of a Foley catheter is not justified unless the patient is haemodynamically compromised. Tissue perfusion monitoring with serial testing for blood lactate levels and near infrared spectroscopy (NIRS) is only necessary in a decompensated phase. Use of central lines (other than umbilical) should be minimized in the preoperative period unless the patient remains critically ill or needs cardiac catheterization.

Provision of nutrition to the neonate with HLHS is a controversial area. Some centres maintain stable neonates with HLHS nil by mouth and undertake surgical S1P within a few days of birth, whereas others advocate enteral feeding in this context [205, 206]. It has been suggested that in stable babies, enteral feeds may even protect against necrotizing enterocolitis (NEC), provided there is adequate enteral flow, as assessed by coeliac arterial Doppler imaging [207, 208]. Stable neonates who will wait longer for an intervention for clinical reasons (e.g. low BW) will by necessity receive enteral feeding. A stable neonate with a longer waiting time to intervention, with an RR <60/min and a HR <130/min (both at rest), may receive nasogastric feeds and accept oral food intake, even from the mother's breast.

5.2.2 The unstable newborn with hypoplastic left heart syndrome. Initial management of the sick neonate with HLHS should focus on stabilization by balancing Qp and Qs to optimize systemic DO_2 [209–211]. Patients with severe metabolic acidosis and cardiogenic shock require emergency measures recommended in neonatal advanced life-support algorithms, including intubation and ventilation [212]. The PGE1 infusion should be started at a higher dose (20 ng/kg/min) while considering which is the appropriate interventional pathway (see also section on h-S1P). Central venous and arterial catheters should be placed for sampling and monitoring. To assess mixed venous SO_2 (SvO_2), consider sampling in the innominate vein to avoid overestimation due to atrial left-to-right and arterial right-to-left shunt dependence.

The level of SaO_2 depends on the proportions and the oxygen saturation (SO_2) of the 2 components of Qs. If the pulmonary venous blood is not fully saturated due to pulmonary parenchymal disease, O_2 should be given, as for any patient with lung disease, the goal being to achieve a maximal SaO_2 of 80–85% (with adequate Qs). In the context of SvO_2 <50% or an arterio-venous SO_2 difference >40%, further therapeutic efforts are directed to improving Qs. In this context, haemoglobin (Hb) >12 g/dl is adequate and 14 g/dl is optimal.

Newborns admitted in shock with metabolic acidosis because of an obstructed DA that is unresponsive to high doses of PGE1 with catecholamine (e.g. norepinephrine) infusion should be considered for a percutaneous or trans-PA ductal stent [213, 214].

If there is evidence of low Qs despite a seemingly adequate DA, especially in the presence of a non-restrictive Qp or r-FO, emergency b-PAB should be considered to limit pulmonary run-off. If, in addition, there is cyanosis and refractory hypoxaemia, the patient should be considered for atrial septostomy followed by b-PAB.

Although intubation and ventilation are required to support the baby, sedation and analgesia should be administered in the form of ketamine or opioids (low-dose morphine or fentanyl) together with benzodiazepines supplemented by non-opioids such as paracetamol. Alternative agents include alpha-2 agonists such as dexmedetomidine or clonidine [215–217].

Once adequate stabilization has been achieved, it may be possible to reduce the PGE1 dosage (5–10 ng/kg/min) unless there is an associated left heart obstruction such as CoA. If catecholamines have been used as a rescue therapy (with high-dose PGE1), both should be reduced if feasible, aiming for normal BP (term neonates > systolic 65 and diastolic >35 mmHg measured in the upper body) supporting adequate perfusion of the coronary and cerebral circulation. Milrinone (0.5–1 µg/kg/min) can be continued until S1P, but catecholamines should be stopped prior to S1P if this procedure is not performed emergently [218]. In a baby who has been successfully weaned from catecholamines and stabilized, extubation to air may be feasible.

DO_2 is limited in HLHS, and one should aim for the lowest effective HR and SVR to optimize diastolic filling time, with SaO_2 maintained between 75% and 85%. Useful medications that can be considered to achieve this are dexmedetomidine, clonidine, digoxin and β1-receptor blockers. Use of continuous milrinone infusion may be helpful [219–221].

Guidelines for therapeutic measures to increase oxygen delivery in hypoplastic left heart syndrome prior to stage 1 palliation

Strategy	Class[a]	Level[b]
Continuous, lowest effective dose of prostaglandin E1 infusion	I	B
Balloon atrial septostomy to treat pulmonary congestion and to increase Qp in cases of insufficient inter-circulatory mixing	I	B
Bilateral pulmonary banding for low cardiac output based on a high Qp and widely patent DA	I	B
Inodilators (milrinone) to support right ventricular function, if adequate coronary perfusion pressure is maintained	IIa	B
Monitor for restrictions at DA, FO and aortic isthmus with echocardiography and clinical assessment	IIa	C
Minimize VO_2 via adequate O_2 carrying capacity. Consider continuous dexmedetomidine or clonidine infusion, oral β1-blocker, digoxin	IIb	B

[a]Class of recommendation.
[b]Level of evidence.
DA: ductus arteriosus; FO: foramen ovale; Qp: pulmonary blood flow; VO_2: oxygen uptake.

5.2.3 Major prematurity and very low birth weight. The incidence of low BW (<2.5 kg) among newborns with HLHS is almost 10–15%, similar to the overall incidence of prematurity or low BW in neonates with other CHD [222, 223]. Low BW is a risk factor for S1P, with technical and physiological challenges [222]. Comorbidities from other organ systems (central nervous system, renal, gastrointestinal) increase the risk in both the short and long term [223–225]. Multi-institutional studies have demonstrated increased mortality rates for low-BW infants with HLHS undergoing S1P, through IS-1 [54]. From a worldwide perspective, several strategies are currently utilized for premature infants with HLHS including compassionate care only, early Norwood procedure, h-S1P for bridging to Norwood, a heart transplant and a hybrid variant consisting of b-PAB with continuous PGE1 infusion [as a bridge to later Norwood or comprehensive S2P (c-S2P)] [199, 200, 224–227]. In preterm newborns the lowest effective dosage of continuous PGE1 infusion should be used (<5 ng/kg/min); in most cases, 1–2 ng/kg/min is sufficient, with or without additional oral caffeine supplementation [211]. Sometimes, continuous positive airway pressure or continuous humidified nasal airflow without O_2 is useful to avoid intubation and ventilation.

6. ANAESTHESIA FOR HYPOPLASTIC LEFT HEART SYNDROME SURGERY

A schematic for SV physiology has the heart receive and mix pulmonary and systemic venous return, then function as a single pumping chamber to supply Qp and Qs in parallel. The primary goal is to balance Qp and Qs throughout a patient's perioperative course. Manipulating vascular resistance and blood flow can be achieved by various means, and understanding these options is important to successful anaesthetic management. Although institutional care will differ, communication and understanding among the various medical teams involved and the patient's parents are important factors for a successful outcome.

6.1 Preoperative assessment

A standard anaesthetic preoperative assessment will be made, but the considerations below are important when tailoring the anaesthetic plan to the timing and type of surgical treatment. Whilst this narrative is relevant to surgical treatment undertaken on cardiopulmonary bypass (CPB), it is also applicable for anaesthetic management during the placement of PABs, h-S1P and non-cardiac procedures (e.g. exploratory laparotomies, line placements, radiologic examinations) for which CPB is not required but anaesthesia is.

6.2 Cardiac diagnosis

Details of the cardiac anatomy of each patient are important because they can affect the conduct and stability of the patient under anaesthesia as well as the overall prognosis [44]. Although controversy exists regarding Asc Ao size as an influence for surgical death, it, along with an r-FO, AV valve regurgitation and/or anomalous coronary and head and neck vessels, will influence the stability of the patient under anaesthesia. Anomalous head and neck vessels will influence placement of monitoring lines. Antegrade flow through the AoV can make interpretation of SaO_2 more difficult. Genetic disorders and other conditions may coexist with HLHS [228]. Syndromes can indicate the potential for a difficult airway. Conditions associated with micrognathia with a small airway require downsizing of the tracheal tube. Turner's syndrome will result in a guarded HLHS prognosis. Patients with DiGeorge syndrome may have abnormal calcium metabolism, and blood products will need to be irradiated if required.

6.3 Current condition of the patient

The timing and the course of any patient's treatment depend on the initial presentation. Over 75% of HLHS cases have an antenatal diagnosis: Once the child is born, 30% will be stable, maintaining a DA for Qs on a PGE1 infusion, self-ventilating in air [113, 142]. Some patients will require inotropic support and/or preoperative ventilation to improve physiological stability, especially those with significantly high Qp/QS. A small subgroup will have an r-FO or IAS and may require urgent treatment to decompress

the LA and pulmonary veins. Because this group has a worse prognosis, many teams advise delivery at a children's hospital with cardiac surgical facilities, where the baby can receive immediate care, be it cannulation for extracorporeal life support (ECLS) or urgent surgical repair [142, 229, 230]. A postnatal diagnosis following DA closure predictably leads to cardiovascular collapse and poor systemic perfusion, requiring resuscitation.

Patients weighing <2 kg and those with significant prematurity or evidence of intrauterine growth retardation can pose technical difficulties. That, coupled with the problems associated with prematurity (neurological sequelae, lung disease, altered drug metabolism) will influence treatment decisions and choices [231, 232].

6.4 Anaesthetic agents

Anaesthetic induction can be via an inhalational or intravenous technique, depending on centre preference. Traditionally, maintenance anaesthesia is opioid based, though doses differ depending on institution. Opioids produce cardiovascular stability and can potentially attenuate inflammatory responses. Doses of fentanyl up to 50 μg/kg have been used [233, 234]. Because high doses of opioids have some disadvantages, some experts advocate a more balanced anaesthesia, adding volatile or hypnotic agents such as isoflurane and ketamine, especially when early weaning from mechanical ventilation is planned [235]. Recently, some centres have converted to remifentanil infusions, which do allow for rapid titration and early tracheal extubation. Use of volatile agents may, in theory, convey cardiac protection by influencing ischaemic preconditioning [236]. In addition, results from some animal studies suggest that volatile anaesthetics may also confer neuroprotection [237].

6.5 Neurodevelopment and anaesthesia

There are concerns with early exposure to anaesthesia as it relates to delayed neurodevelopment [238]. Most anaesthetic agents have been implicated in animal studies to stimulate neuronal apoptosis [239, 240]. Reassuringly, preliminary intermediate results from an RCT show no difference in neurodevelopment at 2 years, comparing 2 treatment strands of an awake local anaesthetic technique versus sevoflurane volatile anaesthesia for inguinal hernia repair in infants. These data may be relevant to the HLHS scenario as well [241].

Alpha-2 agonists such as dexmedetomidine and clonidine are increasingly used in paediatric cardiac anaesthesia as an anaesthetic-opioid sparing adjuncts [242]. Clonidine is useful during h-S1P procedures to control HR and swings in SVR, and these agents may have the additional advantage of preventing tachyarrhythmias [200, 243, 244]. Moreover, these agents have not been shown to cause neuronal apoptosis in animals and may even confer neuroprotection against volatile agent-induced neuronal apoptosis in humans [245]. However, current clinical evidence is conflicting, demonstrating the difficulty in reproducing or extrapolating evidence from animal studies [246, 247].

6.6 Monitoring

At induction of anaesthesia, all patients should have standard monitoring devices in place. The DA makes measuring preductal and post-ductal SaO_2 and plethysmography useful. Given the potential for significant dead space ventilation, the end tidal CO_2 monitor will not always reflect the arterial partial pressure of carbon dioxide (pCO_2), particularly if PABs are in place.

6.6.1 Arterial pressure monitoring. The choice of operation, its various stages and the preferred perfusion techniques during the operation will affect the siting of the arterial lines. Anomalous head and neck vessels will have a bearing on placement. An arterial line in the right arm will be useful if selective regional cerebral perfusion (RCP) is planned. A combination of both a right arm arterial line and one sited in a lower limb, usually a femoral arterial, helps track both cerebral and descending Ao (Desc Ao) perfusion. The use of this configuration may also help to detect a gradient across the neo-Ao and arch, which might signal the need for intraoperative revision. Many centres are utilizing ultrasound guidance for placement of monitoring lines to promote user accuracy and efficiency, reducing stress on the fragile preoperative patient.

6.6.2 Central venous access. The S1P is usually the initial stage in a surgical pathway heading towards a BCPS, and subsequently, a Fontan circulation. Neonates with complex cardiac defects are prone to thrombosis, and central lines are a potential source [248–250]. SVC stenosis or thrombosis can produce significant morbidity, and most centres will initially avoid placing lines in this critically important vessel [251, 252]. Femoral central venous lines are common, but umbilical and direct atrial lines are also used. All can induce thrombosis, but atrial lines may pose more problems if thrombosis occurs, due to the higher risk of emboli. Use of heparin-bonded central venous catheters and infusions of low-dose heparin through these lines are standard of care in many centres, but evidence of benefit is unclear [253]. The incidence of sepsis from indwelling umbilical lines increases exponentially over time, usually prompting their early removal but necessitating other central venous access. An improperly placed umbilical catheter with its tip in the hepatic region can result in liver necrosis or venous obstruction if caustic or if hypertonic solutions are infused. More recently, patients often come to the operating room with peripherally inserted central catheters, which may be less thrombotic. However, their small internal diameter often precludes their reliable use for volume expansion.

6.6.3 Additional monitoring. Intraoperative echocardiography is a standard of care that can be achieved adequately by either epicardial or transoesophageal probes. TOE has the advantage of a continuous monitor and does not interrupt the procedure or preoccupy the surgeon's hands. The probe can cause trauma and perforation to the upper oesophagus and obstruct both the airway and cardiac structures in neonates [254, 255]. The choice usually depends upon the availability of a neonatal size TOE probe and the preference and experience of the cardiac centre (see section on imaging).

Arterial blood gas (ABG), glucose and lactate analyses have been the mainstays for monitoring the adequacy of ventilation, acid-base management on CPB and tissue perfusion. SvO_2 is another marker of DO_2 and oxygen uptake (VO_2) and has been used in the management of cardiac patients both by intermittent sampling or by continuous measurement with direct catheter

placement [256]. Significant interest has developed using NIRS, which correlates well with SvO_2 and has the advantage of being non-invasive [257–259]. Because the normal range of NIRS values has not been established, and individual regional variations in SaO_2 exist, debate rages as to the value of NIRS as a surrogate monitor for global DO_2. In practice, most teams do use intraoperative NIRS in some capacity.

6.7 Precardiopulmonary bypass

6.7.1 Balancing pulmonary blood flow/systemic blood flow and maintaining cardiac output. Balancing anaesthesia according to the cardiovascular status of a patient necessitates careful titration, because most anaesthetic agents can have deleterious cardiovascular effects. Assuming normal pulmonary SO_2 and SvO_2, aiming for SaO_2 between 70% and 85% is the simplest way to balance Qp and Qs, and the ratio ideally should be close to 1. Most patients will have a tendency for excessive Qp with high SaO_2. Increasing the PVR, decreasing the fraction of inspired oxygen (FiO_2) or increasing the pCO_2 represents a traditional compensatory manoeuver [260]. Altering pCO_2 by addition of inspiratory carbon dioxide or by hypoventilation may have more value than reducing FiO_2, although hypoventilation should be used with caution because it may lead to atelectasis. Introducing nitrogen into the circuit has the effect of reducing the FiO_2 below 21%, reducing Qp/Qs [261]. However, when compared to increasing $PaCO_2$, reducing FiO_2 does not seem to improve SvO_2 or increase arterial BP [22]. Conversely, patients with significantly raised PVR, as in r-FO, can be extremely difficult to oxygenate. These patients often exhibit significant cardiovascular instability from the systemic effects of poor DO_2.

Surgical manipulation of cardiac anatomy during dissection can alter the condition of the patient and affect monitoring. If a right innominate shunt (an MBTS) is used for arterial cannulation for CPB, monitoring equipment attached to the right arm will not function properly. Communication with the surgical team is vital to limit any cardiovascular insult during dissection. Preventing a low diastolic BP and maintaining cardiac function, especially in the setting of a small Asc Ao, may require the use of inotropes and vasoactive agents. When appropriate, a surgically placed sling around the right pulmonary artery (RPA) may improve stability during dissection by mechanically increasing PVR but potentially at the cost of SaO_2. Reducing metabolic requirements with mild hypothermia may be beneficial in states of low cardiac output (CO) and reduced DO_2. A neonate's core temperature will drop with exposure during surgery, but surface cooling (ice packs applied to the head) is an easy way to accelerate this process.

6.7.2 Anticoagulation. Full heparinization, monitored by activated clotting time, is required to initiate CPB [262]. Most centres choose a dose between 300 and 400 IU/kg, aiming for an activated clotting time of 300–400 s. Coated circuits are used to minimize thrombin formation and potentially to reduce the inflammatory response [263, 264]. Suboptimal heparinization may promote the coagulopathy seen following CPB, increasing thrombin production. An individually tailored dose of heparin and subsequent protamine may reduce the activation of the coagulation cascade. However, no trials have been undertaken to show clinical benefit using this approach [265–268].

PGE1 infusion is continued as long as there is a requirement for the DA to provide Qs. It can be stopped once on CPB, or if the DA has been stented when an h-S1P is performed.

6.8 Cardiopulmonary bypass

As with repair of other complex CHD, consensus regarding the conduct of CPB bypass during S1P is lacking and there are wide interinstitutional variations [269]. Construction of the neo-Ao is performed commonly under a combination of deep hypothermic circulatory arrest (DHCA), low-flow CPB and RCP.

6.8.1 Hypothermia and circulatory arrest. The use of DHCA for Ao arch reconstruction is a long-standing technique in many institutions, with cooling for at least 20 min on CPB to nasopharyngeal temperatures of 18–20°C before stopping pump flow. Various strategies have been developed to limit the inflammatory response to CPB and reduce end organ damage, particularly cerebral complications [270]. Most evidence focuses on comparing the durations of DHCA and the effects of intermittent cerebral perfusion during DHCA and comparing DHCA with low-flow or selective RCP [271–278]. Although neurological sequelae can occur with any duration of DHCA, they are less likely if DHCA does not exceed 45 min. RCP has not definitively changed the incidence of detrimental neurological effects compared with DHCA. Limiting the duration of DHCA, using intermittent cerebral perfusion for anticipated prolonged periods of arrest and using low-flow or selective RCP remain sensible strategies for most patients undergoing S1P.

6.8.2 Haematocrit. It is important at all temperatures to balance increased blood viscosity [higher haematocrit (Hct)] and reduced O_2 capacity (lower Hct). Haemodilution protocols vary among institutions. A comparison between an Hct of 25% and 35% showed a trend towards better neurological outcomes in the latter group, and although evidence is limited, most centres in practice would aim for 25–30% [279]. There seems to be no clear outcome advantage in using fresh whole blood compared to a combination of packed red blood cells (RBCs) and fresh frozen plasma for priming of the CPB circuit. Retrospective data do suggest reduced donor exposure with fresh whole blood (compared with packed RBCs). There is a theoretical advantage to using RBCs stored fewer than 5 days, with a potential for reduced acid-base and electrolyte disturbance [280–282]. Although it is difficult to extrapolate results from adult studies to paediatric practice, the results of an adult critical care trial showed no difference between outcome and age for volume of red cells transfused [283].

Though there are increasing reports of bloodless cardiac surgery in very small patients, an asanguinous S1P remains elusive goal because blood must generally be added to the CPB prime to avoid marked haemodilution [284]. Aggressive miniaturization of the CPB circuit may be the most efficacious strategy. Minimizing foreign surface contact, in conjunction with biomimetic or biopassive surface coatings, lessens the inflammatory response to bypass. Clearly, a lower volume circuit can minimize the prime volume, the degree of haemodilution and the volume of homologous blood required to attain a desired Hb level. Simple,

carefully designed CPB circuits that can be primed with <100 ml may reduce the need for modified ultrafiltration and retrograde autologous priming in patients with HLHS.

6.8.3 Steroids. Most teams administer steroids to attenuate the inflammatory response to CPB and to the operation and to provide myocardial and cerebral protection. Animal studies and some small paediatric trials support this practice. However, the evidence from paediatric cardiac surgery is mixed, and there are no large-scale RCTs to provide clarity. A large RCT showed no advantage in the administration of steroids in adult cardiac surgery [285–291].

6.8.4 Acid-base and glucose management. An animal study comparing pH-stat versus α-stat acid-base management suggested that pH-stat confers better brain protection during DHCA. A proposed strategy involves using pH-stat during cooling, then switching to α-stat during DHCA [292]. The only RCT in children comparing α-stat and pH-stat showed some early benefit in the clinical state with pH-stat management in the transposition subgroup, but there was no difference in early or midterm neurological outcomes [292, 293]. There is no conclusive evidence to recommend one acid-base strategy over another.

Mitigation of reperfusion injury may also be enhanced by ABG manipulation, with decreased markers of injury when tissues are perfused with normoxic versus hyperoxic blood, especially in cyanotic patients [294].

Glycaemic control to avoid extremes of blood glucose levels might be prudent, but there is no evidence that hyperglycaemia leads to a worse outcome [295]. Tight glycaemic control does not confer any benefit to paediatric cardiac patients but does add the potential risk of more frequent hypoglycaemia episodes [296].

6.8.5 Filtration. Both modified ultrafiltration and standard ultrafiltration are commonly used to reduce postoperative morbidity. A meta-analysis showed that whereas modified ultrafiltration was more beneficial immediately post-CPB secondary to higher Hct and mean BP, there was no further advantage postoperatively between the 2 techniques [297].

6.8.6 Pharmacological protection. Several pharmacological agents have been used to promote cerebral protection during DHCA. An animal study showed a desflurane volatile-based anaesthetic to have significantly improved neurological outcome after DHCA compared with a fentanyl-based technique [237]. As previously discussed, although not investigating neurological sequelae following DHCA, other animal studies show that volatile agents cause neuronal apoptosis. Barbiturates are one of the more common agents used, but the evidence is scarce, and the doses required are likely to exert significant depression of the myocardium as well as to prolong the mechanical ventilation [298]. Recommending specific agents for routine use is not clear-cut, because the evidence is limited and conflicting.

6.9 Separation from cardiopulmonary bypass and immediate management after the procedure

6.9.1 Balancing pulmonary and systemic blood flow and maintaining cardiac output. Separation from CPB is a critical and challenging time. The initial focus is on ventricular function and rhythm. Reduced function or the presence of arrhythmias can indicate myocardial ischaemia. There is a low threshold for inspecting the Ao-PA amalgamation for a gradient across the neo-Ao or mechanical obstruction of the coronary arteries. On-table angiography, if available, may help when the cause of dysfunction is not clear.

The RV–PA conduit confers advantages over the MBTS in the immediate postoperative period (see section on source of Qp for S1P). Compared with the RV–PA conduit, the continuous PA run-off throughout the cardiac cycle with an MBTS risks lower diastolic BP, coronary steal and a circulation overly sensitive to changes in PVR and SVR [299–302].

Similar to the cardiovascular state preoperatively, if there is excessive Qp postoperatively, PVR can be increased by using ventilation strategies, reducing the calibre of the conduit or shunt or tightening b-PABs. Increasing PVR to improve circulatory balance is a valid method, although reducing SVR with systemic vasodilators to balance Qp/Qs maybe a better strategy [303–305]. Conversely, some patients exhibit elevated PVR or reactive pulmonary vasculature following CPB, probably secondary to an inflammatory response, and may benefit from ventilation strategies with inhaled nitric oxide.

Stroke volume is maintained by optimizing preload, reducing afterload and using inotropes to improve ventricular function. An ideal agent (not yet available) would improve cardiac contractility, balance PVR and SVR, improve Qs, maintain systemic diastolic perfusion pressure and have limited systemic or metabolic effects. There is limited quality data comparing inotropes in paediatric cardiac surgery [306]. Inodilators, in particular milrinone, or systemic vasodilators, such as phenoxybenzamine, in combination with agents such as adrenaline, noradrenaline or vasopressin are all in use [202, 304, 307]. Levosimendan (an inodilator with possible lusitropic properties) has been used successfully to augment CO in some centres.

Arrhythmias can present postoperatively, most commonly atrial tachycardias and bradyarrhythmias from sinoatrial node dysfunction [308]. A ventriculotomy for an RV–PA conduit might be arrhythmogenic, but there is no clear evidence of this [309, 310]. Correction of electrolyte imbalance, treatment with magnesium and temperature control are simple therapeutic options. Direct current cardioversion is indicated for acute tachycardias producing cardiovascular instability. Dual chamber epicardial temporary pacing can be used to maintain an adequate HR or sometimes to override atrial or junctional tachyarrhythmias. Subsequent treatment for recurrent tachyarrhythmias with β-blockers or amiodarone may be required, though care is warranted because these agents, especially amiodarone, can significantly reduce ventricular function [311].

Aiming for saturations between 70% and 85% is a simple way to guide balancing of Qp/Qs. A steady improvement in acid-base status and falling lactate levels suggest adequate Qs [312]. Persistent SvO_2 levels <50% indicate a worse outcome [202, 256, 313, 314]. NIRS correlates with SvO_2, is simple to use, and is non-invasive. Because NIRS is useful for detecting problems during CPB, there is a strong attraction to use it to monitor and guide treatment, making it a standard of care in many centres [270, 315–317]. However, the evidence for goal-directed therapy using NIRS in cardiac surgery remains elusive, with recent large adult trials showing no advantage [318–320].

Optimizing Hb to a level between 13 and 16 g/dl will improve DO_2 [303]. Over-transfusion leading to higher Hb levels should

be avoided, because it is likely to be detrimental to the DO_2 [321].

Temperature control (especially avoiding pyrexia) has been shown to be important in many clinical scenarios [322, 323]. Mild hypothermia reduces DO_2 and the tendency towards tachycardia, which can be beneficial in states of low CO or problematic arrhythmias. Potential problems with induced hypothermia include an increased tendency towards infections and a coagulopathic state.

6.9.2 Haemostasis. Bleeding and a coagulopathic state often follow complex neonatal surgery with CPB, despite the initial reversal of heparin with protamine. Because protamine can depress the myocardium and cause significant swings in vascular resistance by reducing SVR and increasing PVR, care is required when administering it [324]. Reducing blood product use to improve patient outcome is another major consideration [321, 325]. How one handles the perfusion procedure, the surgical techniques and the equipment used will influence transfusion requirements. Intraoperative rotational thromboelastometry or thromboelastography to monitor the coagulation cascade for directed treatment has become increasingly common and has reduced the need for red cell transfusions when treating bleeding patients [326–328].

The use of factor concentrates is a potential new avenue. Fibrinogen concentrates, prothrombin complex concentrate, recombinant factor VIIa, and anti-inhibitor coagulant complex have all been used in cardiac surgery [329–334]. The main concern with their use is the tendency for thrombosis, and as yet there are no published large-scale trials. The use of antifibrinolytics such as tranexamic acid can reduce blood loss during cardiac surgery [335, 336]. High-dose tranexamic acid is associated with seizures [337]. The use of aprotinin remains controversial, and although aprotinin is not currently used in North America, it is still used in centres in the UK and Europe. Future data collection should clarify whether the increased adverse event risk in adult aprotinin trials is present in the paediatric cardiac population [338, 339].

6.9.3 Transitioning to the intensive care unit. A certain proportion of patients undergoing a Norwood S1P will be unable to separate from CPB, requiring conversion to ECLS (usually ECMO). In such cases, particular attention during transport is directed to avoidance of decannulation and/or kinking of cannulas and utilizing a low ventilation strategy to minimize lung pressure and volume trauma.

Transfer of the patient to the ICU requires a detailed handoff to the accepting care team using closed loop communication. Recent studies have demonstrated that protocolized checklists result in improved efficiency and patient safety.

6.10 Summary

Research relevant to anaesthesia surrounding the initial treatment for HLHS is limited. As survival continues to improve, the focus will likely shift to improving associated morbidity. This goal will best be accomplished by multicentre collaboration and research.

Anaesthetic management of infants with hypoplastic left heart syndrome

Concept	Class[a]	Level[b]
Reduce SVR and prevent surges in afterload to improve systemic perfusion and maintain a balanced Qp/Qs	IIb	C
Reduce exposure to anaesthetic drugs shown to cause neuroapoptosis	IIb	C
The use of NIRS to monitor perioperative course	IIb	C
The use of TEG or ROTEM to monitor and direct treatment of coagulopathy	IIb	C
Minimization of CPB circuit to limit inflammatory response and haemodilution	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
CPB: cardiopulmonary bypass; NIRS: near infrared spectroscopy; Qp/Qs: pulmonary blood flow/systemic blood flow; ROTEM: rotational thromboelastometry; SVR: systemic vascular resistance; TEG: thromboelastography.

7. PREPARATION AND TIMING FOR STAGE 1 PALLIATION FOR HYPOPLASTIC LEFT HEART SYNDROME

Cases should be discussed by a multidisciplinary team wherever possible, including a paediatric cardiologist, a cardiac surgeon, an intensive care specialist and an anaesthesiologist. A detailed clinical assessment and review of imaging data enable the most appropriate surgical strategy to be chosen, and the operative risks and prognosis established, so that accurate and balanced counselling can be given to the parents.

7.1 Age at surgery

The optimum age for surgery is 2–7 days [137]. This is a class I recommendation (evidence level C) based on extensive published series of Norwood operations, which have demonstrated the best outcomes within this age range. No RCTs examining the impact of exact age (by day of life) have been published, and the wide variation in clinical presentation and physiological stability will have the strongest influence on the precise timing. Surgery has been avoided where possible during the first days of life to allow the postnatal circulation to stabilize and recover from the trauma of childbirth. However, physiological decompensation or restriction to the pulmonary venous return (see below) may necessitate emergency intervention, even on day 1 of life (class I, level C).

Older age at Norwood surgery is also a risk factor (class IIa, level C) [340–345]. There is insufficient evidence to define how risk increases with age beyond 7 days, or whether this risk is incremental with advancing age. Norwood S1P in older infants is commonly related to failed bi-V strategies in those with borderline left heart structures. They constitute a mixed group whose significant comorbidities and previous interventions make it

difficult to interpret the isolated impact of age alone within a host of competing risk factors. There is good evidence that undertaking the Norwood procedure at >14 days carries a significantly increased risk of death and prolonged length of stay. However, there is no evidence to suggest that a Norwood procedure is contraindicated or futile in the older age groups, provided that the RV has been maintained at systemic pressure [346].

It may be safe to establish enteral feeding in some neonates with HLHS prior to surgery, although published practices vary. There is no evidence to suggest that withholding enteral feeding protects against the development of NEC, and this practice does not influence surgical outcomes (class IIa, level C) [347–349]. However, it is prudent to consider the general condition of each baby, especially the adequacy of Qs and the metabolic profile, because individual patients may be at a higher risk of gastrointestinal problems with or without feedings. The importance of an intact gastrointestinal tract in patients with HLHS cannot be overstated.

Preoperative risk factors for mortality after Norwood stage 1 palliation

Preoperative risk factor	Risk	Class[a]	Level[b]
Premature birth	Very high	I	B
Weight <2.5 kg	High	IIa	B
Weight <2.0 kg	Very high	I	C
Genetic or chromosomal anomaly	High[c]	I	B
Preoperative ventilation	Moderate	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
[c]Varies with condition: Turner's and Down's syndromes are both associated with very high operative risk.

7.2 Gestational age

There is strong and increasing evidence that gestational age is an important determinant of clinical outcomes in neonatal surgery, but it can be difficult to separate from low BW. There is class I, level B evidence that prematurity increases the operative risk for death after the Norwood operation [126, 132, 222, 350–354] including evidence from the SVRT [35, 355]. There is also class I, level A evidence that prematurity increases the risk of postoperative morbidity and more prolonged ICU and hospital stays [58, 356]. The risk of prematurity for CPB (especially risk of neurological injury) is well established, with class I, level A evidence. Occasional retrospective studies have not shown prematurity to be an independent risk factor for death, but these are overwhelmingly in the minority [232]. Most evidence is based on the definition of premature birth as being at or before 37/40 weeks of gestation. There has not been any attempt to stratify age by degree of prematurity, although some studies have specified <35 weeks [352]. The majority of studies regarding prematurity in HLHS are based on a categorical yes or no definition, but by extrapolation from wider studies in neonatal CHD, the operative risk for prematurity rises exponentially with decreasing age.

There is limited information as to whether prematurity should influence the age at which S1P should be performed. Delaying the Norwood procedure in a premature infant to allow the organ systems to grow and mature has an appeal, but this is mitigated by the risk of leaving the neonate with an unstable physiology and at risk of interim end organ injury [357]. There is no good evidence that delaying the Norwood procedure beyond the recommended 2- to 6-day-of-age window carries any benefit in premature infants. Nevertheless, there is class IIa (level C) evidence that use of the h-S1P (i.e. avoiding CPB) in premature infants may reduce the otherwise increased mortality and morbidity rates [225, 358].

7.3 Weight

Low BW has been a consistently important risk factor for poor outcomes as an independent variable. Weight as a continuous variable has generally not been proven but discriminant values of <2.5 kg and of <2 kg have class IIa evidence of being risk factors for early and in-hospital death across all surgical techniques [35, 132, 222, 342, 343, 351, 353, 359–364]. BW has been a consistent and important risk factor in all risk-scoring systems for predicting Norwood procedure outcomes. Low weight appears to be an immutable patient risk factor, and there is no evidence that strategies to delay surgery or to try and increase preoperative weight have any influence on improving survival [357]. Enthusiasm for the h-S1P has provided some class IIIa evidence that its use in low BW infants improves outcomes compared to the standard Norwood S1P using CPB, but there have been no RCTs to support this concept [225, 358, 365]. The SVRT has suggested that outcomes for infants <2.5 kg may be better with the MBTS approach than with the RV–PA conduit, although the difference

Anatomical or patient-related risk factors for mortality after Norwood stage 1 palliation

Anatomical feature	Risk	Class[a]	Level[b]
Intact atrial septum	Very severe	I	C
Need for ECMO	Very severe	I	B
Obstructed TAPVD	Severe	IIa	C
Unbalanced AVSD subtype	Moderate–severe	IIa	C
TR ≥ moderate	Severe	I	C
Impaired RV function	Moderate–severe	IIb	C
Asc Ao <2 mm	Moderate	IIa	C
AA/MS subtype	Moderate	IIb	C
Any associated cardiac condition	Moderate	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
AA: aortic atresia; Asc Ao: ascending aorta; AVSD: atrioventricular septal defect; ECMO: extracorporeal membrane oxygenation; MS: mitral stenosis; RV: right ventricle; TAPVD: totally anomalous pulmonary venous drainage; TR: tricuspid regurgitation.

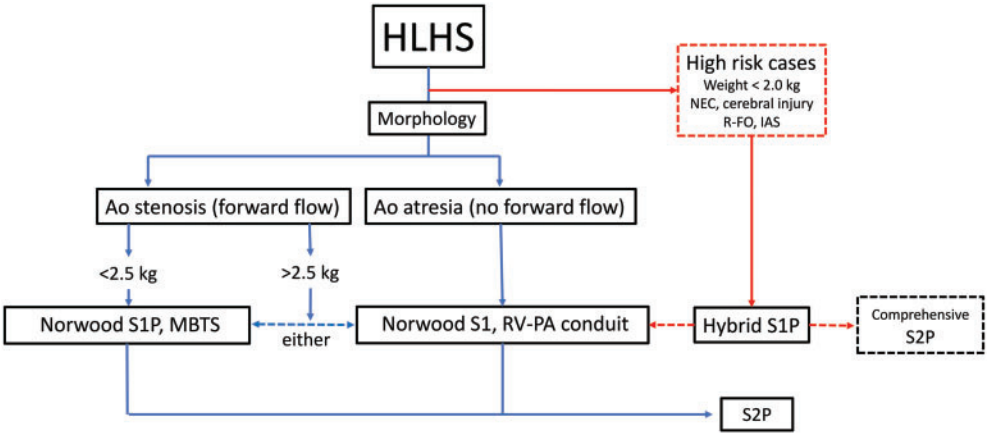

Figure 18: Potential decision tree for the choice of S1P based on the best evidence from the Single Ventricle Reconstruction Trial and published series of the hybrid S1P technique (as the preferred approach). The balance of evidence in favour of the RV–PA conduit has been reduced as the trial period has been extended, but there remains a marginal benefit in the aortic atresia cohort, also supported by data from the Congenital Heart Surgeons' Society. HLHS: hypoplastic left heart syndrome; IAS: intact atrial septum; MBTS: modified Blalock–Taussig shunt; NEC: necrotizing enterocolitis; PA: pulmonary artery; r-FO: restrictive foramen ovale; RV: right ventricle; S1P: stage 1 palliation: S2P: stage 2 palliation.

is small and is mainly from institutions with high-volume Norwood programmes and in patients with AS rather than AA [35]. A summary of the evidence relating age and weight to the choice of Norwood procedure is shown in Fig. 18.

7.4 Preoperative ventilation

There is no evidence that preoperative ventilation improves outcome, even if it used electively [366]. The need for preoperative mechanical ventilation is a risk factor for poor outcome in many series, but not universally [352, 362, 367]. The majority of centres do not use ventilation routinely, so most patients are only ventilated for haemodynamic instability, excessive Qp and resuscitation. Consequently, the need for mechanical preoperative ventilation has been shown to be a risk factor for poor outcome, and there is insufficient data to evaluate the role of elective ventilation. Evidence suggests that stable patients do not require elective ventilation (class IIa, level C). Similarly, elective ventilation for transport in a stable patient is not beneficial and should be avoided if possible (class IIa, level B). Ventilation for preoperative MRI should be avoided if possible.

7.5 Non-cardiac and associated genetic abnormalities

Genetic or chromosomal abnormalities in HLHS are strong and consistent risk factors for poor outcome of the Norwood procedure, both in-hospital and late. There is class I (level B) evidence to support this contention [35, 126, 222, 350, 352, 355, 359, 361, 368, 369]. Most syndromes and genetic defects have been studied in smaller retrospective series, so the evidence for individual genetic anomalies and chromosomal defects is less clear. In keeping with other major congenital heart lesions, comfort care is recommended for trisomy 13 and 18 syndromes (class I, level C) because the outcome of major cardiac surgery in these populations is extremely poor, with no evidence that it alters the severe life-limiting natural history. There is limited evidence for the role of the Norwood procedure in both trisomy 21 and in Turner syndrome, and both carry an increased risk for early death (class I, level C) [369–374]. Mosaic variants of these anomalies may have a better prognosis. The abnormal lymphatic system in trisomy 21 can make S2P and stage 3 palliation high-risk procedures with poor outcome. For these reasons, the Norwood operation might not be offered to such patients after appropriate counselling.

7.6 Anatomical factors

A variety of anatomical factors have been examined, and several have emerged as consistent risk factors for early and in-hospital death following the Norwood operation, with others having mixed evidence. This information should be taken into account when counselling families and assessing suitability for surgery. There is no individual anatomical factor that has been established as an absolute contraindication to S1P, but IAS or severely r-FO in the setting of MA carries an extremely poor prognosis and high operative mortality rate.

7.6.1 Morphological subtype. AA carries a higher operative risk than AS (class IIa, level B) but the increment is small and not reported in all studies [360]. The SVRT showed that the risk of AA was minimized by the use of an RV–PA conduit over the MBTS (class IIa, level B) [35]. The combination of AA/MS carries a significantly higher risk for in-hospital death [40, 44, 196, 375, 376], although not in the SVRT. This may relate to the presence of myocardial sinusoids and coronary steal but is not seen consistently. Despite considerable data on the morphological subtype, there is only class IIa, level C evidence that AA/MS is an independent risk for poor outcome.

7.6.2 Ascending aorta diameter. Small Asc Ao diameter is strongly linked to AA, which confounds the risk factor analysis of size alone. Multiple single-centre retrospective studies have cited small Ao diameter (usually as a categorical variable of <2 mm) as a risk factor for survival following the Norwood procedure [35, 344, 357, 362, 363, 365, 377]. Class IIa (level C) evidence indicates

that an Asc Ao diameter <2 mm carries a slight to moderate increased risk for death following S1P.

7.6.3 Totally anomalous pulmonary venous drainage. TAPVD is not consistently analysed in the literature, because it frequently occurs in the presence of right isomerism or other complex cardiac conditions that carry many other cardiac and non-cardiac morbidities. The evidence suggests that obstructed TAPVD is a severe risk factor for death after the Norwood procedure (class I, level C), but there is no consensus on the impact of unobstructed TAPVD [21, 24, 35, 42, 55]. The combination of HLHS with obstructed TAPVD is extremely high risk, and active treatment may not be offered in severe cases.

7.6.4 Intact atrial septum. r-FO and IAS have been consistently identified as severe risk factors for early and late death after the Norwood procedure [33, 158, 377, 378]. Any patient with IAS, especially in the absence of forwards flow through the left heart, should be considered as very high risk for the Norwood procedure and requires initial emergency decompression of the LA (class I, level C). Antenatally diagnosed cases should have delivery planned close to an available surgical team and have resuscitation and ECMO facilities immediately available. ECMO may be required to stabilize the patient, and urgent decompression is indicated if active treatment is planned. Antenatal diagnosis of pulmonary lymphangiectasia in combination with IAS carries an extremely poor prognosis, and active treatment may not be offered [33]. Choice of operation depends on the overall condition of the baby. Minimizing the duration and complexity of an operation has been advocated by utilizing the h-S1P approach (see subsequent sections) but there is insufficient evidence to support any one strategy over another. Both IAS and obstructed TAPVD are associated with pulmonary lymphangiectasia of the lungs and developmental lung anomalies that strongly influence early and late outcomes.

7.6.5 Ventricular function. All evidence for RV function is based on echocardiographic assessment, usually on a subjective scale of mild, moderate or severe impairment. Function does not feature as an independent risk factor in several studies, but there is class IIb (level C) evidence that ≥moderate RV dysfunction is a risk factor for in-hospital death following the Norwood procedure [132, 365, 381].

7.6.6 Tricuspid regurgitation or common atrioventricular valve regurgitation. There is class I (level C) evidence that preoperative ≥moderate TR (or AVV regurgitation in the setting of unbalanced AVSD) is a major risk factor for early and in-hospital death [132, 351, 353, 367, 368]. TV repair has been advocated in this setting, but there are no RCTs to evaluate the benefit of concomitant valve repair at time of the Norwood procedure. The evidence suggests that TV repair is a safe procedure to undertake at the time of the Norwood operation and should be considered in any case with ≥moderate TR.

7.7 Surgical set-up and bypass management

Median sternotomy is the only recommended surgical approach. The h-S1P has been described as being performed through a left posterolateral thoracotomy with safe outcomes, but midline sternotomy is usually the h-S1P approach [380].

7.7.1 Cannulation. Arterial cannulation can be performed in a variety of ways, all of which have been shown to be safe and reproducible. No strong evidence favours any one technique, but the choice is affected by CPB strategy and individual morphology. Cannulation of the DA is safe but requires changing the cannulation site to the neo-Ao after arch reconstruction. Standard high Ao cannulation can be used in cases with a large Ao and is the simplest technique. The cannula can be advanced into the brachiocephalic artery and snared for antegrade RCP during arch surgery. The most widely currently used arterial cannulation method is placement of a vascular graft on the brachiocephalic artery. This procedure allows secure arterial perfusion throughout the operation and can be used to continue antegrade RCP during arch repair without additional manoeuvres. A 3-mm polytetrafluoroethylene (PTFE) graft is most commonly used, placed above the brachiocephalic vein. In cases with an aberrant subclavian artery, the graft can be placed on the carotid artery.

Cases with IAA should ideally have dual arterial cannulas, 1 placed in the DA and 1 onto a brachiocephalic artery graft (or in the Asc Ao if large enough). Some authors describe cannulating the main PA (MPA) and snaring the branch PAs to avoid instrumenting the duct. The disadvantage is that the branches cannot be separated from the MPA without decannulation, and a longer period of DHCA is required.

Whole-body perfusion during arch reconstruction has been described but is not standard practice for the majority of reporting centres. The technique requires an additional Desc Ao cannulation during arch reconstruction. This cannulation can be performed directly via the posterior pericardium or by inserting and then snaring a perfusion cannula into the lumen of the open Desc Ao after the duct has been excised. These techniques are safe and can be performed with mild hypothermia (32°C), avoiding the need for deep hypothermia. There is a low incidence of renal dysfunction and acidosis postoperatively [381–383]. However, these data are all based on observational studies, with no trials to suggest any survival advantage over standard arterial cannulation. There is class IIa (level B) evidence for less renal impairment and shorter ICU stay.

Single venous cannulation of the RA has been the predominant reported technique. Bicaval cannulation is safe and has the advantage of enabling atrial septectomy to be performed without circulatory arrest. If continuous whole-body perfusion is the chosen CPB strategy, then bicaval cannulation is also favoured. Single cannulation is simpler and keeps the cannula away from the surgical field when the surgeon is working on the RPA and arch. There is no evidence to favour single or dual cannulation as the preferred strategy.

7.7.2 Perfusion strategy. A variety of strategies exist without any dominant technique. There has been a general trend to move away from prolonged periods of DHCA, but the majority of evidence supports the use of at least moderate hypothermia to provide neurological protection and to accommodate periods of less than full perfusion during arch reconstruction. The use of antegrade RCP during arch repair has become increasingly popular, delivered via a PTFE graft on the brachiocephalic artery or an arterial cannula high in the Asc Ao, which can be advanced into the brachiocephalic artery and snared. Both techniques are

acceptable. Published evidence for CPB flow adequacy during RCP recommends 40–50 ml/kg, with pressure monitoring in the upper limb. There are no trials to compare different flow regimens. Temperature management depends on the perfusion strategy. The use of pH verses α-stat strategies is discussed under anaesthetic considerations.

7.7.3 Antegrade regional cerebral perfusion versus deep hypothermia and circulatory arrest. Although there is evidence of increasing use of RCP, there is no evidence of a survival benefit when the 2 techniques are compared. There is class IIa (level C) evidence of lower serum lactate levels and of some protection of renal function with RCP, but no survival benefit [277, 278, 384]. RCP is used routinely for S1P by >80% of US surgeons [385].

7.7.4 Haematocrit and blood product utilization on cardiopulmonary bypass. The use of blood products for the Norwood S1P is unavoidable, and practice is institution specific. Whole blood or packed RBCs with fresh frozen plasma are recommended, for the goal being an Hct >25%, especially during the cooling and rewarming phases when hypoxic and ischaemic brain injuries are most likely to occur. It is recommended that Hct be maintained up to 30% [386, 387]. Fresh blood (<5 days old) is better metabolically balanced, with lower lactate concentrations compared to stored blood and is recommended for neonatal surgery with evidence of fewer pulmonary complications(class I, level B) (see anaesthetic considerations) [280, 281].

The use of DHCA is safe, and there is no evidence to suggest that the use of short periods of DHCA *per se* is associated with additional risk of death. However, because there is class I (level B) evidence that longer periods of DHCA are strongly associated with early mortality, every effort should be made to minimize the duration of DHCA [44, 342, 355].

7.7.5 Antifibrinolytics. The use of aprotinin as an antifibrinolytic agent to reduce bleeding has been shown to be both effective and safe. Evidence comes from large trials and meta-analyses of neonates and infants undergoing CPB and includes patients with HLHS but does not include analyses of the data by diagnostic groups. Nevertheless, the overall findings support the use of aprotinin to reduce postoperative bleeding and for renal protection. The use did not affect the operative mortality rate [388, 389]. Although aprotinin is not currently used in North America and Australia, it is still used in centres in the UK and Europe. Future data collection should clarify whether the increased adverse event risk in adult aprotinin trials is present in the paediatric cardiac population (see anaesthetic considerations).

7.7.6 Delayed sternal closure. An open sternum is used commonly following the Norwood procedure, reflecting the complexity of the surgery and the potential for haemodynamic instability in the early postoperative period. A large multicentre study from the Society of Thoracic Surgeons' database found that the chest was left open in 74% of cases [390]. All large published series and the SVRT show that delayed sternal closure is used to some extent by all centres. Routine use of delayed sternal closure is commonly practiced or can be used based on the surgeon's preference in more complex, unstable or higher risk cases. There is no RCT to support the use of delayed sternal closure, and the evidence is therefore biased in that many centres only utilize this strategy in higher risk and more unstable cases. As a consequence, the SVRT demonstrated a higher early mortality rate associated with delayed sternal closure, reflecting the higher operative risk and comorbidities of the patients [353, 355]. The recommendation is that delayed sternal closure should be considered if there is any concern about haemodynamic instability or postoperative tissue oedema (class IIa with level of evidence C) [353, 355, 379, 390]. Equally, primary chest closure is acceptable in the setting of stable haemodynamics, but the level of evidence is less strong and this procedure should probably be only performed by experienced teams (class IIb, level C).

Intraoperative and institutional risk factors for death after the Norwood stage 1 palliation

Operative factor	Mortality risk	Class[a]	Level[b]
DHCA duration	Progressive	I	B
Use of ECMO	Very high	I	C
Open sternum	Moderate	IIa	B
Institutional volume	Moderate	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
DHCA: deep hypothermic circulatory arrest; ECMO: extracorporeal membrane oxygenation.

7.7.7 Myocardial protection. Standard cardioplegia regimens that are applicable to all neonatal operations are recommended for the Norwood procedure and have been used according to standard institutional preference. Cold-blood intermittent dosing of cardioplegia is the most common method. There is no evidence to suggest 1 type or regime of cardioplegia is of benefit over any other. Myocardial ischaemic time can be reduced by perfusing the Ao root during arch reconstruction but there is no evidence of any survival benefit. In AA, the implantation of the proximal RV–PA conduit can be performed safely without Ao clamping. This reduces the total Ao clamp time but has not been shown to have any clinical benefit. Although there is a trend for the use of a single-dose modified depolarizing intracellular solution like the histidine-tryptophan-ketoglutarate solution or the del Nido solution, there is no evidence in the Norwood operation of any outcome benefit compared to other regimens.

7.7.8 Vasodilatation. The use of systemic vasodilators has gained wide use in CPB and postoperative management of patients having the Norwood procedure. There have been no RCTs, but there is class I (level C) evidence that systemic vasodilatation produces more stable haemodynamics with better tissue DO_2 delivery and reduces the risk of cardiovascular collapse [304, 391, 392]. The use of fixed α-blockers such as phenoxybenzamine has largely been superseded by phosphodiesterase inhibitors [393]. Some centres also use sodium nitroprusside or phentolamine during the cooling and warming phases of CPB.

7.7.9 Role of extracorporeal membrane oxygenation. Circulatory support with ECMO within the operating room has been widely used in the setting of the Norwood procedure when there is failure to wean from CPB, severely deranged metabolic status or borderline haemodynamics (despite high inotropic requirements). It is reasonable to deploy ECMO in such circumstances (class IIa, level C), but only after remediable anatomical lesions have been addressed. The predicted hospital survival (25–30%) for ECMO in these circumstances is poor compared to other neonatal cardiac conditions, and the need to use ECMO has been shown to be a highly significant risk factor for postoperative death [394, 395].

7.7.10 Institutional volume/caseload. The relationship between case volume and outcome has been analysed in congenital heart surgery, with the Norwood operation being the most extensively studied index procedure. The Norwood caseload for both a unit and an individual surgeon has been strongly associated with improved survival in retrospective multi-institutional studies [396–399]. The SVRT showed a stronger association with decreased morbidity than with survival [35, 355, 379]. Although a strong trend, the relationship is not always upheld, and many small-volume centres have reported good outcomes. There is a stronger relationship for institutional volumes compared with individual surgeon volumes. It is recommended that centres should undertake >10 Norwood procedures per year to optimize outcomes (class IIa, level B).

8. MANAGEMENT OF THE PULMONARY ARTERIES, AORTIC ARCH AND ATRIAL SEPTUM DURING THE NORWOOD STAGE 1 PALLIATION

8.1 Management of the pulmonary arteries

Good development of the PAs in HLHS (central and peripheral) is crucial for the future effectiveness of the Fontan circulation. All surgical procedures regarding the PAs, starting from the neonatal period, should focus on promoting growth and avoidance of distortion and scar tissue.

The level of the MPA transection should be planned together with the type of Ao arch reconstruction. Most surgeons prefer to divide the MPA immediately below the bifurcation. The bifurcation end of the MPA can be closed directly (preferably with a vertical technique to prevent stenosis), but usually a small autologous pericardial or pulmonary homograft patch is recommended [400–405]. Neither of these techniques has demonstrated superiority, but loss of continuity between the RPA and left pulmonary artery (LPA) has been observed when the distal PA was primarily sutured. Surgeons who prefer the RV–PA conduit use this aperture for the distal graft anastomosis, with or without an additional patch. Depending on the position of the PTFE graft in relation to the neo-Ao, careful analysis of the geometry can prevent distortion or compression of the central PAs by the distal graft. There are several techniques for distal shunt anastomosis, but none is superior (see shunt section). The ligated DA stump is usually left in place and does not require additional patch-plasty. Care should be taken not to obstruct the branch PAs with a too proximally situated ligature.

The Norwood operation after h-SP1 with b-PAB requires a careful assessment of the PAs after band removal. In most cases a Hegar dilator alone (4–6 mm) is sufficient to address the PAB-induced narrowing. However, discontinuity of the branch PAs as a complication of the PAB should be addressed as early as possible to promote critically important PA development. In these cases, an additional patch (autologous pericardium, PA homograft) reconstruction is recommended.

The techniques with complete division of the PA branches from the MPA (e.g. 'PA trunk-saving' method and 'chimney reconstruction') require subsequent end-to-end anastomosis of the left and RPAs, with the risk of stenosis, and are recommended only during the c-S2P [406, 407].

Pulmonary arteries

Recommendations	Class[a]	Level[b]
Patch reconstruction of the central PAs	IIa	C
Direct closure of the central PAs	IIb	C
Division of the branch PAs	III	C
Ligature of the proximal ductus arteriosus, no patch	I	C

[a]Class of recommendation.
[b]Level of evidence.
PAs: pulmonary arteries.

8.2 Arch reconstruction techniques

The techniques of cannulation and management of CPB are strongly dependent on the method chosen for reconstruction of the arch and the Asc Ao. After several modifications of the original technique, a 'classic' Norwood now usually implies PA homograft patch augmentation of the entire arch and Asc Ao, with proximal anastomosis of Asc Ao to MPA, without resection of the Ao isthmus [341, 408–411] (Fig. 19A–C).

For a Norwood procedure with DHCA, the RA (venous) and MPA (arterial) just above the sinuses of Valsalva are cannulated. Dissection and mobilization of the arch and the Desc Ao are done during cooling, separating the small Asc Ao from the MPA. The Desc Ao should be dissected at least 2 cm below the junction with the DA, but sacrifice of intercostal arteries is usually not necessary [412]. In DHCA, the head arteries are snared and the cardioplegic solution is administrated through a cannula in the innominate artery. Arterial and venous cannulas may be removed to assess the geometry of the reconstructed vessels [401, 403]. The PA end of the DA is ligated (see above), and all other DA tissue should be resected. One should excise all the tissue macroscopically identified as ductal (thicker walled and more friable than Ao) [405, 413]. It is usually unnecessary to transect or resect the isthmus. Resection of the isthmus may require ligation of the left subclavian artery, because its orifice is adjacent [414]. The Desc Ao should be opened at least 7–10 mm beyond the DA insertion. Identification of the intercostal arteries is helpful for orientation, because they arise from the Desc Ao and not from the DA.

The Ao arch is opened along the (lesser) inner curvature. The Asc Ao should be opened along the left lateral wall adjacent to

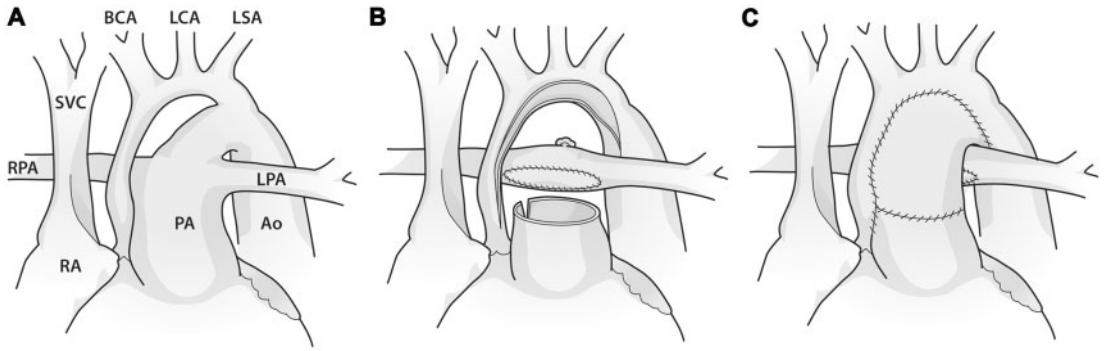

Figure 19: (**A–C**) Classical aortic arch reconstruction technique for hypoplastic left heart syndrome (PA homograft patch augmentation of the entire arch and ascending aorta, with proximal anastomosis of the ascending Ao to the main PA, without resection of the aortic isthmus). Ao: aorta; BCA: brachiocephalic artery; LCA: left coronary artery; LPA: left pulmonary artery; LSA: left subclavian artery; RA: right atrium; PA: pulmonary artery RPA: right pulmonary artery; SVC: superior vena cava.

the MPA. If the Asc Ao is small (1–3 mm), the incision line should reach more deeply into the Ao root (which is usually larger than the diminutive Asc Ao) to the level of the transected MPA (Fig. 19B). A CoA shelf on the posterior wall of the isthmus (a ridge of intima and media) should be addressed and can be peeled off without sharp dissection [415].

The material for the patch reconstruction of the Ao can be autologous (pericardium) [401, 415–417], homologous (Ao, pericardium, PA) or xenologous (bovine or porcine pericardium) [416–419]. In most cases, surgeons prefer a PA homograft, not only because of its pliability, handling and haemostatic properties but also due to its thickness, which corresponds to that of the neonatal Ao wall. The important disadvantage of homograft patches is the lack of availability. The patch is roughly triangular, oval at the top and wide at the base to fit the circumference of the MPA (shield-shaped). Reconstruction is started in the descending part, progressing to the arch and Asc Ao using a continuous polypropylene suture. At every stage of reconstruction, the shape of the patch should be analysed and, if necessary, tailored, because kinking or redundancy around very narrow areas can cause early or late obstruction, which is poorly tolerated by the SV. Appropriate tailoring of the patch is also essential to avoid excessive dilation of the Asc Ao and compression of the LPA or left bronchus. The golden rule 'a patch as small as possible but without kinking' should be kept in mind.

Before completion of the Ao reconstruction, the proximal MPA artery is longitudinally incised (3–5 mm), exactly adjacent to the aortic root incision. The facing sides of the 2 roots are anastomosed directly using a continuous suture. This step is probably the most critical part of the Norwood procedure, because minimal distortion in this region can result in poor coronary perfusion. In a very small Ao, the scar tissue developing in the anastomosis can cause stenosis and impair coronary blood supply. Alternatively, a double-barrelled technique can be used after transection of the Asc Ao immediately above the sinotubular junction. Reconstruction of the Ao is completed by end-to-end anastomosis between the patched Ao and the proximal MPA. After Ao reconstruction, the same purse string suture in the proximal MPA (neo-Ao) can be used for arterial recannulation (Fig. 19C).

Patch augmentation provides a more standardized, reproducible and easier surgical procedure, irrespective of arch morphology or degree of Asc Ao hypoplasia. The posterior Ao wall in the isthmus region can be left in continuity [420, 421]. One modification using patch material involves initial complete reconstruction of the arch with a homologous patch. The patch on the undersurface of the arch is then incised, and the distal end of the MPA is sutured to the opening in an end-to-side fashion to complete the proximal anastomosis.

There are a variety of modifications of the classical Norwood technique employing direct anastomosis of the proximal PA and Ao arch with or without opening of the Asc Ao, and with or without aortic isthmus and CoA resection. They are generically termed 'autologous techniques' [401, 402, 406, 407, 412] (Fig. 20A and B). A tension-free reconstruction of the Ao arch is usually possible by extensively mobilizing the arch branches and Desc Ao. In cases with AA and a very small Asc Ao it may be necessary to transect and re-implant the Ao into the innominate artery or MPA. The autologous techniques reduce DHCA time and address possible disadvantages of the exogenous patches (lack of growth, degeneration, possible transmission of viral infection, availability). Relative contraindications to this technique include long, diminutive Asc Ao (≤2.5 mm in diameter), DA tissue in the Ao arch between the left carotid and left subclavian artery, a long DA and an aberrant right subclavian artery [43, 401]. Possible disadvantages related to this method are compression of the branch PAs and left bronchus by the short arch. Saving autologous material from the MPA for arch reconstruction to protect the LPA from compression comes at the expense of the central PA tissue [406, 407]. The most important issue with the autologous techniques can be coronary perfusion (precoronary stenosis), notably in cases with AA and a small Asc Ao. This is an important risk factor for postoperative death [401, 417, 422, 423].

In the 'interdigitating' technique, after resection of the isthmus, 2 longitudinal incisions are made in the anterior and posterior walls of the Desc Ao (Fig. 20C). An extended end-to-end anastomosis is made between the distal Ao arch and the posterior Desc Ao [424]. This method may require a patch for arch augmentation and classical amalgamation with the proximal PA. The rationale of this technique is based on the histological examination of the Ao isthmus in specimens with HLHS, proving that DA tissue encircles the Ao lumen, with extension into the Ao both proximally and distally from the DA orifice [425]. Potential residual DA tissue is split longitudinally in the anterior and posterior portions, and the incisions are augmented with autologous tissue posteriorly and the patch anteriorly.

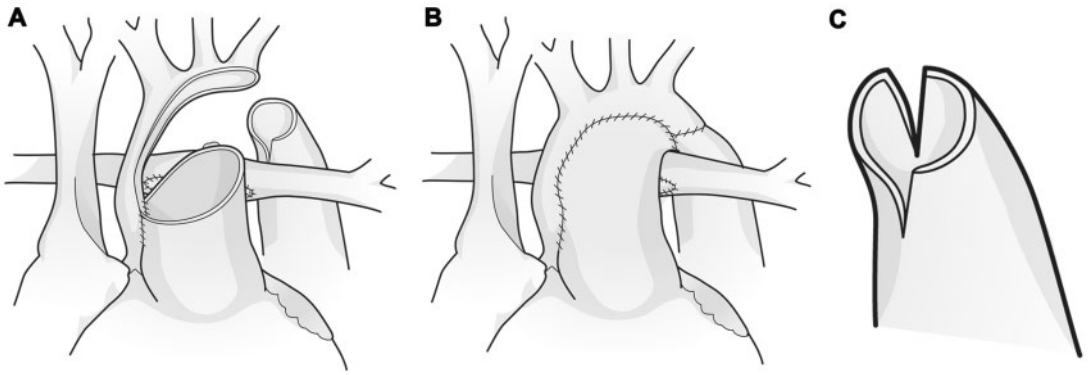

Figure 20: (**A** and **B**) Direct anastomosis of the proximal pulmonary artery and aortic arch with or without opening of the ascending aorta and with or without aortic isthmus and resection of the coarctation of the aorta ('autologous' techniques). (**C**) Incisions in the distal aorta for the 'interdigitating' technique for direct aortic arch reconstruction.

In the presence of a larger diameter Asc Ao (4–5 mm), the longitudinal incision of the Ao can be extended just to the origin of the innominate artery. The arch can be anastomosed directly to the MPA or partially anastomosed (just the posterior aortic wall) with augmentation of the anterior wall using a patch (Fig. 21).

A right Ao arch is extremely unusual in HLHS but can be seen in other forms of SV requiring the Norwood-type reconstruction. In children with an additional IAA arch, it is usually possible to anastomose the posterior wall of the aortic branches directly side to side. Then the reconstruction can be completed by augmentation with a patch and amalgamation with the proximal MPA as in the classic Norwood procedure [428]. In transposition of the great arteries or malposition of the great arteries, an unobstructed anastomosis of the Ao root, Asc Ao and the MPA can be achieved with the 'double-barrelled' technique or the two-patch technique (Fig. 22A–C) [426–428]. Disconnecting the proximal Asc Ao from the distal Asc Ao in strategies other than the double barrel technique can cause distortion, affecting the coronary supply, especially if the native Ao is very small (<2 mm); thus it is generally not recommended. An aberrant right subclavian artery can be left in place, and division is not recommended by any level of evidence. In the rare case of an IAA with HLHS, the same general principles of reconstruction apply, except that the 2 segments of the arch will always be separated and an anastomosis will be required between the Ao arch and the Desc Ao, incorporating the MPA, usually with patch augmentation.

Recurrent CoA or arch obstruction requiring intervention is common (7–36%), especially in non-HLHS forms of an SV undergoing S1P [66, 400, 413, 416, 419, 424, 429–432]. Echocardiographic criteria for recurrent CoA include a Doppler maximum instantaneous gradient in the Desc Ao >30 mmHg and/or a CoA index (ratio between the narrowest diameter of the Desc Ao and the widest portion of the Desc Ao) <0.7 [433]. The diagnosis by catheterization is angiographic narrowing of the Ao with a peak systolic ejection gradient of >20 mmHg. Most obstructions develop within 1–6 months after the Norwood procedure, and even mild degrees of obstruction can be clinically significant, with signs of low Qs. Recurrent Ao arch obstruction after S1P is associated with worse RV systolic function at the time of S2P [415]. Early catheterization intervention is recommended in patients with moderate or severe ventricular dysfunction, moderate or severe TR or an abnormal Doppler flow pattern in the abdominal Ao [66, 432, 434].

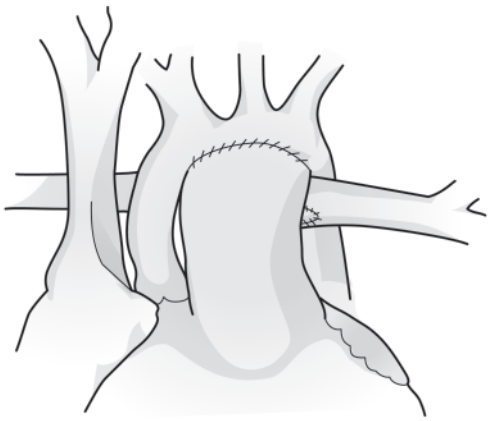

Figure 21: In the presence of a larger diameter ascending aorta (4–5 mm), the longitudinal incision of the aorta can be extended just to the origin of the innominate artery. The arch can then be anastomosed directly to the main pulmonary artery or to the posterior wall of the arch directly with augmentation of the anterior wall using a patch.

Recoarctation and acute arch angles increase wall shear stress and energy loss, but stiff vessel walls after patch reconstruction also consume energy resulting in an increased cardiac workload [414]. Elasticity of the reconstructed Ao (compliance) is crucial for single RV function. Patients with HLHS after the Norwood operation have increased Ao stiffness and decreased distensibility [435]. A persistent increase in stiffness within the Ao after successful repair of CoA, even without patch material, is well known [436, 437]. Interestingly, nearly all arch obstruction after the Norwood happens in the first several months of life, which is probably related to technical problems in reconstruction rather than to non-growth of the patch-augmented Ao. The growth of the reconstructed arch is similar to that of the normal population and occurs in the native tissue that comprises at least a part of the circumference of the Ao at every level [438].

The types of the arch reconstruction and the patch material do not affect the incidence of arch or isthmus preintervention as much as the residual DA tissue and surgical technique do, i.e. without extra material versus homograft patch, isthmus resection versus no resection, homograft versus bovine pericardium [43, 66, 400, 413, 416, 419, 420, 424, 430, 432, 439]. Studies

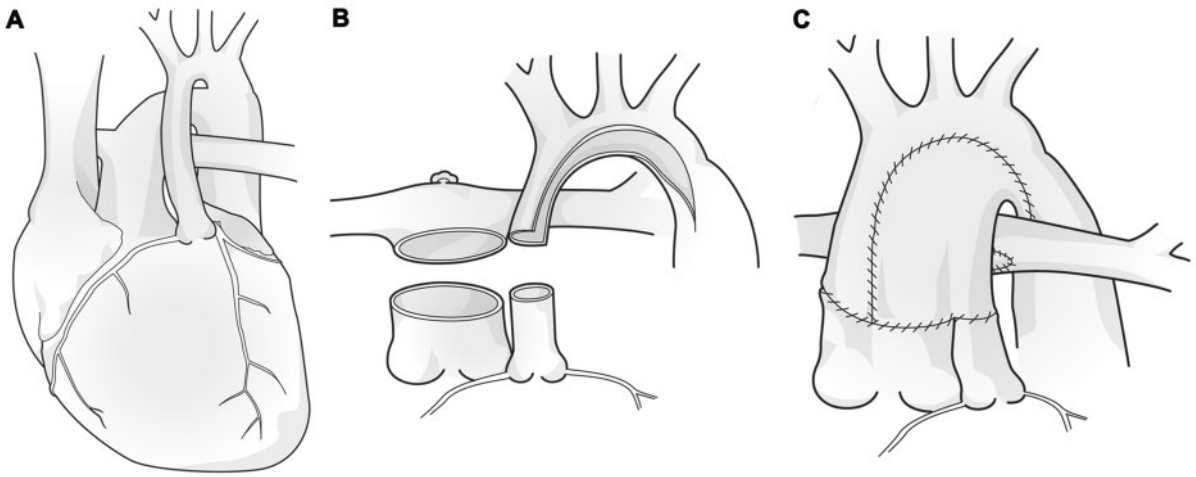

Figure 22: (**A–C**) In transposition or malposition of the great arteries, an unobstructed anastomosis of the aortic root, the ascending aorta and the main pulmonary artery can be achieved with the 'double-barrelled' anastomotic technique.

assessing the 'interdigitating' technique report a lower incidence of recurrent obstruction (0–13.7%) [340, 424, 440, 441]. Coarctectomy seems to result in a lower incidence of neo-Ao arch and isthmus obstruction in comparison with the classical technique, but the SVRT did not support this experience [416, 431].

In Norwood procedures, an optimal technical performance may attenuate the effects of poor preoperative physiological status and high case complexity, with a reduced hospital mortality probability. Inadequate technical performance resulted in poor outcomes regardless of preoperative status [442].

Aortic arch reconstruction

Recommendations	Class[a]	Level[b]
Resection of the macroscopically identified ductal tissue	I	C
Resection of the posterior coarctation shelf	I	C
Resection of the isthmus (coarctectomy)	IIa	C
Reconstruction of the aortic arch without extra material	IIb	C
Transection and reimplantation of the diminutive ascending aorta	IIb	C
Incision of the descending aorta 5–10 mm beyond the ductus insertion	I	C
Interdigitating technique	IIa	C
Longitudinal incision and direct 'side-to-side' anastomosis of the adjacent (facing sides) pulmonary and aortic roots	I	C

[a]Class of recommendation.
[b]Level of evidence.

8.3 Atrial septectomy

An unobstructed FO is crucial at each stage of HLHS treatment. The main issue with restriction of the FO is cyanosis and, less often, congestion in the lungs. The Rashkind procedure pre-S1P is rarely recommended, because it can cause unlimited Qp at the expense of Qs. Creation of an unobstructed interatrial communication during S1P is recommended; if is done effectively, a repeat septectomy is not required [443]. If the anatomy of the atrial septum is normal, the septectomy can be performed through the cannulation site of the RA appendage [401, 405, 420]. Resection of the whole septum primum and as much as possible of the septum secundum (after identification of the TV) is recommended [408]. The atrial septectomy can be made at different stages of the Norwood procedure, but the majority of surgeons perform it as a first procedure after cardioplegic arrest. Abnormal anatomy of the atrial septum or LA (displacement of septum primum, intact or very thick septum, cor triatriatum) is not uncommon and is an indication for full atriotomy for better visualization of the septum and assessment of the pulmonary veins. Posterior deviation (leftward displacement) of the septum primum occurs in ∼55% of patients, and only 26% of children with HLHS have normal atrial septal morphological characteristics [444]. In children with persistent left SVC draining to the coronary sinus, the septum primum is smaller and the resection can be more difficult [443]. If a retrograde flow in a levoatrial cardinal vein is an LA decompression pathway, then an r-FO or IAS should be suspected [22]. IAS, present in ∼5% of children with HLHS, can cause maldevelopment of the pulmonary vasculature (dilated lymphatic vessels and arterialization of the pulmonary veins), which contributes to a very high mortality rate [22, 411].

Recurrent restriction at the atrial level is rare (4.1%), manifesting as severe cyanosis [443]. Only restriction at presentation (pre-S1P) is associated with the risk of developing an r-FO after the S1P operation. In some cases, the atrial septum may be prone to pathological hyperplasia after S1P [443]. Restriction that has to be addressed during the S2P procedure is rare (3–4%) [43, 445]. Transcatheter interventions (balloon septostomy, balloon dilation) are recommended for a recurrent r-FO, but they not universally effective.

Atrial septum

Recommendations	Class[a]	Level[b]
Wide resection of the septum primum in normal atrial anatomy through the atrial cannulation side	I	C
Atriotomy for atrial septectomy in case of abnormal interatrial anatomy	I	C

[a]Class of recommendation.
[b]Level of evidence.

9. SOURCE OF PULMONARY BLOOD FLOW

9.1 Norwood stage 1 palliation and pulmonary blood flow

As a consequence of the utilization of the MPA and PV for the systemic outflow, Qp must be provided by creation of a reliable, effective and durable source. In addition, one of the essential goals of the Norwood procedure is to control Qp in order to allow for appropriate growth and development of the pulmonary vasculature in preparation for a BCPS. At the time of the Norwood S1P, the Qp can be provided by a systemic-to-pulmonary arterial shunt or a conduit between the RV and PA.

9.2 Systemic to pulmonary artery shunts

9.2.1 Central shunt. Central shunts, which originate from the Ao and communicate directly or indirectly to a central PA, were used in the early stages of development of the Norwood procedure [412, 448]. Because they usually have a shorter length, they provide more flow and a higher perfusion pressure. These factors have been associated with improved development of the central PAs and a lower risk of shunt thrombosis, particularly with smaller shunts (3.0 mm) [447–449] (class IIa, level C). However, central shunts, where there is a direct anastomosis of the Ao and a branch PA, are particularly difficult to calibrate, leading to excessive Qp and significant PA distortion. They may also be difficult to control at the time of reintervention [410, 446, 450] (class IIb, level C). In light of the delicate circulatory balance required by S1P physiology, excessive Qp is associated with significant morbidity and mortality, in particular when recurrent Ao arch obstruction is present [408, 451]. Nevertheless, it should be noted that a central shunt constructed with a short PTFE conduit can be beneficial in specific circumstances, for example, when patients have elevated PVR as a result of r-FO, have initial palliation beyond 14 days of age or have with significant hypoplasia of the branch PAs [341, 342, 346, 452] (class II, level C).

9.2.2 Modified Blalock–Taussig shunt. As an alternative, the MBTS has been utilized for decades as the preferred source of Qp during the Norwood procedure. The perceived advantages include origin from the innominate artery, since the size of this vessel functions as an additional resistor to regulate Qp [408, 453–456] (class IIa, level C). However, the diameter of a PTFE shunt is the primary determinant of its resistance. Alterations in the length of the tube or in its position on the arterial tree have a smaller but still important influence on the effective Qp [456]. In neonates weighing 3.5 kg, a 3.5-mm shunt is usually appropriate to achieve a balanced Qp/Qs near 1 [341, 408, 412, 457] (class IIa, level C). In addition, when compared to the central shunt, the location of an MBTS between the reconstructed neo Asc Ao and the SVC makes it substantially easier to control at the time of reoperation [447] (class IIa, level C). As with central shunts, systemic-to-PA shunts allow diastolic flow run-off from the systemic into the pulmonary circulation, which causes reversal of flow in the Asc Ao and coronary arteries [458]. This diastolic flow reversal results in decreased coronary blood flow reserve and has been associated with myocardial ischaemia. Typically this process is associated with dynamic changes in the systemic/pulmonary resistance ratio, promoting excessive Qp at the expense of systemic perfusion and increased myocardial work [459]. This phenomenon contributes to the significant morbidity and mortality of IS-1 [450, 460–463] (class II, level B). Moreover, MBTS shunt size has been directly associated with the magnitude of TR at the time of S2P [464] (class IIb, level C)

Although the use of a smaller shunt potentially mitigates excessive diastolic run-off, unless it is in a central position, the use of shunts <3.5 mm carries an increased risk of thrombosis, which can be a life-threatening complication [465] (class IIb, level C). Extrinsic manipulation of the shunt in order to reduce its size and control Qp has been successfully utilized in the immediate perioperative period. This adjustment would facilitate the management of patients who have excessive Qp [466] (class IIa, level C).

Due to ease of exposure, reliability and control, placing a PTFE shunt on the innominate artery has become a common practice [27, 43, 342, 352, 360, 408, 412, 447, 451, 453, 455–458, 465, 467–469]. This PTFE shunt not only can be used as the source of Qp at the conclusion of the procedure, it is also frequently used to provide antegrade systemic perfusion during cooling and RCP during arch reconstruction [470–473]. The belief in the salutary effect of RCP and the anticipated duration of the arch reconstruction will affect the timing of relocation of the arterial cannula to the reconstructed neo-Ao. It should be clear that despite the intuitive appeal of RCP, the effectiveness of the cerebral protection conferred has not been demonstrated in several neurodevelopmental studies, including 3 RCTs, and therefore should be used with caution [277, 278, 384, 474, 475] (class II, level A).

When utilizing RCP, it is common practice to perform the proximal MBTS anastomosis on CPB during the period of cooling or even prior to heparinization and CPB in order to minimize bleeding. The PA anastomosis is then constructed during the warming phase after arch reconstruction has been completed [470, 476]. Arterial cannulation is shifted to the MPA for the anastomosis between the PTFE shunt and the RPA.

An aberrant subclavian artery presents an additional challenge to the insertion of a systemic-to-PA shunt, which in this scenario would originate from the common carotid artery opposite to the side of the Ao arch. Frequently, this is a smaller vessel and therefore has the increased risk of shunt inflow problems and a potential compromise of cerebral blood flow. The presence of an aberrant subclavian artery has been associated with a higher risk of both mortality and reintervention following the Norwood procedure, however, not in all published series [43, 401] (class II, level C). An alternate approach is to avoid manipulating the carotid artery and use a central shunt or an RV–PA conduit as the source of Qp.

Systemic-to-PA shunt stenosis and/or thrombosis is a well-described phenomenon associated with significant morbidity and mortality that may require immediate intervention [477]. Catheter intervention has been described as an effective means to diagnose and manage shunt issues, including stenting of the shunt and balloon dilatation of a stenotic innominate artery (class IIa, level C). Prompt ECMO support is as an effective management strategy in cases of acute and life-threatening hypoxia associated with shunt occlusion [394, 395] (class IIa, level C). The use of aspirin following placement of an MBTS is common and may have some clinical benefits. However, assessing its actual effectiveness is complicated by the presence of resistance to antiplatelet agents, even in high doses [478–481] (class II, level C). Anecdotally, heparin-bonded PTFE shunts have been utilized with success [482] (class II, level C).

9.3 Right ventricle–pulmonary artery conduit

The use of an RV–PA conduit has regained significant interest and popularity. The original description by Norwood *et al.* [410, 446] included an RV–PA conduit to provide a reliable source of blood flow to the central PAs. This technique was quickly abandoned due to the unavailability of an appropriately sized conduit for a neonate [454]. Since then, the use of the RV–PA conduit has been revisited and quickly embraced, based on its inherent advantage of haemodynamic stability due to elimination of diastolic run-off from the systemic (and coronary) circulations [300, 471, 472, 483–485]. Despite initial success and improved survival reported in single-centre studies, significant concerns remain regarding the ventriculotomy associated with an RV–PA conduit and the potential for late ventricular dysfunction and dysrhythmias [64, 100, 310, 452, 486, 487] (class IIb, level B).

PTFE is the most commonly used material for the RV–PA conduit. It is inexpensive and readily available in a broad range of suitable sizes. Alternatively, in order to reduce the regurgitation fraction into the RV, small homografts (surgically reduced) or saphenous vein grafts have been successfully used for RV–PA conduits [488, 489]. Nevertheless, considering the inherently lower volume load associated with an RV–PA conduit and the limited time prior to S2P (6 months or less), there is no evidence of clinical improvement to support their use, which therefore remains at the discretion of the surgeon [488–490]. (class II, level C).

The most common conduit size used is 5 mm for patients between 2.5 and 4 kg. Six-millimetre tubes are used for larger patients or those with possibly high PVR (restrictive ASD anomalous pulmonary venous connection with obstruction). Four-millimetre conduits are reserved for patients with BW <2.5 kg [299, 300, 355, 360, 467, 469, 483–485, 491–494] (class II. level C). Alternately, if excessive Qp is present, the conduit could be calibrated to a smaller cross-section by placing partially occluding vascular clips externally. This particular approach would permit increasing the cross-section of the conduit by ballooning the area crimped by the clips, effectively allowing growth without a need for surgical revision of the conduit.

The technique for insertion requires the anastomosis of the distal end of the conduit, which is bevelled with the toe towards the RPA (if the conduit is placed to the left of the neo-Ao), to a patch of pericardium, pulmonary homograft or PTFE. This patch facilitates and augments the anastomosis to the distal MPA or central PA. Alternately, where commercially available, a PTFE conduit attached to a segment of PTFE membrane has been successfully utilized [300, 483, 484] (class IIa, level C).

The proximal anastomosis is constructed using a limited ventriculotomy in the infundibulum of the RV, avoiding any important epicardial vessels. The site of the incision should be chosen carefully and located at least 5–10 mm below the semilunar valve annulus in order to preserve the integrity and function of the native PV and to avoid important coronary arteries, either with the incision or the suture line. The incision should accommodate a 5- to 6-mm conduit and full-thickness suture line and is constructed incorporating the epicardium and endocardium in order to avoid obstruction of the conduit inflow by protrusion of the RV muscle at the proximal anastomosis. Alternately, the infundibulotomy can be expanded, separating the muscle fibres bluntly or using a coronary punch to create a larger and well-defined edge, albeit with a larger RV muscle resection [222, 300, 359, 360, 467, 484, 489, 492, 494, 495]. In addition, the edges of the ventriculotomy could be undermined in order to prevent obstruction by the RV muscle. However, undermining the RV wall should be limited because this procedure can lead to significant thinning and weakening, resulting in a pseudoaneurysm [496, 497] (class IIb, level C). The use of this type of Qp has gained widespread acceptance but has been associated with a significant increase in the need for reinterventions to address stenosis of the conduit either at the proximal or distal anastomotic site or the proximal origin of the branch PAs [498–500] (class IIb, level C).

Various technical modifications have been described to avoid obstruction of the conduit, including the use of a ring-reinforced PTFE conduit that can be pushed through the infundibulotomy at the proximal and/or distal anastomotic site, known colloquially as the 'dunk' or 'double dunk' technique [501–504] (class II, level C).

The insertion of an RV–PA conduit can be staged during the procedure, depending on surgeon preference. Construction of the distal anastomosis is performed after transection of the MPA and commonly follows the reconstruction of the neo-Ao arch. It is important to complete the distal anastomosis and remove any pericardial traction to allow structures to resume their normal position in the mediastinum prior to determining the length of the conduit. This procedure facilitates estimating the appropriate length of the conduit to reach the ventriculotomy without compressing the heart and coronary arteries or kinking if the conduit is too long. Similarly, the proximal anastomosis can be performed after reperfusion of the heart, minimizing myocardial ischaemic time and allowing assessment of neoaortic regurgitation through the ventriculotomy.

Positioning of the conduit both to the left and right of the reconstructed neo-Ao has been described with similar outcomes. This preference is largely based on institutional experience, the goal being to avoid central PA distortion and compression by the sternum. Lateral positioning also facilitates addressing a right branch PA stenosis, if needed, at the time of S2P. An important consideration when placing the conduit to the right of the neo-Ao is the potential for conduit laceration or disruption at the time of sternal re-entry [467, 484, 485, 491, 492, 500] (class II, level C).

9.4 Single Ventricle Reconstruction Trial

Following the introduction of an RV–PA conduit for Qp, a multitude of studies reported opposing conclusions about improved

outcomes with this modification. Equipoise regarding choices for Qp was established and to answer this question, a multicentre prospective RCT was undertaken by the Paediatric Heart Network in 155 institutions in North America to compare the outcomes of the Norwood procedure, randomizing the source of Qp between MPBT shunts and RV–PA conduits [299].

9.4.1 Primary outcome. Following randomization of 555 subjects, the intention to treat analysis demonstrated that the transplant-free survival at 12 months was 10% higher (74% vs 64%) following Norwood procedures utilizing RV–PA conduits for Qp. The relative risk of death or need for transplant with the RV–PA conduit (compared to an MBTS) was 0.72. Events within 30 days (death, acute shunt failure, cardiac arrest, ECMO, unplanned cardiovascular reoperation or NEC) occurred in 28/274 (10%) infants in the RV–PA conduit group and in 38/275 (14%) in the MBTS group. From postoperative day 30 to S2P, events occurred in 29/243 infants (12%) versus 52/236 (22%), respectively.

The mean follow-up time for survivors who did not undergo a transplant was 32 ± 11 months (range 12–52 months). On the basis of all follow-up data, the difference in transplant-free survival between the 2 groups was no longer significant after 12 months ($P = 0.06$), primarily because most of the mortality in the MBTS group occurred early in the follow-up period. Non-proportional hazards testing showed that the treatment effect differed in the periods before and after 12 months ($P = 0.02$). After 12 months, 10 deaths and 6 transplants occurred in the RV–PA group, compared to 7 deaths and 0 transplant in the MBTS group (8% vs 4% of infants who survived >12 months), therefore eliminating the superiority of the RV–PA in terms of transplant-free survival [57].

It should be noted that although there was ∼10% crossover from 1 group to the other, the primary reason for crossover was anatomical, and most of these events (84%) occurred during the original procedure. There was no difference in crossover incidence between groups. Similarly, the incidence of shunt revision was 5%, without differences between groups. Analysis of non-intention to treat (shunt actually received) revealed that the transplant-free survival advantage beyond 12 months remained significantly better in the RV–PA group compared to the MBTS group (25.6% vs 37.3%, with an absolute increase of 11.7% in survival; $P = 0.003$) (class IIa, level B). This early difference in the mortality probability may be explained by the physiological advantages of the RV–PA conduit in the early postoperative period.

9.4.2 Secondary outcome. Although morbidity during the Norwood admission was similar between the shunt groups, fewer patients in the RV–PA conduit group required early BCPS resuscitation for hypoxaemia after the Norwood procedure. This result is a likely reflection of the less vulnerable physiology afforded patients who do not have parallel circulations connected at the arterial level [474] (class IIa, level B).

Importantly, patients with an RV–PA conduit required more unplanned cardiovascular interventions in the first 12 months. These were largely balloonings and stent placements in the PTFE graft or PAs arteries initially, but more commonly following discharge in the RV–PA group [57]. Comparison of the effect of the MBTS versus the RV–PA conduit on RV function and PA growth revealed that the use of an RV–PA conduit was associated with a lower end-diastolic volume and higher RV ejection fraction following the Norwood procedure. However, these differences were not demonstrable by 12 months after randomization. In addition, angiographic assessment prior to S2P demonstrated a higher Nakata index and better RPA growth in the patients who received an MBTS [299].

Additional analysis of the impact the Qp type may have on non-modifiable factors (prematurity, BW, patency of the AoV) revealed that the RV–PA conduit was associated with a significant survival advantage in term babies with AA (51% of the cohort). The mortality rate in this group was 31% less with the RV–PA conduit than with the MBTS (class IIa, level B). Qp type had no influence on the outcome of term patients with a patent AoV and preterm patients with AA (45% of the cohort).

Unexpectedly, the RV–PA shunt may have been associated with a survival advantage in preterm patients with a patent AoV; however, the numbers were too small to be conclusive about this association [35] (class IIa, level B).

Qp source type was not associated with an indication for a heart transplant, and the variables associated with listing for a heart transplant included poor RV function pre-Norwood, diagnosis other than HLHS and number of interventions prior to the Norwood procedure. Nevertheless, an RV–PA conduit was associated with better survival during the wait-list period [86] (class IIa, level B).

It appears that surgeon and institutional experience with a particular strategy (whether MBTS or RV–PA conduit) may be the most important determinant of institutional outcomes (rather than choosing a strategy successful elsewhere). Only site volume showed an interaction, with higher volume negating the advantage of the RV–PA conduit with respect to transplant-free survival. This finding may reflect the expertise of individual surgeons or

Modified Blalock-Taussig shunt

Recommendations	Class[a]	Level[b]
MBTS facilitates regulation of Qp	IIa	C
MBTS facilitates Qp control at the time of reoperation	IIa	C
MBTS facilitates titration of excessive Qp	IIa	C
MBTS facilitates implementation of RCP	IIa	C
MBTS is associated with diastolic run-off away from Asc Ao and higher IS-1 mortality rate	IIb	C
Use of MBTS more difficult with aberrant subclavian artery	II	C
Catheter intervention can be effective to resolve shunt stenosis	IIa	C
ECMO is a useful adjunct to manage acute shunt failure	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
Asc Ao: ascending aorta; ECMO: extracorporeal membrane oxygenation; IS-1: interstage 1; MBTS: modified Blalock–Taussig shunt; Qp: pulmonary blood flow; RCP: regional cerebral perfusion.

greater institutional experience in the perioperative care of patients with an MBTS.

Neurodevelopmental impairment is higher in survivors of the Norwood procedure than in the normal population. Analysis of this cohort, including formal neurodevelopmental testing at 14 months of age, revealed impairment was highly associated with innate patient factors and overall morbidity in the first year rather than with the intraoperative management strategies (including source of Qp or perfusion strategy utilized for the Norwood procedure [41] class II, level B).

Source of pulmonary blood flow

Recommendations	Class[a]	Level[b]
Central shunt is associated with increased pulmonary blood flow	IIb	C
Central shunt may be indicated for high PVR (restrictive atrial septal defect, age >14 days)	IIa	C
Innominate artery insertion	IIa	C
Central pulmonary artery growth is enhanced by central shunts	IIa	C
Central shunts are more prone to morbidity	IIb	B

[a]Class of recommendation.
[b]Level of evidence.
PVR: pulmonary vascular resistance.

10. SPECIAL SURGICAL CONSIDERATIONS

10.1 Restrictive atrial septal defect and anomalous pulmonary veins

IAS or r-FO is a predictor of poor outcome among patients with HLHS. Despite aggressive postnatal treatment, the perioperative mortality rate can exceed 50% [22, 35]. Patients with an r-FO exhibit more significant pulmonary venous thickening, lymphatic dilatation, hypoplastic PAs and a tendency towards persistence of high-resistance foetal vessels compared to patients with a non-r-FO [35, 505, 506]. The currently accepted definition of IAS or highly r-FO includes the following:

1. The atrial septum is intact on either a prenatal or postnatal echocardiogram.
2. A prenatal echocardiogram shows a small FO with prominent pulmonary venous flow reversal.
3. The neonate requires urgent catheter LA decompression for clinical signs of LA hypertension (severe hypoxia, haemodynamic instability or both).

Prenatal diagnosis of this condition is of paramount importance (see foetal diagnosis section). As discussed previously, prenatal examination allows one to stratify the risk of emergency septostomy and to plan appropriate delivery and postnatal treatment [143, 153]. After birth, r-FO is defined by both clinical and imaging criteria [378]. Nevertheless, clinical rather than echocardiographic criteria should guide decision-making and timing for intervention [230]. The SVRT reported a preoperative mortality rate of 23% for newborns with this condition [34].

Newborns with HLHS and obstruction to pulmonary venous return with deep cyanosis after birth are initially managed by rapid institution of mechanical ventilation with high FiO_2 (0.5–1.0) and low inspiratory mean pressure to avoid further decrease in Qp. Inotropic treatment with dopamine, epinephrine or norepinephrine is added to support cardiac function, increase SVR and promote Qp [507]. Use of sodium bicarbonate to compensate respiratory acidosis is not recommended in this setting because its hydrolysis causes a further increase in CO_2, worsening the acidosis. In patients who remain very unstable despite medical management, ECMO support should be considered. After stabilization, further management should be directed to solve the obstruction to the pulmonary venous return as quickly as possible. According to the severity of obstruction, clinical picture and morphology of the atrial septum, several strategies have been described.

A surgical approach, either by septectomy or the Norwood operation, carries an extremely high operative risk, with survival ~20% [158]. This is true even with a planned caesarean delivery, probably because an operation with CPB is poorly tolerated in critically ill neonates with severe pulmonary congestion. The most reasonable approach is immediate postnatal transcatheter intervention [141, 158]. Depending on the septal anatomy, the procedure can be accomplished by a traditional balloon septostomy, a static balloon dilation or placement of a stent. With IAS, it is necessary to create a defect by puncture, with successive balloon dilation and/or stent placement.

Rarely, for patients in whom prenatal examination predicts a catastrophic clinical picture after delivery, an *ex utero* intrapartum therapy has been described [153]. With this strategy, the head of the infant is delivered via a caesarean delivery so that ECMO support can be initiated before separation from the placenta. Subsequently, a transcatheter procedure is performed under ECMO support.

In addition to the high risk of death, transcatheter procedures carry a relatively high incidence of complications, including stent dislocation and haemorrhage from perforation of the atrial wall, both of which are life-threatening. The small LA typically seen in this condition raises the technical challenge and risk of complications [230].

After successful septostomy, evolution of PVR can be difficult to predict. In some patients, decompression of the LA can lead to early excessive Qp and congestive heart failure, requiring urgent intervention. It is reasonable to proceed with a S1P Norwood or h-S1P procedure as soon the patient is stable and recovers end organ function, usually within 3–5 days [141, 158]. The need for emergency b-PAB after septostomy has been also reported.

The perioperative management of the Norwood operation can also be complicated. Even after septostomy, patients can have high PVR, exacerbated by CPB. Larger shunts may be required, at least in the immediate postoperative course. Subsequently, when PVR decreases, the clinical picture could turn towards excessive Qp, heart failure and circulatory collapse. A higher incidence of shunt revision and postoperative ECMO support has been reported [141]. A strategy with neonatal h-S1P followed by a c-S2P a few months later certainly avoids a complex procedure that requires CPB in these sick newborns. However, at the moment, there is no evidence that delaying the operation improves early and intermediate outcomes [508].

Despite some improvement in the early survival of patients who had a successful postnatal transcatheter procedure followed by an interval Norwood procedure, there is a decreased 1-year survival rate, with a significant number of deaths during IS-1 [132]. These findings suggest that patients with r-FO have pulmonary vascular abnormalities that place them at higher risk for all surgical interventions [148].

In the last decade an increasing number of prenatal procedures have been offered for foetuses with HLHS with r-FO/IAS [143]. Although procedural success can be achieved in a good proportion of cases, it does not always translate to a patent FO after delivery. For patients with FO patency without severe restriction at birth, early outcome in terms of stability, incidence of complications and survival to S1P has improved. Longer-term benefits including normalization of PVR are speculative.

Anomalous pulmonary venous connection is a relatively common finding in SV lesions associated with heterotaxy syndrome (right isomerism), but it has also been described in HLHS [191]. The anomalous connection should be repaired at the time of the Norwood procedure by anastomosis between the pulmonary venous confluence and the most convenient part of the common atrium, basically adopting the same techniques used to repair TAPVD in bi-V circulation. The connecting vein could be left open at this stage but should be occluded at S2P to avoid a right-to-left shunt thereafter. Prognosis of these patients, especially those with obstructed TAPVD, remains poor, with a substantial early and midterm mortality rate. Only a few will reach Fontan completion. Similarly, for patients with r-FO/IAS, anomalies in the pulmonary vascular tree and lung development are common findings. A heart transplant has been proposed, but this option, in addition to the operative risk, is, in practice, limited by organ shortages. In any case, high PVR is a risk factor for a heart transplant as well.

10.2 Inferences

There is evidence that severe r-FO/IAS and obstructive TAPVD increase the mortality rate of patients with HLHS. The increased risk phase concerns not only the prenatal and immediate postoperative period but continues during follow-up:

- A transcatheter procedure should be considered to be first-line treatment in patients born with HLHS and r-FO/IAS, despite a high incidence of complications.
- A primary surgical approach either by atrial septectomy or emergency Norwood operation carries a much higher risk than a transcatheter approach and is not recommended. Conversely, surgery should be performed immediately in patients with anomalous pulmonary venous connection with obstruction.
- After a transcatheter procedure, provided that the obstruction to the pulmonary venous return is resolved, it is reasonable to proceed with a Norwood S1P within a short time.
- There is no evidence that MBTS is superior to an RV–PA conduit in patients with obstruction to pulmonary venous return. The postoperative period can be stormy, even requiring revision of the shunt and ECMO support.

The rationale for foetal procedures to decompress pulmonary venous return is based on the possibility of improvement in vascular and lung development. Due to the high risk of maternal–foetal complications, prenatal procedures should be concentrated in centres with high expertise.

Restrictive foramen ovale and obstructed totally anomalous pulmonary venous drainage

Recommendations	Risk	Class[a]	Level[b]
IAS or r-FO predictors poor outcome for HLHS	Severe	I	B
Prenatal diagnosis: allows risk stratification and planning appropriate delivery and postnatal treatmentAfter birth: clinical not instrumental criteria should guide decision-making and timing for intervention		IIa	C
A transcatheter procedure should be considered first-line treatment in patients born with HLHS and r-FO/IAS, despite a high incidence of complications		IIa	C
A primary surgical approach (atrial septostomy or emergency Norwood procedure) carries a much higher risk than the transcatheter approach and is not recommended		IIa	C
It is reasonable to proceed with an S1P (hybrid or Norwood) shortly after a successful transcatheter procedure. No evidence of a superiority strategy (Norwood versus h-S1P; MBTS versus RV–PA conduit)		IIa	C
Surgery should be performed as early as possible in patients with anomalies of pulmonary venous connection with obstruction. The anomalous connection should be repaired by anastomosis between the common pulmonary vein and the most convenient part of the common atrium		IIb	C

[a]Class of recommendation.
[b]Level of evidence.
h-S1P: hybrid S1P; HLHS: hypoplastic left heart syndrome; IAS: intact atrial septum; MBTS: modified Blalock–Taussig shunt; PA: pulmonary artery; RV: right ventricle; S1P: stage 1 palliation; r-FO: restrictive foramen ovale; TAPVD: totally anomalous pulmonary venous drainage.

Tricuspid valve

Concept-strategy	Risk	Class[a]	Level[b]
TR ≥moderate increases mortality and morbidity rates and prevents completion of the SV pathway	Severe	I	B
Transthoracic 2-dimensional and colour Doppler echocardiography remain the most common tools to evaluate TV function and assess anatomical mechanisms responsible for TR. 3D technology could improve evaluation of TV anatomy and function		IIa	C
Newborns with severe TR, especially with RV dysfunction, carry a high risk for surgical palliation and should be considered for a heart transplant. Valve repair could be attempted only if RV function is not impaired		IIa	C
The majority of TV procedures are performed at S2P, during IS-2 or at Fontan completion		IIa	C
Optimal repair depends on correct identification of mechanisms that sustain TR. Closure of clefts and commissures, edge-to-edge repair and annuloplasty are the most common techniques adopted for repair of the TV in newborns concomitantly or immediately after a Norwood procedure. Partial annuloplasty creating a bicuspid valve yields better results than other types of annuloplasty		IIb	C
Progressive RV dilation and dysfunction play a major role in late TV failure despite an initially successful repair		IIb	C

[a]Class of recommendation.
[b]Level of evidence.
IS-2: interstage 2; RV: right ventricle; S2P: stage 2 palliation; SV: single ventricle; TR: tricuspid regurgitation; TV: tricuspid valve.

10.3 Tricuspid valve

TR is a relatively common problem in patients with HLHS. About 25% will have moderate or severe TV dysfunction, requiring surgical repair along the SV pathway [509, 510]. There is also evidence that moderate–severe TR is related to poor survival, increased morbidity, decreased long-term functional results and prevention of completion of the SV pathway [35, 77, 368]. Severe TR already existing at first presentation frequently becomes more obvious after surgical palliation.

Pathophysiological mechanisms responsible for TR are often multiple. Annular dilation caused by volume load has been considered the 'trigger' mechanism [511]. On the other hand, TV structural abnormalities, both of leaflets (dysplasia, clefts, defects in tissue) and the subvalvular apparatus (abnormal papillary muscle and chordae), have been described [103, 511, 512]. Improvements in echocardiographic and MRI techniques have allowed us to look deeply into the pathophysiological mechanisms of the systemic RV, identifying other more complex mechanisms responsible for TR. It is becoming more evident that the RV *per se* is poorly adapted to the systemic workload and often remodels in an unfavourable manner. Intraventricular dys-synchrony, displacement of papillary muscles with prolapse or tethering of the valve and change in the spatial arrangement of the interventricular septum due to altered interaction with the small LV can all contribute to development of TR [104, 107].

After S1P, TR could be related to myocardial damage due to ischaemia (coronary insufficiency, insufficient myocardial protection, use of large shunts and high afterload related to residual arch obstruction) [510]. The Qp source used at the first stage (MBTS versus RV–PA conduit) does not correlate with the development of TR [513]. In any case, different mechanisms may coexist in the same patient, so TR is frequently a mix of organic and functional disease, making repair challenging.

Transthoracic 2D and colour Doppler echocardiography remain the most common tools to evaluate TV function and assess anatomical mechanisms responsible for TR. Each component of the valve should be systematically analysed, including the annulus, leaflets and subvalvular apparatus. Interest is evolving in better evaluation of TV anatomy and function using 3D technology, with the goal of designing innovative surgical procedures [106, 499, 514]. MRI and cardiac catheterization are important during IS-1 and interstage 2 (IS-2) for better assessment of RV function and arch anatomy. Direct valve inspection with a saline injection test could underestimate the dynamic aspect related to papillary muscles and ventricular function. There is wide variability between echocardiographic and surgical assessment of TV function. Structural leaflet abnormalities are more commonly diagnosed by surgeons whereas prolapse or restriction is more commonly seen by echocardiographers [104].

Severe TR presenting at birth remains an extremely challenging problem, with poor early and IS-1 prognosis. Surgical abstention, a heart transplant and, recently, the h-S1P procedure have been advocated [515]. Pre-S1P treatment of significant TR is based on control of SV volume load by medical management, ensuring DA patency and the use of mechanical ventilation to control Qp [516]. The majority of TV procedures are performed at S2P, during IS-2 or at the completion Fontan procedure [511, 517, 518]. There are few reports in which TR is specifically addressed concomitantly or around S1P. The indication for a concurrent valve procedure has been severe TR, but more often these reports come from institutions where a primary heart transplant is not available [519–521].

During S1P, valve repair is performed with cardioplegic arrest before or after arch repair. DHCA is avoided with the use of bicaval cannulation. As in any valve operation, optimal repair depends on correct identification of the mechanisms that sustain TR. Indeed, when repair is performed concomitantly with S1P, it is usually limited to commissural obliteration, cleft closure and annuloplasty. Commissural obliteration is done when TR is related to anterior leaflet prolapse that more frequently occurs at the anteroseptal or posteroseptal commissures. The most common technique for correction consists of obliteration with either doubly armed pledgetted sutures or 2–3 separate sutures of 6/0

or 7/0 polypropylene [511, 517]. Individual clefts or other tissue defects are also closed by simple interrupted sutures. Annuloplasty in newborns and small infants cannot include rigid or semi-rigid rings and is generally partial. The most common technique involves running parallel mattress sutures along the annulus from the anteroposterior to the posteroseptal commissure, essentially obliterating the posterior leaflet, creating a bicuspid valve [517]. A classical De Vega annuloplasty has also been described but seems to be less effective and less durable. To avoid an excessively narrow valve, the new orifice size is calibrated at 100% of normal TV diameter [522].

Patients with unbalanced AVSD with LV hypoplasia and DA-dependent Qs treated initially by the SV pathway require special attention. The AV junction is characterized by a common dysplastic valve, with multiple clefts and commissures. Frequently, portions of the leaflets are poorly supported by chordae causing prolapse [523]. These valves are particularly prone to develop AVV regurgitation, often present at birth, that would require treatment concomitant with S1P. In this situation, closure of clefts and leaking commissures is particularly important. Prolapse of leaflets could be treated by means of an edge-to-edge technique, creating a double or triple orifice. Suturing adjacent portions of the valve (to avoid tension that could tear the tissue) is important [523]. Competence of the valve can occasionally be improved by complete obliteration of a diminutive component.

The survival rate of patients with moderate or greater TR around S1P is much worse than that of patients who develop TR at a later time [35]. Despite an initially successful repair with significative reduction in TR, outcomes are restricted by limited repair durability, with recurrent significant TR in more than one-third of the patients. RV dilation and dysfunction in these patients are progressive, suggesting a main role in valve repair failure and transplant-free survival [523, 524]. Only patients with little post-operative residual TR and preserved ventricular function have a survival equivalent to that of patients who have a Norwood procedure without a TV procedure [525]. There is no clear evidence that valve repair around S1P can improve long-term survival; therefore, no definitive recommendation for S1P during IS-1 can be provided.

10.4 Inferences

- TR is relatively common in patients with HLHS, although severe TR at birth is much less frequent.
- Severe TR significatively increases mortality and morbidity during staged palliation, impairs right ventricular function and could prevent completion of the SV pathway.
- Anatomical and functional mechanisms are equally involved in the development of TR.
- Echocardiography is the standard diagnostic tool to assess TV morphology and function. TV evaluation should include anatomical and functional details of the annulus, leaflet and subvalvular apparatus. Use of 3D technology may contribute to understanding anatomical and functional mechanisms of TR.
- Newborns with severe TR, especially with RV dysfunction, carry a high risk for surgical palliation and should be considered for a heart transplant. Valve repair could be attempted only if RV function is not impaired.
- Closure of clefts and commissures, edge-to edge repair and annuloplasty are the most common techniques adopted for repair of TV in newborns concomitantly or immediately after a Norwood procedure. Partial annuloplasty is most commonly performed, creating a bicuspid valve. This technique has better results compared to other types of annuloplasties. Use of rigid rings in newborns and small infants is precluded by size.
- TV-plasty is effective in reducing TR in most cases, but a significant number of patients have recurrence related principally to RV dysfunction.

10.5 Aortic valve

Occasionally a Norwood procedure is performed to rescue neonates after failure of a bi-V repair, typically after an attempt at Ao balloon valvuloplasty. In the presence of severe aortic regurgitation, the valve must be repaired, usually by suturing the tear produced by the balloon. In this setting, early reintervention usually implies a poor prognosis and might reflect incorrect management decisions [49, 525].

Interest is growing in a staged bi-V repair for patients with relatively milder forms of HLHS [526]. Besides the Norwood procedure, LV recruitment includes resection of EFE, restriction of ASD and management of AS and MS. In newborns, the MV is best approached through the septum. Valvuloplasty, depending on the lesion, entails separation of fused papillary muscles, thinning of leaflets, commissurotomy and division of accessory or secondary chords [527]. Ao valvuloplasty techniques include commissurotomy, primary repair of leaflet tear when present and debridement of leaflets. Extensive valvular reconstruction is more frequently performed in association with S2P and the Fontan operation [526, 528].

10.6 Dysplastic pulmonary valve

A dysplastic, functionally stenotic PV is extremely rare in patients with HLHS [529]. During foetal development, severe degrees of PV stenosis are not tolerated, causing heart failure, hydrops and foetal death [530]. Few reports describe the clinical course of patients born with this associated anomaly. Severe pulmonary stenosis is probably a contraindication for the Norwood S1P, and such patients should be immediately listed for a heart transplant, possibly staged by h-S1P. A balloon valvuloplasty could help to stabilize the baby, paying attention to balloon size to minimize risk of regurgitation [531, 532]. Mild or moderate degrees of PV stenosis increase the risk but not are an absolute contraindication for Norwood palliation. In this case, to decrease the amount of total CO that crosses the systemic outflow, it is better to perform S1P with an RV–PA conduit [533].

10.7 Coronary anomalies

Three main coronary anomalies have been described in HLHS: anomalous Ao origin, anomalous origin from MPA or branch PA and fistula or ventriculocoronary connections [534]. All of these anomalies have been described in patients with AA and have a potential implication for surgery. A recent autopsy study found 22% specimens that had coronary anomalies that correlated with the patient's death [164].

Failure to recognize an anomalous origin of the Ao or PA could result in coronary damage, with catastrophic consequences, when the vessels are incised or transected for the Norwood

procedure [535]. Anomalous origin from a PA branch could have implications in h-S1P because the PAB could affect coronary perfusion by direct compression or when placed proximally to the coronary origin. Therefore, coronary imaging is recommended in routine echocardiography before all types of S1P. When a coronary anomaly is suspected, the diagnosis should be confirmed by CT scan, MRI or angiography [536] (see Imaging section).

Several case reports describe coronary arteries originating from the MPA or the RPA in HLHS. Anomalies reported include the LCA from the RPA, the circumflex coronary artery from the RPA and the right CA from the RPA. Once the diagnosis is made, a coronary button could be harvested, mobilized and preimplanted successfully in the reconstructed neo-Ao as in the arterial switch operation [537]. At the beginning of CPB, attention is paid to snare the PA distal to the coronary origin, and myocardial protection should be assured by infusion of cardioplegia both in the Asc Ao and the MPA. To overcome the higher operative risk of reimplantation in the setting of a Norwood procedure, alternatives would be an h-S1P with a PAB distal to the anomalous left coronary artery from the PA, followed by reimplantation at the time of c-S2P or of a heart transplant [536].

The second group of anomalies is described almost exclusively in patients with AA/MS, a high-risk variant of HLHS [376]. These hearts are characterized by the presence EFE and by coronary vessels that are more tortuous, with increased medial thickness [534, 538]. The typical anomaly is an LV-to-subepicardial coronary (ventriculocoronary) communication or fistula. It has been hypothesized that ventricular–coronary fistulae may occur as a consequence of a hypertensive LV, a finding more common in AA/MS. Diagnosis of a ventriculocoronary fistula is made by echocardiography, showing a vascular channel with a trans-myocardial course, from the LV cavity to an epicardial coronary artery. There is turbulent colour Doppler flow in the vascular channel, usually with a retrograde systolic and antegrade diastolic flow pattern across the LV myocardium, remote from the MV orifice [40, 163].

Coronary hypoperfusion may occur once a heart is decompressed on CPB, and inadequate myocardial protection by administration of antegrade cardioplegia could explain the risk of failure of S1P in patients with MS-AA and fistulae. The mechanisms are not yet fully understood, and there is probably wide variability in the degree of ventriculocoronary connections. LV-dependent studies identified AA/MS as a risk factor for death, whereas others, including the SVRT, did not [35, 163]. In the absence of specific protocols to analyse the number, the magnitude and the significance of ventriculocoronary connections, there is no specific recommendation for surgical management of patients with AA/MS besides the general survival advantage for patients with AA when an RV–PA conduit is adopted for Qp [35, 539].

11. POSTOPERATIVE MANAGEMENT

Early postoperative outcomes after S1P have improved considerably in the last 20 years. However, the immediate postoperative period remains a critical phase in the HLHS journey, as demonstrated by the early mortality rate, which in current registry reports is ∼15%, and by the prevalence of postoperative adverse events (e. g. the need for ECLS), which arise significantly more frequently than after lower risk operations [540, 541].

11.1 Admission from the operating room

Neonates with HLHS who are admitted to the ICU following S1P have considerable circulatory vulnerability due to the inflammatory impact of CPB, a period of myocardial ischaemia, reperfusion injury, a potential for Ao-coronary flow limitation and an inefficient parallel circulation. The period of transfer from the operating room, the handover to the ICU team and the first postoperative 24 h represent key milestones. Arrival of the patient in the ICU should be immediately followed by a detailed handover from the operating team to the accepting ICU team, according to the World Health Organization's surgical safety checklist guidelines [542]. Beyond the safety checklist report, specific issues germane to the patient with HLHS should be covered, including:

- Preprocedural risk factors such as associated genetic or congenital abnormalities, low BW (especially < 2.5 kg), prematurity, adverse cardiovascular features of r-FO, AVV regurgitation or poor RV function [355].
- Anaesthetic issues, such as the status (grade) of the airway, endotracheal tube size, medications administered, blood products transfused, inotrope dosage, antibiotics and pain relief.

Intraoperative aspects covering a complete account of the surgical procedure, any technical difficulties encountered, CPB and myocardial/circulatory arrest strategies and times, all adjuncts related to the operation including pacing wires, drains, status of sternal closure and ECLS cannulation sites (if applicable).

11.2 Standard monitoring

All patients require standard monitoring of ECG, peripheral SaO_2, end tidal CO_2, peripheral and central temperature and central venous access for secure delivery of medications and preload monitoring of [543, 544]. The preferred location is based on the preference of the centre preference and includes internal jugular vein (with the tip in the SVC) and lines placed directly into the common atrium during the operation. Both sites provide SvO_2

Coronary anomalies

Recommendations	Class[a]	Level[b]
Coronary anomalies can negatively impact survival after stage 1 palliation. Preoperative evaluation should be performed by echocardiography if a coronary anomaly is suspected	IIa	C
Aortic atresia/mitral stenosis associated with a ventriculocoronary connection is associated with a higher mortality rate and requires a particular strategy for stage 1 palliation	IIb	C

[a]Class of recommendation.
[b]Level of evidence.

monitoring; however, the SVC site is more reliable [544]. The femoral vein is the back-up site; however, SO_2 values from that site are not a true reflection of SvO_2. An invasive arterial line for continuous monitoring of systolic/diastolic and mean systemic BP and for blood sampling for ABG is also essential.

11.3 Imaging

Upon arrival in the ICU, a chest X-ray should be taken to identify the position of the endotracheal tube, the nasogastric tubes and the central venous lines, and the status of the lung fields. If feasible, a transthoracic echocardiogram should be performed, with attention to global and regional ventricular function, adequacy of the surgical repair, residual or newly acquired lesions, size of the FO and AVV competence. Although many centres advocate TOE, a probe in the oesophagus may compromise ventilation and compress the LA and/or the Ao arch. There are also rare reports of oesophageal perforation by the echocardiographic probe. Because the Ao arch is poorly visualized by an oesophageal probe, and because many centres utilizing epicardial echocardiography obtain similar results compared to TOE, this may not be justified in all patients undergoing S1P [545]. In practice most postoperative imaging is transthoracic.

11.4 Blood sampling and investigations

11.4.1 Haematological values. A haematological profile, including complete blood count and clotting screen, should be checked on arrival in the ICU and regularly thereafter, based on clinical progress.

The Transfusion and Anaemia Expertise Initiative recommended that prior to red cell transfusion, the risks and benefits and optimization of all physiological contributors to DO_2 should be considered [248]. Given the precarious circulation and cyanosis early after S1P, the Hct should be maintained between 40% and 45% in order to maximize O_2 carrying capacity and DO_2 while avoiding hyperviscosity. The threshold for transfusion of red cells should be reviewed as the patient is stabilized over the postoperative period. The Transfusion and Anaemia Expertise Initiative proposed that a 'solely Hb-based transfusion' should be avoided when the level is >9 g/dl; however, this expert group acknowledged that evidence supporting the application of these permissive transfusion thresholds after S1P is extremely weak [248]. Indeed, the decision to transfuse red cells to infants after S1P is rarely (if ever) based on the Hb level alone.

By virtue of the immature hepatic function in the neonate, liver-dependent coagulation factors will be diminished. Compounding this potential for coagulopathy is the presence of cyanosis and the recent exposure to haemodilution and hypothermia, and the inflammatory response from CPB [546, 547]. These factors increase the risk of bleeding in the immediate postoperative period. Although blood product transfusion algorithms have shown value in the adult cardiac patient, they have not been shown to be useful in neonates [548, 549]. After S1P, the coagulation studies, thromboelastography and platelet counts guide clinicians as to what product is actually needed in the bleeding patient [550]. If the coagulation profile has normalized, persistent postoperative bleeding or sudden cessation of drainage demands prompt communication with the surgeon and possible mediastinal exploration [550].

11.4.2 Biochemical considerations. Serum biochemical assessment including electrolytes, calcium and magnesium should be checked on arrival in the ICU and regularly thereafter [551]. The ionized calcium, serum sodium, magnesium and potassium levels should be maintained within normal limits with supplementation following a protocol in order to protect the vulnerable myocardium from arrhythmias [552].

ABG should be checked on admission, regularly and with any clinical concern. Arterial lactate levels, a surrogate monitor for systemic perfusion and DO_2, should also be checked frequently. Serial lactate measurements are a useful adjunct to monitoring SVO_2, and high lactate levels are linked to adverse events and poorer outcomes after S1P [312]. Some institutions use lactate algorithms to guide inotrope support or the escalation to ECLS [553].

11.5 Haemodynamics and tissue perfusion monitoring

11.5.1 Oxygen saturation, flow and cardiac output. The balance between Qp and Qs is determined by PVR/SVR. The Qp/Qs is calculated using the formula (SaO_2 - SvO_2/pulmonary venous SO_2 - SvO_2). The pulmonary venous SO_2 is assumed to be 100%, and the SvO_2 can be measured (by sampling from a central venous catheter).

Excessive QP results from combinations of high SVR, an inadequately resistant shunt or low PVR [554]. High SVR can occur with vasoconstrictive drugs, pain, fever, acidosis, hypovolaemia and residual anatomical lesions [554]. High Qp/Qs with high systemic SVR is an important cause of low CO and circulatory collapse following S1P [304, 555]. For this reason, it is important to maintain a favourable and steady physiological state, avoiding high-dose inotropes, promoting comfort, normothermia and euvolaemia, and searching for residual lesions.

With normal pulmonary venous SO_2 and SVO_2, an arterial partial pressure of oxygen between 40 and 45 mmHg or 5.3 and 6.0 kPa (corresponding to a peripheral arterial SO_2 between 75% and 85%) is evidence of a well-balanced circulation. In the circumstance of suspected excessive Qp, the strategy of using hypoventilation to elevate the pCO_2 and raise PVR can lead to atelectasis and intrapulmonary desaturation and is not recommended.

CO depends on Qp/Qs, an unobstructed pathway from the RV to the coronary arteries and Ao, an unobstructed pulmonary venous return, a reliable and suitably resistive source of Qp and reasonable ventricular function [391, 556, 557]. Postoperative management that relies solely on keeping the peripheral SO_2 between 75% and 85% is an oversimplification, because several assumptions are required, and the practice has been linked to adverse postoperative events [555]. Changes in sympathetic tone can lead to increased SVR, raising Qp/Qs, but at the expense of DO_2 [555]. In simulation studies of SV circulations, there is a non-linear relationship between DO_2 and SaO_2, such that, as the peripheral SaO_2 increases, DO_2 increases to a point but then rapidly diminishes [558]. Following serial or continuous SVO_2 readings is a more effective way to monitor global oxygen economy and enables tailoring of therapy to immediate need. SVO_2 monitoring from a catheter located in the SVC has lessened the incidence of cardiovascular collapse in some institutions, particularly if an intervention is initiated once a threshold of 30–40% is

reached [314, 559]. The use of SVO_2 monitoring has been a key factor in improving survival following S1P [202].

11.5.2 Near infrared spectroscopy. NIRS provides a continuous evaluation of DO_2. Although it is not universally available, it has become a standard of care in many institutions. The primary benefit of NIRS monitoring is the detection of trends, looking for deviations from the patient's baseline. Absolute acceptable or dangerous levels have yet to be identified, and translatable protocols for routine bedside use are needed. However, an NIRS cerebral SaO_2 <55% in the first 48 h following S1P has been linked to adverse outcome [317]. Low cerebral NIRS values have also been linked to neurological events after cardiac operations, including S1P [560]. Some institutions track the difference between the cerebral and somatic measurements as a way to monitor circulatory impairment [561].

11.6 Data integration methods

The use of vital sign data integration methods is an emerging area of practice for future consideration. Sophisticated computational analytics, applied to the paediatric cardiac patient, harness a large volume of data, in the hope of identifying patients at risk for deterioration early on. Use of mathematical models may in time supplement the intensivist's clinical acumen to promote proactive behaviour and improve patient survival rates. Next-generation analytic technology has been tested in patients with HLHS and other infants undergoing cardiac surgery [562]. Proponents of Etiometry (Boston, MA, USA) contend that their proprietary algorithms can predict which patients are at risk for inadequate DO_2 following cardiac surgery [563].

11.7 Important haemodynamic issues

11.7.1 Source of pulmonary blood flow. Small-diameter PTFE tube grafts are vulnerable to clot formation [550]. Therefore, heparin anticoagulation is recommended in the postoperative period [248, 554]. For a given Qp/Qs and CO, the pulse pressure is wider and the diastolic pressure lower in patients with MBTS compared to those with an RV–PA conduit. A high SVR will increase the Qp/Qs, increase aortic diastolic run-off, favour Qp and compromise systemic DO_2 [555]. To mitigate these effects, afterload reduction should be achieved with phenoxybenzamine or milrinone [304]. Of note, the SVRT demonstrated that the MBTS was an independent risk factor for cardiac arrest in the postoperative period, emphasizing further the importance of measures to promote reduction in SVR [355].

11.7.2 Right ventricle-to-pulmonary artery conduit. The RV–PA conduit in S1P requires a small ventriculotomy that may impair regional wall motion. This conduit is generally non-valved, resulting in some degree of pulmonary regurgitation and volume burden to the RV. Because Qp originates from the RV rather than from the systemic circulation and the relatively long conduit imposes resistance, patients with an RV–PA conduit are less vulnerable to sudden adverse events in the postoperative period [355, 458]. Aggressive treatment of high SVR with afterload reduction may result in a lower Qp/Qs in patients with an RV–PA conduit than in those with an MBTS.

11.7.3 Residual lesions. As part of a quality improvement initiative, a method for evaluating the technical success of various operations has been proposed [557]. In a study of surgical factors within the cohort of patients in the SVRT, the 'technical performance score' was calculated for 356 (65%) cases based on standardized review of the echocardiogram [58]. The grade of the 'technical performance score' was strongly linked to the duration of the hospital stay, the mortality rate, the preintervention incidence and even neurodevelopmental outcomes at 1 year. This result emphasizes the importance of the bedside team being aware of possible residual lesions and their potential effect on the postoperative course (see Imaging section).

11.7.4 Tamponade. Cardiac tamponade after S1P is a complex anatomical and physiological problem due to the extreme sensitivity to cardiovascular compression for any reason. Suspicion of cardiac tamponade is raised when tachycardia, hypotension, narrow pulse pressure and elevated filling pressures occur, particularly with increasing or decreasing mediastinal tube drainage. Reopening of the sternum should not be delayed while awaiting echocardiographic confirmation. Tamponade can occur, however, even in electively open-sternum cases. The use of fresh whole blood intraoperatively has reduced the need for mediastinal re-exploration from 3% to 0.8% amongst all paediatric cardiac surgery cases and should therefore be considered [564].

11.7.5 Arrhythmias. A recent report from the SVRT indicated that the most common electrophysiological issue after S1P was tachyarrhythmia (20%) followed by AV block (4%) [309]. Tachyarrhythmias can lower CO by compromising diastolic filling of the coronaries or by depressing systolic function. Third-degree AV block may diminish CO by impairing the contribution from the atrium by eliminating AV synchrony. Risk factors include the MBTS, age at Norwood procedure and concomitant procedures, particularly those on the TV. Arrhythmias were associated with longer ventilation time and longer hospital stays [309]. Medical therapy for arrhythmias in HLHS is complex and critical and should be undertaken on a case by case basis in discussion with electrophysiologists.

11.8 Management strategies for postoperative care: ventilation

Immediately after S1P, the infant should be placed on mechanical ventilation with the goal of maintaining a normal pH, a normal pCO_2 and arterial pO_2 between 40 and 45 mmHg or 5.3 and 6.0 kPa [304, 555]. In many infants, the optimum strategy is to ventilate in air with oxygenation in the stated range.

If the patient becomes hypoxaemic (pO_2 < 40 mmHg or 5.3 kPa or a peripheral SaO_2 < 75%), detailed evaluation is needed, with treatment under all circumstances. Causes include pulmonary venous desaturation due to a malpositioned endotracheal tube, pulmonary consolidation, pleural effusion/haemothorax or pneumothorax, most of which may be resolved with appropriate remedial actions. More profound hypoxaemia (SaO_2 < 70%) may be cardiac in origin, potentially due to impaired Qp, such as from a blocked, compressed or kinked MBTS or RV–PA conduit. This scenario requires emergency investigation, imaging and treatment. Interventions for shunt obstruction include increasing the shunt perfusion pressure (adrenaline,

noradrenaline, phenylephrine), anticoagulation with heparin, minimizing VO_2(sedation, muscle relaxation), supplemental oxygen to increase pulmonary venous SO_2 and an intervention on the shunt (catheterization, surgery) [554, 565].

The duration of postoperative ventilation after S1P varies among studies, with a median of 7 days in the SVRT, but patients should be extubated when clinically ready. A recent large single-centre study indicated that after a period of postoperative recovery, 64% of infants were extubated onto temporary support with continuous positive airway pressure [566]. This non-invasive respiratory support is beneficial as a preventive measure against failure of extubation, which is relatively common after S1P. Parents and clinical teams should be prepared for this scenario. In the same study, 16% of patients required reintubation, with failure linked to a higher risk of postoperative death [566].

Failure to be weaned from ventilation, with persistent respiratory distress, desaturation or heart failure 7–10 days after Norwood surgery may indicate the presence of a residual haemodynamic lesion or in rare cases diaphragmatic paralysis [567]. If this occurs, further imaging and investigation are indicated and should be planned in conjunction with the entire team. A minority of more complex patients with HLHS end up requiring long-term ventilation via a tracheostomy [568]. The requirement for chronic ventilation via a tracheostomy has negative implications for medium-term outcome and requires a multidisciplinary approach to management [569] (Table 12).

11.9 Therapies to optimize haemodynamics

Common atrial pressure (indicating cardiac preload) should be maintained at an adequate level with judicious colloid administration (boluses of 5–10 ml/kg), tailored on a case by case basis considering specific factors such as degree of TR. All patients require pharmacological afterload reduction early after S1P, and most require inotropes. A standard regimen is low-dose adrenaline (0.02–0.05 μg/kg/min). The predominant afterload reducing agents are milrinone and phenoxybenzamine [305, 307]. The evolution of low CO syndrome (LCOS) may be ameliorated by milrinone, which is a lusitrope with proven benefits [307, 570]. The recommended dose range is 0.25–0.75 μg/kg/min. A dose at the lower end of the range should be considered as the starting point early after S1P, because of reduced renal clearance of the drug in this setting.

Patients with MBTS have greater systolic and diastolic flow into the Qp and therefore may have diastolic hypotension, requiring the addition of a noradrenaline infusion. All catecholamines lead to increases in SVR at higher doses, and this scenario should be avoided [571]. If hypotension triggers the use of escalating catecholamine doses, then ECLS should be considered a safer option.

Patients will require titration of opiate medications after S1P to maintain an appropriate level of analgesia, based on the COMFORT Behaviour scale [572]. Patients who are less stable or who have an open sternum may require muscle relaxants as well [573].

11.10 Low cardiac output state

Manifestations of LCOS include low pulse volume, prolonged capillary refill time, low BP, metabolic acidosis, high lactate and oligoanuria [48]. In LCOS, the SVO_2 is low (i.e. <75% of the SaO_2). Although based on older data from a different congenital heart defect, there is evidence applicable to S1P, indicating that the nadir for CO occurs to 12 h after CPB; therefore patients should not be weaned aggressively until this period has passed, usually meaning after the first postoperative night [574].

If LCOS does occur, it may be necessary to increase the inotropic support and level of afterload reduction. Further measures

Table 12: Factors contributing to hypoxaemia and ventilator dependence after stage 1 palliation

Factor	Possible cause	Diagnostic measures
Pulmonary venous desaturation	• Ventilation/perfusion mismatch: malpositioned endotracheal tube, pleural effusion, haemothorax, pneumothorax, chylothorax, pulmonary oedema, atelectasis, pneumonia, pneumonitis and AV malformation	• Chest radiogram • Lung ultrasound • Bubble echocardiography/angio-CT/cardiac catheter for arteriovenous malformation
Systemic venous desaturation	• Low DO_2: anaemia, LCOS, impaired coronary perfusion, ventricular dysfunction, TR or TS, neo AR or AS, CoA, pericardial effusion/tamponade, arrhythmia • Increased VO_2: sepsis, hyperthermia, pain, agitation, seizures	• NIRS, SvO_2 • Haemoglobin • Temperature • ECG, atrial ECG, Holter monitor • ECHO • Cardiac catheter
Inadequate Qp	• Low SVR (in patient with MBTS): sepsis, hyperthermia, systemic vasodilators • High PVR: lung disease, pulmonary vascular disease, pulmonary vein stenosis, r-FO/IAS, TR, TS, RV, arch obstruction • Obstruction: shunt-conduit stenosis • PA branches: stenosis, kinking, tenting, thrombosis, thromboembolism • Small MBTS or RV–PA conduit	• Echocardiogram • Cardiac catheter, angio-CT • Anatomical evaluation of MBTS, RV–PA conduit, PA branches, pulmonary veins • PVR study

AR: aortic regurgitation; AS: aortic stenosis; AV: atrioventricular; CoA: coarctation of the aorta; CT: computed tomography; DO_2: oxygen delivery; ECG: electrocardiogram; ECHO: echocardiogram; IAS: intact atrial septum; LCOS: low cardiac output syndrome; MBTS: modified Blalock–Taussig shunt; NIRS: near infrared spectrum; PA: pulmonary artery; PVR: pulmonary vascular resistance; Qp: pulmonary blood flow; r-FO: restrictive foramen ovale; RV: right ventricle; SvO_2: mixed venous oxygen saturation; SVR: systemic vascular resistance; TR: tricuspid regurgitation; TS: tricuspid stenosis; VO_2: oxygen uptake.

for treatment of hypotension with LCOS, for which robust clinical trial data do not exist, include mild cooling of the patient to 35°C (with muscle relaxation) and administration of stress dose hydrocortisone [575]. In this setting, VO_2 should be minimized by keeping the patient sedated and muscle relaxed.

Cardiac arrest, which is usually a complication of LCOS, is more common after S1P than after most other operations. Importantly, patients who had cardiac arrest following S1P were found to have a poorer outcome than those in other patient categories in a registry-based study of arrest outcomes [576]. For patients deteriorating towards cardiac arrest, or in cardiac arrest, ECLS should be initiated.

Delayed sternal closure is another frequently used (78% of patients) adjunct for prevention or treatment of LCOS (see surgical sections) [577]. In 1 study, the median time to sternal closure was 4 days, with an important number of infants experiencing failure requiring an emergency reopening. The strongest predictor of successful sternal closure in this study was the SVO_2, implying that moving to chest closure is best undertaken when CO has improved [578]. Furthermore, a reduced 'technical performance score' was strongly linked to failed closure. Therefore, consideration of readiness should entail a review of haemodynamic risk factors. Patients with open chest and delayed sternal closure should be treated with prophylactic antibiotics based on local protocols.

11.11 Extracorporeal life support/extracorporeal membrane oxygenation

After S1P, indications for ECLS include LCOS, acute hypoxaemia due to malfunction of an MBTS or an RV–PA conduit and cardiac arrest (for which cases ECLS is termed ECPR) [394, 395, 579]. ECLS (usually as ECMO) is deployed after S1P in 17% of cases, which is high in comparison to other operations [495, 541]. The incidence of ECMO in European settings is lower; however, multicentre data are lacking. The fact that the survival rate in the subset of patients needing ECMO is relatively poor, reported as 57% in a registry-based study, should be considered [541]. Outcome may be influenced by the reason for ECMO deployment, with better survival reported for patients with a remediable cause such as MBTS blockage, and poor results in patients who are not able to separate from CPB [394]. In practice, most teams consider any S1P patient to be a candidate should the need arise.

For patients with an MBTS, effective ECMO requires specific management of Qp through the MBTS during ECMO. Poor outcomes have been reported when the MBTS is fully occluded in this setting, and it is rarely required [580]. Current strategies for management of shunt run-off include the use of higher (supranormal 150–200 ml/kg/min) ECMO flow to provide increased Qs and CO. However, if CO remains insufficient despite increased ECMO flows, 1 option is to surgically restrict flow through the MBTS.

All patients on ECMO after S1P require careful management of anticoagulation to avoid major bleeding and thrombosis. Patients with uncontrolled fluid overload should receive continuous venoveno haemofiltration via the ECMO circuit.

Patients who suffer cardiac arrest and those who undergo ECLS (usually ECMO), both relatively prevalent after S1P, have a higher risk of having an acute neurological event and should be monitored carefully with electroencephalograms and cranial ultrasound. In particular this applies to patients with profound shock and acidosis prior to ECLS, who were reported in a registry study to have a 22% incidence of major acute neurological complications, many lethal [581].

The level of experience that ICU teams have in dealing with postoperative complications such as cardiac arrest and need for ECMO, which are highly relevant to S1P, has been assessed in the study of a concept referred to as 'failure to rescue'. In a large study, lower mortality rates were strongly linked to the success achieved in such a rescue, which emphasizes the importance of the experience that ICU teams gain in dealing with major complications [397, 582].

11.12 Fluid management

Fluid overload and acute kidney injury are relatively common after S1P, contributing to postoperative morbidity. Both are more likely to occur in the context of LCOS [583–585]. In patients with preserved renal function who are responsive to diuretics, administration of furosemide (by bolus or infusion) and fluid restriction will be sufficient to deal with postoperative fluid overload. Patients with fluid overload who do not respond to diuretics and those with more severe acute kidney injury should be managed with dialysis [583, 586, 587]. The most common approach is peritoneal dialysis, which is safe and effective in this setting [588]. However, the exact threshold at which dialysis should be started is unclear and varies from centre to centre.

11.13 Nutrition

There is a relatively high risk of NEC after S1P, which is exacerbated by low CO [349, 589]. However, caloric supplementation is important to recovery, and enteral feeding is the preferred approach given that it has physiological advantages for maintaining gut integrity [590, 591]. Therefore, milk feeds should be started by nasogastric tube when there is reasonable CO, usually at the earliest 48 h after surgery. Given the fragile circulation and risk of NEC, feeds should be introduced slowly, starting at 0.5–1 ml/kg/h with spaced small advances based on a feeding protocol that includes checks of gastric residual volumes [205, 592] The optimal feed is expressed breast milk, but if this is not available then an alternate starting infant formula should be selected based on the guidance of local dieticians. Patients who are not fit to receive enteral feeds because of LCOS or NEC should receive total parenteral nutrition with the maximum possible caloric content feasible given the fluid restrictions in this setting [593]. Patients with more prolonged dependence on intravenous therapies such as parenteral nutrition may require more long-lasting forms of central venous access.

11.14 Parental distress and social support

The postoperative period is a very stressful time for parents, particularly when there are complications or prolonged hospitalization [594]. Provision of psychological support should be provided to families during this period, either via psychologists or by specialist nurses [595]. Although beyond the scope of this discussion, this is critically important to both the family and the clinical care team and requires specific expertise.

Postoperative management

Recommendations	Class[a]	Level[b]
Compliance with an operating room checklist and a rigorous handover to the ICU team based on an algorithm	I	A
In the early postoperative period a steady physiological state with euvolaemia, low SVR and balanced laboratory values to prevent adverse events	I	C
Postoperative pharmacological support should include an inodilator or vasodilator to promote stable and low SVR to optimize CO	I	B
In the early postoperative period, alongside standard ICU monitoring, the SvO2 should be tracked as part of the overall management pathway (site of measurement based on local policies and individual patient factors)	I	C
Heparin anticoagulation is recommended in the postoperative period	IIa	C
Postoperative hypoxaemia requires urgent evaluation and treatment including assessment of the lungs and the source of Qp	I	C
Patients with acute kidney injury that are unresponsive to diuretics should receive dialysis	IIa	C
Enteral feeds are recommended postoperatively when there is reasonable CO, based on the local feeding protocol	IIa	C
ECLS should initiation for postoperative cardiac arrest, acute loss of Qp and other causes of severe low CO unresponsive to other therapies	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
CO: cardiac output; ECLS: extracorporeal life support; ICU: intensive care unit; Qp: pulmonary blood flow; SvO_2: mixed venous oxygen saturation; SVR: systemic vascular resistance.

12. HYBRID STRATEGIES FOR HYPOPLASTIC LEFT HEART SYNDROME: STAGE 1 PALLIATION

12.1 Timing for hybrid stage 1 palliation

The h-S1P approach for HLHS was introduced in the early 1990s to achieve palliation without CPB and circulatory arrest [596]. Norwood S1P had unacceptable mortality and morbidity rates at the time [225]. A heart transplant was an alternative, but only in affluent countries [201, 597]. The neonatal h-S1P initially had limitations relating to technique and available materials [598]. In 1998, the first h-S1P followed by a successful c-S2P was performed [599]. Initially, 2 centres (in Europe and the USA) replaced the neonatal Norwood S1P with h-S1P, followed by others worldwide [213, 508, 600–603]. In most centres with an established Norwood programme, the h-S1P is used primarily for high-risk neonates and to delay complex CPB surgery beyond the neonatal period for any indication [226, 227]. However, using h-S1P only in high-risk patients may dilute the experience that is necessary for success (class IIa, level B).

For a neonate with HLHS and a normal risk level, an elective h-S1P is performed within the first week of life [200, 604]. The procedure is suitable for almost all left-sided obstructive cardiac lesions with DA-dependent Qs, regardless of age, weight or haemodynamics [605–607]. The neonatal h-S1P is currently achievable with an average mortality rate of <5%, including newborns admitted in cardiogenic shock and resuscitated by the hybrid approach [601, 608, 609].

An elective h-S1P is best performed before tachypnoea ensues, because the diastolic left-right DA shunt increases or the dilated RV shows progressive TR [200, 609]. Therefore, b-PAB should be performed during the first week, usually within the first 2–5 days. For emergencies, 1 or all h-S1P components can be used, depending on the cause of cardiovascular failure. An atrial septal manipulation might be necessary immediately or in the first few hours of life, even after a foetal intervention. An h-S1P has been used at a weight of almost 1000 g and in untreated infants up to age 8 months, followed by successful c-S2P and Fontan [608].

Timing of hybrid stage 1 palliation

Best timing of hybrid stage 1 palliation	Impact on outcome	Class[a]	Level[b]
Elective approach, first postnatal week	Very high	I	B
Bilateral pulmonary artery banding as an emergency	High	IIa	B
Ductus arteriosus stent as an emergency	High	IIa	B
Balloon atrial septostomy as an emergency	High	IIa	B
Hybrid stage 1 palliation in a premature infant	high	IIa	B

[a]Class of recommendation.
[b]Level of evidence.

12.2 Principles of the hybrid approach

The h-S1P should provide sufficient Qs via an unobstructed DA and Ao arch, a protected Qp and laminar pulmonary vein flow.

The hybrid concept, sequentially or in a single procedure, was applied at first to high-risk Norwood candidates to move extensive surgery beyond the neonatal period [599, 600, 608]. The h-S1P is followed by a c-S2P at 4–6 months. C-S2P combines removal of a b-PAB and a DA stent, BCPS, reconstruction of the systemic SV outlet and Ao arch repair, comparable to a Norwood S1P [600, 608]. The h-S1P or parts thereof can serve as a rescue procedure or as a simpler alternative to an elective Norwood S1P [200]. Some centres also utilize the h-S1P for bridging to a Norwood procedure beyond the neonatal period [600, 608]. A reverse MBTS has been introduced as an additional variant of the h-S1P to deal with CoA-mediated restriction of retrograde Ao arch flow [516].

12.3 Pathophysiological issues

The h-S1P aims to balance Qp and Qs to avoid myocardial ischaemia. Pulmonary vein blood flow should be unobstructed and fully oxygenated from all parts of both lungs. Excessive Qp and protection against pulmonary vascular obstructive disease must be achieved by b-PAB and postcapillary PHT (despite b-PAB), by an unobstructed FO. The h-S1P has been successfully performed in single or even single hypoplastic lung physiology in newborns with diaphragmatic hernia [610].

The Qs should be distributed to all organs without obstruction and with a sufficient DO_2. A balanced Qp/Qs is achieved when the SaO_2 is ∼80%, relating to an SvO_2 of 50–60%. The coronary and cerebral blood flow should not be impeded; likewise, the abdominal perfusion. An adequate DA guarantees sufficient Qs, including the cerebral as well as the coronary circulation, but Ao obstruction needs to be excluded. A large DA promotes the 'Windkessel' effect by connecting the systemic circulation to a dilated MPA [220]. A diastolic left-to-right shunt is favoured, so even with effective b-PAB and no pulmonary regurgitation, the SVR needs to be so low as possible without jeopardizing cerebral and coronary perfusion pressure. The Doppler flow pattern and measurements across a native or stented DA may reveal obstruction, estimate systolic blood flow and determine the diastolic left-to-right shunt. The area under the curve of the diastolic trace shows pulmonary reflow [220]. A negative diastolic blood flow obtained from the anterior cerebral artery and coeliac trunk would also be relevant. Therefore, repetitively performed echocardiographic Doppler measurements are essential to a comprehensive evaluation. The consequences of a significantly restrictive DA are immediate shock and death, but excessive pulmonary run-off is a silent killer of myocardial performance. DA stenting alone does not guarantee good flow because non-covered parts of the DA may obstruct. Also, in-stent stenosis is related to stent material and the unique DA tissue [611].

An h-S1P might be contraindicated in the rare morphological constellation of MA/AS with a restrictive interventricular communication, in which the coronary perfusion is dependent on a progressively narrowing VSD. Compromised coronary perfusion can also result from insufficient antegrade flow through the AoV and retrograde arch obstruction, in particular during IS-1. Similar consequences could relate to coronary fistulae or obstructions [196]. Even an ideal h-S1P will trigger RV myocardial hypertrophy.

In a borderline LV with a sufficient antegrade flow reaching the innominate artery, harlequin head perfusion can be observed, with a normal SaO_2 on the right and deoxygenated blood on the left side. A moderately r-FO with a pressure gradient of 5–15 mmHg may be desirable in a borderline LV with the potential for bi-V repair to induce LV growth, if a genetically predetermined factor such as EFE is excluded [20, 606, 607].

12.4 Surgical bilateral pulmonary artery banding technique

Balanced Qp/Qs is currently best accomplished by placing b-PAB via a median sternotomy [612, 613]. Usually, b-PAB is performed before the DA is stented (class IIa, level B). In case of prior high-urgency isolated DA stenting, there is a risk of a stent obstruction, in particular if a balloon-expandable stent was used [516, 605]. With a previously stented DA, the left PA is harder to isolate and the stent is at greater risk for distortion [614].

In a stable patient, an open DA with PGE1 infusion has several advantages. The technique for b-PAB becomes easier and has lower risk. Any stent-related haemodynamic problems can be avoided, and even a slightly obstructed Ao isthmus can be improved with the PGE1 (class IIa, level B). A stent within an unobstructed DA does not change *per se* the patient's haemodynamics or add stability. However, an adequately placed b-PAB will improve the haemodynamics by balancing the circulation by improving Qs. A standard 3.5-mm PTFE tube graft (3 mm for BW < 2.5) cut to a 1- to 2-mm wide ring serves as the PAB [612] (class IIa, level B). Exposure of the RPA is straightforward, but exposure on the LPA is more difficult [613]. The right PAB is positioned between the Asc Ao and the SVC, proximal to the RPA bifurcation and fixed to the adventitia. Bands performed in premature babies should be secured with a 6-0 suture, so that dilation with a 3- to 4-mm coronary balloon catheter can be performed during a follow-up procedure if needed [10]. Additionally, a poststenotic branch dilatation may be induced by the small band with a width of 1–2 mm (class IIa, level B). A wide band has to be avoided, because the risk for development of hypoplastic PA branches is significant (class IIa, level B).

The efficacy of a PAB can immediately be observed by an increase in systemic BP and an ideal decrease of SaO_2. There is usually no need for direct pressure measurements across the band (class IIa, level B). Doppler measurements can be performed to analyse the pressure gradient across both PABs by the systolic flow pattern, estimating the postcapillary pressure, if the BP is additionally measured and a pressure gradient across the DA is excluded [213]. The diastolic component of the systolic-diastolic Doppler flow pattern indicates the effectiveness of the PAB. A purely systolic flow pattern independent of its calculated pressure gradient does not. An end-diastolic flow pattern above 50% of the systolic Doppler flow curve might be associated with a narrow PAB [211] (class IIa, level B) (Table 13).

12.5 Transpulmonary ductus arteriosus stenting technique

DA stenting is not always required, because PGE1 can be administered long term [211]. However, stent placement is preferred to palliate until c-S2P, to avoid the side effects of long-term PGE1 infusion and central lines. For a one-stage h-S1P, stent placement is performed after b-PAB, when the haemodynamics are stabilized (class IIa, level B). For transpulmonary DA stenting, a sheath is placed in the MPA as proximally as possible just above the sinotubular junction [613, 615]. The sheath size (4, 5 or 6 Fr)

Table 13: Criteria, techniques and issues for bilateral PA banding in hypoplastic left heart syndrome

1. PAB size and objective
• PAB lumen by cut and resutured small (1–2 mm) PTFE tube (3.5 vs 3.0 mm, based on BW <3/2.5 kg)
• Pulsed-wave Doppler flow pattern across the banded PA; systolic gradient (systolic PA pressure - post-PAB pressure level); diastolic flow component = efficacy of the PAB
2. Anatomical variants (RPA vs LPA size)
• Indicates different PAB sizes (example: right 3.5-mm vs left 3-mm PTFE tube)
3. Timing
• At any time in the setting of high pulmonary run-off and progressive low CO (salvage procedure)
4. Risk factors for procedure-related losses:
• Opening of pericardium in unstable patients
• Loose PAB (suture failure, wrong PAB)
• PA hypoplasia by a too wide band
• PAB placement in context of unrecognized duct obstruction

BW: birth weight; CO: cardiac output; LPA: left PA; PA: pulmonary artery; PAB: pulmonary artery banding; PTFE: polytetrafluoroethylene; RPA: right PA.

depends on the stent design. A silk suture is placed around the distal sheath ∼2 mm from the tip to serve as an external marker for depth of insertion. Deep insertion could hinder deployment of the stent to cover the entire length of the DA. A small hand injection of contrast through the sidearm of the sheath defines the DA, left PA, Desc Ao and retrograde Ao flow. The DA length and diameter are angiographically measured at the distal, middle and proximal ends, and the appropriate stent is chosen. Balloon-expandable or the preferred self-expandable stents can be used (class IIa, level B). A balloon-expandable stent requires more space between the inserted sheath and the pulmonary end of the DA, and the ductal flow will be briefly interrupted. In most newborns with HLHS, an 8-mm stent is utilized [613, 615]. The entire length of the DA tissue must be covered, which typically spans from the origin of the left PA to beyond the transverse arch (class IIa, level B). Further manipulations after stent placement are usually not possible. Additionally, transpulmonary DA stenting is a manipulation with its own risk to destabilize the sensitive haemodynamics of the patient with HLHS [200]. This part of the h-S1P has a learning curve and requires sufficient training. The current approach of combining b-PAB with transpulmonary DA stenting has a mortality rate of 5–25% [225, 600, 609, 616, 617]. It is an exacting procedure, which requires the full attention of all participants.

12.6 Anaesthetic management

Details are critical and are covered in the anaesthesia section of the HLHS guidelines [235, 618, 619]. Briefly, a full general anaesthetic is used, as in neonatal surgery with CPB. All drugs for resuscitation, including those for treating arrhythmias and even cardiogenic shock, should be prepared, and catecholamines should be connected prophylactically. A critical time is the period in which the patient needs to be sedated under PGE1, due to the augmented risk of apnoea. The side effects of anaesthetic drugs can lead immediately to a resuscitative condition, which can be almost impossible in patients with HLHS. Extreme dependency of an adequate coronary perfusion pressure on the one side and high sensitivity to over-dosed catecholamines on the other side can be fatal. The tiny Asc Ao could constrict with high dosages of norepinephrine, which may lead to fatal myocardial ischaemia, often starting with ventricular arrhythmia (class IIa, level B). Therefore, balanced anaesthesia with repetitive small dosages of midazolam (0.1–0.2 mg/kg) and fentanyl (5–10 μg/kg) and the addition of 0.5–1% isoflurane as an induction dose are preferred. Ketamine (0.5–1 mg/kg) is preferentially used in unstable patients because it liberates endogenous norepinephrine (class IIa, level B). Short-acting analgesic-sedative drugs are also preferred for weaning and early extubation. Dexmedetomidine and clonidine are increasingly used after h-S1P for the first few days in the ICU (class IIa, level B). The general haemodynamic support immediately after h-S1P does not change significantly from the postnatal strategy (see other sections regarding postoperative management in the HLHS guidelines).

12.7 Postoperative management in the intensive care unit

The ICU team must be prepared for and familiar with the newborn with HLHS after h-S1P [620, 621]. The postoperative course is determined decisively by the preoperative condition. Taking this into account, the first measure is not to perform h-S1P too late. H-S1P performed at a mean age of the 12th postnatal day was reported to lead to acute kidney dysfunction in 16% versus in 53% following a Norwood operation [583]. When morphological or functional problems are excluded by echocardiography, the second therapeutic measure consists of early extubation, sometimes in the operating room [613]. Only patients in whom the h-S1P was performed as a rescue approach need a longer recovery time.

Risks for postoperative LCOS, tamponade and arrhythmias are low, but not zero. Postoperative capillary leak, oedema formation (including the myocardium) and vascular paralysis, as often seen after the Norwood procedure, are rare (class IIa, level B). The ventilator setting and the monitoring of an intubated patient should be similar to the situation during open-chest surgery. A low-frequency ventilation with a slightly increased tidal volume (10 ml/kg, depending on chest excursions and auscultation) serves as an antiatelectasis measure but does not exclude a slightly permissive hypercapnic ventilation with positive base excess and lowest effective mean airway pressure. Early extubation with spontaneous breathing (with or without high-flow support) is an important safety measure after h-S1P (class IIa, level B). The need for treatment with catecholamine is rare. In some centres, milrinone and clonidine are used together to achieve low SVR (Qp/Qs balance), optimize HR and diastolic ventricular filling and smooth out analgesia and sedation.

12.8 Elective percutaneous ductus arteriosus stenting

DA in some institutions is an elective transcatheter procedure, in a spontaneous breathing, sedated newborn, at times with an additional atrioseptostomy [213, 599, 605]. For percutaneous stent placement, femoral vein or arterial access is utilized [214]. In case of an additional atrial septum manipulation, a 5- or 6-Fr

sheath is placed in the femoral vein and a 4-Fr sheath in the artery. Exact transvenous stent placement is monitored by a catheter advanced through the femoral artery access. Following intravenous heparinization of 100 IU/kg, a multipurpose catheter is positioned in the junction of the DA and the Asc-Desc Ao, and a coronary guidewire through the catheter within the Ao arch. Utilizing a haemostatic valve, continuous BP monitoring and hand injection of contrast can be performed. For transvenous DA stenting, an end-open 4-Fr wedge catheter is floated by an inflated balloon across the TV within the RV. A soft coronary wire is advanced through the balloon catheter still positioned within the RV across the PV valve, DA and in the Desc Ao. The balloon catheter is exchanged for a 4-Fr, 2.5 curved right Judkins catheter, which is positioned over the wire in the MPA opposite the junction of the PA and the duct. For venous, trans-RV ductal stenting, an additional stiff coronary wire should be placed within the Desc Ao and the soft wire removed. Together with the multipurpose catheter placed in the DA-Desc Ao junction, a sufficient delineation of duct morphology can be assessed angiographically by hand injections of contrast medium through the Judkins 4 Fr or arterially placed multipurpose catheter, sometimes even simultaneously. Biplane assessment by 90° lateral and 30° right anterior oblique views allows one to demonstrate the DA: in the lateral projection, one sees the duct-PA insertion, and in the 30° right anterior oblique, the Ao-DA junction, respectively.

The described catheter strategy reduces total catheter time and improves the safety of percutaneous ductal stenting (class IIa, level B). Placement of a trans-ventricular long sheath is not necessary, thereby avoiding haemodynamic instability. Currently, if a highly obstructed DA is excluded (which would favour a premounted balloon-expandable stent), self-expandable stents are preferred. Placement of self-expandable stents avoids ductal flow interruption and the high risk of stent slipping, as seen in particular when utilizing balloon-expandable stents for non-constricted, widely patent ducts. PGE1 infusion need not further be stopped until a slight DA obstruction is observed (class IIa, level B).

In Europe, a new generation of self-expandable stents has been developed with a CE-mark for ductal stenting in newborns [213, 583]. Arterial access facilitates DA stenting in terms of efficacy and safety. Another advantage is the chance for analysing the Ao isthmus before and after stent placement [213, 214]. Even a slightly obstructed isthmus should be dilated with a balloon diameter 5–6 mm prior to DA stenting. If a significant CoA persists after stent placement, an effective treatment can be performed by a second stent, which can be placed through the open-cell struts or beyond the stented duct (class IIa, level B). Coronary or specially designed self-expandable stents with a width of 5 or 6 mm and a length of 9–12 mm are used primarily for additional CoA stenting [213, 608].

Considering a DA without obstruction, the self-expandable stent diameter has to be at least 1–2 mm above the minimal DA diameter, but in any case, exceeding the diameter of the Desc Ao (class IIa, level B). This last recommendation is of particular importance in newborns with IAA [606]. By choosing such a ratio of stent to Desc Ao diameter, stent embolization can be avoided (class IIa, level B). Taking into account technical and material details, percutaneous duct stenting can be performed with almost no deaths [606, 608]. As a prerequisite, the stock of materials in the catheter laboratory in which percutaneous DA stenting is performed must be sufficient to allow the operator to anticipate any complication [213]. However, in the majority of countries, self-expandable stents are only available for introducer sheaths of 5 or 6 Fr, which might be inconvenient when using femoral artery access (Table 14).

Table 14: Criteria, technique and issues of percutaneous DA stenting

1. Echocardiographic screening and angiographic duct delineation
• Depending on imaging, the chosen stents should be longer and the width 1–2 mm larger than the measured DA. The stent should exceed the diameter of the Desc Ao
• Non-obstructed ducts should preferentially be stented by self-expandable stents
• DA obstruction is an indication for a balloon-expandable stent
2. Risk assessment based on morphological variants of the Ao arch
• Stent placement from the PA to the Desc Ao arch
• Stenting across the Desc Ao arch
• CoA with recommended predilation and/or post-ductal CoA stenting
• DA stenting in the context of an aberrant subclavian artery or other arch anomalies
3. Timing
• At any time in the setting of PGE1-resistant DA obstruction (acidosis)
• Consider risk factors for procedure-related losses: duct irritation with consecutive constriction and hyperproliferation, open-cell device with residual kinking, obstruction or still un-covered duct tissue (requiring PGE1 despite stented duct) heparin, clopidogrel are recommended

Ao: aorta; CoA: coarctation of the Ao; DA: ductus arteriosus; Desc Ao: descending Ao; PA: pulmonary artery; PGE1: prostaglandin E1.

12.9 Atrial septal manipulation

Atrioseptostomy becomes necessary in almost 50% of newborns with HLHS, either as part of S1P or during the IS-1 [142, 622]. Standard balloon atrioseptostomy is often difficult, due to the size and location of the defect, the size of the LA and the instability of the patient. Therefore, not only the timing of the procedure but also the technique itself has to be variable. The techniques include:

1. Gradual static balloon dilatation with or without utilizing cutting balloons and follow-up Rashkind ballooning
2. Perforation of the atrial septum by a Brockenbrough needle or a radio frequency technique, followed by stent placement.

No technique yielded a reliable, reproducible result until the current one (class IIa, level B). Sometimes delay of the balloon septostomy by nearly a week, which allows some growth of the LA, yields a more substantial and durable opening in the atrial septum (if a 2 cc balloon is accommodated). The Brockenbrough needle technique in a small LA has been described (class IIa, level B). Septal puncture is performed utilizing a transseptal needle loaded into a 6-Fr, 48-cm-long sheath (Cook-Medical®). Under biplane fluoroscopy (anterior–posterior and 90° lateral), the ensemble of sheath, mandrel and needle (1–2 mm behind the tip) is pulled back from the SVC into the fossa ovalis and contrast is continuously applied via a 5-ml Luer Lock syringe fixed at the needle. In contact with the fossa ovalis, only the needle is advanced to deposit contrast medium in the atrial septum and then further advanced in the LA, still by application of contrast by which the LA cavity can be easily demonstrated. A coronary guidewire (Whisper, Abbott Laboratories, Chicago, IL, USA) is

advanced through the needle and positioned in a left-sided pulmonary vein. After careful removal of the needle and mandrel, with the sheath still on the RA side, gradual dilation of the septum can be performed, starting with 1- to 3-mm coronary balloon until a 5- to 7-mm balloon allows advancement the 6-Fr long-sheath into the LA. The interatrial septum can be easily stented using a balloon-expandable or self-expandable stent [213, 613, 623]. A slightly diabolo-shaped stent pattern reduces the risk of stent embolization. With a self-expandable stent, the septum determinates the dog-bone shape in any case, and sometimes the stent needs to be slightly and carefully redilated. An 8-mm balloon-expandable stent is already fully expanded at the ends, but in the area of the stented IAS it may still have a width of 6–7 mm. Despite the diablo-shape of the stent, careful removal of the deflated balloon is necessary to avoid stent embolization [214, 608]. Redilatation of the atrial stent in follow-up is safer than full expansion during placement (class IIa, level B) (Table 15).

Table 15: Criteria for atrial septostomy/stent implantation in hypoplastic left heart syndrome with restrictive foramen ovale/intact atrial septum

1. Severe restriction on echocardiography, hypoxaemia, tachypnoea
• Foramen ovale diameter ≤1 mm on colour Doppler scan or closed or a decompressing vein from the left atrium with flow obstruction
• Pulmonary venous Doppler flow pattern consistent with high atrial pressure (to-and-fro flow, forward/reverse velocity time integral <3)
• Pulmonary venous A-wave duration ≥90 ms
2. Anatomical subtypes necessitating manipulations: large versus small left atrium, floppy versus thick atrial septum, atypical position of a restrictive foramen ovale, intact atrial septum, pulmonary vein obstructions
3. Timing
• At any time in the setting of pulmonary congestion-related hypoxaemia (salvage procedure)
• Consider risk factors for procedure-related losses: access, left atrial size, Brockenbrough technique and atrial septal stenting for creation of definitive defects

12.10 Hybrid approach as a rescue measure

The components of the h-S1 can be used as rescue measures for compromised newborns with HLHS [599, 605, 615, 624]. Percutaneous DA stenting and, with some reservations, transpulmonary stenting, are the procedures of choice for PGE1-refractory DA obstruction, as observed in newborns admitted in cardiogenic shock and metabolic acidosis (class IIa, level B) [200]. Atrial manipulation (balloon septostomy with or without stenting) is the preferred method to treat severe hypoxaemia attributable to significantly r-FO or IAS [365, 624]. Obstructed pulmonary venous blood flow associated with TAPVD return can also be palliated by transcatheter techniques (class IIb, level B). Stenting of the obstructed vertical vein is described as well as direct connection of the TAPVD confluence with the LA following radiofrequency perforation and stent placement or pure ballooning [365, 625]. Neonates admitted with systemic low CO t caused by high Qp can be resuscitated by b-PAB, using a short, comprehensive open-chest approach (class IIa, level B). The technical details are in principle not different compared to those used with h-S1P.

12.11 Hybrid interstage 1

The IS-1 requires not only a successful initial h-S1P with a well-balanced circulation but also appropriate and assiduous follow-up monitoring (class IIa, level B), including detailed instructions for physicians and parents [200]. Lacking evidence-based drug trials, medications are used on the level of expert opinion but based on pathophysiological and current pharmacological knowledge [142, 220]. Commonly used medications include diuretics (despite questionable indications) with and without digoxin, HR-oriented β1-receptor blockers combined with spironolactone (cardiac fibrosis influencing dosage) and angiotensin-converting enzyme (ACE) inhibitors in case of persistently increased SVR. Regarding the important role of the parents, cardiovascular drugs need to be safe, well understood and easily administrable [142, 220]. The best IS-1 monitors are well enlightened parents familiar with the importance of the RR during the baby's sleep, the quality and quantity of oral milk intake and weight gain (class IIa, level B). In addition, successful IS-1 management requires close outpatient evaluation by experienced paediatric cardiologists able to detect haemodynamic imbalance in advance of cardiovascular emergencies [608]. Complete echocardiographic assessment within a time interval of 8–10 days is mandatory, including interior vena cava and hepatic vein diameters and flow characteristics and Desc Ao and coeliac trunk blood flow. Other critical areas include cardiac morphology, atrial and ventricular function and size, quality of atrial communication, atrial pressure gradient (near zero in HLHS, up to 12–15 mmHg in patients with HLHC). Furthermore, active exclusion of any (even single) pulmonary vein obstruction is repetitively necessary. Finally, one should assess AVV and PV characteristics and function, flow patterns, velocity with calculated gradient, area under the Doppler curve, diastolic left-to-right shunt and the DA-Ao junction with the quality and amount of retrograde arch flow (in the context of BP, RR rate and SO_2). Interventional transcatheter procedures should be pursued for detected or suspected haemodynamic abnormalities during IS-1 (class IIa, level B). Catheter-based solutions can successfully address obstructions within the stented DA, FO or even Desc Ao and can be performed in experienced centres without general anaesthesia [600, 608]. Based on a combined parent-physician monitoring programme, the mortality rate for IS-1 is <5% for patients with HLHS and almost zero for h-S1P-treated patients with HLHC. This rate is comparable with that of the best surveillance programme following the Norwood S1P procedure [628, 629] (see also IS-1 management section). Routine evaluation prior to c-S2P is based on echocardiography and cardiac MRI techniques. Summarizing the data of centres that have replaced routine Norwood surgery with h-S1P, the c-S2P can be performed with a mortality rate of <5% [601, 608, 609, 628, 629].

12.12 Outcomes for hybrid stage 1 palliation using different strategies

The short- and long-term outcomes in HLHS or HLHC reflect the widely variable surgical and interventional techniques [225, 516, 600–603, 606, 608, 609, 628]. Postponing an advanced open-heart surgery from the neonatal period to infancy achieves potential benefits for long-term outcomes, including neurodevelopment, if the components of the h-S1P are performed with that

ultimate goal [630–635]. The concept of stabilization of the SV circulation with b-PAB and of maintenance of ductal patency has significantly widened the therapeutic spectrum for HLHS [636].

13. INTERSTAGE MANAGEMENT

IS-1 mortality in SV patients occurs between hospital discharge following S1P and admission for S2P. Patients considered stable may have sudden, unexpected deterioration or may die while at home. Whereas the risk of IS-1 death is associated with residual anatomical issues and other patient factors, the common exposure is the vulnerable circulatory arrangement. Efforts to characterize risk factors have failed to identify a specific target for improvement strategies. It is clear that the causes of IS-1 deaths are multiple and unlikely to respond to a single medical or surgical intervention [340, 342, 362, 637, 638]. In 2003, Ghanayem *et al.* [627] described the positive impact of a home surveillance programme to identify patients at risk prior to circulatory collapse. They demonstrated a reduction in the IS-1 mortality rate from 15.8% to 0% after implementation. An update to the series demonstrated sustained improvement in IS-1 survival with home monitoring, with 98% survival in 157 consecutive patients from 2000 to 2010 [639]. This experience has been reproduced elsewhere and has led to significant reduction in IS-1 mortality in centres participating in the National Paediatric Cardiology Quality Improvement Collaborative (Table 16) [640–642]. However, the SVRT still reported a 12% overall IS-1 mortality [643]. Research efforts and improvements to care models continue to focus on risk stratification, enhanced screening for residual haemodynamic lesions and surveillance through IS-1 home monitoring protocols. Beyond the prevention of mortality, an important goal of IS-1 care is optimized growth, development and quality of life. Key studies reporting IS-1 outcomes are listed in Table 16.

13.1 Interstage 1 physiology and risk factors

The IS-1 physiology is characterized by an inefficient parallel circulation, with an RV volume load of varying degree, depending on shunt size, patient size and TV function. Residual or recurrent anatomical lesions (CoA, r-FO) impart important additional loads. Hypovolaemia, tachycardia and changes in SVR associated with normal childhood illnesses can acutely destabilize IS-1 physiology [304, 391, 644].

At baseline, patients may have signs of heart failure (tachypnoea, pulmonary congestion, limited energy reserves and growth failure). High caloric intake is required to achieve normal growth and development during this phase, and poor weight gain is an important modifiable predictor of outcome [645–648].

Risk factors for adverse outcome include anatomical and physiological issues, non-cardiac comorbidities, postoperative complications and demographic factors. In an effort to prevent IS-1 deaths and to risk-stratify patients, investigators have identified specific risk factors predicting adverse IS-1 events (see Hypoplastic left heart syndrome guidelines, Risk factors for death during IS-1).

In the SVRT, patients undergoing a modified MBTS were at higher risk of death during IS-1 than those receiving an RV–PA conduit [301, 643]. The influence of the Qp source on IS-1 mortality varied by the degree of TR, with a significant relationship between MBTS and mortality with no or mild TR. With greater degrees of TR there was no significant difference between MBTS and RV–PA conduit [643]. A single-centre comparison of survival highlighted the interaction between shunt/conduit type and duration of IS-1, with 120-day survival significantly higher in the RV–PA conduit group (92% vs 63%) [649]. The authors noted that although there was no difference in IS-1 deaths between groups (5% vs 4%), most IS-1 deaths in the RV–PA conduit group occurred beyond 120 days. The conclusion was that the survival advantage of the RV–PA conduit may be enhanced through earlier S2P.

Postoperative cardiac factors that affect CO at times of increased SVR include TR, arrhythmias and poor ventricular function. Moderate to severe TR represents an important risk factor for IS-1 death, as noted in several studies including the SVRT [643]. Significant TR leads to volume load and reduced effectiveness of CO during periods of circulatory challenge. Impaired RV function is more prevalent in patients with RV–PA conduits than

Table 16: Studies reporting interstage 1 mortality

Study[a]	Period	Population	Results/comments
Mahle *et al.* (2000) (CHOP, USA)	1984–1999	*n* = 840	ISD = 13.9% (no HMP)
Ghanayem *et al.* (2003) (CHW, USA)	1996–2001	*n* = 87	Pre-HMP = 15.8%; HMP = 0%
Fenton *et al.* (2003) (PITT, USA)	1991–2000	*n* = 146	ISD = 14% (no HMP)
Simsic *et al.* (2005) (MUSC, USA)	1996–2001	*n* = 50	ISD = 16% (no HMP)
Hehir *et al.* (2009) (CHOP, USA)	1998–2005	*n* = 368	ISD = 10.5% (no HMP)
Furck *et al.* (2010) (Kiel)	1996–2007	*n* = 157	Pre-HMP = 15.8%; HMP = 0%
Hansen *et al.* (2011) (Kiel)	1996–2009	*n* = 187	Pre-HMP = 12.4%; HMP = 2.2%
Dobrolet *et al.* (2011) (Miami, USA)	2006–2010	*n* = 59	Control = 6%; HMP = 3%
Petit *et al.* (2011) (TCH, USA)	2007–2010	*n* = 230	Pre-HMP = 12%; HMP = 8%
Ghanayem *et al.* (2012) (SVRT, NIH)	2005–2008	*n* = 426, 15 centres	ISD =12% (HMP unknown)
Siehr *et al.* (2014) (Stanford, USA)	2005–2019	*n* = 134	Pre-HMP = 7%; HMP = 0%
Rudd *et al.* (2014) (CHW, USA)	2000–2010	*n* = 157	ISD = 2% (with HMP)
Anderson *et al.* (2015) (NPCQIC)	2010–2014	*n* = 1163, 52 centres	ISD improved from 9.5% to 5.3%

[a]References [44, 340, 341, 478, 627, 639–641, 643–647].

CHOP: Children's Hospital of Philadelphia; CHW: Children's Hospital of Wisconsin; HMP: home monitoring programme; ISD: interstage death; Kiel: University Hospital Schleswig-Holstein, Kiel, Germany; Miami: Miami Children's Hospital and Arnold Palmer Children's Hospital, Miami; MUSC: Medical University of South Carolina; NCH: Nationwide Children's Hospital, Columbus Ohio; NPCQIC: National Paediatric Cardiology Quality Improvement Collaborative; PITT: Children's Hospital of Pittsburgh; SVRT: Single Ventricle Reconstruction Trial; TCH: Texas Children's Hospital.

with an MBTS, but the clinical significance has been questioned. Nonetheless, the SVRT suggested that dysfunction predicts mortality before reaching S2P [650, 651].

Single-centre retrospective studies have identified an association between arrhythmia following S1P and IS-1 deaths, without a clear mechanistic relationship [308]. A prospective assessment of postoperative arrhythmias in 120 patients undergoing S1P found arrhythmia in 78%, with two-thirds requiring intervention [310]. In this series, ventricular arrhythmias were more common after RV–PA conduit S1P and conveyed a hazard ratio of 14 for long-term deaths after S2P. No association was found between ventricular arrhythmias and IS-1 deaths.

Social and economic determinants of IS-1 outcome vary based on geographic region and health care system, implying there may be impairments to health care based on these factors [643, 652, 653]. The SVRT, based in the USA, found a strong link between Hispanic ethnicity, census block poverty level, and the IS-1 mortality rate, suggesting that patients from more deprived backgrounds had a higher incidence of adverse events [643]. Conversely, registry-based studies from the UK found no evidence that socioeconomic status was linked to IS-1 mortality rates. However, there was evidence that in the UK, South Asian ethnicity was linked to worse in-hospital outcomes, and patients with an ethnic background linked to status as a new migrant had a greater number of adverse events IS [652, 654].

Risk factors for death during interstage 1

Risk factor	Risk level	Class[a]	Level[b]
Gestational age	Moderate	I	B
Birth weight	Moderate	I	C
Aortic atresia	Moderate	IIa	B
Ascending aorta diameter	Moderate	IIa	C
Restrictive foramen ovale	Severe	I	C
Postoperative arrhythmia	Moderate	IIa	C
MBTS versus RV–PA conduit	Moderate	IIa	B
Tricuspid regurgitation ≥ moderate	Severe	I	B
Impaired right ventricular function	Moderate	IIb	C
Hospital length of stay	Moderate	IIa	C
Number of postoperative complications	Mild	IIa	B
No oral feeds at discharge	Mild	IIb	C
Race	Moderate	IIb	B
Poverty	Moderate	IIb	B
Genetic or extracardiac syndrome	Mild	IIa	C
Interstage 1 weight gain	Moderate	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
MBTS: modified Blalock–Taussig shunt; PA: pulmonary artery; RV: right ventricle.

13.2 Interstage 1 mortality rate in hybrid stage 1 palliation

Use of the h-S1P has been associated with IS-1 mortality rates similar to those of traditional S1P in single-centre reports [655, 656]. Although the hybrid reduces exposure to complications of complex early CPB surgery, especially in low BW and premature newborns, the circulatory arrangement poses specific problems requiring interstage monitoring. These may include the need for reintervention due to retrograde CoA, stent stenosis or r-FO. A single-centre study in which h-S1P was the primary strategy reported a 75% readmission rate during IS-1, with a 7% IS-1 mortality rate. Also, 11/57 required catheter reintervention during IS-1 [656]. A recent meta-analysis comparing hybrid and surgical approaches did not find any important differences in IS-1 mortality rates [617]. In the analysis, the in-hospital mortality rate was higher in the hybrid group, with the survival difference persisting at 6 and 12 months. This survival difference was not influenced by IS-1 events, and hybrid patients did require more IS-1 interventions in this meta-analysis (see also Hybrid section).

13.3 Preparing for interstage 1 care: postoperative phase and discharge preparation

When a patient survives S1P only to die during or after IS-1, it is devastating to families and the care team alike. Therefore, it is critical that patient physiology be optimized and that patients and families be well prepared for discharge. This preparation includes identification of any important residual or recurrent cardiac anatomical issues that may progress during IS-1, optimization of medical therapy and screening for other medical and sociodemographic risk factors. In many centres, the medical team may elect to keep a patient in hospital during IS-1 due to identified risk factors.

13.4 Medications used in interstage 1 care

Optimization of the circulation is advantageous during IS-1 and may include medical management with diuretics, digoxin and ACE inhibitors for heart failure and TR, but the evidence base is limited (Recommendations for medications during IS-1). The use of ACE inhibitors was the focus of the Infants with Single Ventricle (ISV) study from the Paediatric Heart Network [657]. This multicentre RCT of enalapril versus placebo in survivors of S1P found no differences in IS-1 growth, ventricular function or heart failure between groups. The authors concluded there is no evidence for empiric IS-1 use of ACE inhibitors. However, there may be indications for targeted use in scenarios where it is advantageous to lower SVR or prevent ventricular remodelling (e.g. excessive Qp, moderate or greater TR, ventricular dysfunction). A non-randomized study from the NPCQIC and an additional *post hoc* analysis of the public use data set of the SVRT both concluded that administration of digoxin in patients without arrhythmia during IS-1 was associated with a reduction in IS-1 deaths [221, 658]. However, an analysis of the ISV study data set noted only a trend towards increased survival and poorer weight gain with digoxin use [659]. A recent consensus-based review from Germany supported the use of diuretics, ACE inhibitors and in some cases bisoprolol for interstage management of patients with HLHS with a hybrid circulation [220].

Medications during interstage 1

Recommendations	Class[a]	Level[b]
Empiric digoxin is associated with improved interstage 1 survival	IIa	C
Empirically administered enalapril has no clear benefit	IIa	B
Aspirin may be associated with improved survival	IIa	C
Aspirin may be associated with lower incidence of shunt thrombosis	IIa	C

[a]Class of recommendation.
[b]Level of evidence.

13.5 Principles of successful discharge preparation

An organized approach or protocol for discharge preparation has been shown to improve readiness and reduce complications and readmissions in high-risk populations [654, 660–662]. During preparations for discharge after S1P, it is important to consider the patient and family risk profile based on medical risk factors (TR, poor ventricular function, comorbidity, prolonged hospitalization and psycho-social risk factors, poor economic circumstances, familial learning difficulties, language barriers). Prior to discharge it is necessary to supply general information to parents about their child's condition and to meet parental educational requirements. In addition, it is necessary to provide adequate psycho-social support, specialist training and equipment to meet the needs of the child. It is important to share complete and relevant information about the child with involved health professionals outside the tertiary centre, inclusive of guidance on how to handle a deterioration in the child's condition and follow-up arrangements [660]. Resources and checklists to facilitate discharge preparation have been previously published and are available through the NPCQIC website [640, 663].

13.6 Principles and components of interstage 1 home monitoring protocols

The concept of IS-1 home monitoring arose in response to an unacceptably high rate of sudden deaths at home [627]. The principles of IS-1 home monitoring are founded on providing an inexpensive, non-invasive method of detecting early physiological variances in SO_2 and somatic growth, which may precede more severe deterioration. Prior to discharge, caregivers are provided extensive education on warning signs and specific criteria (see Table 9) to alert the IS-1 care team (Table 17). The infrastructure required for implementation and makeup of home monitoring is described extensively elsewhere and may vary among programmes [639, 664–666] (see Hypoplastic left heart syndrome guidelines, Components of IS-1 monitoring programmes). More important than the specific monitoring criteria are the benefits of a standardized programmatic format. The home monitoring programme is, in effect, a medical home-enhancing care coordination and creating a safety net for the patient and family.

Table 17: Sample 'red flag' criteria for interstage 1 home monitoring programmes

Criterion	Frequency	Threshold
SO_2	Daily	<75% or >90%
Weight loss	Daily	Any weight loss
Weight gain	Daily	Failure to gain >20 g/day for 3 days
Enteral intake	Daily	Intake <100 ml/kg/day

SO_2: oxygen saturation.

Concepts common to a successful programme include the following:

1. Engagement of an interdisciplinary team of physician specialists, advanced practice nurses, nutrition specialists, social workers, therapists, patients and families
2. Use of a care bundle or standard IS-1 protocol
3. Emphasis on continuity of care with dedicated IS-1 team members, bridging all phases of care from ICU to home
4. A focus on transparent and free communication among the IS-1 team, the primary care team and the caregivers
5. Empowerment of families and caregivers through education, connection to support groups and advocacy networks and unfettered access to the IS-1 care team for questions and concerns [640, 641, 667, 668].

There is no consensus on ideal frequency of clinic visits, IS-1 monitoring or testing (echocardiography, cardiac catheterization, biomarker evaluation). The intent of these measures is to detect problems before they become critical; however, the ability to do so depends on the nature of the problem. In the case of progressive myocardial dysfunction, worsening TR or diminishing Qp, daily measure of SO_2 or weight may detect early changes

Components of interstage 1 monitoring programmes

Recommendations	Class[a]	Level[b]
Dedicated IS-1 care team	I	B
IS-1 clinic	I	B
Provision of red flag action plan	I	B
Standardized discharge process including family education and rooming in	I	C
Written communication with primary paediatrician and cardiologist	IIa	C
Involvement of registered dietician	IIa	C
Feeding/nutrition protocol including clear daily weight change goals	IIa	B
Use of telehealth visits	IIb	C
Use of tablet or phone app	IIb	C

[a]Class of recommendation.
[b]Level of evidence.
IS-1: interstage 1.

preceding more serious events. However, sudden events such as acute shunt thrombosis or ventricular arrhythmias are unlikely to be prevented by such a strategy. Therefore, IS-1 monitoring in its current form is just one part of a broader strategy to predict and prevent mortality. A criticism of IS-1 home monitoring is the potential burden and cost of interim clinic visits, testing and readmissions based solely on red flags. In an analysis of the NPCQIC data set, Oster found that 47% of home-monitored patients had at least 1 hospital readmission [626]. The longitudinal experience from Milwaukee documented 161 IS-1 events in 96 patients (59% of cohort) [639]. The authors noted that despite the high number of readmissions, no patient was admitted in shock or respiratory failure, validating the objective of early (pre-crisis) identification of problems.

13.7 Monitoring for progression of anatomical lesions and heart failure

Residual anatomical lesions are perhaps the most obvious target for enhanced surveillance and early reintervention during IS-1, because 'technical performance scores' following S1P have been associated with outcome [58] (see Imaging and Postoperative ICU care sections). Reintervention during IS-1 is common, with interventional catheterization procedures undertaken approximately twice as often as surgical procedures [652, 669]. An analysis of the NPCQIC data set found that of 1156 patients discharged home following S1P, 50% required reintervention during the S1P hospitalization or during the IS-1 period [498]. In this cohort, arch interventions were more common in those with an MBTS, whereas PA and shunt interventions were more common in the RV–PA conduit group. Perhaps the most important problem to arise during the IS-1 is recurrent arch obstruction. In the SVR trial, 18% of patients underwent a reintervention for CoA, and 70% of the interventions were catheter based [431]. There remains some controversy in the gold standard screening test to predict significant recurrent arch obstruction and the need for intervention during IS-1 [670, 671]. Upper and lower BP measurements are technically difficult and user-dependent. Palpation of normal pulses may be confounded by a wide pulse pressure associated with shunt physiology. In a study of echocardiographic predictors of catheter intervention during IS, a peak gradient of 26 mmHg had a 100% sensitivity for predicting subsequent arch intervention [671]. This study, like many others, suffers from the fact that the outcome of interest (significant recurrent arch obstruction) is defined by the intervention itself (catheter balloon dilation) rather than a well-defined pathophysiological criterion.

The potential for serum biomarkers of heart failure to be helpful in monitoring IS-1 patients has been assessed in a few single-centre studies as well as in a *post hoc* analysis of the ISV study [670, 672]. In the ISV cohort, type B natriuretic peptide (BNP) levels remained elevated prior to S2P but fell significantly afterwards [673]. Those with higher BNP levels were found by echocardiography to have greater ventricular dilation, a higher degree of TR and impaired growth. Although BNP levels are uniformly high in the early post-S1P period, they undergo a predictable decline in the stable patient during IS-1 as the patient grows and as relative Qp lessens. Therefore, if a patient has an increase in BNP level during this period, it suggests a new, progressive or recurrent problem placing a load on the RV [670]. The main value of these and other biomarkers is the ability to correlate an easily measurable, objective value to an important haemodynamic change during IS-1.

13.8 Role of telehealth and phone apps during interstage 1

Recent innovations in IS care have focused on leveraging technology to improve real-time communication and monitoring during IS. The use of virtual home visits utilizing teleconferencing has been described and is feasible in regions with the infrastructure to support the technology. It is unclear whether this offers an advantage over traditional communication [674, 675]. The use of digital apps, either through tablet computers or cell phones, is a natural evolution from the traditional three-ring binders used for home monitoring communication, education and data collection. Results from a randomized crossover study showed significant advantages to the use of a tablet-based platform compared with handwritten records, with increased sensitivity of red flags through automatic alerts to the care team. Cell phone apps are particularly appealing to a generation of parents who are acclimated to their use throughout their daily lives. Linkage of Blue Tooth enabled scales and pulse oximeters with devices connected in real time to the IS-1 care team through the electronic health record (with the capability to generate auto-alerts) may further improve monitoring sensitivity.

13.9 Patients remaining in the hospital during interstage 1

A significant proportion of patients surviving S1P remain in hospital until S2P due to social or medical barriers to safe and timely hospital discharge. The Milwaukee programme reported that from 2000 to 2010, 15% (29/186) remained in hospital during IS-1 due to haemodynamic instability, labile oxygenation or extracardiac organ dysfunction [639]. These patients represented a sicker cohort than those discharged home, with longer surgical times, more frequent use of ECMO postoperatively (24% vs 5%) and more preoperative risk factors. This group also suffered worse 1-year (75% vs 97%) and 5-year (66% vs 95%) survival rates compared to those discharged following S1P. In the SVRT (2005–2008), 22/549 (4%) remained in-hospital prior to S2P [643]. A US registry study of 5374 infants with HLHS from 2004 to 2013 found that 5.8% of patients remained in-hospital prior to S2P [676]. Interestingly, the percentage remaining in-hospital increased from 3.8% in the early era to 9% in the later era of the study. This difference may be related to the greater number of complex neonates surviving S1P or to trends in management over time to reduce IS-1 mortality rates.

13.10 Impact of interstage 1 variables on timing of stage 2 palliation

Reports suggest that the timing of S2P has become progressively earlier, coincident with increased enrolment in IS-1 home monitoring programmes [652, 676–679]. A recent registry-based study from the UK linked improvement in HLHS outcomes to a reduction in the median age of S2P from 5.7 to 5.1 months, a rise in IS-1 interventions and a reduction in the variability of the age at S2P [652]. This finding is in line with a study from the USA that linked a decrease in IS-1 deaths to the introduction of a

standardized home monitoring programme and an S2P age reduction to 4.1 months [678]. Conversely, those children who remain hospitalized due to ongoing haemodynamic instability and receive S2P at a particularly early age have worse outcomes [679]. A recent study from the Congenital Heart Surgeons' Society critical left ventricular tract outflow obstruction cohort concluded that performing S2P after 3 months of age is optimal for low-to-medium risk infants and further that high-risk infants are less likely to survive an S2P before 3 months of age [63]. In an analysis of the NPCQIC data set comparing care practices from 2008 to 2010 to those from a later era (2014), there was a shift in average age at S2P from 153 (IQR = 59) to 140 (IQR = 43) days [663]. In the later era, more patients were enrolled in home monitoring; the use of the RV–PA conduit was more common; and there were significant reductions in preoperative risk factors such as acidosis and the need for intubation. In a study comparing IS-1 outcomes in NPCQIC centres grouped by timing of S2P, Hill *et al.* [680] found that those who had S2P late had a higher IS-1 mortality rate (10% vs 5.7%). Importantly, in neither study were there meaningful differences in outcome at S2P between groups.

13.11 Role of nutrition and growth in interstage 1 outcomes

Growth and feeding have become intrinsically connected to IS management, because weight gain is both a non-specific marker of cardiovascular health and a modifiable risk factor for surgical outcomes. Children with SV lesions have a high incidence of growth failure, which is most pronounced in the perioperative and IS-1 periods. Contributing factors are multifactorial, and growth velocity is associated with both short- and long-term outcomes [645, 648, 681–683]. However, the goal of normal infant growth patterns can be achieved during IS-1 in a home monitoring programme, with involvement of a registered dietician [647, 677]. Improving IS-1 nutrition and feeding has become 1 of 3 key drivers for the NPCQIC efforts to improve outcomes for S1P.

Prior to the widespread implementation of IS-1 monitoring programmes, growth failure during IS-1 was common and to some degree normalized and accepted. As a result, this population historically experienced significant failure to thrive during a phase when adequate protein and energy balance is critical for normal growth and development. Patients with an ongoing nutritional deficit undergoing S2P had worse surgical outcomes [645]. Multiple studies have demonstrated an acute decline in weight-for-age *z*-scores during the early postoperative phase, with the average score at the time of discharge ranging from -1.4 to -2 [684–686]. In these single-centre studies, lower hospital weight gain was associated with increasing patient complexity and ICU complications, including ICU length of stay, need for postoperative ECMO, longer postoperative ventilation time and greater TR. Hong *et al.* [686] documented a significant drop in weight-for-age *z*-scores during neonatal hospitalization in patients with a median caloric intake in the ICU of 54 kcal/kg/day and a median intake at the time of discharge of 107 kcal/kg/day. The authors concluded that the early postoperative period is marked by suboptimal calorie delivery and that efforts to optimize enteral intake should result in improved growth. Li *et al.* found a high energy deficit in the early postoperative period, using indirect calorimetry . Neonates in this study were hypermetabolic and did not reach a positive energy balance until postoperative day 3 with standard parenteral nutrition regimens. Prolonged time to reach nutritional goals has also been recognized as a problem in the general paediatric ICU population and represents a potential target for process improvement. However, the association of overfeeding and death in critically ill patients highlights the impact of patient condition on outcomes related to feeding and nutrition [687]. It may be counterproductive to focus improvement efforts on weight gain during a period where patients are critically ill and in a catabolic state.

Although in-hospital growth remains suboptimal, IS-1 growth has improved through implementation of home monitoring. Earlier studies commonly documented failure to thrive during IS-1. In a study of 100 patients undergoing S2P, Anderson *et al.* [645] reported a decrease in the median weight-for-age *z*-score from -1.4 to -2 during IS, with an average weight gain of 18 g/day in. Patients with a lower score experienced worse S2P outcomes. In contrast, patients enrolled in monitoring at Children's Hospital of Wisconsin achieved a normal IS-1 growth velocity of 26.8 g per day [647]. On average, these patients required 117 kcal/kg/day to achieve this result. This strategy was associated with 98% IS-1 survival. This finding has been replicated in other centres employing a multidisciplinary team approach with involvement of a nutrition specialist, utilizing protocols targeting normal weight gain and high caloric intake goals [641, 642, 677]. Individual nutrition protocols vary but commonly include daily weight at home combined with weekly calls to allow changes to the feeding plan.

Although there is consensus on the need for increased caloric support for infants in IS-1, the preferred feeding mode varies. In a large multicentre cohort, Hill *et al.* [688] found no difference in growth during IS-1 based on a supplementary tube feeding modality. The authors concluded that different feeding modalities may achieve adequate growth within the context of IS-1 management using standardized calorie and weight goals. Some centres have elected not to discharge patients home with nasoenteral feeding tubes due to concerns for aspiration or tube misplacement. The use of IS-1 nasogastric tube feeding was not associated with increased IS-1 mortality rates in an analysis of the NPCQIC cohort [689]. The authors did see higher IS-1 mortality rates in the group fed via gastrostomy plus fundoplication, which may be a marker for patient complexity. Given the importance of adequate and safe caloric intake, if family home circumstances are challenging, travel times are long or infants are at high medical risk, centres may elect to keep patients requiring supplemental tube feedings in-hospital during the IS period [690].

13.12 Family considerations

Family engagement is pivotal in successful IS-1 management. A priority of home monitoring is to empower caregivers by providing education to understand the disease process and warning signs, to provide immediate access to the IS-1 team when needed and to connect caregivers to the network of families living with SV as added support. Various studies have demonstrated a high level of parental stress in households of children with a SV, especially at the time of initial hospital discharge [691–696]. The home monitoring programme provides a support network for families and can offer resources beyond medical interventions. The involvement of parents in local support groups and national organizations advocating for children and families with CHD may help alleviate family stress and provide a much-needed support structure.

14. CONCLUSION

Opportunities to improve IS-1 outcomes include improved risk stratification, optimized screening for residual haemodynamic lesions and enhanced surveillance through refinement of IS-1 monitoring protocols. Beyond the prevention of death, an important goal of IS-1 care is improved growth, development and quality of life.

15. OUTCOME DATA FROM THE CONGENITAL HEART SURGERY AND THE EUROPEAN CONGENITAL HEART SURGEONS ASSOCIATION DATABASES REGARDING HYPOPLASTIC LEFT HEART SYNDROME

Multi-institutional databases and registries allow benchmarking of an institution's outcome data against national and international multi-institutional data. Benchmarking can facilitate the assessment and improvement of quality in paediatric cardiac surgery [540, 697, 698].

For the purposes of these guidelines, data from the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS CHSD) and the European Congenital Heart Surgeons Association (ECHSA) Congenital Database have been assembled and are presented in Tables 18–23.

The STS CHSD receives data from over 95% of the hospitals in the USA in which paediatric cardiac surgery is performed and is the largest database for paediatric and congenital cardiac operations. STS CHSD captured data for 122 212 cardiac operations and 101 769 index cardiac operations performed from 1 July 2013 to 30 June 2017 [699]. Table 18 documents the number and proportion of operations in the STS CHSD performed for patients with a primary diagnosis of HLHS during this 4-year analytic window. Table 19 documents the number and percentage of operations in the STS CHSD with a primary procedure related to HLHS during the same period.

The ECHSA Congenital Database contains data from multiple countries both within and outside Europe. Table 20 documents the number and proportion of operations performed for patients with a primary diagnosis of HLHS in the entire ECHSA Congenital Database from 1 July 2013 to 30 June 2017. Table 21 shows the number and proportion of operations with a primary procedure related to HLHS during the same 4-year window.

Table 22 shows the number and proportion of operations for patients with a primary diagnosis of HLHS in the ECHSA Congenital Database in an analysis restricted to data from European countries from 1 July 2013 to 30 June 2017. Table 23 documents the number and proportion of operations with a primary procedure related to HLHS in the ECHSA Congenital Database in an analysis restricted to data from European countries from 1 July 2013 to 30 June 2017.

Table 18: STS CHSD: hypoplastic left heart syndrome as primary diagnosis

Primary diagnosis	Number	Proportion of all operations in STS CHSD (%)
Hypoplastic left heart syndrome	7248	5.9
Shone's syndrome	52	0.0

STS CHSD: Society of Thoracic Surgeons Congenital Heart Surgery Database.

Table 20: ECHSA Congenital Database: hypoplastic left heart syndrome as primary diagnosis

Primary diagnosis	Number	Proportion of all operations in the ECHSA CHSD (%)
Hypoplastic left heart syndrome	3419	4.09
Shone's syndrome	172	0.21

CHSD: Congenital Heart Surgery Database; ECHSA: European Congenital Heart Surgeons Association.

Table 19: STS CHSD: hypoplastic left heart syndrome primary procedure

Primary procedure	Number	Proportion of all operations in STS CHSD (%)	Operative mortality rate (%)
Norwood procedure	2795	2.5	14.3
Biventricular repair	77	0.1	9.1
RV–PA conduit + intraventricular tunnel (LV-Ao) + arch reconstruction (Yasui operation)	68	0.1	8.8
h-S1P, b-PAB application	205	0.2	38.5
h-S1P, stent placement in DA	24	0.0	0.0
h-S1P, stent placement in DA + application of b-PAB	318	0.3	18.9
h-S2P, Ao-PA amalgamation + BCPS + PAB removal + Ao arch repair	131	0.1	6.9
h-S2P, Ao-PA amalgamation + BCPS + PAB removal (no Ao arch repair)	10	0.0	0.0

Ao: aortic; b-PAB: bilateral pulmonary artery banding; BCPS: bidirectional cavopulmonary shunt; DA: ductus arteriosus; h-S1P: hybrid stage 1 palliation; h-S2P: hybrid stage 2 palliation; LV: left ventricle; PA: pulmonary artery; RV: right ventricle; STS CHSD: Society of Thoracic Surgeons Congenital Heart Surgery Database.

Table 21: ECHSA Congenital Database: hypoplastic left heart syndrome primary procedure

Primary procedure	Number	Percentage of all operations in ECHSA Congenital Database (%)	Operative mortality rate (%)
Norwood S1P	1041	1.24	22.85
Biventricular repair	73	0.09	12.33
h-S1P, application of b-PAB	106	0.13	10.58
h-S1P, stent placement in DA	7	0.01	0.00
h-S1P, stent placement in DA + application of b-PAB	52	0.06	40.38
h-S2P, Ao-PA amalgamation + BCPS + PAB removal + Ao arch repair	28	0.03	11.11
h-S2P, Ao-PA amalgamation + BCPS + PAB removal (no Ao arch repair)	1	0.00	100.00

Ao: aortic; b-PAB: bilateral pulmonary artery banding; BCPS: bidirectional cavopulmonary shunt; DA: ductus arteriosus; ECHSA: European Congenital Heart Surgeons Association; h-S1P: hybrid stage 1 palliation; h-S2P: hybrid stage 2 palliation; PA: pulmonary artery; S1P: stage 1 palliation.

Table 22: ECHSA Congenital Database (Europe only): hypoplastic left heart syndrome as primary diagnosis

Primary diagnosis	Number	Proportion of all operations in ECHSA Congenital Database (%)
Hypoplastic left heart syndrome	2709	5.72
Shone's syndrome	134	0.28

ECHSA: European Congenital Heart Surgeons Association.

15.1 Other registry outcome data

The National Congenital Heart Disease Audit publishes data for all paediatric centres in the UK. Currently available HLHS data for 2015–2018 include 295 Norwood procedures. The 30-day survival rate for this period is 93.2%, with 100% of cases included in follow-up. Some of these cases are also included in the STS and/or ECHSA databases.

15.2 Nomenclature for use in studies and databases

The International Paediatric and Congenital Cardiac Code (IPCCC) (www.ipccc.net) was produced and has been maintained by the International Society for Nomenclature of Paediatric and Congenital Heart Disease (ISNPCHD) [15, 16, 700, 701]. The IPCCC is widely used for most paediatric and congenital cardiac registries and databases, including the STS CHSD and the ECHSA Congenital Database. ISNPCHD has submitted a hierarchical nomenclature tree for paediatric and congenital cardiac disease to the World Health Organization that will become the paediatric and congenital cardiac component of the International Classification of Diseases 11th Revision [16]. ISNPCHD has provided corresponding definitions for all of the paediatric and congenital cardiac terms in the International Classification of Diseases 11th Revision and also definitions for a variety of related terms [15, 16, 700].

15.3 Summary and recommendations

The IPCCC is a standardized international system of paediatric and congenital cardiac nomenclature that should be used in all registries, databases and research studies in the domain of paediatric and congenital cardiac care, including those related to HLHS. This recommendation is level 1 class C [15, 16, 700].

Multi-institutional databases and registries allow benchmarking of data concerning death, patterns of practice, morbidity and postoperative length of stay [540]. As a level 1 class C recommendation, all paediatric and congenital cardiac teams should routinely assess their own data against national and international benchmarks using multi-institutional databases and registries [540, 697–699, 701].

Analysis of outcome data

Recommendations	Class[a]	Level[b]
The International Paediatric and Congenital Cardiac Code should be used in all registries, databases and research studies in paediatric and congenital cardiac care, including those related to hypoplastic left heart syndrome	I	C
All paediatric and congenital cardiac teams should routinely assess their data against national and international benchmarks using multi-institutional databases and registries	I	C

[a]Class of recommendation.
[b]Level of evidence.

Table 23: ECHSA Congenital Database (Europe only): hypoplastic left heart syndrome

Primary procedure	Number	Proportion of all operations in ECHSA Congenital Database (%)	Operative mortality rate (%)
Norwood procedure	846	1.79	21.02
Biventricular repair	63	0.13	7.94
h-S1P, application of b-PAB	100	0.21	8.16
h-S1P, stent placement in DA	3	0.01	0.00
h-S1P, stent placement in DA + application of b-PAB	27	0.06	14.81
h-S2P, Ao-PA amalgamation + BCPS + PAB removal + Ao arch repair	25	0.05	8.33
h-S2P, Ao-PA amalgamation + BCPS + PAB removal (no Ao arch repair)	0	0.00	0.00

Ao: aortic; b-PAB: bilateral pulmonary artery banding; BCPS: bidirectional cavopulmonary shunt; DA: ductus arteriosus; ECHSA: European Congenital Heart Surgeons Association; h-S1P: hybrid stage 1 palliation; h-S2P: hybrid stage 2 palliation; PA: pulmonary artery.

Conflict of interest: none declared.

REFERENCES

[1] Lev M. Pathologic anatomy and interrelationship of hypoplasia of the aortic tract complexes. Lab Invest 1952;1:61–70.

[2] Noonan JA, Nadas AS. The hypoplastic left heart syndrome; an analysis of 101 cases. Pediatr Clin North Am 1958;5:1029–56.

[3] Talner CN. Report of the New England Regional Infant Cardiac Program, by Donald C. Fyler, MD, Pediatrics, 1980; 65(suppl):375–461. Pediatrics 1998;102:258–9.

[4] Barber G. Hypoplastic left heart syndrome. In: Garson A, Bricker JT, Fisher DJ, Neish SR (eds). The Science and Practice of Pediatric Cardiology, 2nd edn. Baltimore: Williams and Wilkins, 1998, 1316–33.

[5] Šamánek M, Slavík Z, Zbořilová B, Hroboňová V, Voříšková M, Škovránek J. Prevalence, treatment, and outcome of heart disease in live-born children: a prospective analysis of 91,823 live-born children. Pediatr Cardiol 1989;10:205–11.

[6] Morris CD, Outcalt J, Menashe VD. Hypoplastic left heart syndrome: natural history in a geographically defined population. Pediatrics 1990; 85:977–83.

[7] Ferencz C, Rubin JD, Mccarter RJ, Brenner JI, Neill CA, Perry LW *et al.* Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. Am J Epidemiol 1985;121:31–6.

[8] Schwedler G, Lindinger A, Lange PE, Sax U, Olchvary J, Peters B *et al.* Frequency and spectrum of congenital heart defects among live births in Germany: a study of the Competence Network for Congenital Heart Defects. Clin Res Cardiol 2011;100:1111–17.

[9] Birth Statistics Canada: Published by the Authority of the Minister responsible for Statistics Canada. Minister of Industry. Ottawa: Statistics Canada, 1999. Annual Number of Births, in Canada, Provinces, and Territories for the Year Ending June 30 (1997–1998).

[10] Vital Statistics: US Birth Rates. National Center for Health Statistics. United States Department of Health and Human Services. Annual Report for the Year 1997. In: Farrugetti R (ed.). The World Almanac and Book of Facts. Mahwah: PRIMEDIA Reference Inc., 1999, 1998.

[11] Razzouk AJ, Chinnock RE, Gundry SR, Johnston JK, Larsen RL, Baum MF *et al.* Transplantation as a primary treatment for hypoplastic left heart syndrome: intermediate-term results. Ann Thorac Surg 1996;62:1–7; discussion 8.

[12] Caplan WD, Cooper TR, Garcia-Prats JA, Brody BA. Diffusion of innovative approaches to managing hypoplastic left heart syndrome. Arch Pediatr Adolesc Med 1996;150:487–90.

[13] Gillum RF. Epidemiology of congenital heart disease in the United States. Am Heart J 1994;127:919–27.

[14] Sousa-Uva M, Head SJ, Thielmann M, Cardillo G, Benedetto U, Czerny M *et al.* Methodology manual for European Association for Cardio-Thoracic Surgery (EACTS) clinical guidelines. Eur J Cardiothorac Surg 2015;48:809–16.

[15] Tchervenkov CI, Jacobs JP, Weinberg PM, Aiello VD, Béland MJ, Colan SD *et al.* The nomenclature, definition and classification of hypoplastic left heart syndrome. Cardiol Young 2006;16:339–68.

[16] Franklin RCG, Béland MJ, Colan SD, Walters HL, Aiello VD, Anderson RH *et al.* Nomenclature for congenital and paediatric cardiac disease: the International Paediatric and Congenital Cardiac Code (IPCCC) and the Eleventh Iteration of the International Classification of Diseases (ICD-11). Cardiol Young 2017;27:1872–938.

[17] Guidelines for the management of congenital heart diseases in childhood and adolescence. Cardiol Young 2017;27:S1–105.

[18] Barron DJ, Kilby MD, Davies B, Wright JGC, Jones TJ, Brawn WJ. Hypoplastic left heart syndrome. Lancet 2009;374:551–64.

[19] Roeleveld PP, Axelrod DM, Klugman D, Jones MB, Chanani NK, Rossano JW *et al.* Hypoplastic left heart syndrome: from fetus to Fontan. Cardiol Young 2018;28:1275–88.

[20] Crucean A, Alqahtani A, Barron DJ, Brawn WJ, Richardson RV, O'Sullivan J *et al.* Re-evaluation of hypoplastic left heart syndrome from a developmental and morphological perspective. Orphanet J Rare Dis 2017; 12:138.

[21] Kearney DL. The pathological spectrum of left-ventricular hypoplasia. Semin Cardiothorac Vasc Anesth 2013;17:105–16.

[22] Rychik J, Rome JJ, Collins MH, DeCampli WM, Spray TL. The hypoplastic left heart syndrome with intact atrial septum: atrial morphology, pulmonary vascular histopathology and outcome. J Am Coll Cardiol 1999; 34:554–60.

[23] Vogel M, McElhinney DB, Wilkins-Haug LE, Marshall AC, Benson CB, Juraszek AL *et al.* Aortic stenosis and severe mitral regurgitation in the fetus resulting in giant left atrium and hydrops: pathophysiology, outcomes, and preliminary experience with pre-natal cardiac intervention. J Am Coll Cardiol 2011;57:348–55.

[24] van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM *et al.* Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:2241–7.

[25] Egbe A, Uppu S, Lee S, Stroustrup A, Ho D, Srivastava S. Temporal variation of birth prevalence of congenital heart disease in the United States. Congenit Heart Dis 2015;10:43–50.

[26] Hawkins JA, Doty DB. Aortic atresia: morphologic characteristics affecting survival and operative palliation. J Thorac Cardiovasc Surg 1984; 88:620–6.

[27] Bove EL, Lloyd TR. Staged reconstruction for hypoplastic left heart syndrome. Contemporary results. Ann Surg 1996;224:387–94; discussion 394–5.

[28] Yagi H, Liu X, Gabriel GC, Wu Y, Peterson K, Murray SA *et al.* The genetic landscape of hypoplastic left heart syndrome. Pediatr Cardiol 2018; 39:1069–81.

[29] Perry DJ, Mullen CR, Carvajal HG, Brar AK, Eghtesady P. Familial screening for left-sided congenital heart disease: what is the evidence? What is the cost? Diseases 2017;5:29.

[30] Zakaria D, Tang X, Bhakta R, ElHassan NO, Prodhan P. Chromosomal abnormalities affect the surgical outcome in infants with hypoplastic left heart syndrome: a large cohort analysis. Pediatr Cardiol 2018;39:11–18.

[31] Cole CR, Eghtesady P. The myocardial and coronary histopathology and pathogenesis of hypoplastic left heart syndrome. Cardiol Young 2016; 26:19–29.

[32] Salih C, Sheppard MN, Ho SY. Morphometry of coronary capillaries in hypoplastic left heart syndrome. Ann Thorac Surg 2004;77:903–7; discussion 907.

[33] Saul D, Degenhardt K, Iyoob SD, Surrey LF, Johnson AM, Johnson MP *et al.* Hypoplastic left heart syndrome and the nutmeg lung pattern in utero: a cause and effect relationship or prognostic indicator? Pediatr Radiol 2016;46:483–9.
[34] Atz AM, Travison TG, Williams IA, Pearson GD, Laussen PC, Mahle WT *et al.* Prenatal diagnosis and risk factors for preoperative death in neonates with single right ventricle and systemic outflow obstruction: screening data from the Pediatric Heart Network Single Ventricle Reconstruction trial. J Thorac Cardiovasc Surg 2010;140:1245–50.
[35] Tweddell JS, Sleeper LA, Ohye RG, Williams IA, Mahony L, Pizarro C *et al.* Intermediate-term mortality and cardiac transplantation in infants with single-ventricle lesions: risk factors and their interaction with shunt type. J Thorac Cardiovasc Surg 2012;144:152–9.
[36] Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK *et al.* Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010;23:465–95; quiz 576–7.
[37] Bellsham-Revell H, Masani N. Educational series in congenital heart disease: the sequential segmental approach to assessment. Echo Res Pract 2019;6:R1–8.
[38] Hosein RBM, Clarke AJB, McGuirk SP, Griselli M, Stumper O, De Giovanni JV *et al.* Factors influencing early and late outcome following the Fontan procedure in the current era. The "Two Commandments"? Eur J Cardiothorac Surg 2007;31:344–52; discussion 353.
[39] Jonas RA, Hansen DD, Cook N, Wessel D. Anatomic subtype and survival after reconstructive operation for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 1994;107:1121–7; discussion 1127–8.
[40] Vida VL, Bacha EA, Larrazabal A, Gauvreau K, Dorfman AL, Marx G *et al.* Surgical outcome for patients with the mitral stenosis-aortic atresia variant of hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2008; 135:339–46.
[41] Lloyd TR, Evans TC, Marvin WJ Jr. Morphologic determinants of coronary blood flow in the hypoplastic left heart syndrome. Am Heart J 1986;112:666–71.
[42] Matsushima S, Oshima Y, Matsuhisa H. Aortic arch reconstruction using a Kommerell diverticulum for hypoplastic left heart syndrome with a right aortic arch. J Thorac Cardiovasc Surg 2016;152:e35–7.
[43] Ishino K, Stümper O, De Giovanni JJ, Silove ED, Wright JG, Sethia B *et al.* The modified Norwood procedure for hypoplastic left heart syndrome: early to intermediate results of 120 patients with particular reference to aortic arch repair. J Thorac Cardiovasc Surg 1999;117:920–30.
[44] Furck AK, Uebing A, Hansen JH, Scheewe J, Jung O, Fischer G *et al.* Outcome of the Norwood operation in patients with hypoplastic left heart syndrome: a 12-year single-center survey. J Thorac Cardiovasc Surg 2010;139:359–65.
[45] Grosse-Wortmann L, Yun TJ, Al-Radi O, Kim S, Nii M, Lee KJ *et al.* Borderline hypoplasia of the left ventricle in neonates: insights for decision-making from functional assessment with magnetic resonance imaging. J Thorac Cardiovasc Surg 2008;136:1429–36.
[46] Tuo G, Khambadkone S, Tann O, Kostolny M, Derrick G, Tsang V *et al.* Obstructive left heart disease in neonates with a "borderline" left ventricle: diagnostic challenges to choosing the best outcome. Pediatr Cardiol 2013;34:1567–76.
[47] Rhodes LA, Colan SD, Perry SB, Jonas RA, Sanders SP. Predictors of survival in neonates with critical aortic stenosis. Circulation 1991; 84:2325–35.
[48] Lofland GK, McCrindle BW, Williams WG, Blackstone EH, Tchervenkov CI, Sittiwangkul R *et al.* Critical aortic stenosis in the neonate: a multi-institutional study of management, outcomes, and risk factors. Congenital Heart Surgeons Society. J Thorac Cardiovasc Surg 2001; 121:10–27.
[49] Hickey EJ, Caldarone CA, Blackstone EH, Lofland GK, Yeh T, Pizarro C *et al.* Critical left ventricular outflow tract obstruction: the disproportionate impact of biventricular repair in borderline cases. J Thorac Cardiovasc Surg 2007;134:1429–36; discussion 1436–7.
[50] Overman DM, Baffa JM, Cohen MS, Mertens L, Gremmels DB, Jegatheeswaran A *et al.* Unbalanced atrioventricular septal defect: definition and decision-making. World J Pediatr Congenit Heart Surg 2010;1:91–6.
[51] Jegatheeswaran A, Pizarro C, Caldarone CA, Cohen MS, Baffa JM, Gremmels DB *et al.* Echocardiographic definition and surgical decision-making in unbalanced atrioventricular septal defect: a Congenital Heart Surgeons' Society multiinstitutional study. Circulation 2010; 122:S209–15.
[52] Cohen MS, Jegatheeswaran A, Baffa JM, Gremmels DB, Overman DM, Caldarone CA *et al.* Echocardiographic features defining right dominant unbalanced atrioventricular septal defect: a multi-institutional Congenital Heart Surgeons' Society study. Circ Cardiovasc Imaging 2013;6:508–13.
[53] Hascoët S, Peyre M, Hadeed K, Alacoque X, Chausseray G, Fesseau R *et al.* Safety and efficiency of the new micro-multiplane transoesophageal probe in paediatric cardiology. Arch Cardiovasc Dis 2014; 107:361–70.
[54] Pushparajah K, Miller OI, Rawlins D, Barlow A, Nugent K, Simpson JM. Clinical application of a micro multiplane transoesophageal probe in congenital cardiac disease. Cardiol Young 2012;22:170–7.
[55] Costa P, Moura C, Areias JC, Sousa AR. Intraoperative transesophageal echocardiogram using an intracardiac ultrasound catheter in a congenital heart surgery: a case report. Pediatr Cardiol 2013;34: 1911–13.
[56] DeGroff CG. Transesophageal echocardiography in critically ill acute postoperative infants: comparison of AcuNav intracardiac echocardiographic and microTEE miniaturized transducers. J Am Soc Echocardiogr 2013;26:103.
[57] Mertens LL, Friedberg MK. Imaging the right ventricle—current state of the art. Nat Rev Cardiol 2010;7:551–63.
[58] Nathan M, Sleeper LA, Ohye RG, Frommelt PC, Caldarone CA, Tweddell JS *et al.* Technical performance score is associated with outcomes after the Norwood procedure. J Thorac Cardiovasc Surg 2014;148:2208–13, 2214.e1–6.
[59] Karamlou T. Utility of the technical performance score for the Norwood operation … every score should know its limitations. J Thorac Cardiovasc Surg 2014;148:2214–15.
[60] Hussain T, Lossnitzer D, Bellsham-Revell H, Valverde I, Beerbaum P, Razavi R *et al.* Three-dimensional dual-phase whole-heart MR imaging: clinical implications for congenital heart disease. Radiology 2012; 263:547–54.
[61] Muthurangu V, Taylor AM, Hegde SR, Johnson R, Tulloh R, Simpson JM *et al.* Cardiac magnetic resonance imaging after stage I Norwood operation for hypoplastic left heart syndrome. Circulation 2005;112:3256–63.
[62] Brown DW, Gauvreau K, Powell AJ, Lang P, Colan SD, Del Nido PJ *et al.* Cardiac magnetic resonance versus routine cardiac catheterization before bidirectional Glenn anastomosis in infants with functional single ventricle: a prospective randomized trial. Circulation 2007;116:2718–25.
[63] Meza JM, Hickey EJ, Blackstone EH, Jaquiss RDB, Anderson BR, Williams WG *et al.* The optimal timing of stage 2 palliation for hypoplastic left heart syndrome: an analysis of the pediatric heart network Single Ventricle Reconstruction trial public data set. Circulation 2017;136:1737–48.
[64] Wong J, Lamata P, Rathod RH, Bertaud S, Dedieu N, Bellsham-Revell H *et al.* Right ventricular morphology and function following stage I palliation with a modified Blalock-Taussig shunt versus a right ventricle-to-pCO2 conduit. Eur J Cardiothorac Surg 2017;51:50–7.
[65] Eckhauser A, Pasquali SK, Ravishankar C, Lambert LM, Newburger JW, Atz AM *et al.* Variation in care for infants undergoing the Stage II palliation for hypoplastic left heart syndrome. Cardiol Young 2018; 28:1109–15.
[66] Krupickova S, Vazquez-Garcia L, Obeidat M, Banya W, DiSalvo G, Ghez O *et al.* Accuracy of computed tomography in detection of great vessel stenosis or hypoplasia before superior bidirectional cavopulmonary connection: comparison with cardiac catheterization and surgical findings. Arch Cardiovasc Dis 2019;112:12–21.
[67] Jones BO, Ditchfield MR, Cahoon GD, Hardy P, d'Udekem Y, Brizard CP *et al.* Cardiac magnetic resonance imaging prior to bidirectional cavopulmonary connection in hypoplastic left heart syndrome. Heart Lung Circ 2010;19:535–40.
[68] Chaosuwannakit N, Makarawate P. Diagnostic accuracy of low-dose dual-source cardiac computed tomography as compared to surgery in univentricular heart patients. J Cardiothorac Surg 2018;13:39.
[69] Goo HW. Serial changes in anatomy and ventricular function on dual-source cardiac computed tomography after the Norwood procedure for hypoplastic left heart syndrome. Pediatr Radiol 2017;47:1776–86.
[70] Khoo NS, Smallhorn JF, Kaneko S, Myers K, Kutty S, Tham EB. Novel insights into RV adaptation and function in hypoplastic left heart syndrome between the first 2 stages of surgical palliation. JACC Cardiovasc Imaging 2011;4:128–37.
[71] Bellsham-Revell HR, Tibby SM, Bell AJ, Witter T, Simpson J, Beerbaum P *et al.* Serial magnetic resonance imaging in hypoplastic left heart syndrome gives valuable insight into ventricular and vascular adaptation. J Am Coll Cardiol 2013;61:561–70.

[72] Gewillig M, Brown SC, Heying R, Eyskens B, Ganame J, Boshoff DE *et al.* Volume load paradox while preparing for the Fontan: not too much for the ventricle, not too little for the lungs. Interact CardioVasc Thorac Surg 2010;10:262–5.
[73] Lu X, Nadvoretskiy V, Bu L, Stolpen A, Ayres N, Pignatelli RH *et al.* Accuracy and reproducibility of real-time three-dimensional echocardiography for assessment of right ventricular volumes and ejection fraction in children. J Am Soc Echocardiogr 2008;21:84–9.
[74] Leibundgut G, Rohner A, Grize L, Bernheim A, Kessel-Schaefer A, Bremerich J *et al.* Dynamic assessment of right ventricular volumes and function by real-time three-dimensional echocardiography: a comparison study with magnetic resonance imaging in 100 adult patients. J Am Soc Echocardiogr 2010;23:116–26.
[75] Bell A, Rawlins D, Bellsham-Revell H, Miller O, Razavi R, Simpson J. Assessment of right ventricular volumes in hypoplastic left heart syndrome by real-time three-dimensional echocardiography: comparison with cardiac magnetic resonance imaging. Eur Heart J Cardiovasc Imaging 2014;15:257–66.
[76] Altmann K, Printz BF, Solowiejczyk DE, Gersony WM, Quaegebeur J, Apfel HD. Two-dimensional echocardiographic assessment of right ventricular function as a predictor of outcome in hypoplastic left heart syndrome. Am J Cardiol 2000;86:964–8.
[77] Kulkarni A, Neugebauer R, Lo Y, Gao Q, Lamour JM, Weinstein S *et al.* Outcomes and risk factors for listing for heart transplantation after the Norwood procedure: an analysis of the Single Ventricle Reconstruction trial. J Heart Lung Transplant 2016;35:306–11.
[78] Bellsham-Revell HR, Simpson JM, Miller OI, Bell AJ. Subjective evaluation of right ventricular systolic function in hypoplastic left heart syndrome: how accurate is it? J Am Soc Echocardiogr 2013;26:52–6.
[79] Zaidi SJ, Penk J, Cui VW, Kanjanauthai S, Roberson DA. Right Ventricular Systolic Function Parameters in Hypoplastic Left Heart Syndrome. Pediatr Cardiol 2018;39:1423–32.
[80] Forsha D, Li L, Joseph N, Kutty S, Friedberg MK. Association of left ventricular size with regional right ventricular mechanics in hypoplastic left heart syndrome. Int J Cardiol 2020;298:66–71.
[81] Rösner A, Bharucha T, James A, Mertens L, Friedberg MK. Impact of right ventricular geometry and left ventricular hypertrophy on right ventricular mechanics and clinical outcomes in hypoplastic left heart syndrome. J Am Soc Echocardiogr 2019;32:1350–8.
[82] Colquitt JL, Loar RW, Morris SA, Feagin DK, Sami S, Pignatelli RH. Serial strain analysis identifies hypoplastic left heart syndrome infants at risk for cardiac morbidity and mortality: a pilot study. J Am Soc Echocardiogr 2019;32:643–50.
[83] Friedberg MK, Dragulescu A. Serial assessment of right ventricular strain in hypoplastic left heart syndrome: deformation imaging in deformed hearts. J Am Soc Echocardiogr 2019;32:651–4.
[84] Lin LQ, Conway J, Alvarez S, Goot B, Serrano-Lomelin J, Colen T *et al.* Reduced right ventricular fractional area change, strain, and strain rate before bidirectional cavopulmonary anastomosis is associated with medium-term mortality for children with hypoplastic left heart syndrome. J Am Soc Echocardiogr 2018;31:831–42.
[85] Zaidi SJ, Penk J, Cui VW, Roberson DA. Right ventricular mechanical dyssynchrony in hypoplastic left heart syndrome: correlation with systolic function and QRS duration. Pediatr Cardiol 2019;40:934–42.
[86] Petko C, Möller P, Hoffmann U, Kramer H-H, Uebing A. Comprehensive evaluation of right ventricular function in children with different anatomical subtypes of hypoplastic left heart syndrome after Fontan surgery. Int J Cardiol 2011;150:45–9.
[87] Goldberg DJ, French B, Szwast AL, McBride MG, Paridon SM, Rychik J *et al.* Tricuspid annular plane systolic excursion correlates with exercise capacity in a cohort of patients with hypoplastic left heart syndrome after Fontan operation. Echocardiography 2016;33:1897–902.
[88] Ruotsalainen HK, Bellsham-Revell HR, Bell AJ, Pihkala JI, Ojala TH, Simpson JM. Right ventricular systolic function in hypoplastic left heart syndrome: a comparison of manual and automated software to measure fractional area change. Echocardiography 2017;34:587–93.
[89] Ruotsalainen H, Bellsham-Revell H, Bell A, Pihkala J, Ojala T, Simpson J. Right ventricular systolic function in hypoplastic left heart syndrome: a comparison of velocity vector imaging and magnetic resonance imaging. Eur Heart J Cardiovasc Imaging 2016;17:687–92.
[90] Michelfelder EC, Vermilion RP, Ludomirsky A, Beekman RH, Lloyd TR. Comparison of simultaneous Doppler- and catheter-derived right ventricular dP/dt in hypoplastic left heart syndrome. Am J Cardiol 1996; 77:212–14.
[91] Christensen D, Cardis B, Mahle W, Lewis R, Huckaby J, Favaloro-Sabatier J *et al.* Pre- and postoperative quantitation of right ventricular tissue Doppler velocities in infants with hypoplastic left heart syndrome. Echocardiography 2006;23:303–7.
[92] Bellsham-Revell HR, Tibby SM, Bell AJ, Miller OI, Razavi R, Greil GF *et al.* Tissue Doppler time intervals and derived indices in hypoplastic left heart syndrome. Eur Heart J Cardiovasc Imaging 2012;13:400–7.
[93] Wisler J, Khoury PR, Kimball TR. The effect of left ventricular size on right ventricular hemodynamics in pediatric survivors with hypoplastic left heartsyndrome. J Am Soc Echocardiogr 2008;21:464–9.
[94] Williams RV, Ritter S, Tani LY, Pagotto LT, Minich LL. Quantitative assessment of ventricular function in children with single ventricles using the Doppler myocardial performance index. Am J Cardiol 2000;86:1106–10.
[95] Mahle WT, Coon PD, Wernovsky G, Rychik J. Quantitative echocardiographic assessment of the performance of the functionally single right ventricle after the Fontan operation. Cardiol Young 2001;11:399–406.
[96] Friedberg MK, Silverman NH. The systolic to diastolic duration ratio in children with hypoplastic left heart syndrome: a novel Doppler index of right ventricular function. J Am Soc Echocardiogr 2007;20:749–55.
[97] Kutty S, Graney BA, Khoo NS, Li L, Polak A, Gribben P *et al.* Serial assessment of right ventricular volume and function in surgically palliated hypoplastic left heart syndrome using real-time transthoracic three-dimensional echocardiography. J Am Soc Echocardiogr 2012;25:682–9.
[98] Friedberg MK, Silverman NH, Dubin AM, Rosenthal DN. Right ventricular mechanical dyssynchrony in children with hypoplastic left heart syndrome. J Am Soc Echocardiogr 2007;20:1073–9.
[99] Petko C, Hoffmann U, Möller P, Scheewe J, Kramer H-H, Uebing A. Assessment of ventricular function and dyssynchrony before and after stage 2 palliation of hypoplastic left heart syndrome using two-dimensional speckle tracking. Pediatr Cardiol 2010;31:1037–42.
[100] Hill GD, Frommelt PC, Stelter J, Campbell MJ, Cohen MS, Kharouf R *et al.* Impact of initial Norwood shunt type on right ventricular deformation: the Single Ventricle Reconstruction trial. J Am Soc Echocardiogr 2015;28:517–21.
[101] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321–60.
[102] Margossian R, Sleeper LA, Pearson GD, Barker PC, Mertens L, Quartermain MD *et al.* Assessment of diastolic function in single-ventricle patients after the Fontan procedure. J Am Soc Echocardiogr 2016; 29:1066–73.
[103] Stamm C, Anderson RH, Ho SY. The morphologically tricuspid valve in hypoplastic left heart syndrome. Eur J Cardiothorac Surg 1997; 12:587–92.
[104] Bharucha T, Honjo O, Seller N, Atlin C, Redington A, Caldarone CA *et al.* Mechanisms of tricuspid valve regurgitation in hypoplastic left heart syndrome: a case-matched echocardiographic-surgical comparison study. Eur Heart J Cardiovasc Imaging 2013;14:135–41.
[105] Mart CR, Eckhauser AW, Murri M, Su JT. A systematic method for using 3D echocardiography to evaluate tricuspid valve insufficiency in hypoplastic left heart syndrome. Ann Pediatr Card 2014;7:193–200.
[106] Kutty S, Colen T, Thompson RB, Tham E, Li L, Vijarnsorn C *et al.* Tricuspid regurgitation in hypoplastic left heart syndrome: mechanistic insights from 3-dimensional echocardiography and relationship with outcomes. Circ Cardiovasc Imaging 2014;7:765–72.
[107] Colen T, Kutty S, Thompson RB, Tham E, Mackie AS, Li L *et al.* Tricuspid valve adaptation during the first interstage period in hypoplastic left heart syndrome. J Am Soc Echocardiogr 2018;31:624–33.
[108] Bharucha T, Khan R, Mertens L, Friedberg MK. Right ventricular mechanical dyssynchrony and asymmetric contraction in hypoplastic heart syndrome are associated with tricuspid regurgitation. J Am Soc Echocardiogr 2013;26:1214–20.
[109] van Velzen CL, Clur SA, Rijlaarsdam MEB, Pajkrt E, Bax CJ, Hruda J *et al.* Prenatal diagnosis of congenital heart defects: accuracy and discrepancies in a multicenter cohort. Ultrasound Obstet Gynecol 2016; 47:616–22.
[110] Marek J, Tomek V, Skovránek J, Povysilová V, Samánek M. Prenatal ultrasound screening of congenital heart disease in an unselected national population: a 21-year experience. Heart 2011;97:124–30.
[111] Quartermain MD, Pasquali SK, Hill KD, Goldberg DJ, Huhta JC, Jacobs JP *et al.* Variation in prenatal diagnosis of congenital heart disease in infants. Pediatrics 2015;136:e378–85.

[112] Quartermain MD, Hill KD, Goldberg DJ, Jacobs JP, Jacobs ML, Pasquali SK *et al.* Prenatal diagnosis influences preoperative status in neonates with congenital heart disease: an analysis of the society of thoracic surgeons congenital heart surgery database. Pediatr Cardiol 2019; 40:489–96.
[113] Sivarajan V, Penny DJ, Filan P, Brizard C, Shekerdemian LS. Impact of antenatal diagnosis of hypoplastic left heart syndrome on the clinical presentation and surgical outcomes: the Australian experience. J Paediatr Child Health 2009;45:112–17.
[114] Markkanen HK, Pihkala JI, Salminen JT, Saarinen MM, Hornberger LK, Ojala TH. Prenatal diagnosis improves the postnatal cardiac function in a population-based cohort of infants with hypoplastic left heart syndrome. J Am Soc Echocardiogr 2013;26:1073–9.
[115] Weber RW, Stiasny B, Ruecker B, Fasnacht M, Cavigelli-Brunner A, Valsangiacomo Buechel ER. Prenatal diagnosis of single ventricle physiology impacts on cardiac morbidity and mortality. Pediatr Cardiol 2019; 40:61–70.
[116] Holland BJ, Myers JA, Woods CR. Prenatal diagnosis of critical congenital heart disease reduces risk of death from cardiovascular compromise prior to planned neonatal cardiac surgery: a meta-analysis. Ultrasound Obstet Gynecol 2015;45:631–8.
[117] Thakur V, Dutil N, Schwartz SM, Jaeggi E. Impact of prenatal diagnosis on the management and early outcome of critical duct-dependent cardiac lesions. Cardiol Young 2018;28:548–53.
[118] Wernovsky G, Licht DJ. Neurodevelopmental outcomes in children with congenital heart disease-what can we impact? Pediatr Crit Care Med 2016;17:S232–42.
[119] Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL *et al.* Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. Circulation 2010; 121:26–33.
[120] Peyvandi S, De Santiago V, Chakkarapani E, Chau V, Campbell A, Poskitt KJ *et al.* Association of prenatal diagnosis of critical congenital heart disease with postnatal brain development and the risk of brain injury. JAMA Pediatr 2016;170:e154450.
[121] McBrien A, Hornberger LK. Early fetal echocardiography. Birth Defects Res 2019;111:370–9.
[122] De Robertis V, Rembouskos G, Fanelli T, Volpe G, Muto B, Volpe P. The three-vessel and trachea view (3VTV) in the first trimester of pregnancy: an additional tool in screening for congenital heart defects (CHD) in an unselected population. Prenat Diagn 2017;37:693–8.
[123] Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A *et al.*; American Heart Association Adults with Congenital Heart Disease Joint Committee of the Council on Cardiovascular Disease in the Young and Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Council on Cardiovascular and Stroke Nursing. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation 2014;129:2183–242.
[124] International Society of Ultrasound in Obstetrics and Gynecology, Carvalho JS, Allan LD, Chaoui R, Copel JA, DeVore GR *et al.* ISUOG practice guidelines (updated): sonographic screening examination of the fetal heart. Ultrasound Obstet Gynecol 2013;41:348–59.
[125] American Institute of Ultrasound in Medicine. AIUM practice guideline for the performance of fetal echocardiography. J Ultrasound Med 2013; 32:1067–82.
[126] Alsoufi B, Mori M, Gillespie S, Schlosser B, Slesnick T, Kogon B *et al.* Impact of patient characteristics and anatomy on results of Norwood operation for hypoplastic left heart syndrome. Ann Thorac Surg 2015; 100:591–8.
[127] Gaynor JW, Wernovsky G, Jarvik GP, Bernbaum J, Gerdes M, Zackai E *et al.* Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. J Thorac Cardiovasc Surg 2007;133:1344–53, 1353.e1–3.
[128] Alsaied T, Tseng S, King E, Hahn E, Divanovic A, Habli M *et al.* Effect of fetal hemodynamics on growth in fetuses with single ventricle or transposition of the great arteries. Ultrasound Obstet Gynecol 2018; 52:479–87.
[129] Kinnear C, Haranal M, Shannon P, Jaeggi E, Chitayat D, Mital S. Abnormal fetal cerebral and vascular development in hypoplastic left heart syndrome. Prenat Diagn 2019;39:38–44.
[130] Liu MY, Zielonka B, Snarr BS, Zhang X, Gaynor JW, Rychik J. Longitudinal assessment of outcome from prenatal diagnosis through Fontan operation for over 500 fetuses with single ventricle-type congenital heart disease: the Philadelphia Fetus-to-Fontan Cohort Study. J Am Heart Assoc 2018;7:e009145.
[131] Beroukhim RS, Gauvreau K, Benavidez OJ, Baird CW, LaFranchi T, Tworetzky W. Perinatal outcome after prenatal diagnosis of single-ventricle cardiac defects. Ultrasound Obstet Gynecol 2015;45:657–63.
[132] Rychik J, Szwast A, Natarajan S, Quartermain M, Donaghue DD, Combs J *et al.* Perinatal and early surgical outcome for the fetus with hypoplastic left heart syndrome: a 5-year single institutional experience. Ultrasound Obstet Gynecol 2010;36:465–70.
[133] Hellmund A, Berg C, Herberg U, Geipel A, Kempe A, Gembruch U. Levoatrial cardinal vein in a series of five prenatal cases with hypoplastic left heart syndrome and intact atrial septum. Ultraschall in Med 2017; 38:206–11.
[134] Morris SA, Ethen MK, Penny DJ, Canfield MA, Minard CG, Fixler DE *et al.* Prenatal diagnosis, birth location, surgical center, and neonatal mortality in infants with hypoplastic left heart syndrome. Circulation 2014;129:285–92.
[135] Peterson AL, Quartermain MD, Ades A, Khalek N, Johnson MP, Rychik J. Impact of mode of delivery on markers of perinatal hemodynamics in infants with hypoplastic left heart syndrome. J Pediatr 2011;159:64–9.
[136] Miller TA, Ghanayem NS, Newburger JW, McCrindle BW, Hu C, DeWitt AG *et al.*; for the Pediatric Heart Network Investigators. Gestational age, birth weight, and outcomes six years after the Norwood procedure. Pediatrics 2019;143:e20182577.
[137] Costello JM, Pasquali SK, Jacobs JP, He X, Hill KD, Cooper DS *et al.* Gestational age at birth and outcomes after neonatal cardiac surgery: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. Circulation 2014;129:2511–17.
[138] Herberg U, Berg C, Geipel A, Gembruch U, Breuer J. Foetal therapy: what works? Closed interatrial septum. Cardiol Young 2014;24:47–54.
[139] Arai S, Fujii Y, Kotani Y, Kuroko Y, Kasahara S, Sano S. Surgical outcome of hypoplastic left heart syndrome with intact atrial septum. Asian Cardiovasc Thorac Ann 2015;23:1034–8.
[140] Sathanandam SK, Philip R, Gamboa D, Van Bergen A, Ilbawi MN, Knott-Craig C *et al.* Management of hypoplastic left heart syndrome with intact atrial septum: a two-centre experience. Cardiol Young 2016; 26:1072–81.
[141] Vida VL, Bacha EA, Larrazabal A, Gauvreau K, Thiagaragan R, Fynn-Thompson F *et al.* Hypoplastic left heart syndrome with intact or highly restrictive atrial septum: surgical experience from a single center. Ann Thorac Surg 2007;84:581–5; discussion 586.
[142] Vlahos AP, Lock JE, McElhinney DB, van der Velde ME. Hypoplastic left heart syndrome with intact or highly restrictive atrial septum: outcome after neonatal transcatheter atrial septostomy. Circulation 2004; 109:2326–30.
[143] Jantzen DW, Moon-Grady AJ, Morris SA, Armstrong AK, Berg C, Dangel J *et al.* Hypoplastic left heart syndrome with intact or restrictive atrial septum: a report from the International Fetal Cardiac Intervention Registry. Circulation 2017;136:1346–9.
[144] Gellis L, Drogosz M, Lu M, Sleeper LA, Cheng H, Allan C *et al.* Echocardiographic predictors of neonatal illness severity in fetuses with critical left heart obstruction with intact or restrictive atrial septum. Prenat Diagn 2018;38:788–94.
[145] Sanapo L, Moon-Grady AJ, Donofrio MT. Perinatal and delivery management of infants with congenital heart disease. Clin Perinatol 2016; 43:55–71.
[146] Lowenthal A, Kipps AK, Brook MM, Meadows J, Azakie A, Moon-Grady AJ. Prenatal diagnosis of atrial restriction in hypoplastic left heart syndrome is associated with decreased 2-year survival. Prenat Diagn 2012; 32:485–90.
[147] Taketazu M, Barrea C, Smallhorn JF, Wilson GJ, Hornberger LK. Intrauterine pulmonary venous flow and restrictive foramen ovale in fetal hypoplastic left heart syndrome. J Am Coll Cardiol 2004; 43:1902–7.
[148] Goltz D, Lunkenheimer J-M, Abedini M, Herberg U, Berg C, Gembruch U *et al.* Left ventricular obstruction with restrictive inter-atrial communication leads to retardation in fetal lung maturation. Prenat Diagn 2015; 35:463–70.
[149] Seed M, Bradley T, Bourgeois J, Jaeggi E, Yoo S-J. Antenatal MR imaging of pulmonary lymphangiectasia secondary to hypoplastic left heart syndrome. Pediatr Radiol 2009;39:747–9.
[150] Victoria T, Andronikou S. The fetal MR appearance of "nutmeg lung": findings in 8 cases linked to pulmonary lymphangiectasia. Pediatr Radiol 2014;44:1237–42.

[151] Lloyd DF, van Amerom JF, Pushparajah K, Simpson JM, Zidere V, Miller O *et al.* An exploration of the potential utility of fetal cardiovascular MRI as an adjunct to fetal echocardiography. Prenat Diagn 2016;36:916–25.
[152] Chintala K, Tian Z, Du W, Donaghue D, Rychik J. Fetal pulmonary venous Doppler patterns in hypoplastic left heart syndrome: relationship to atrial septal restriction. Heart 2008;94:1446–9.
[153] Divanović A, Hor K, Cnota J, Hirsch R, Kinsel-Ziter M, Michelfelder E. Prediction and perinatal management of severely restrictive atrial septum in fetuses with critical left heart obstruction: clinical experience using pulmonary venous Doppler analysis. J Thorac Cardiovasc Surg 2011;141:988–94.
[154] Jaeggi E, Renaud C, Ryan G, Chaturvedi R. Intrauterine therapy for structural congenital heart disease: contemporary results and Canadian experience. Trends Cardiovasc Med 2016;26:639–46.
[155] Szwast A, Tian Z, McCann M, Donaghue D, Rychik J. Vasoreactive response to maternal hyperoxygenation in the fetus with hypoplastic left heart syndrome. Circ Cardiovasc Imaging 2010;3:172–8.
[156] Enzensberger C, Axt-Fliedner R, Degenhardt J, Kawecki A, Tenzer A, Kohl T *et al.* Pulmonary vasoreactivity to materno-fetal hyperoxygenation testing in fetuses with hypoplastic left heart. Ultraschall in Med 2016;37:195–200.
[157] Schidlow DN, Donofrio MT. Prenatal maternal hyperoxygenation testing and implications for critical care delivery planning among fetuses with congenital heart disease: early experience. Am J Perinatol 2018; 35:16–23.
[158] Glatz JA, Tabbutt S, Gaynor JW, Rome JJ, Montenegro L, Spray TL *et al.* Hypoplastic left heart syndrome with atrial level restriction in the era of prenatal diagnosis. Ann Thorac Surg 2007;84:1633–8.
[159] Marshall AC, Levine J, Morash D, Silva V, Lock JE, Benson CB *et al.* Results of in utero atrial septoplasty in fetuses with hypoplastic left heart syndrome. Prenat Diagn 2008;28:1023–8.
[160] Donofrio MT, Skurow-Todd K, Berger JT, McCarter R, Fulgium A, Krishnan A *et al.* Risk-stratified postnatal care of newborns with congenital heart disease determined by fetal echocardiography. J Am Soc Echocardiogr 2015;28:1339–49.
[161] Hancock HS, Romano JC, Armstrong A, Yu S, Lowery R, Gelehrter S. Single ventricle and total anomalous pulmonary venous connection: implications of prenatal diagnosis. World J Pediatr Congenit Heart Surg 2018;9:434–9.
[162] Axt-Fliedner R, Tenzer A, Kawecki A, Degenhardt J, Schranz D, Valeske K *et al.* Prenatal assessment of ventriculocoronary connections and ventricular endocardial fibroelastosis in hypoplastic left heart. Ultraschall in Med 2014;35:357–63.
[163] Sathanandam S, Cui W, Nguyen NV, Husayni TS, Van Bergen AH, Sajan I *et al.* Ventriculocoronary artery connections with the hypoplastic left heart: a 4-year prospective study: incidence, echocardiographic and clinical features. Pediatr Cardiol 2010;31:1176–85.
[164] Nathan M, Williamson AK, Mayer JE, Bacha EA, Juraszek AL. Mortality in hypoplastic left heart syndrome: review of 216 autopsy cases of aortic atresia with attention to coronary artery disease. J Thorac Cardiovasc Surg 2012;144:1301–6.
[165] Hornberger LK, Sanders SP, Rein AJ, Spevak PJ, Parness IA, Colan SD. Left heart obstructive lesions and left ventricular growth in the midtrimester fetus. A longitudinal study. Circulation 1995;92:1531–8.
[166] Simpson JM, Sharland GK. Natural history and outcome of aortic stenosis diagnosed prenatally. Heart 1997;77:205–10.
[167] Kovacevic A, Ohman A, Tulzer G, Herberg U, Dangel J, Carvalho JS *et al.*; the Fetal Working Group of the AEPC. Fetal hemodynamic response to aortic valvuloplasty and postnatal outcome: a European multicenter study. Ultrasound Obstet Gynecol 2018;52:221–9.
[168] Wohlmuth C, Wertaschnigg D, Wieser I, Arzt W, Tulzer G. Tissue Doppler imaging in fetuses with aortic stenosis and evolving hypoplastic left heart syndrome before and after fetal aortic valvuloplasty. Ultrasound Obstet Gynecol 2016;47:608–15.
[169] Ishii T, McElhinney DB, Harrild DM, Marcus EN, Sahn DJ, Truong U *et al.* Ventricular strain in fetuses with aortic stenosis and evolving hypoplastic left heart syndrome before and after prenatal aortic valvuloplasty. Fetal Diagn Ther 2013;35:18–26.
[170] Arzt W, Wertaschnigg D, Veit I, Klement F, Gitter R, Tulzer G. Intrauterine aortic valvuloplasty in fetuses with critical aortic stenosis: experience and results of 24 procedures. Ultrasound Obstet Gynecol 2011;37:689–95.
[171] Tulzer G, Arzt W. Fetal cardiac interventions: rationale, risk and benefit. Semin Fetal Neonatal Med 2013;18:298–301.
[172] Freud LR, McElhinney DB, Marshall AC, Marx GR, Friedman KG, del Nido PJ *et al.* Fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome: postnatal outcomes of the first 100 patients. Circulation 2014;130:638–45.
[173] MäKikallio K, McElhinney DB, Levine JC, Marx GR, Colan SD, Marshall AC *et al.* Fetal aortic valve stenosis and the evolution of hypoplastic left heart syndrome: patient selection for fetal intervention. Circulation 2006;113:1401–5.
[174] Gardiner HM, Kovacevic A, Tulzer G, Sarkola T, Herberg U, Dangel J *et al.*; Fetal Working Group of the AEPC. Natural history of 107 cases of fetal aortic stenosis from a European multicenter retrospective study. Ultrasound Obstet Gynecol 2016;48:373–81.
[175] Friedman KG, Sleeper LA, Freud LR, Marshall AC, Godfrey ME, Drogosz M *et al.* Improved technical success, postnatal outcome and refined predictors of outcome for fetal aortic valvuloplasty. Ultrasound Obstet Gynecol 2018;52:212–20.
[176] Moon-Grady AJ, Morris SA, Belfort M, Chmait R, Dangel J, Devlieger R *et al.* International fetal cardiac intervention registry: a worldwide collaborative description and preliminary outcomes. J Am Coll Cardiol 2015;66:388–99.
[177] Tulzer A, Arzt W, Gitter R, Prandstetter C, Tulzer G. In-utero aortic valvuloplasty in fetuses with critical aortic stenosis and evolving hypoplastic left heart syndrome: effects on the fetal heart and on outcome. A single center analysis of 80 patients. Cardiol Young 2019;29:S39.
[178] Lisanti AJ. Parental stress and resilience in CHD: a new frontier for health disparities research. Cardiol Young 2018;28:1142–50.
[179] Lisanti AJ, Allen LR, Kelly L, Medoff-Cooper B. Maternal stress and anxiety in the pediatric cardiac intensive care unit. Am J Crit Care 2017; 26:118–25.
[180] Bratt E-L, Järvholm S, Ekman-Joelsson B-M, Mattson L-Å, Mellander M. Parent's experiences of counselling and their need for support following a prenatal diagnosis of congenital heart disease—a qualitative study in a Swedish context. BMC Pregnancy Childbirth 2015;15:171.
[181] Gutgesell HP, Massaro TA. Management of hypoplastic left heart syndrome in a consortium of university hospitals. Am J Cardiol 1995; 76:809–11.
[182] Rosenthal A. Physiology, diagnosis and clinical profile of the hypoplastic left heart syndrome. Progress Ped Cardiol 1996;5:19–22.
[183] Oster ME, Aucott SW, Glidewell J, Hackell J, Kochilas L, Martin GR *et al.* Lessons learned from newborn screening for critical congenital heart defects. Pediatrics 2016;137:e20154573–e20154573.
[184] Manzoni P, Martin GR, Sanchez Luna M, Mestrovic J, Simeoni U, Zimmermann L *et al.* Pulse oximetry screening for critical congenital heart defects: a European consensus statement. Lancet Child Adolesc Health 2017;1:88–90.
[185] Grosse SD, Peterson C, Abouk R, Glidewell J, Oster ME. Cost and cost-effectiveness assessments of newborn screening for critical congenital heart disease using pulse oximetry: a review. Int J Neonatal Screen 2017; 3:34.
[186] Ross RD, Bollinger RO, Pinsky WW. Grading the severity of congestive heart failure in infants. Pediatr Cardiol 1992;13:72–5.
[187] Mercer-Rosa L, Goldberg DJ. Prognostic value of serial echocardiography in hypoplastic left heart syndrome: smaller hearts, better results. Circ Cardiovasc Imaging 2018;11:e008006.
[188] Fraser CD, Carberry KE. Congenital heart disease. In: Townsend CM, Beauchamp RD, Evers BM, Mattox KL (eds). Sabiston Textbook of Surgery, 19th edn. Philadelphia: Elsevier, Saunders, 2012, 1611–49.
[189] Fricker FJ. Hypoplastic left heart syndrome: diagnosis and early management. NeoReviews 2008;9:e253–61.
[190] Gordon BM, Rodriguez S, Lee M, Chang R-K. Decreasing number of deaths of infants with hypoplastic left heart syndrome. J Pediatr 2008; 153:354–8.
[191] Gaynor JW, Collins MH, Rychik J, Gaughan JP, Spray TL. Long-term outcome of infants with single ventricle and total anomalous pulmonary venous connection. J Thorac Cardiovasc Surg 1999;117:506–13; discussion 513–14.
[192] Monaco MA, Liberman L, Starc TJ, Silver ES. Defining the electrocardiogram in the neonate with hypoplastic left heart syndrome. Pediatr Cardiol 2015;36:1014–18.
[193] Marx GR, Shirali G, Levine JC, Guey LT, Cnota JF, Baffa JM *et al.* Multicenter study comparing shunt type in the Norwood procedure for single-ventricle lesions: three-dimensional echocardiographic analysis. Circ Cardiovasc Imaging 2013;6:934–42.

[194] den Dekker MHT, Slieker MG, Blank AC, Haas F, Freund MW. Comparability of Z-score equations of cardiac structures in hypoplastic left heart complex. J Am Soc Echocardiogr 2013;26:1314–21.
[195] O'Connor WN, Cash JB, Cottrill CM, Johnson GL, Noonan JA. Ventriculocoronary connections in hypoplastic left hearts: an autopsy microscopic study. Circulation 1982;66:1078–86.
[196] Siehr SL, Maeda K, Connolly AA, Tacy TA, Reddy VM, Hanley FL *et al.* Mitral stenosis and aortic atresia—a risk factor for mortality after the modified Norwood operation in hypoplastic left heart syndrome. Ann Thorac Surg 2016;101:162–7.
[197] Nguyen T, Miller M, Gonzalez J, Nardell K, Galas J, John JB *et al.* Echocardiography of hypoplastic left heart syndrome. Cardiol Young 2011;21:28–37.
[198] Gossett JG, Rocchini AP, Lloyd TR, Graziano JN. Catheter-based decompression of the left atrium in patients with hypoplastic left heart syndrome and restrictive atrial septum is safe and effective. Cathet Cardiovasc Intervent 2006;67:619–24.
[199] Yabrodi M, Mastropietro CW. Hypoplastic left heart syndrome: from comfort care to long-term survival. Pediatr Res 2017;81:142–9.
[200] Ohye RG, Schranz D, D'Udekem Y. Current therapy for hypoplastic left heart syndrome and related single ventricle lesions. Circulation 2016; 134:1265–79.
[201] Bailey L, Concepcion W, Shattuck H, Huang L. Method of heart transplantation for treatment of hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 1986;92:1–5.
[202] Tweddell JS, Hoffman GM, Mussatto KA, Fedderly RT, Berger S, Jaquiss RDB *et al.* Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: lessons learned from 115 consecutive patients. Circulation 2002;106(12 Suppl 1):I82–9.
[203] Stieh J, Fischer G, Scheewe J, Uebing A, Dütschke P, Jung O *et al.* Impact of preoperative treatment strategies on the early perioperative outcome in neonates with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2006;131:1122–9.
[204] Johnson BA, Mussatto K, Uhing MR, Zimmerman H, Tweddell J, Ghanayem N. Variability in the preoperative management of infants with hypoplastic left heart syndrome. Pediatr Cardiol 2008;29:515–20.
[205] Slicker J, Hehir DA, Horsley M, Monczka J, Stern KW, Roman B *et al.* Nutrition algorithms for infants with hypoplastic left heart syndrome; birth through the first interstage period. Congenit Heart Dis 2013;8:89–102.
[206] Carpenito K-R, Prusinski R, Kirchner K, Simsic J, Miao Y, Luce W *et al.* Results of a feeding protocol in patients undergoing the hybrid procedure. Pediatr Cardiol 2016;37:852–9.
[207] Iannucci GJ, Oster ME, Mahle WT. Necrotising enterocolitis in infants with congenital heart disease: the role of enteral feeds. Cardiol Young 2013;23:553–9.
[208] Hebra A, Brown MF, Hirschl RB, McGeehin K, O'Neill JA, Norwood WI *et al.* Mesenteric ischemia in hypoplastic left heart syndrome. J Pediatr Surg 1993;28:606–11.
[209] Akkinapally S, Hundalani SG, Kulkarni M, Fernandes CJ, Cabrera AG, Shivanna B *et al.* Prostaglandin E1 for maintaining ductal patency in neonates with ductal-dependent cardiac lesions. Cochrane Database Syst Rev 2018;2:CD011417.
[210] Shivananda S, Kirsh J, Whyte HE, Muthalally K, McNamara PJ. Accuracy of clinical diagnosis and decision to commence intravenous prostaglandin E1 in neonates presenting with hypoxemia in a transport setting. J Crit Care 2010;25:174.e1–9.
[211] Huang F-K, Lin C-C, Huang T-C, Weng K-P, Liu P-Y, Chen Y-Y *et al.* Reappraisal of the prostaglandin E1 dose for early newborns with patent ductus arteriosus-dependent pulmonary circulation. Pediatr Neonatol 2013;54:102–6.
[212] Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM *et al.* Part 13: neonatal resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:S543–60.
[213] Schranz D, Akintuerk H. Hypoplastic left heart syndrome: the Giessen approach; history, technique, and results. In: Butera G, Cheatham J, Pedra C, Schranz D, Tulzer G (eds). Fetal and Hybrid Procedures in Congenital Heart Diseases. New York: Springer, 2016, 209–20.
[214] Schranz D, Michel-Behnke I. Advances in interventional and hybrid therapy in neonatal congenital heart disease. Semin Fetal Neonatal Med 2013;18:311–21.
[215] Koroglu A, Teksan H, Sagir O, Yucel A, Toprak HI, Ersoy OM. A comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. Anesth Analg 2006;103:63–7.
[216] Su F, Nicolson SC, Gastonguay MR, Barrett JS, Adamson PC, Kang DS *et al.* Population pharmacokinetics of dexmedetomidine in infants after open heart surgery. Anesth Analg 2010;110:1383–92.
[217] Hünseler C, Balling G, Röhlig C, Blickheuser R, Trieschmann U, Lieser U *et al.* Continuous infusion of clonidine in ventilated newborns and infants: a randomized controlled trial. Pediatr Crit Care Med 2014; 15:511–22.
[218] Pichot C, Ghignone M, Quintin L. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting? J Intensive Care Med 2012;27:219–37.
[219] Zuppa AF, Nicolson SC, Adamson PC, Wernovsky G, Mondick JT, Burnham N *et al.* Population pharmacokinetics of milrinone in neonates with hypoplastic left heart syndrome undergoing stage I reconstruction. Anesth Analg 2006;102:1062–9.
[220] Schranz D, Voelkel NF. "Nihilism" of chronic heart failure therapy in children and why effective therapy is withheld. Eur J Pediatr 2016; 175:445–55.
[221] Oster ME, Kelleman M, McCracken C, Ohye RG, Mahle WT. Association of digoxin with interstage mortality: results from the pediatric heart network Single Ventricle Reconstruction trial public use dataset. J Am Heart Assoc 2016;5:e002566.
[222] Stasik CN, Gelehrter S, Goldberg CS, Bove EL, Devaney EJ, Ohye RG. Current outcomes and risk factors for the Norwood procedure. J Thorac Cardiovasc Surg 2006;131:412–17.
[223] Desai J, Aggarwal S, Lipshultz S, Agarwal P, Yigazu P, Patel R *et al.* Surgical interventions in infants born preterm with congenital heart defects: an analysis of the kids' inpatient database. J Pediatr 2017; 191:103–9.
[224] Siffel C, Riehle-Colarusso T, Oster ME, Correa A. Survival of children with hypoplastic left heart syndrome. Pediatrics 2015;136:e864–70.
[225] Lloyd DFA, Cutler L, Tibby SM, Vimalesvaran S, Qureshi SA, Rosenthal E *et al.* Analysis of preoperative condition and interstage mortality in Norwood and hybrid procedures for hypoplastic left heart syndrome using the Aristotle scoring system. Heart 2014;100:775–80.
[226] Morray BH, Albers EL, Jones TK, Kemna MS, Permut LC, Law YM. Hybrid stage 1 palliation as a bridge to cardiac transplantation in patients with high-risk single ventricle physiology. Pediatr Transplant 2018;22:e13307.
[227] Ota N, Murata M, Tosaka Y, Ide Y, Tachi M, Ito H *et al.* Is routine rapid-staged bilateral pulmonary artery banding before stage 1 Norwood a viable strategy? J Thorac Cardiovasc Surg 2014;148:1519–25.
[228] Natowicz M, Chatten J, Clancy R, Conard K, Glauser T, Huff D *et al.* Genetic disorders and major extracardiac anomalies associated with the hypoplastic left heart syndrome. Pediatrics 1988;82:698–706.
[229] Canter CE, Moorehead S, Huddleston CB, Spray TL. Restrictive atrial septal communication as a determinant of outcome of cardiac transplantation for hypoplastic left heart syndrome. Circulation 1993; 88:II456–60.
[230] Hoque T, Richmond M, Vincent JA, Bacha E, Torres A. Current outcomes of hypoplastic left heart syndrome with restrictive atrial septum: a single-center experience. Pediatr Cardiol 2013;34:1181–9.
[231] Gelehrter S, Fifer CG, Armstrong A, Hirsch J, Gajarski R. Outcomes of hypoplastic left heart syndrome in low-birth-weight patients. Pediatr Cardiol 2011;32:1175–81.
[232] Kalfa D, Krishnamurthy G, Levasseur S, Najjar M, Chai P, Chen J *et al.* Norwood stage I palliation in patients less than or equal to 2.5 kg: outcomes and risk analysis. Ann Thorac Surg 2015;100:167–73.
[233] Hansen DD, Hickey PR. Anesthesia for hypoplastic left heart syndrome: use of high-dose fentanyl in 30 neonates. Anesth Analg 1986;65:127–32.
[234] Duncan HP, Cloote A, Weir PM, Jenkins I, Murphy PJ, Pawade AK *et al.* Reducing stress responses in the pre-bypass phase of open heart surgery in infants and young children: a comparison of different fentanyl doses. Br J Anaesth 2000;84:556–64.
[235] Naguib AN, Winch P, Schwartz L, Isaacs J, Rodeman R, Cheatham JP *et al.* Anesthetic management of the hybrid stage 1 procedure for hypoplastic left heart syndrome (HLHS). Paediatr Anaesth 2010;20: 38–46.
[236] Joint Professional Guidance on the Use of General Anaesthesia in Young Children. Royal College of Anesthetists of Great Britain and Ireland. https://www.anaesthesia.ie/latest-news/joint-professional-guidance-on-the-use-of-general-anaesthesia-in-young-children-2/ (16 December 2019, date last accessed).
[237] Kurth CD, Priestley M, Watzman HM, McCann J, Golden J. Desflurane confers neurologic protection for deep hypothermic circulatory arrest in newborn pigs. Anesthesiology 2001;95:959–64.

[238] Kunst G, Klein AA. Peri-operative anaesthetic myocardial preconditioning and protection—cellular mechanisms and clinical relevance in cardiac anaesthesia. Anaesthesia 2015;70:467–82.
[239] Brambrink AM, Back SA, Riddle A, Gong X, Moravec MD, Dissen GA *et al.* Isoflurane-induced apoptosis of oligodendrocytes in the neonatal primate brain. Ann Neurol 2012;72:525–35.
[240] Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Martin LD *et al.* Ketamine-induced neuroapoptosis in the fetal and neonatal rhesus macaque brain. Anesthesiology 2012;116:372–84.
[241] Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G *et al.* Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 2016; 387:239–50.
[242] Lam F, Bhutta AT, Tobias JD, Gossett JM, Morales L, Gupta P. Hemodynamic effects of dexmedetomidine in critically ill neonates and infants with heart disease. Pediatr Cardiol 2012;33:1069–77.
[243] Kadam SV, Tailor KB, Kulkarni S, Mohanty SR, Joshi PV, Rao SG. Effect of dexmeditomidine on postoperative junctional ectopic tachycardia after complete surgical repair of tetralogy of Fallot: a prospective randomized controlled study. Ann Card Anaesth 2015;18:323–8.
[244] Gianfranco B. Hybrid approach in hypoplastic left heart syndrome (HLHS). In: Schranz D (ed.). Cardiac Catheterisation for Congenital Heart Disease: From Fetal life to Adulthood, Vol. 38. New York: Springer, 2015, 649–66.
[245] Walker SM, Grafe M, Yaksh TL. Intrathecal clonidine in the neonatal rat: dose-dependent analgesia and evaluation of spinal apoptosis and toxicity. Anesth Analg 2012;115:450–60.
[246] Perez-Zoghbi JF, Zhu W, Grafe MR, Brambrink AM. Dexmedetomidine-mediated neuroprotection against sevoflurane-induced neurotoxicity extends to several brain regions in neonatal rats. Br J Anaesth 2017; 119:506–16.
[247] Lee J-R, Lin EP, Hofacer RD, Upton B, Lee SY, Ewing L *et al.* Alternative technique or mitigating strategy for sevoflurane-induced neurodegeneration: a randomized controlled dose-escalation study of dexmedetomidine in neonatal rats. Br J Anaesth 2017;119:492–505.
[248] Cholette JM, Willems A, Valentine SL, Bateman ST, Schwartz SM. Pediatric critical care transfusion and anemia expertise initiative (TAXI), et al. recommendations on RBC transfusion in infants and children with acquired and congenital heart disease from the pediatric critical care transfusion and anemia expertise initiative. Pediatr Crit Care Med 2018; 19(9S Suppl 1):S137–48.
[249] Petäjä J, Lundström U, Sairanen H, Marttinen E, Griffin JH. Central venous thrombosis after cardiac operations in children. J Thorac Cardiovasc Surg 1996;112:883–9.
[250] Emani S, Zurakowski D, Baird CW, Pigula FA, Trenor C, Emani SM. Hypercoagulability markers predict thrombosis in single ventricle neonates undergoing cardiac surgery. Ann Thorac Surg 2013;96:651–6.
[251] Wu ET, Takeuchi M, Imanaka H, Higuchi T, Kagisaki K. Chylothorax as a complication of innominate vein thrombosis induced by a peripherally inserted central catheter. Anaesthesia 2006;61:584–6.
[252] Trezzi M, Bradley SM, Bandisode V, Baker H, Kavarana MN. Prior innominate vein occlusion does not preclude successful bidirectional superior cavopulmonary connection. Ann Thorac Surg 2015; 100:162–6.
[253] Anton N, Cox PN, Massicotte MP, Chait P, Yasui Y, Dinyari PM *et al.* Heparin-bonded central venous catheters do not reduce thrombosis in infants with congenital heart disease: a blinded randomized, controlled trial. Pediatrics 2009;123:e453–8.
[254] Tsai SK, Chang CI, Wang MJ, Chen SJ, Chiu IS, Chen YS *et al.* The assessment of the proximal left pulmonary artery by transesophageal echocardiography and computed tomography in neonates and infants: a case series. Anesth Analg 2001;93:594–7.
[255] Chang Y-Y, Chang C-I, Wang M-J, Lin S-M, Chen Y-S, Tsai S-K *et al.* The safe use of intraoperative transesophageal echocardiography in the management of total anomalous pulmonary venous connection in newborns and infants: a case series. Paediatr Anaesth 2005;15:939–43.
[256] Tweddell JS, Ghanayem NS, Mussatto KA, Mitchell ME, Lamers LJ, Musa NL *et al.* Mixed venous oxygen saturation monitoring after stage 1 palliation for hypoplastic left heart syndrome. Ann Thorac Surg 2007; 84:1301–10; discussion 1310–11.
[257] Johnson BA, Hoffman GM, Tweddell JS, Cava JR, Basir M, Mitchell ME *et al.* Near-infrared spectroscopy in neonates before palliation of hypoplastic left heart syndrome. Ann Thorac Surg 2009;87:571–7; discussion 577–9.
[258] Tortoriello TA, Stayer SA, Mott AR, McKenzie ED, Fraser CD, Andropoulos DB *et al.* A noninvasive estimation of mixed venous oxygen saturation using near-infrared spectroscopy by cerebral oximetry in pediatric cardiac surgery patients. Paediatr Anaesth 2005;15:495–503.
[259] Chakravarti SB, Mittnacht AJC, Katz JC, Nguyen K, Joashi U, Srivastava S. Multisite near-infrared spectroscopy predicts elevated blood lactate level in children after cardiac surgery. J Cardiothorac Vasc Anesth 2009; 23:663–7.
[260] Ramamoorthy C, Tabbutt S, Kurth CD, Steven JM, Montenegro LM, Durning S *et al.* Effects of inspired hypoxic and hypercapnic gas mixtures on cerebral oxygen saturation in neonates with univentricular heart defects. Anesthesiology 2002;96:283–8.
[261] Shime N, Hashimoto S, Hiramatsu N, Oka T, Kageyama K, Tanaka Y. Hypoxic gas therapy using nitrogen in the preoperative management of neonates with hypoplastic left heart syndrome. Pediatr Crit Care Med 2000;1:38–41.
[262] Shore-Lesserson L, Baker RA, Ferraris VA, Greilich PE, Fitzgerald D, Roman P *et al.* The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of ExtraCorporeal Technology: clinical practice guidelines—anticoagulation during cardiopulmonary bypass. Ann Thorac Surg 2018;105:650–62.
[263] Miyaji K, Hannan RL, Ojito J, Jacobs JP, White JA, Burke RP. Heparin-coated cardiopulmonary bypass circuit: clinical effects in pediatric cardiac surgery. J Cardiac Surgery 2000;15:194–8.
[264] Böning A, Scheewe J, Ivers T, Friedrich C, Stieh J, Freitag S *et al.* Phosphorylcholine or heparin coating for pediatric extracorporeal circulation causes similar biologic effects in neonates and infants. J Thorac Cardiovasc Surg 2004;127:1458–65.
[265] Codispoti M, Ludlam CA, Simpson D, Mankad PS. Individualized heparin and protamine management in infants and children undergoing cardiac operations. Ann Thorac Surg 2001;71:922–7; discussion 927–8.
[266] Guzzetta NA, Bajaj T, Fazlollah T, Szlam F, Wilson E, Kaiser A *et al.* A comparison of heparin management strategies in infants undergoing cardiopulmonary bypass. Anesth Analg 2008;106:419–25.
[267] Guzzetta NA, Miller BE, Todd K, Szlam F, Moore RH, Tosone SR. An evaluation of the effects of a standard heparin dose on thrombin inhibition during cardiopulmonary bypass in neonates. Anesth Analg 2005; 100:1276–82.
[268] Gruenwald CE, Manlhiot C, Crawford-Lean L, Foreman C, Brandão LR, McCrindle BW *et al.* Management and monitoring of anticoagulation for children undergoing cardiopulmonary bypass in cardiac surgery. J Extra Corpor Technol 2010;42:9–19.
[269] Reagor JA, Clingan S, Kulat BT, Matte GS, Voss J, Tweddell JS. The Norwood Stage 1 procedure—conduct of perfusion: 2017 survey results from NPC-QIC member institutions. Perfusion 2018;33:667–78.
[270] Hirsch JC, Jacobs ML, Andropoulos D, Austin EH, Jacobs JP, Licht DJ *et al.* Protecting the infant brain during cardiac surgery: a systematic review. Ann Thorac Surg 2012;94:1365–73; discussion 1373.
[271] Wypij D, Newburger JW, Rappaport LA, duPlessis AJ, Jonas RA, Wernovsky G *et al.* The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: the Boston Circulatory Arrest trial. J Thorac Cardiovasc Surg 2003; 126:1397–403.
[272] Langley SM, Chai PJ, Miller SE, Mault JR, Jaggers JJ, Tsui SS *et al.* Intermittent perfusion protects the brain during deep hypothermic circulatory arrest. Ann Thorac Surg 1999;68:4–12; discussion 12–13.
[273] Newburger JW, Jonas RA, Wernovsky G, Wypij D, Hickey PR, Kuban KC *et al.* A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. N Engl J Med 1993;329:1057–64.
[274] Bellinger DC, Wypij D, duPlessis AJ, Rappaport LA, Jonas RA, Wernovsky G *et al.* Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest trial. J Thorac Cardiovasc Surg 2003;126:1385–96.
[275] Myung RJ, Petko M, Judkins AR, Schears G, Ittenbach RF, Waibel RJ *et al.* Regional low-flow perfusion improves neurologic outcome compared with deep hypothermic circulatory arrest in neonatal piglets. J Thorac Cardiovasc Surg 2004;127:1051–6; discussion 1056–7.
[276] Andropoulos DB, Stayer SA, McKenzie ED, Fraser CD. Regional low-flow perfusion provides comparable blood flow and oxygenation to both cerebral hemispheres during neonatal aortic arch reconstruction. J Thorac Cardiovasc Surg 2003;126:1712–17.
[277] Visconti KJ, Rimmer D, Gauvreau K, del Nido P, Mayer JE, Hagino I *et al.* Regional low-flow perfusion versus circulatory arrest in neonates: one-

year neurodevelopmental outcome. Ann Thorac Surg 2006;82:2207–11; discussion 2211–13.
[278] Goldberg CS, Bove EL, Devaney EJ, Mollen E, Schwartz E, Tindall S *et al.* A randomized clinical trial of regional cerebral perfusion versus deep hypothermic circulatory arrest: outcomes for infants with functional single ventricle. J Thorac Cardiovasc Surg 2007;133:880–7.
[279] Newburger JW, Jonas RA, Soul J, Kussman BD, Bellinger DC, Laussen PC *et al.* Randomized trial of hematocrit 25% versus 35% during hypothermic cardiopulmonary bypass in infant heart surgery. J Thorac Cardiovasc Surg 2008;135:347–54, 354.e1–4.
[280] Mou SS, Giroir BP, Molitor-Kirsch EA, Leonard SR, Nikaidoh H, Nizzi F *et al.* Fresh whole blood versus reconstituted blood for pump priming in heart surgery in infants. N Engl J Med 2004;351:1635–44.
[281] Sümpelmann R, Schürholz T, Thorns E, Hausdörfer J. Acid-base, electrolyte and metabolite concentrations in packed red blood cells for major transfusion in infants. Paediatr Anaesth 2001;11:169–73.
[282] Jobes DR, Sesok-Pizzini D, Friedman D. Transfusion requirement with use of fresh whole blood in pediatric cardiac surgical procedures. Ann Thorac Surg 2015;99:1706–11.
[283] Cooper DJ, McQuilten ZK, Nichol A, Ady B, Aubron C, Bailey M *et al.* Age of red cells for transfusion and outcomes in critically ill adults. N Engl J Med 2017;377:1858–67.
[284] Redlin M, Habazettl H, Boettcher W, Kukucka M, Schoenfeld H, Hetzer R *et al.* Effects of a comprehensive blood-sparing approach using body weight-adjusted miniaturized cardiopulmonary bypass circuits on transfusion requirements in pediatric cardiac surgery. J Thorac Cardiovasc Surg 2012;144:493–9.
[285] Scrascia G, Rotunno C, Guida P, Amorese L, Polieri D, Codazzi D *et al.* Perioperative steroids administration in pediatric cardiac surgery: a meta-analysis of randomized controlled trials. Pediatr Crit Care Med 2014;15:435–42.
[286] Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J *et al.*; SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet 2015;386:1243–53.
[287] Shum-Tim D, Tchervenkov CI, Jamal AM, Nimeh T, Luo CY, Chedrawy E *et al.* Systemic steroid pretreatment improves cerebral protection after circulatory arrest. Ann Thorac Surg 2001;72:1465–71; discussion 1471–2.
[288] Shum-Tim D, Tchervenkov CI, Laliberté E, Jamal A-M, Nimeh T, Luo C-Y *et al.* Timing of steroid treatment is important for cerebral protection during cardiopulmonary bypass and circulatory arrest: minimal protection of pump prime methylprednisolone. Eur J Cardiothorac Surg 2003; 24:125–32.
[289] Langley SM, Chai PJ, Jaggers JJ, Ungerleider RM. Preoperative high dose methylprednisolone attenuates the cerebral response to deep hypothermic circulatory arrest. Eur J Cardiothorac Surg 2000; 17:279–86.
[290] Bronicki RA, Backer CL, Baden HP, Mavroudis C, Crawford SE, Green TP. Dexamethasone reduces the inflammatory response to cardiopulmonary bypass in children. Ann Thorac Surg 2000;69:1490–5.
[291] Heying R, Wehage E, Schumacher K, Tassani P, Haas F, Lange R *et al.* Dexamethasone pretreatment provides antiinflammatory and myocardial protection in neonatal arterial switch operation. Ann Thorac Surg 2012;93:869–76.
[292] Priestley MA, Golden JA, O'Hara IB, McCann J, Kurth CD. Comparison of neurologic outcome after deep hypothermic circulatory arrest with alpha-stat and pH-stat cardiopulmonary bypass in newborn pigs. J Thorac Cardiovasc Surg 2001;121:336–43.
[293] Du Plessis AJ, Jonas RA, Wypij D, Hickey PR, Riviello J, Wessel DL *et al.* Perioperative effects of alpha-stat versus pH-stat strategies for deep hypothermic cardiopulmonary bypass in infants. J Thorac Cardiovasc Surg 1997;114:991–1000; discussion 1000–1.
[294] Caputo M, Mokhtari A, Miceli A, Ghorbel MT, Angelini GD, Parry AJ *et al.* Controlled reoxygenation during cardiopulmonary bypass decreases markers of organ damage, inflammation, and oxidative stress in single-ventricle patients undergoing pediatric heart surgery. J Thorac Cardiovasc Surg 2014;148:792–801.e8; discussion 800–1.
[295] de Ferranti S, Gauvreau K, Hickey PR, Jonas RA, Wypij D, Du Plessis A *et al.* Intraoperative hyperglycemia during infant cardiac surgery is not associated with adverse neurodevelopmental outcomes at 1, 4, and 8 years. Anesthesiology 2004;100:1345–52.
[296] Agus MSD, Wypij D, Hirshberg EL, Srinivasan V, Faustino EV, Luckett PM *et al.* Tight glycemic control in critically ill children. N Engl J Med 2017; 376:e48–741.
[297] Kuratani N, Bunsangjaroen P, Srimueang T, Masaki E, Suzuki T, Katogi T. Modified versus conventional ultrafiltration in pediatric cardiac surgery: a meta-analysis of randomized controlled trials comparing clinical outcome parameters. J Thorac Cardiovasc Surg 2011;142:861–7.
[298] Nussmeler NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 1986;64:165–70.
[299] Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M *et al.* Comparison of shunt types in the Norwood procedure for single-ventricle lesions. N Engl J Med 2010;362:1980–92.
[300] Sano S, Ishino K, Kawada M, Honjo O. Right ventricle-pulmonary artery shunt in first-stage palliation of hypoplastic left heart syndrome. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2004;7:22–31.
[301] Bradley SM, Simsic JM, McQuinn TC, Habib DM, Shirali GS, Atz AM. Hemodynamic status after the Norwood procedure: a comparison of right ventricle-to-pulmonary artery connection versus modified Blalock-Taussig shunt. Ann Thorac Surg 2004;78:933–41; discussion 933–41.
[302] Edwards L, Morris KP, Siddiqui A, Harrington D, Barron D, Brawn W. Norwood procedure for hypoplastic left heart syndrome: BT shunt or RV-PA conduit? Arch Dis Child Fetal Neonatal Ed 2007;92:F210–14.
[303] Li J, Zhang G, McCrindle BW, Holtby H, Humpl T, Cai S *et al.* Profiles of hemodynamics and oxygen transport derived by using continuous measured oxygen consumption after the Norwood procedure. J Thorac Cardiovasc Surg 2007;133:441–8.
[304] Hoffman GM, Tweddell JS, Ghanayem NS, Mussatto KA, Stuth EA, Jaquis RDB *et al.* Alteration of the critical arteriovenous oxygen saturation relationship by sustained afterload reduction after the Norwood procedure. J Thorac Cardiovasc Surg 2004;127:738–45.
[305] Tweddell JS, Hoffman GM, Fedderly RT, Berger S, Thomas JP Jr, Ghanayem NS *et al.* Phenoxybenzamine improves systemic oxygen delivery after the Norwood procedure. Ann Thorac Surg 1999;67:161–7; discussion 167–8.
[306] Cavigelli-Brunner A, Hug MI, Dave H, Baenziger O, Buerki C, Bettex D *et al.* Prevention of low cardiac output syndrome after pediatric cardiac surgery: a double-blind randomized clinical pilot study comparing dobutamine and milrinone. Pediatr Crit Care Med 2018;19:619–25.
[307] Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC *et al.* Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107:996–1002.
[308] Trivedi B, Smith PB, Barker PC, Jaggers J, Lodge AJ, Kanter RJ. Arrhythmias in patients with hypoplastic left heart syndrome. Am Heart J 2011;161:138–44.
[309] Oster ME, Chen S, Dagincourt N, Bar-Cohen Y, Brothers M, Cain N *et al.*; Pediatric Heart Network Investigators. Development and impact of arrhythmias after the Norwood procedure: a report from the Pediatric Heart Network. J Thorac Cardiovasc Surg 2017;153:638–45.
[310] Hall EJ, Smith AH, Fish FA, Bichell DP, Mettler BA, Crum K *et al.* Association of shunt type with arrhythmias after Norwood procedure. Ann Thorac Surg 2018;105:629–36.
[311] Kovacikova L, Hakacova N, Dobos D, Skrak P, Zahorec M. Amiodarone as a first-line therapy for postoperative junctional ectopic tachycardia. Ann Thorac Surg 2009;88:616–22.
[312] Murtuza B, Wall D, Reinhardt Z, Stickley J, Stumper O, Jones TJ *et al.* The importance of blood lactate clearance as a predictor of early mortality following the modified Norwood procedure. Eur J Cardiothorac Surg 2011;40:1207–14.
[313] Fenton KN, Lessman K, Glogowski K, Fogg S, Duncan KF. Cerebral oxygen saturation does not normalize until after stage 2 single ventricle palliation. Ann Thorac Surg 2007;83:1431–6.
[314] Hoffman GM, Ghanayem NS, Kampine JM, Berger S, Mussatto KA, Litwin SB *et al.* Venous saturation and the anaerobic threshold in neonates after the Norwood procedure for hypoplastic left heart syndrome. Ann Thorac Surg 2000;70:1515–20; discussion 1521.
[315] Orihashi K, Sueda T, Okada K, Imai K. Near-infrared spectroscopy for monitoring cerebral ischemia during selective cerebral perfusion. Eur J Cardiothorac Surg 2004;26:907–11.
[316] Gottlieb EA, Fraser CD, Andropoulos DB, Diaz LK. Bilateral monitoring of cerebral oxygen saturation results in recognition of aortic cannula malposition during pediatric congenital heart surgery. Paediatr Anaesth 2006;16:787–9.
[317] Phelps HM, Mahle WT, Kim D, Simsic JM, Kirshbom PM, Kanter KR *et al.* Postoperative cerebral oxygenation in hypoplastic left heart syndrome after the Norwood procedure. Ann Thorac Surg 2009;87:1490–4.

[318] Hoffman GM, Mussatto KA, Brosig CL, Ghanayem NS, Musa N, Fedderly RT *et al.* Systemic venous oxygen saturation after the Norwood procedure and childhood neurodevelopmental outcome. J Thorac Cardiovasc Surg 2005;130:1094–100.
[319] Rogers CA, Stoica S, Ellis L, Stokes EA, Wordsworth S, Dabner L *et al.* Randomized trial of near-infrared spectroscopy for personalized optimization of cerebral tissue oxygenation during cardiac surgery. Br J Anaesth 2017;119:384–93.
[320] Lei L, Katznelson R, Fedorko L, Carroll J, Poonawala H, Machina M *et al.* Cerebral oximetry and postoperative delirium after cardiac surgery: a randomized controlled trial. Anesthesia 2017;72:1465–6.
[321] Blackwood J, Joffe AR, Robertson CMT, Dinu IA, Alton G, Penner K *et al.* Association of hemoglobin and transfusion with outcome after operations for hypoplastic left heart. Ann Thorac Surg 2010; 89:1378–84.e1–2.
[322] Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C *et al.* Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197–206.
[323] Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E *et al.* Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009;361:1349–58.
[324] Shapira N, Schaff HV, Piehler JM, White RD, Sill JC, Pluth JR. Cardiovascular effects of protamine sulfate in man. J Thorac Cardiovasc Surg 1982;84:505–14.
[325] Salvin JW, Scheurer MA, Laussen PC, Wypij D, Polito A, Bacha EA *et al.* Blood transfusion after pediatric cardiac surgery is associated with prolonged hospital stay. Ann Thorac Surg 2011;91:204–10.
[326] Romlin BS, Wåhlander H, Berggren H, Synnergren M, Baghaei F, Nilsson K *et al.* Intraoperative thromboelastometry is associated with reduced transfusion prevalence in pediatric cardiac surgery. Anesth Analg 2011; 112:30–6.
[327] Nakayama Y, Nakajima Y, Tanaka KA, Sessler DI, Maeda S, Iida J *et al.* Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery. Br J Anaesth 2015;114:91–102.
[328] Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. Anaesthesia 2017;72:519–31.
[329] Song HK, Tibayan FA, Kahl EA, Sera VA, Slater MS, Deloughery TG *et al.* Safety and efficacy of prothrombin complex concentrates for the treatment of coagulopathy after cardiac surgery. J Thorac Cardiovasc Surg 2014;147:1036–40.
[330] Maeda K, Asija R, Hollander S, Williams G, Yeh J, Rosenthal D *et al.* Low dose factor eight inhibitor bypassing activity (FEIBA) for incessant bleeding in pediatric patients on mechanical circulatory support (MCS). J Heart Lung Transpl 2013;32:S290.
[331] Bui JD, Despotis GD, Trulock EP, Patterson GA, Goodnough LT. Fatal thrombosis after administration of activated prothrombin complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received activated recombinant factor VII. J Thorac Cardiovasc Surg 2002;124:852–4.
[332] Pychyńska-Pokorska M, Moll JJ, Krajewski W, Jarosik P. The use of recombinant coagulation factor VIIa in uncontrolled postoperative bleeding in children undergoing cardiac surgery with cardiopulmonary bypass. Pediatr Crit Care Med 2004;5:246–50.
[333] Ekert H, Brizard C, Eyers R, Cochrane A, Henning R. Elective administration in infants of low-dose recombinant activated factor VII (rFVIIa) in cardiopulmonary bypass surgery for congenital heart disease does not shorten time to chest closure or reduce blood loss and need for transfusions: a randomized, double-blind, parallel group, placebo-controlled study of rFVIIa and standard haemostatic replacement therapy versus standard haemostatic replacement therapy. Blood Coagul Fibrinolysis 2006;17:389–95.
[334] Fenger-Eriksen C, Lindberg-Larsen M, Christensen AQ, Ingerslev J, Sørensen B. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. Br J Anaesth 2008;101:769–73.
[335] Muthialu N, Balakrishnan S, Sundar R, Muralidharan S. Efficacy of tranexamic acid as compared to aprotinin in open heart surgery in children. Ann Card Anaesth 2015;18:23–6.
[336] Schouten ES, van de Pol AC, Schouten ANJ, Turner NM, Jansen NJG, Bollen CW. The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis. Pediatr Crit Care Med 2009;10:182–90.
[337] Sharma V, Katznelson R, Jerath A, Garrido-Olivares L, Carroll J, Rao V *et al.* The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11 529 patients. Anaesthesia 2014;69:124–30.
[338] Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM *et al.* A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319–31.
[339] Pagano D, Howell NJ, Freemantle N, Cunningham D, Bonser RS, Graham TR *et al.* Bleeding in cardiac surgery: the use of aprotinin does not affect survival. J Thorac Cardiovasc Surg 2008;135:495–502.
[340] Hehir DA, Dominguez TE, Ballweg JA, Ravishankar C, Marino BS, Bird GL *et al.* Risk factors for interstage death after stage 1 reconstruction of hypoplastic left heart syndrome and variants. J Thorac Cardiovasc Surg 2008;136:94–9, 99.e1–3.
[341] Mahle WT, Spray TL, Wernovsky G, Gaynor JW, Clark BJ. Survival after reconstructive surgery for hypoplastic left heart syndrome: a 15-year experience from a single institution. Circulation 2000;102:III-136–41.
[342] Ashburn DA, McCrindle BW, Tchervenkov CI, Jacobs ML, Lofland GK, Bove EL *et al.* Outcomes after the Norwood operation in neonates with critical aortic stenosis or aortic valve atresia. J Thorac Cardiovasc Surg 2003;125:1070–82.
[343] Gomide M, Furci B, Mimic B, Brown KL, Hsia T-Y, Yates R *et al.* Rapid 2-stage Norwood I for high-risk hypoplastic left heart syndrome and variants. J Thorac Cardiovasc Surg 2013;146:1146–51; discussion 1151–2.
[344] Alsoufi B, Manlhiot C, Al-Ahmadi M, Al-Halees Z, McCrindle BW, Mousa AY *et al.* Older children at the time of the Norwood operation have ongoing mortality vulnerability that continues after cavopulmonary connection. J Thorac Cardiovasc Surg 2011;142:142–7.e2.
[345] Karamlou T, Sexson K, Parrish A, Welke KF, McMullan DM, Permut L *et al.* One size does not fit all: the influence of age at surgery on outcomes following Norwood operation. J Cardiothorac Surg 2014;9:100.
[346] Sames-Dolzer E, Hakami L, Innerhuber M, Tulzer G, Mair R. Older age at the time of the Norwood procedure is a risk factor for early postoperative mortality. Eur J Cardiothorac Surg 2015;47:257–61; discussion 261.
[347] Howley LW, Kaufman J, Wymore E, Thureen P, Magouirk JK, McNair B *et al.* Enteral feeding in neonates with prostaglandin-dependent congenital cardiac disease: international survey on current trends and variations in practice. Cardiol Young 2012;22:121–7.
[348] Willis L, Thureen P, Kaufman J, Wymore E, Skillman H, da Cruz E. Enteral feeding in prostaglandin-dependent neonates: is it a safe practice? J Pediatr 2008;153:867–9.
[349] McElhinney DB, Hedrick HL, Bush DM, Pereira GR, Stafford PW, Gaynor JW *et al.* Necrotizing enterocolitis in neonates with congenital heart disease: risk factors and outcomes. Pediatrics 2000;106:1080–7.
[350] Cross RR, Harahsheh AS, McCarter R, Martin GR; for the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC). Identified mortality risk factors associated with presentation, initial hospitalisation, and interstage period for the Norwood operation in a multi-centre registry: a report from the national pediatric cardiology-quality improvement collaborative. Cardiol Young 2014; 24:253–62.
[351] Sano S, Huang SC, Kasahara S, Yoshizumi K, Kotani Y, Ishino K. Risk factors for mortality after the Norwood procedure using right ventricle to pulmonary artery shunt. Ann Thorac Surg 2009;87:178–85; discussion 185–6.
[352] Jacobs JP, O'Brien SM, Chai PJ, Morell VO, Lindberg HL, Quintessenza JA. Management of 239 patients with hypoplastic left heart syndrome and related malformations from 1993 to 2007. Ann Thorac Surg 2008; 85:1691–6; discussion 1697.
[353] Gupta P, Chakraborty A, Gossett JM, Rettiganti M. A prognostic tool to predict outcomes in children undergoing the Norwood operation. J Thorac Cardiovasc Surg 2017;154:2030–7.e2.
[354] DiBardino DJ, Gomez-Arostegui J, Kemp A, Raviendran R, Hegde S, Devaney EJ *et al.* Intermediate results of hybrid versus primary Norwood operation. Ann Thorac Surg 2015;99:2141–7; discussion 2147–9.
[355] Tabbutt S, Ghanayem N, Ravishankar C, Sleeper LA, Cooper DS, Frank DU *et al.* Risk factors for hospital morbidity and mortality after the Norwood procedure: a report from the Pediatric Heart Network Single Ventricle Reconstruction trial. J Thorac Cardiovasc Surg 2012; 144:882–95.
[356] Hansen JH, Rotermann I, Logoteta J, Jung O, Dütschke P, Scheewe J *et al.* Neurodevelopmental outcome in hypoplastic left heart syndrome: impact of perioperative cerebral tissue oxygenation of the Norwood procedure. J Thorac Cardiovasc Surg 2016;151:1358–66.

[357] Hickey EJ, Nosikova Y, Zhang H, Caldarone CA, Benson L, Redington A *et al.* Very low-birth-weight infants with congenital cardiac lesions: is there merit in delaying intervention to permit growth and maturation? J Thorac Cardiovasc Surg 2012;143:126–36, 136.e1.
[358] Pizarro C, Derby CD, Baffa JM, Murdison KA, Radtke WA. Improving the outcome of high-risk neonates with hypoplastic left heart syndrome: hybrid procedure or conventional surgical palliation? Eur J Cardiothorac Surg 2008;33:613–18.
[359] Gaynor JW, Mahle WT, Cohen MI, Ittenbach RF, DeCampli WM, Steven JM *et al.* Risk factors for mortality after the Norwood procedure. Eur J Cardiothorac Surg 2002;22:82–9.
[360] Tabbutt S, Dominguez TE, Ravishankar C, Marino BS, Gruber PJ, Wernovsky G *et al.* Outcomes after the stage I reconstruction comparing the right ventricular to pulmonary artery conduit with the modified Blalock Taussig shunt. Ann Thorac Surg 2005;80:1582–90; discussion 1590–1.
[361] Chowdhury SM, Graham EM, Atz AM, Bradley SM, Kavarana MN, Butts RJ. Validation of a simple score to determine risk of hospital mortality after the Norwood procedure. Semin Thorac Cardiovasc Surg 2016; 28:425–33.
[362] Azakie T, Merklinger SL, McCrindle BW, Van Arsdell GS, Lee KJ, Benson LN *et al.* Evolving strategies and improving outcomes of the modified Norwood procedure: a 10-year single-institution experience. Ann Thorac Surg 2001;72:1349–53.
[363] McGuirk SP, Stickley J, Griselli M, Stumper OF, Laker SJ, Barron DJ *et al.* Risk assessment and early outcome following the Norwood procedure for hypoplastic left heart syndrome. Eur J Cardiothorac Surg 2006; 29:675–81.
[364] Artrip JH, Campbell DN, Ivy DD, Almodovar MC, Chan K-C, Mitchell MB *et al.* Birth weight and complexity are significant factors for the management of hypoplastic left heart syndrome. Ann Thorac Surg 2006; 82:1252–7; discussion 1258–9.
[365] Guleserian KJ, Barker GM, Sharma MS, Macaluso J, Huang R, Nugent AW *et al.* Bilateral pulmonary artery banding for resuscitation in high-risk, single-ventricle neonates and infants: a single-center experience. J Thorac Cardiovasc Surg 2013;145:206–13; discussion 213–14.
[366] Meckler GD, Lowe C. To intubate or not to intubate? Transporting infants on prostaglandin E1. Pediatrics 2009;123:e25–30.
[367] Shamszad P, Gospin TA, Hong BJ, McKenzie ED, Petit CJ. Impact of preoperative risk factors on outcomes after Norwood palliation for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2014; 147:897–901.
[368] Newburger JW, Sleeper LA, Gaynor JW, Hollenbeck-Pringle D, Frommelt PC, Li JS *et al.*; On behalf of the Pediatric Heart Network Investigators. Transplant-free survival and interventions at 6 years in the SVR trial. Circulation 2018;137:2246–53.
[369] Patel A, Hickey E, Mavroudis C, Jacobs JP, Jacobs ML, Backer CL *et al.* Impact of noncardiac congenital and genetic abnormalities on outcomes in hypoplastic left heart syndrome. Ann Thorac Surg 2010; 89:1805–13; discussion 1813–14.
[370] Lara DA, Ethen MK, Canfield MA, Nembhard WN, Morris SA. A population-based analysis of mortality in patients with Turner syndrome and hypoplastic left heart syndrome using the Texas Birth Defects Registry. Congenit Heart Dis 2017;12:105–12.
[371] Reis PM, Punch MR, Bove EL, van de Ven CJ. Outcome of infants with hypoplastic left heart and Turner syndromes. Obstet Gynecol 1999;93:532–5.
[372] Philip J, Gupta D, Bleiweis MS, Pietra BA, Vyas HV. Hypoplastic left heart in Turner's syndrome: a primary indication for transplant? Cardiol Young 2018;28:458–60.
[373] Ooi YK, Sinha P, Gierdalski M, Harahsheh A. High-risk single ventricle palliation in children with Down syndrome: single institution experience. Cardiol Young 2015;25:539–43.
[374] Gupta-Malhotra M, Larson VEV, Rosengart RM, Guo H, Moller JH. Mortality after total cavopulmonary connection in children with the Down syndrome. Am J Cardiol 2010;105:865–8.
[375] Murtuza B, Stumper O, Wall D, Stickley J, Jones TJ, Barron DJ *et al.* The effect of morphologic subtype on outcomes following the Sano-Norwood procedure. Eur J Cardiothorac Surg 2012;42:787–93.
[376] Glatz JA, Fedderly RT, Ghanayem NS, Tweddell JS. Impact of mitral stenosis and aortic atresia on survival in hypoplastic left heart syndrome. Ann Thorac Surg 2008;85:2057–62.
[377] Sata S, Sinzobahamvya N, Arenz C, Zartner P, Asfour B, Hraska V. Restrictive atrial septum defect becomes a risk factor for Norwood palliation of hypoplastic left heart syndrome only when it is combined with mitral or aortic atresia. Thorac Cardiovasc Surg 2015;63:354–9.
[378] Photiadis J, Urban AE, Sinzobahamvya N, Fink C, Schindler E, Schneider M *et al.* Restrictive left atrial outflow adversely affects outcome after the modified Norwood procedure. Eur J Cardiothorac Surg 2005;27:962–7.
[379] Newburger JW, Sleeper LA, Frommelt PC, Pearson GD, Mahle WT, Chen S *et al.*; Pediatric Heart Network Investigators. Transplantation-free survival and interventions at 3 years in the Single Ventricle Reconstruction trial. Circulation 2014;129:2013–20.
[380] Bockeria L, Alekyan B, Berishvili D, Pursanov M, Krupianko SM, Zarginava G *et al.* A modified hybrid stage I procedure for treatment of hypoplastic left heart syndrome: an original surgical approach. Interact CardioVasc Thorac Surg 2010;11:142–5.
[381] Rajagopal SK, Emani SM, Roy N, Westgate L, Bacha EA. Acute kidney injury and regional abdominal perfusion during neonatal aortic arch reconstruction. J Thorac Cardiovasc Surg 2010;140:453–8.
[382] Kreuzer M, Sames-Dolzer E, Schausberger L, Tulzer A, Ratschiller T, Haizinger B *et al.* Double-arterial cannulation: a strategy for whole body perfusion during aortic arch reconstruction. Interact CardioVasc Thorac Surg 2018;27:742–8.
[383] Hammel JM, Deptula JJ, Karamlou T, Wedemeyer E, Abdullah I, Duncan KF. Newborn aortic arch reconstruction with descending aortic cannulation improves postoperative renal function. Ann Thorac Surg 2013; 96:1721–6; discussion 1726.
[384] Algra SO, Jansen NJG, van der Tweel I, Schouten ANJ, Groenendaal F, Toet M *et al.* Neurological injury after neonatal cardiac surgery: a randomized, controlled trial of 2 perfusion techniques. Circulation 2014;129:224–33.
[385] Ohye RG, Goldberg CS, Donohue J, Hirsch JC, Gaies M, Jacobs ML *et al.* The quest to optimize neurodevelopmental outcomes in neonatal arch reconstruction: the perfusion techniques we use and why we believe in them. J Thorac Cardiovasc Surg 2009;137:803–6.
[386] Jonas RA, Wypij D, Roth SJ, Bellinger DC, Visconti KJ, Du Plessis AJ *et al.* The influence of hemodilution on outcome after hypothermic cardiopulmonary bypass: results of a randomized trial in infants. J Thorac Cardiovasc Surg 2003;126:1765–74.
[387] Wypij D, Jonas RA, Bellinger DC, Del Nido PJ, Mayer JE, Bacha EA *et al.* The effect of hematocrit during hypothermic cardiopulmonary bypass in infant heart surgery: results from the combined Boston hematocrit trials. J Thorac Cardiovasc Surg 2008;135:355–60.
[388] Pasquali SK, Li JS, He X, Jacobs ML, O'Brien SM, Hall M *et al.* Comparative analysis of antifibrinolytic medications in pediatric heart surgery. J Thorac Cardiovasc Surg 2012;143:550–7.
[389] Arnold DM, Fergusson DA, Chan AKC, Cook RJ, Fraser GA, Lim W *et al.* Avoiding transfusions in children undergoing cardiac surgery: a meta-analysis of randomized trials of aprotinin. Anesth Analg 2006;102:731–7.
[390] Johnson JN, Jaggers J, Li S, O'Brien SM, Li JS, Jacobs JP, Jacobs ML *et al.* Center variation and outcomes associated with delayed sternal closure after stage 1 palliation for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2010;139:1205–10.
[391] De Oliveira NC, Ashburn DA, Khalid F, Burkhart HM, Adatia IT, Holtby HM *et al.* Prevention of early sudden circulatory collapse after the Norwood operation. Circulation 2004;110:II-133–8.
[392] Furck AK, Hansen JH, Uebing A, Scheewe J, Jung O, Kramer H-H. The impact of afterload reduction on the early postoperative course after the Norwood operation—a 12-year single-centre experience. Eur J Cardiothorac Surg 2010;37:289–95.
[393] Mills KI, Kaza AK, Walsh BK, Bond HC, Ford M, Wypij D *et al.* Phosphodiesterase inhibitor-based vasodilation improves oxygen delivery and clinical outcomes following stage 1 palliation. J Am Heart Assoc 2016;5:e003554.
[394] Allan CK, Thiagarajan RR, del Nido PJ, Roth SJ, Almodovar MC, Laussen PC. Indication for initiation of mechanical circulatory support impacts survival of infants with shunted single-ventricle circulation supported with extracorporeal membrane oxygenation. J Thorac Cardiovasc Surg 2007;133:660–7.
[395] Ravishankar C, Dominguez TE, Kreutzer J, Wernovsky G, Marino BS, Godinez R *et al.* Extracorporeal membrane oxygenation after stage I reconstruction for hypoplastic left heart syndrome. Pediatr Crit Care Med 2006;7:319–23.
[396] Hirsch JC, Gurney JG, Donohue JE, Gebremariam A, Bove EL, Ohye RG. Hospital mortality for Norwood and arterial switch operations as a function of institutional volume. Pediatr Cardiol 2008;29:713–17.
[397] Pasquali SK, Jacobs JP, He X, Hornik CP, Jaquiss RD, Jacobs ML *et al.* The complex relationship between center volume and outcome in patients undergoing the Norwood operation. Ann Thorac Surg 2012; 93:1556–62.

[398] Checchia PA, McCollegan J, Daher N, Kolovos N, Levy F, Markovitz B. The effect of surgical case volume on outcome after the Norwood procedure. J Thorac Cardiovasc Surg 2005;129:754–9.
[399] Hornik CP, He X, Jacobs JP, Li JS, Jaquiss RDB, Jacobs ML *et al.* Relative impact of surgeon and center volume on early mortality after the Norwood operation. Ann Thorac Surg 2012;93:1992–7.
[400] Ferns SJ, El Zein C, Maruboyina SP, Subramanian S, Van Bergen AH, Ilbawi MN. Improved results of aortic arch reconstruction in the Norwood procedure. Ann Thorac Surg 2016;102:178–85.
[401] Poirier NC, Drummond-Webb JJ, Hisamochi K, Imamura M, Harrison AM, Mee RB. Modified Norwood procedure with a high-flow cardiopulmonary bypass strategy results in low mortality without late arch obstruction. J Thorac Cardiovasc Surg 2000;120:875–84.
[402] Fraser CD, Mee RB. Modified Norwood procedure for hypoplastic left heart syndrome. Ann Thorac Surg 1995;60:S546–9.
[403] Norwood WI. Hypoplastic left heart syndrome. Ann Thorac Surg 1991; 52:688–95.
[404] Januszewska K, Kozlik-Feldmann R, Dalla-Pozza R, Greil S, Abicht J, Netz H *et al.* Right ventricle-to-pulmonary artery shunt related complications after Norwood procedure. Eur J Cardiothorac Surg 2011;40:584–90.
[405] Tweddell JS. The Norwood procedure with an innominate artery-to-pulmonary artery shunt. Oper Tech Thorac Cardiovasc Surg 2005; 10:123–40.
[406] Konuma T, Sakamoto S, Toba S, Futsuki A, Yamamoto N, Kanemitsu S *et al.* Novel aortic arch reconstruction using a modified Norwood procedure based on hypoplastic left heart syndrome-specific anatomical malformations. Interact CardioVasc Thorac Surg 2018;27:243–9.
[407] Asada S, Yamagishi M, Itatani K, Yaku H. Chimney reconstruction of the aortic arch in the Norwood procedure. J Thorac Cardiovasc Surg 2017; 154:e51–4.
[408] Jonas RA, Lang P, Hansen D, Hickey P, Castaneda AR. First-stage palliation of hypoplastic left heart syndrome. The importance of coarctation and shunt size. J Thorac Cardiovasc Surg 1986;92:6–13.
[409] Norwood WI, Kirklin JK, Sanders SP. Hypoplastic left heart syndrome: experience with palliative surgery. Am J Cardiol 1980;45:87–91.
[410] Norwood WI, Lang P, Hansen DD. Physiologic repair of aortic atresia-hypoplastic left heart syndrome. N Engl J Med 1983;308:23–6.
[411] Bove EL. Current status of staged reconstruction for hypoplastic left heart syndrome. Pediatr Cardiol 1998;19:308–15.
[412] Bu'Lock FA, Stumper O, Jagtap R, Silove ED, De Giovanni JV, Wright JG *et al.* Surgery for infants with a hypoplastic systemic ventricle and severe outflow obstruction: early results with a modified Norwood procedure. Br Heart J 1995;73:456–61.
[413] Hansen JH, Petko C, Bauer G, Voges I, Kramer H-H, Scheewe J. Fifteen-year single-center experience with the Norwood operation for complex lesions with single-ventricle physiology compared with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2012;144:166–72.
[414] Itatani K, Miyaji K, Qian Y, Liu JL, Miyakoshi T, Murakami A *et al.* Influence of surgical arch reconstruction methods on single ventricle workload in the Norwood procedure. J Thorac Cardiovasc Surg 2012; 144:130–8.
[415] Larrazabal LA, Selamet Tierney ES, Brown DW, Gauvreau K, Vida VL, Bergersen L *et al.* Ventricular function deteriorates with recurrent coarctation in hypoplastic left heart syndrome. Ann Thorac Surg 2008; 86:869–74; discussion 869–74.
[416] Bautista-Hernandez V, Marx GR, Gauvreau K, Pigula FA, Bacha EA, Mayer JE *et al.* Coarctectomy reduces neoaortic arch obstruction in hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2007; 133:1540–6.
[417] Hasegawa T, Oshima Y, Maruo A, Matsuhisa H, Tanaka A, Noda R *et al.* Aortic arch geometry after the Norwood procedure: the value of arch angle augmentation. J Thorac Cardiovasc Surg 2015;150:358–66.
[418] Gargiulo G, Pace Napoleone C, Solinas M, Frascaroli G, Pierangeli AA. New patch for the Norwood procedure. Ann Thorac Surg 1999; 68:1873–4.
[419] Morell VO, Wearden PA. Experience with bovine pericardium for the reconstruction of the aortic arch in patients undergoing a Norwood procedure. Ann Thorac Surg 2007;84:1312–15.
[420] Griselli M, McGuirk SP, Stümper O, Clarke AJB, Miller P, Dhillon R *et al.* Influence of surgical strategies on outcome after the Norwood procedure. J Thorac Cardiovasc Surg 2006;131:418–26.
[421] Jacobs ML. Aortic reconstruction in hypoplastic left heart syndrome—a reappraisal. J Thorac Cardiovasc Surg 2000;120:872–4.
[422] Bichell DP, Lamberti JJ, Pelletier GJ, Hoecker C, Cocalis MW, Ing FF *et al.* Late left pulmonary artery stenosis after the Norwood procedure is prevented by a modification in shunt construction. Ann Thorac Surg 2005;79:1656–60; discussion 1660–1.
[423] Menon A, Jones T, Barron D, Stumper O, Brawn W. Posterior reduction aortoplasty for left pulmonary artery compression after Norwood procedure. Ann Thorac Surg 2011;91:1300–1.
[424] Burkhart HM, Ashburn DA, Konstantinov IE, De Oliviera NC, Benson L, Williams WG *et al.* Interdigitating arch reconstruction eliminates recurrent coarctation after the Norwood procedure. J Thorac Cardiovasc Surg 2005;130:61–5.
[425] Machii M, Becker AE. Nature of coarctation in hypoplastic left heart syndrome. Ann Thorac Surg 1995;59:1491–4.
[426] Jacobs ML, Rychik J, Murphy JD, Nicolson SC, Steven JM, Norwood WI. Results of Norwood's operation for lesions other than hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 1995;110:1555–61; discussion 1561–2.
[427] Thistlewaite PA, Myers JL, Siewers RD, Ettedgui JA. Technique for repair of single-ventricle hearts with transposition of the great arteries and aortic arch hypoplasia. Ann Thorac Surg 1999;67:260–2.
[428] van Son JA, Reddy VM, Haas GS, Hanley FL. Modified surgical techniques for relief of aortic obstruction in [S, L, L] hearts with rudimentary right ventricle and restrictive bulboventricular foramen. J Thorac Cardiovasc Surg 1995;110:909–15.
[429] Zeltser I, Menteer J, Gaynor JW, Spray TL, Clark BJ, Kreutzer J *et al.* Impact of re-coarctation following the Norwood operation on survival in the balloon angioplasty era. J Am Coll Cardiol 2005;45:1844–8.
[430] Zellers TM. Balloon angioplasty for recurrent coarctation of the aorta in patients following staged palliation for hypoplastic left heart syndrome. Am J Cardiol 1999;84:231–3, A9.
[431] Hill KD, Rhodes JF, Aiyagari R, Baker GH, Bergersen L, Chai PJ *et al.* Intervention for recoarctation in the Single Ventricle Reconstruction trial: incidence, risk, and outcomes. Circulation 2013;128:954–61.
[432] Tworetzky W, McElhinney DB, Burch GH, Teitel DF, Moore P. Balloon arterioplasty of recurrent coarctation after the modified Norwood procedure in infants. Catheter Cardiovasc Interv 2000;50:54–8.
[433] Lemler MS, Zellers TM, Harris KA, Ramaciotti C. Coarctation index: identification of recurrent coarctation in infants with hypoplastic left heart syndrome after the Norwood procedure. Am J Cardiol 2000;86:697–9, A9.
[434] Januszewska K, Kozlik-Feldmann R, Kordon Z, Urschel S, Netz H, Reichart B *et al.* Significance of the residual aortic obstruction in multistage repair of hypoplastic left heart syndrome. Eur J Cardiothorac Surg 2011;40:508–13.
[435] Cardis BM, Fyfe DA, Mahle WT. Elastic properties of the reconstructed aorta in hypoplastic left heart syndrome. Ann Thorac Surg 2006; 81:988–91.
[436] Ong CM, Canter CE, Gutierrez FR, Sekarski DR, Goldring DR. Increased stiffness and persistent narrowing of the aorta after successful repair of coarctation of the aorta: relationship to left ventricular mass and blood pressure at rest and with exercise. Am Heart J 1992; 123:1594–600.
[437] Kim GB, Kang SJ, Bae EJ, Yun YS, Noh CI, Lee JR *et al.* Elastic properties of the ascending aorta in young children after successful coarctoplasty in infancy. Int J Cardiol 2004;97:471–7.
[438] Mahle WT, Rychik J, Weinberg PM, Cohen MS. Growth characteristics of the aortic arch after the Norwood operation. J Am Coll Cardiol 1998; 32:1951–4.
[439] Sivanandam S, Mackey-Bojack SM, Moller JH. Pathology of the aortic arch in hypoplastic left heart syndrome: surgical implications. Pediatr Cardiol 2011;32:189–92.
[440] Lamers LJ, Frommelt PC, Mussatto KA, Jaquiss RDB, Mitchell ME, Tweddell JS. Coarctectomy combined with an interdigitating arch reconstruction results in a lower incidence of recurrent arch obstruction after the Norwood procedure than coarctectomy alone. J Thorac Cardiovasc Surg 2012;143:1098–102.
[441] Haller C, Chetan D, Saedi A, Parker R, Van Arsdell GS, Honjo O. Geometry and growth of the reconstructed aorta in patients with hypoplastic left heart syndrome and variants. J Thorac Cardiovasc Surg 2017; 153:1479–87.e1.
[442] Karamichalis JM, Thiagarajan RR, Liu H, Mamic P, Gauvreau K, Bacha EA. Stage I Norwood: optimal technical performance improves outcomes irrespective of preoperative physiologic status or case complexity. J Thorac Cardiovasc Surg 2010;139:962–8.
[443] Mahle WT, Rychik J, Gaynor JW, Spray TL, Rome JJ. Restrictive interatrial communication after reconstructive surgery for hypoplastic left heart syndrome. Am J Cardiol 2001;88:1454–7, A9.

[444] Weinberg PM, Chin AJ, Murphy JD, Pigott JD, Norwood WI. Postmortem echocardiography and tomographic anatomy of hypoplastic left heart syndrome after palliative surgery. Am J Cardiol 1986; 58:1228–32.
[445] Forbess JM, Cook N, Serraf A, Burke RP, Mayer JE, Jonas RA. An institutional experience with second- and third-stage palliative procedures for hypoplastic left heart syndrome: the impact of the bidirectional cavopulmonary shunt. J Am Coll Cardiol 1997;29:665–70.
[446] Norwood WI, Lang P, Castaneda AR, Campbell DN. Experience with operations for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 1981;82:511–19.
[447] Lamberti JJ, Carlisle J, Waldman JD, Lodge FA, Kirkpatrick SE, George L *et al.* Systemic-pulmonary shunts in infants and children. Early and late results. J Thorac Cardiovasc Surg 1984;88:76–81.
[448] Amato JJ, Marbey ML, Bush C, Galdieri RJ, Cotroneo JV, Bushong J. Systemic-pulmonary polytetrafluoroethylene shunts in palliative operations for congenital heart disease. Revival of the central shunt. J Thorac Cardiovasc Surg 1988;95:62–9.
[449] Vitanova K, Leopold C, von Ohain J, Wolf C, Beran E, Lange R *et al.* Reasons for failure of systemic-to-pulmonary artery shunts in neonates. Thorac Cardiovasc Surg 2019;67:2–7.
[450] Bartram U, Grünenfelder J, Van Praagh R. Causes of death after the modified Norwood procedure: a study of 122 postmortem cases. Ann Thorac Surg 1997;64:1795–802.
[451] Murdison KA, Baffa JM, Farrell PE, Chang AC, Barber G, Norwood WI *et al.* Hypoplastic left heart syndrome. Outcome after initial reconstruction and before modified Fontan procedure. Circulation 1990; 82:IV199–207.
[452] Alboliras ET, Chin AJ, Barber G, Helton JG, Pigott JD, Norwood WI. Pulmonary artery configuration after palliative operations for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 1989;97:878–85.
[453] Kanter KR, Miller BE, Cuadrado AG, Vincent RN. Successful application of the Norwood procedure for infants without hypoplastic left heart syndrome. Ann Thorac Surg 1995;59:301–4.
[454] Lang P, Norwood WI. Hemodynamic assessment after palliative surgery for hypoplastic left heart syndrome. Circulation 1983;68:104–8.
[455] Bove EL, Sondheimer HM, Kavey RE, Byrum CJ, Blackman MS, Parker FB. Subclavian-pulmonary artery shunts with polytetrafluorethylene interposition grafts. Ann Thorac Surg 1984;37:88–91.
[456] Donahoo JS, Gardner TJ, Zahka K, Kidd BS. Systemic-pulmonary shunts in neonates and infants using microporous expanded polytetrafluoroethylene: immediate and late results. Ann Thorac Surg 1980;30:146–50.
[457] Bando K, Turrentine MW, Sun K, Sharp TG, Caldwell RL, Darragh RK *et al.* Surgical management of hypoplastic left heart syndrome. Ann Thorac Surg 1996;62:70–6; discussion 76–7.
[458] Maher KO, Pizarro C, Gidding SS, Januszewska K, Malec E, Norwood WI *et al.* Hemodynamic profile after the Norwood procedure with right ventricle to pulmonary artery conduit. Circulation 2003;108:782–4.
[459] Mroczek T, Małota Z, Wójcik E, Nawrat Z, Skalski J. Norwood with right ventricle-to-pulmonary artery conduit is more effective than Norwood with Blalock-Taussig shunt for hypoplastic left heart syndrome: mathematic modeling of hemodynamics. Eur J Cardiothorac Surg 2011; 40:1412–17; discussion 1417–18.
[460] Harrison AM, Davis S, Reid JR, Morrison SC, Arrigain S, Connor JT *et al.* Neonates with hypoplastic left heart syndrome have ultrasound evidence of abnormal superior mesenteric artery perfusion before and after modified Norwood procedure. Pediatr Crit Care Med 2005; 6:445–7.
[461] Johnson JN, Ansong AK, Li JS, Xu M, Gorentz J, Hehir DA *et al.* Celiac artery flow pattern in infants with single right ventricle following the Norwood procedure with a modified Blalock-Taussig or right ventricle to pulmonary artery shunt. Pediatr Cardiol 2011;32:479–86.
[462] Mahle WT, Spray TL, Gaynor JW, Clark BJ. Unexpected death after reconstructive surgery for hypoplastic left heart syndrome. Ann Thorac Surg 2001;71:61–5.
[463] Donnelly JP, Raffel DM, Shulkin BL, Corbett JR, Bove EL, Mosca RS *et al.* Resting coronary flow and coronary flow reserve in human infants after repair or palliation of congenital heart defects as measured by positron emission tomography. J Thorac Cardiovasc Surg 1998;115:103–10.
[464] Asakai H, Galati JC, Weskamp S, Jones B, Millar J, Konstantinov IE *et al.* Impact of Blalock-Taussig shunt size on tricuspid regurgitation in hypoplastic left heart syndrome. Ann Thorac Surg 2014;97:2123–8.
[465] Myers JW, Ghanayem NS, Cao Y, Simpson P, Trapp K, Mitchell ME *et al.* Outcomes of systemic to pulmonary artery shunts in patients weighing less than 3 kg: analysis of shunt type, size, and surgical approach. J Thorac Cardiovasc Surg 2014;147:672–7.
[466] Schmid FX, Kampmann C, Kuroczynski W, Choi YH, Knuf M, Tzanova I *et al.* Adjustable tourniquet to manipulate pulmonary blood flow after Norwood operations. Ann Thorac Surg 1999;68:2306–9.
[467] McGuirk SP, Griselli M, Stumper OF, Rumball EM, Miller P, Dhillon R *et al.* Staged surgical management of hypoplastic left heart syndrome: a single institution 12 year experience. Heart 2006;92:364–70.
[468] Pizarro C, Davis D, Galantowicz M, Munro H, Gidding S, Norwood W. Stage I palliation for hypoplastic left heart syndrome in low birth weight neonates: can we justify it? Eur J Cardiothorac Surg 2002;21:716–20.
[469] Rüffer A, Danch A, Gottschalk U, Mir T, Lacour-Gayet F, Haun C *et al.* The Norwood procedure—does the type of shunt determine outcome? Thorac Cardiovasc Surg 2009;57:270–5.
[470] Gates RN, Palafox BA, Parker B. Technique for the Norwood procedure using normothermic selective cerebral perfusion. ASAIO J 2007;53:655–8.
[471] Imoto Y, Kado H, Shiokawa Y, Fukae K, Yasui H. Norwood procedure without circulatory arrest. Ann Thorac Surg 1999;68:559–61.
[472] Kishimoto H, Kawahira Y, Kawata H, Miura T, Iwai S, Mori T. The modified Norwood palliation on a beating heart. J Thorac Cardiovasc Surg 1999;118:1130–2.
[473] Pigula FA, Nemoto EM, Griffith BP, Siewers RD. Regional low-flow perfusion provides cerebral circulatory support during neonatal aortic arch reconstruction. J Thorac Cardiovasc Surg 2000;119:331–9.
[474] Newburger JW, Sleeper LA, Bellinger DC, Goldberg CS, Tabbutt S, Lu M *et al.* Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies: the Single Ventricle Reconstruction trial. Circulation 2012;125:2081–91.
[475] Vuylsteke A, Sharples L, Charman G, Kneeshaw J, Tsui S, Dunning J *et al.* Circulatory arrest versus cerebral perfusion during pulmonary endarterectomy surgery (PEACOG): a randomised controlled trial. Lancet 2011; 378:1379–87.
[476] Hammel JM, Deptula JJ, Siecke R, Abdullah I, Duncan KF. Descending aortic and innominate artery cannulation for aortic arch repair with mildly hypothermic continuous cardiopulmonary bypass in infants and children. World J Pediatr Congenit Heart Surg 2013;4:418–21.
[477] Do N, Hill KD, Wallace AS, Vricella L, Cameron D, Quintessenza J *et al.* Shunt failure-risk factors and outcomes: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. Ann Thorac Surg 2018;105:857–64.
[478] Fenton KN, Siewers RD, Rebovich B, Pigula FA. Interim mortality in infants with systemic-to-pulmonary artery shunts. Ann Thorac Surg 2003;76:152–6; discussion 156–7.
[479] Truong DT, Johnson JT, Bailly DK, Clawson JR, Sheng X, Burch PT *et al.* Platelet inhibition in shunted infants on aspirin at short and midterm follow-up. Pediatr Cardiol 2017;38:401–9.
[480] Emani S, Trainor B, Zurakowski D, Baird CW, Fynn-Thompson FE, Pigula FA *et al.* Aspirin unresponsiveness predicts thrombosis in high-risk pediatric patients after cardiac surgery. J Thorac Cardiovasc Surg 2014; 148:810–14; discussion 814–16.
[481] Saini A, Joshi AD, Cowan KM, Wayne Gatewood C, Kumar STK, Allen J *et al.* High acetylsalicylic acid dosing in infants after modified Blalock-Taussig shunt. Cardiol Young 2019;29:389–97.
[482] Ambarsari YA, Purbojo A, Blumauer R, Glöckler M, Toka O, Cesnjevar RA *et al.* Systemic-to-pulmonary artery shunting using heparin-bonded grafts. Interact CardioVasc Thorac Surg 2018;27:591–7.
[483] Malec E, Januszewska K, Kolcz J, Mroczek T. Right ventricle-to-pulmonary artery shunt versus modified Blalock-Taussig shunt in the Norwood procedure for hypoplastic left heart syndrome—influence on early and late haemodynamic status. Eur J Cardiothorac Surg 2003; 23:728–33; discussion 733–4.
[484] Pizarro C, Malec E, Maher KO, Januszewska K, Gidding SS, Murdison KA *et al.* Right ventricle to pulmonary artery conduit improves outcome after stage I Norwood for hypoplastic left heart syndrome. Circulation 2003;108:II-155–60.
[485] Mair R, Tulzer G, Sames E, Gitter R, Lechner E, Steiner J *et al.* Right ventricular to pulmonary artery conduit instead of modified Blalock-Taussig shunt improves postoperative hemodynamics in newborns after the Norwood operation. J Thorac Cardiovasc Surg 2003;126:1378–84.
[486] Menon SC, Erickson LK, McFadden M, Miller DV. Effect of ventriculotomy on right-ventricular remodeling in hypoplastic left heart syndrome: a histopathological and echocardiography correlation study. Pediatr Cardiol 2013;34:354–63.
[487] Tanoue Y, Kado H, Shiokawa Y, Fusazaki N, Ishikawa S. Midterm ventricular performance after Norwood procedure with right ventricular-

pulmonary artery conduit. Ann Thorac Surg 2004;78:1965–71; discussion 1971.
[488] Briceno-Medina M, Kumar TKS, Sathanandam S, Boston U, Perez M, Allen J *et al.* Femoral vein homograft as Sano shunt results in improved pulmonary artery growth after Norwood operation. Cardiol Young 2018;28:118–25.
[489] Reinhartz O, Reddy VM, Petrossian E, MacDonald M, Lamberti JJ, Roth SJ *et al.* Homograft valved right ventricle to pulmonary artery conduit as a modification of the Norwood procedure. Circulation 2006;114:I-594–9.
[490] Kumar TKS, Zurakowski D, Briceno-Medina M, Shah A, Sathanandam S, Allen J *et al.* Experience of a single institution with femoral vein homograft as right ventricle to pulmonary artery conduit in stage 1 Norwood operation. J Thorac Cardiovasc Surg 2019;158:853–62.e1.
[491] Gist KM, Barrett CS, Graham DA, Crumback SL, Schuchardt EL, Erickson B *et al.* Pulmonary artery interventions after Norwood procedure: does type or position of shunt predict need for intervention? J Thorac Cardiovasc Surg 2013;145:1485–92.
[492] Januszewska K, Kozlik-Feldmann R, Abicht J, Dalla-Pozza R, Malec E. Right ventricle-to-pulmonary artery shunt in Norwood procedure: early results. World J Pediatr Congenit Heart Surg 2010;1:44–50.
[493] Kolcz J, Skladzien T, Kordon Z, Rudzinski A, Skalski J. Impact of right ventricle-pulmonary artery conduit placement on pulmonary artery development after the Norwood procedure in hypoplastic left heart syndrome. Eur J Cardiothorac Surg 2012;42:218–23; discussion 223–4.
[494] Photiadis J, Sinzobahamvya N, Haun C, Schneider M, Zartner P, Schindler E *et al.* Does the shunt type determine mid-term outcome after Norwood operation? Eur J Cardiothorac Surg 2012;42:209–15; discussion 215–16.
[495] Ohye RG, Ludomirsky A, Devaney EJ, Bove EL. Comparison of right ventricle to pulmonary artery conduit and modified Blalock-Taussig shunt hemodynamics after the Norwood operation. Ann Thorac Surg 2004; 78:1090–3.
[496] Karimi M, Farouk A, Stork J, Hennein HA. Right ventricular aneurysm following modified Norwood-Sano operation for hypoplastic left heart syndrome. Interact CardioVasc Thorac Surg 2008;7:664–6.
[497] Mahle WT, Cuadrado AR, Tam V. Early experience with a modified Norwood procedure using right ventricle to pulmonary artery conduit. Ann Thorac Surg 2003;76:1084–8; discussion 1089.
[498] Buelow MW, Rudd N, Tanem J, Simpson P, Bartz P, Hill G. Reintervention following stage 1 palliation: a report from the NPC-QIC Registry. Congenit Heart Dis 2018;13:919–26.
[499] Fischbach J, Sinzobahamvya N, Haun C, Schindler E, Zartner P, Schneider M *et al.* Interventions after Norwood procedure: comparison of Sano and modified Blalock-Taussig shunt. Pediatr Cardiol 2013; 34:112–18.
[500] Rumball EM, McGuirk SP, Stümper O, Laker SJ, de Giovanni JV, Wright JG *et al.* The RV-PA conduit stimulates better growth of the pulmonary arteries in hypoplastic left heart syndrome. Eur J Cardiothorac Surg 2005;27:801–6.
[501] Mascio CE, Spray TL. Distal dunk for right ventricle to pulmonary artery shunt in stage 1 palliation. Ann Thorac Surg 2015;100:2381–2.
[502] Mroczek T, Sacharczuk J, Żurek R, Morka A, Szypulski A, Jarosz J *et al.* The "double dunk" technique for a right ventricle to pulmonary artery conduit implantation during the Norwood procedure reduces unintended shunt-related events. Kardiol Pol 2018;76:1697–704.
[503] Schreiber C, Kasnar-Samprec J, Hörer J, Eicken A, Cleuziou J, Prodan Z *et al.* Ring-enforced right ventricle-to-pulmonary artery conduit in Norwood stage I reduces proximal conduit stenosis. Ann Thorac Surg 2009;88:1541–5.
[504] Tsukashita M, Mosca RS. Periscope modification of right ventricle-to-pulmonary artery shunt in Norwood operation. Ann Thorac Surg 2014; 98:2244–6.
[505] Graziano JN, Heidelberger KP, Ensing GJ, Gomez CA, Ludomirsky A. The influence of a restrictive atrial septal defect on pulmonary vascular morphology in patients with hypoplastic left heart syndrome. Pediatr Cardiol 2002;23:146–51.
[506] Maeda K, Yamaki S, Kado H, Asou T, Murakami A, Takamoto S. Hypoplasia of the small pulmonary arteries in hypoplastic left heart syndrome with restrictive atrial septal defect. Circulation 2004;110:II-139–46.
[507] Atz AM, Feinstein JA, Jonas RA, Perry SB, Wessel DL. Preoperative management of pulmonary venous hypertension in hypoplastic left heart syndrome with restrictive atrial septal defect. Am J Cardiol 1999; 83:1224–8.
[508] Murphy MO, Bellsham-Revell H, Morgan GJ, Krasemann T, Rosenthal E, Qureshi SA *et al.* Hybrid procedure for neonates with hypoplastic left heart syndrome at high-risk for Norwood: midterm outcomes. Ann Thorac Surg 2015;100:2286–90; discussion 2291–2.
[509] Barber G, Helton JG, Aglira BA, Chin AJ, Murphy JD, Pigott JD *et al.* The significance of tricuspid regurgitation in hypoplastic left-heart syndrome. Am Heart J 1988;116:1563–7.
[510] Elmi M, Hickey EJ, Williams WG, Van Arsdell G, Caldarone CA, McCrindle BW. Long-term tricuspid valve function after Norwood operation. J Thorac Cardiovasc Surg 2011;142:1341–7.e4.
[511] Bautista-Hernandez V, Brown DW, Loyola H, Myers PO, Borisuk M, del Nido PJ *et al.* Mechanisms of tricuspid regurgitation in patients with hypoplastic left heart syndrome undergoing tricuspid valvuloplasty. J Thorac Cardiovasc Surg 2014;148:832–8; discussion 838–40.
[512] Pigula FA, Mettler B. Management of tricuspid regurgitation in patients with hypoplastic left heart syndrome. Semin Thorac Cardiovasc Surg 2017;29:64–9.
[513] Frommelt PC, Gerstenberger E, Cnota JF, Cohen MS, Gorentz J, Hill KD *et al.* Impact of initial shunt type on cardiac size and function in children with single right ventricle anomalies before the Fontan procedure: the Single Ventricle Reconstruction extension trial. J Am Coll Cardiol 2014; 64:2026–35.
[514] Takahashi K, Inage A, Rebeyka IM, Ross DB, Thompson RB, Mackie AS *et al.* Real-time 3-dimensional echocardiography provides new insight into mechanisms of tricuspid valve regurgitation in patients with hypoplastic left heart syndrome. Circulation 2009;120:1091–8.
[515] Tsang VT, Raja SG. Tricuspid valve repair in single ventricle: timing and techniques. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2012;15:61–8.
[516] Baba K, Honjo O, Chaturvedi R, Lee K-J, Van Arsdell G, Caldarone CA *et al.* "Reverse Blalock-Taussig shunt": application in single ventricle hybrid palliation. J Thorac Cardiovasc Surg 2013;146:352–7.
[517] Ohye RG, Gomez CA, Goldberg CS, Graves HL, Devaney EJ, Bove EL. Tricuspid valve repair in hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2004;127:465–72.
[518] Alsoufi B, Sinha R, McCracken C, Figueroa J, Altin F, Kanter K. Outcomes and risk factors associated with tricuspid valve repair in children with hypoplastic left heart syndrome. Eur J Cardiothorac Surg 2018; 54:993–1000.
[519] Huang S-C, Chen Y-S, Chang C-I, Chiu I-S. Outcome of tricuspid valve plasty in Norwood stage I operation. Circ J 2016;80:1362–70.
[520] Sugiura J, Nakano T, Oda S, Usui A, Ueda Y, Kado H. Effects of tricuspid valve surgery on tricuspid regurgitation in patients with hypoplastic left heart syndrome: a non-randomized series comparing surgical and non-surgical cases. Eur J Cardiothorac Surg 2014;46:8–13.
[521] Ota N, Ikai A, Hirose K, Sakamoto K. Retrospective analysis of stage I Norwood procedures with tricuspid valve insufficiency in the past 5 years. Interact CardioVasc Thorac Surg 2007;6:121–3.
[522] Sano S, Fujii Y, Arai S, Kasahara S, Tateishi A. Atrioventricular valve repair for patient with heterotaxy syndrome and a functional single ventricle. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2012; 15:88–95.
[523] Honjo O, Atlin CR, Mertens L, Al-Radi OO, Redington AN, Caldarone CA *et al.* Atrioventricular valve repair in patients with functional single-ventricle physiology: impact of ventricular and valve function and morphology on survival and reintervention. J Thorac Cardiovasc Surg 2011; 142:326–35.e2.
[524] Ugaki S, Khoo NS, Ross DB, Rebeyka IM, Adatia I. Tricuspid valve repair improves early right ventricular and tricuspid valve remodeling in patients with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2013;145:446–50.
[525] Hickey EJ, Caldarone CA, Blackstone EH, Williams WG, Yeh T, Pizarro C *et al.* Biventricular strategies for neonatal critical aortic stenosis: high mortality associated with early reintervention. J Thorac Cardiovasc Surg 2012;144:409–17, 417.e1.
[526] Emani SM, Bacha EA, McElhinney DB, Marx GR, Tworetzky W, Pigula FA *et al.* Primary left ventricular rehabilitation is effective in maintaining two-ventricle physiology in the borderline left heart. J Thorac Cardiovasc Surg 2009;138:1276–82.
[527] Myers PO, Baird CW, Del Nido PJ, Pigula FA, Lang N, Marx GR *et al.* Neonatal mitral valve repair in bi-Ventricular repair, single ventricle palliation, and secondary left ventricular recruitment: indications, techniques, and mid-term outcomes. Front Surg 2015;2:59.
[528] Emani SM, McElhinney DB, Tworetzky W, Myers PO, Schroeder B, Zurakowski D *et al.* Staged left ventricular recruitment after single-

ventricle palliation in patients with borderline left heart hypoplasia. J Am Coll Cardiol 2012;60:1966–74.
[529] Bharati S, Nordenberg A, Brock RR, Lev M. Hypoplastic left heart syndrome with dysplastic pulmonary valve with stenosis. Pediatr Cardiol 1984;5:127–30.
[530] Cantinotti M, Costa S, Assanta N. Prenatal diagnosis of a rare case of hypoplastic left heart syndrome associated with pulmonary valve stenosis. Pediatr Cardiol 2010;31:745–6.
[531] Farra H, Kort HW. Hypoplastic left heart syndrome and valvar pulmonary stenosis: presentation and management. Pediatr Cardiol 2005; 26:680–2.
[532] Aggarwal S, Delius RE, Walters HL, Natarajan G. Hypoplastic left heart syndrome, restrictive patent foramen ovale, and pulmonary valve stenosis: an unusual combination. Pediatr Cardiol 2012;33:357–9.
[533] Huang S-C, Shih J-C, Lin M-T, Wu E-T. Hypoplastic left heart syndrome with valvular pulmonary stenosis: successful management with Norwood staged reconstruction. Ann Thorac Surg 2011;92:1115–16.
[534] Baffa JM, Chen SL, Guttenberg ME, Norwood WI, Weinberg PM. Coronary artery abnormalities and right ventricular histology in hypoplastic left heart syndrome. J Am Coll Cardiol 1992;20:350–8.
[535] Saroli T, Gelehrter S, Gomez-Fifer CA, van der Velde ME, Bove EL, Ensing GJ. Anomalies of left coronary artery origin affecting surgical repair of hypoplastic left heart syndrome and Shone complex. Echocardiography 2008;25:727–31.
[536] Nathan M, Emani S, Marx G, Pigula F. Anomalous left coronary artery arising from the pulmonary artery in hypoplastic left hearts: case series and review of literature. J Thorac Cardiovasc Surg 2011;142:225–7.
[537] Turiy Y, Douglas W, Balaguru D. Anomalous origin of coronary artery from main pulmonary artery in hypoplastic left heart syndrome. Ann Thorac Surg 2015;100:2346–8.
[538] Sauer U, Gittenberger-de Groot AC, Geishauser M, Babic R, Bühlmeyer K. Coronary arteries in the hypoplastic left heart syndrome. Histopathologic and histometrical studies and implications for surgery. Circulation 1989;80:I168–76.
[539] Polimenakos AC, Sathanandam SK, Husayni TS, El Zein CF, Roberson DA, Ilbawi MN. Hypoplastic left heart syndrome and aortic atresia-mitral stenosis variant: role of myocardial protection strategy and impact of ventriculo-coronary connections after stage I palliation. Pediatr Cardiol 2011;32:929–39.
[540] Jacobs JP, Mayer JE, Pasquali SK, Hill KD, Overman DM, St Louis JD *et al.* The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2019 update on outcomes and quality. Ann Thorac Surg 2019; 107:691–704.
[541] Mascio CE, Austin EH, Jacobs JP, Jacobs ML, Wallace AS, He X *et al.* Perioperative mechanical circulatory support in children: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. J Thorac Cardiovasc Surg 2014;147:658–64; discussion 664–5.
[542] Bergs J, Hellings J, Cleemput I, Zurel Ö, De Troyer V, Van Hiel M *et al.* Systematic review and meta-analysis of the effect of the World Health Organization surgical safety checklist on postoperative complications. Br J Surg 2014;101:150–8.
[543] Sivarajan VB, Bohn D. Monitoring of standard hemodynamic parameters: heart rate, systemic blood pressure, atrial pressure, pulse oximetry, and end-tidal CO2. Pediatr Crit Care Med 2011;12(4 Suppl):S2–11.
[544] Checchia PA, Laussen PC. The cardiac intensive care unit perspective on hemodynamic monitoring of oxygen transport balance. Pediatr Crit Care Med 2011;12(4 Suppl):S69–71.
[545] Muhiudeen IA, Roberson DA, Silverman NH, Haas GS, Turley K, Cahalan MK. Intraoperative echocardiography for evaluation of congenital heart defects in infants and children. Anesthesiology 1992;76:165–72.
[546] Agarwal HS, Barrett SS, Barry K, Xu M, Saville BR, Donahue BS *et al.* Association of blood products administration during cardiopulmonary bypass and excessive post-operative bleeding in pediatric cardiac surgery. Pediatr Cardiol 2015;36:459–67.
[547] Székely A, Cserép Z, Sápi E, Breuer T, Nagy CA, Vargha P *et al.* Risks and predictors of blood transfusion in pediatric patients undergoing open heart operations. Ann Thorac Surg 2009;87:187–97.
[548] Capraro L, Kuitunen A, Salmenperä M, Kekomäki R. On-site coagulation monitoring does not affect hemostatic outcome after cardiac surgery. Acta Anaesthesiol Scand 2001;45:200–6.
[549] Ootaki Y, Yamaguchi M, Yoshimura N, Oka S, Yoshida M, Hasegawa T. Efficacy of a criterion-driven transfusion protocol in patients having pediatric cardiac surgery. J Thorac Cardiovasc Surg 2004;127:953–8.
[550] Giglia TM, Witmer C. Bleeding and thrombosis in pediatric cardiac intensive care. Pediatr Crit Care Med 2016;17(8 Suppl 1):S287–95.
[551] Beke DM, Braudis NJ, Lincoln P. Management of the pediatric postoperative cardiac surgery patient. Crit Care Nurs Clin North Am 2005; 17:405–16, xi.
[552] Rhodes LA, Wall KM, Abernathy SL, Moellinger AB, Borasino S, Alten JA. Decreasing IV potassium in pediatric cardiac intensive care: quality improvement project. Pediatr Crit Care Med 2016;17:772–8.
[553] Rossi AF, Khan DM, Hannan R, Bolivar J, Zaidenweber M, Burke R. Goal-directed medical therapy and point-of-care testing improve outcomes after congenital heart surgery. Intensive Care Med 2005;31:98–104.
[554] Tabbutt S, Tweddell JS, Ghanayem N. Hypoplastic left heart syndrome and other shunt-dependent single ventricles. Pediatr Crit Care Med 2016;17(8 Suppl 1):S318–22.
[555] Wright GE, Crowley DC, Charpie JR, Ohye RG, Bove EL, Kulik TJ. High systemic vascular resistance and sudden cardiovascular collapse in recovering Norwood patients. Ann Thorac Surg 2004;77:48–52.
[556] Karamichalis JM, del Nido PJ, Thiagarajan RR, Jenkins KJ, Liu H, Gauvreau K *et al.* Early postoperative severity of illness predicts outcomes after the stage I Norwood procedure. Ann Thorac Surg 2011; 92:660–5.
[557] Bacha EA, Larrazabal LA, Pigula FA, Gauvreau K, Jenkins KJ, Colan SD *et al.* Measurement of technical performance in surgery for congenital heart disease: the stage I Norwood procedure. J Thorac Cardiovasc Surg 2008;136:993–7, 997.e1–2.
[558] Poullis M. Estimation of oxygen delivery in newborns with a univentricular circulation. Circulation 1999;100:685–8.
[559] Crowley R, Sanchez E, Ho JK, Lee KJ, Schwarzenberger J, Marijic J *et al.* Prolonged central venous desaturation measured by continuous oximetry is associated with adverse outcomes in pediatric cardiac surgery. Anesthesiology 2011;115:1033–43.
[560] Andropoulos DB, Hunter JV, Nelson DP, Stayer SA, Stark AR, McKenzie ED *et al.* Brain immaturity is associated with brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring. J Thorac Cardiovasc Surg 2010;139:543–56.
[561] Hoffman GM, Stuth EA, Jaquiss RD, Vanderwal PL, Staudt SR, Troshynski TJ *et al.* Changes in cerebral and somatic oxygenation during stage 1 palliation of hypoplastic left heart syndrome using continuous regional cerebral perfusion. J Thorac Cardiovasc Surg 2004;127:223–33.
[562] Baronov D, McManus M, Butler E, Chung D, Almodovar MC. Next generation patient monitor powered by in-silico physiology. Conf Proc IEEE Eng Med Biol Soc 2015;2015:4447–53.
[563] Salvin J, Baronov D, Laussen P. The impact of a Real Time Physiologic Data Analytic Index on LOS in neonates following surgery for congenital heart disease. Circulation 2018;136:A20603.
[564] Gruenwald CE, McCrindle BW, Crawford-Lean L, Holtby H, Parshuram C, Massicotte P *et al.* Reconstituted fresh whole blood improves clinical outcomes compared with stored component blood therapy for neonates undergoing cardiopulmonary bypass for cardiac surgery: a randomized controlled trial. J Thorac Cardiovasc Surg 2008;136:1442–9.
[565] Giglia TM, Massicotte MP, Tweddell JS, Barst RJ, Bauman M, Erickson CC *et al.* Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. Circulation 2013;128:2622–703.
[566] Scodellaro T, McKenzie JM, d'Udekem Y, Butt W, Namachivayam SP. Extubation failure is associated with increased mortality following first stage single ventricle reconstruction operation. Pediatr Crit Care Med 2017;18:1136–44.
[567] Brown KL, Ridout DA, Goldman AP, Hoskote A, Penny DJ. Risk factors for long intensive care unit stay after cardiopulmonary bypass in children. Crit Care Med 2003;31:28–33.
[568] Prodhan P, Agarwal A, ElHassan NO, Bolin EH, Beam B, Garcia X *et al.* Tracheostomy among infants with hypoplastic left heart syndrome undergoing cardiac operations: a multicenter analysis. Ann Thorac Surg 2017;103:1308–14.
[569] Hoskote A, Cohen G, Goldman A, Shekerdemian L. Tracheostomy in infants and children after cardiothoracic surgery: indications, associated risk factors, and timing. J Thorac Cardiovasc Surg 2005;130:1086–93.
[570] Chang AC, Atz AM, Wernovsky G, Burke RP, Wessel DL. Milrinone: systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. Crit Care Med 1995;23:1907–14.
[571] Barrington K, Chan W. The circulatory effects of epinephrine infusion in the anesthesized piglet. Pediatr Res 1993;33:190–4.
[572] Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: the COMFORT scale. J Pediatr Psychol 1992;17:95–109.

[573] Lucas SS, Nasr VG, Ng AJ, Joe C, Bond M, DiNardo JA. Pediatric Cardiac Intensive Care Society 2014 consensus statement: pharmacotherapies in cardiac critical care: sedation, analgesia and muscle relaxant. Pediatr Crit Care Med 2016;17:S3–15.
[574] Wernovsky G, Wypij D, Jonas RA, Mayer JE, Hanley FL, Hickey PR *et al.* Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 1995;92:2226–35.
[575] Soto-Rivera CL, Agus MSD, Sawyer JE, Macrae DJ. Pediatric Cardiac Intensive Care Society 2014 consensus statement: pharmacotherapies in cardiac critical care hormone replacement therapy. Pediatr Crit Care Med 2016;17:S59–68.
[576] Alten JA, Klugman D, Raymond TT, Cooper DS, Donohue JE, Zhang W *et al.* Epidemiology and outcomes of cardiac arrest in pediatric cardiac ICUs. Pediatr Crit Care Med 2017;18:935–43.
[577] Pasquali SK, Ohye RG, Lu M, Kaltman J, Caldarone CA, Pizarro C *et al.* Variation in perioperative care across centers for infants undergoing the Norwood procedure. J Thorac Cardiovasc Surg 2012;144:915–21.
[578] Mills KI, van den Bosch SJ, Gauvreau K, Allan CK, Thiagarajan RR, Hoganson DM *et al.* Physiologic effects of delayed sternal closure following stage 1 palliation. Cardiol Young 2018;28:1393–403.
[579] Sherwin ED, Gauvreau K, Scheurer MA, Rycus PT, Salvin JW, Almodovar MC *et al.* Extracorporeal membrane oxygenation after stage 1 palliation for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2012; 144:1337–43.
[580] Jaggers JJ, Forbess JM, Shah AS, Meliones JN, Kirshbom PM, Miller CE *et al.* Extracorporeal membrane oxygenation for infant postcardiotomy support: significance of shunt management. Ann Thorac Surg 2000; 69:1476–83.
[581] Barrett CS, Bratton SL, Salvin JW, Laussen PC, Rycus PT, Thiagarajan RR. Neurological injury after extracorporeal membrane oxygenation use to aid pediatric cardiopulmonary resuscitation. Pediatr Crit Care Med 2009;10:445–51.
[582] Pasquali SK, He X, Jacobs JP, Jacobs ML, O'Brien SM, Gaynor JW. Evaluation of failure to rescue as a quality metric in pediatric heart surgery: an analysis of the STS Congenital Heart Surgery Database. Ann Thorac Surg 2012;94:573–9; discussion 579–80.
[583] Garcia RU, Natarajan G, Walters HL, Delius RE, Aggarwal S. Acute kidney injury following first-stage palliation in hypoplastic left heart syndrome: hybrid versus Norwood palliation. Cardiol Young 2018;28:261–8.
[584] Wong JH, Selewski DT, Yu S, Leopold KE, Roberts KH, Donohue JE *et al.* Severe acute kidney injury following stage 1 Norwood palliation: effect on outcomes and risk of severe acute kidney injury at subsequent surgical stages. Pediatr Crit Care Med 2016;17:615–23.
[585] Welke KF, Dearani JA, Ghanayem NS, Beland MJ, Shen I, Ebels T. Renal complications associated with the treatment of patients with congenital cardiac disease: consensus definitions from the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease. Cardiol Young 2008;18:222–5.
[586] Kakajiwala A, Kim JY, Hughes JZ, Costarino A, Ferguson J, Gaynor JW *et al.* Lack of furosemide responsiveness predicts acute kidney injury in infants after cardiac surgery. Ann Thorac Surg 2017;104:1388–94.
[587] Brown KL, Pagel C, Brimmell R, Bull K, Davis P, Franklin RC *et al.* Definition of important early morbidities related to paediatric cardiac surgery. Cardiol Young 2017;27:747–56.
[588] Kwiatkowski DM, Goldstein SL, Cooper DS, Nelson DP, Morales DLS, Krawczeski CD. Dialysis vs furosemide for prevention of fluid overload in infants after cardiac surgery: a randomized clinical trial. JAMA Pediatr 2017;171:357–64.
[589] Ghanayem NS, Dearani JA, Welke KF, Béland MJ, Shen I, Ebels T. Gastrointestinal complications associated with the treatment of patients with congenital cardiac disease: consensus definitions from the Multi-Societal Database Committee for Pediatric and Congenital Heart Disease. Cardiol Young 2008;18:240–4.
[590] Mehta NM, Bechard LJ, Leavitt K, Duggan C. Cumulative energy imbalance in the pediatric intensive care unit: role of targeted indirect calorimetry. JPEN J Parenter Enteral Nutr 2009;33:336–44.
[591] Mehta NM, Compher C; A.S.P.E.N. Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr 2009;33:260–76.
[592] Briassoulis GC, Zavras NJ, Hatzis MDTD. Effectiveness and safety of a protocol for promotion of early intragastric feeding in critically ill children. Pediatr Crit Care Med 2001;2:113–21.
[593] Allin B, Long A-M, Gupta A, Knight M, Lakhoo K; British Association of Paediatric Surgeons Congenital Anomalies Surveillance System Necrotising Enterocolitis Collaboration. Erratum: Corrigendum: A UK wide cohort study describing management and outcomes for infants with surgical Necrotising Enterocolitis. Sci Rep 2017;7:41149.
[594] Geoghegan S, Oulton K, Bull C, Brierley J, Peters M, Wray J. The experience of long-stay parents in the ICU: a qualitative study of parent and staff perspectives. Pediatr Crit Care Med 2016;17:e496–501.
[595] Geoghegan S, Oulton K, Bull C, Brierley J, Peters M, Wray J. The challenges of caring for long-stay patients in the PICU. Pediatr Crit Care Med 2016;17:e266–71.
[596] Gibbs JL, Wren C, Watterson KG, Hunter S, Hamilton JR. Stenting of the arterial duct combined with banding of the pulmonary arteries and atrial septectomy or septostomy: a new approach to palliation for the hypoplastic left heart syndrome. Br Heart J 1993;69:551–5.
[597] Dapper F, Bauer J, Kroll J, Zickmann B, Bohle RM, Hagel KJ *et al.* Clinical experience with heart transplantation in infants. Eur J Cardiothorac Surg 1998;14:1–5; discussion 5–6.
[598] Gibbs JL, Uzun O, Blackburn ME, Wren C, Hamilton JR, Watterson KG. Fate of the stented arterial duct. Circulation 1999;99:2621–5.
[599] Akintuerk H, Michel-Behnke I, Valeske K, Mueller M, Thul J, Bauer J *et al.* Stenting of the arterial duct and banding of the pulmonary arteries: basis for combined Norwood stage I and II repair in hypoplastic left heart. Circulation 2002;105:1099–103.
[600] Galantowicz M, Cheatham JP, Phillips A, Cua CL, Hoffman TM, Hill SL *et al.* Hybrid approach for hypoplastic left heart syndrome: intermediate results after the learning curve. Ann Thorac Surg 2008;85:2063–70; discussion 2070–1.
[601] Yerebakan C, Valeske K, Elmontaser H, Yörüker U, Mueller M, Thul J *et al.* Hybrid therapy for hypoplastic left heart syndrome: myth, alternative, or standard? J Thorac Cardiovasc Surg 2016;151:1112–21, 1123. e1–5.
[602] Pedra CA, Pedra S, Jatene MB, The Brazilian hybrid approach for hypoplastic left heart syndrome. In: Butera G, Cheatham J, Schranz D, Tulzer G (eds). Fetal and Hybrid Procedures in Congenital Heart Diseases. New York: Springer, 2016, 229–41.
[603] Faria RM, Pacheco JT, de Oliveira IR, Vidal JM, Junior ABR, Costa ALL *et al.* Modified hybrid procedure in hypoplastic left heart syndrome: initial experience of a center in Northeastern Brazil. Braz J Cardiovasc Surg 2017;32:210–14.
[604] Lacour-Gayet F, Clarke D, Jacobs J, Comas J, Daebritz S, Daenen W *et al.* The Aristotle score: a complexity-adjusted method to evaluate surgical results. Eur J Cardiothorac Surg 2004;25:911–24.
[605] Michel-Behnke I, Akintuerk H, Marquardt I, Mueller M, Thul J, Bauer J *et al.* Stenting of the ductus arteriosus and banding of the pulmonary arteries: basis for various surgical strategies in newborns with multiple left heart obstructive lesions. Heart 2003;89: 645–50.
[606] Yerebakan C, Murray J, Valeske K, Thul J, Elmontaser H, Mueller M *et al.* Long-term results of biventricular repair after initial Giessen hybrid approach for hypoplastic left heart variants. J Thorac Cardiovasc Surg 2015;149:1112–20; discussion 1120–2.e2.
[607] Higashida A, Hoashi T, Kitano M, Shimada M, Nakata T, Ozawa H *et al.* Application of hybrid stage I palliation for patients with two ventricular cavities and hypoplastic left heart structures. Interact CardioVasc Thorac Surg 2018;26:906–11.
[608] Schranz D, Bauer A, Reich B, Steinbrenner B, Recla S, Schmidt D *et al.* Fifteen-year single center experience with the "Giessen Hybrid" approach for hypoplastic left heart and variants: current strategies and outcomes. Pediatr Cardiol 2015;36:365–73.
[609] Galantowicz M, Yates AR. Improved outcomes with the comprehensive stage 2 procedure after an initial hybrid stage 1. J Thorac Cardiovasc Surg 2016;151:424–9.
[610] Cvetkovic D, Giamelli J, Lyew M, Erb M, Sett S, DiStefano Y. Hybrid stage I procedure as initial palliation for neonate with hypoplastic left heart syndrome and right congenital diaphragmatic hernia. Semin Cardiothorac Vasc Anesth 2017;21:145–51.
[611] Egan MJ, Trask AJ, Baker PB, Lawrence J, Ladich E, Virmani R *et al.* Histopathologic evaluation of patent ductus arteriosus stents after hybrid stage I palliation. Pediatr Cardiol 2011;32:413–17.
[612] Galantowicz M, Cheatham JP. Lessons learned from the development of a new hybrid strategy for the management of hypoplastic left heart syndrome. Pediatr Cardiol 2005;26:190–9.
[613] Galantowicz M, Cheatham JP, Phillips A, Holzer RJ, Hill SL, Olshove VF. Hybrid procedures for congenital heart disease. In: Butera G, Chessa M, Eicken A, Thomson JD (eds). Cardiac Catheterization for Congenital Heart Disease. New York: Springer, 2015, 301–8.

[614] Galantowicz M, Yates AR. Improved outcomes with the comprehensive stage 2 procedure after an initial hybrid stage 1. J Thorac Cardiovasc Surg 2016;151:424–9. I
[615] Holzer RJ, Chisolm JL, Hill SL, Olshove V, Phillips A, Cheatham JP *et al.* "Hybrid" stent delivery in the pulmonary circulation. J Invasive Cardiol 2008;20:592–8.
[616] Cua CL, McConnell PI, Meza JM, Hill KD, Zhang S, Hersey D *et al.* Hybrid palliation: outcomes after the comprehensive stage 2 procedure. Ann Thorac Surg 2018;105:1455–60.
[617] Cao JY, Lee SY, Phan K, Ayer J, Celermajer DS, Winlaw DS. Early outcomes of hypoplastic left heart syndrome infants: meta-analysis of studies comparing the hybrid and Norwood procedures. World J Pediatr Congenit Heart Surg 2018;9:224–33.
[618] Fischer T. A combined stage 1 and 2 repair for hypoplastic left heart syndrome: anaesthetic considerations. Paediatr Anaesth 2004;14:525–6; author reply 526–7.
[619] Jiang W, Liu X, Liu F, Huang S, Yuan J, Shi Y *et al.* Safety and benefit of pre-operative oral carbohydrate in infants: a multi-center study in China. Asia Pac J Clin Nutr 2018;27:975–9.
[620] Moore J, Paulus D, Cua CL, Kertesz NJ, Miao Y, Cheatham JP *et al.* Arrhythmias after stage I hybrid palliation in single-ventricle patients. Pediatr Cardiol 2016;37:1416–21.
[621] Winch P, Khan S, Naguib A, Yates AR, Rice J, Barry N *et al.* Transportation of patients following surgery for congenital heart disease: a process review prompted by the opening of a new hospital. Int J Clin Exp Med 2014;7:411–15.
[622] Goreczny S, Qureshi S, Rosenthal E, Krasemann T, Bedair R, Salih C *et al.* Self-expanding stent implantation in arterial duct during hybrid palliation of hypoplastic left heart syndrome: midterm experience with a specially designed stent. EuroIntervention 2015;10:1318–25.
[623] Marshall AC. Cardiac catheterization and fetal intervention. In: Sellke FW, del Nido PJ, Swanson SJ (eds). Sabiston and Spencer Surgery of the Chest, 9th edn. Philadelphia, PA: Elsevier, Saunders, 2016, 1915–36.
[624] Rupp S, Michel-Behnke I, Valeske K, Akintürk H, Schranz D. Implantation of stents to ensure an adequate interatrial communication in patients with hypoplastic left heart syndrome. Cardiol Young 2007; 17:535–40.
[625] Feltes TF, Bacha E, Beekman RH, Cheatham JP, Feinstein JA, Gomes AS *et al.* Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation 2011;123:2607–52.
[626] Oster ME, Ehrlich A, King E, Petit CJ, Clabby M, Smith S *et al.* Association of interstage home monitoring with mortality, readmissions, and weight gain: a multicenter study from the national pediatric cardiology quality improvement collaborative. Circulation 2015;132:502–8.
[627] Ghanayem NS, Hoffman GM, Mussatto KA, Cava JR, Frommelt PC, Rudd NA *et al.* Home surveillance program prevents interstage mortality after the Norwood procedure. J Thorac Cardiovasc Surg 2003;126:1367–77.
[628] Yörüker U, Akintürk H. Giessen procedure as comprehensive stage II palliation with aortic arch reconstruction after hybrid bilateral pulmonary artery banding and ductal stenting for hypoplastic left heart syndrome. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2018; 21:19–27.
[629] Sojak V, Bokenkamp R, Kuipers I, Schneider A, Hazekamp M. Biventricular repair after the hybrid Norwood procedure. Eur J Cardiothorac Surg 2019;56:110–16.
[630] Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC *et al.* Brain maturation is delayed in infants with complex congenital heart defects. J Thorac Cardiovasc Surg 2009;137:529–36; discussion 536–7.
[631] Mahle WT, Visconti KJ, Freier MC, Kanne SM, Hamilton WG, Sharkey AM *et al.* Relationship of surgical approach to neurodevelopmental outcomes in hypoplastic left heart syndrome. Pediatrics 2006;117:e90–7.
[632] Knirsch W, Liamlahi R, Hug MI, Hoop R, von Rhein M, Prêtre R *et al.* Mortality and neurodevelopmental outcome at 1 year of age comparing hybrid and Norwood procedures. Eur J Cardiothorac Surg 2012; 42:33–9.
[633] Reich B, Heye K, Tuura R, Beck I, Wetterling K, Hahn A *et al.* Neurodevelopmental outcome and health-related quality of life in children with single-ventricle heart disease before Fontan procedure. Semin Thorac Cardiovasc Surg 2017;S1043-0697 (17)30288-5.
[634] Heye KN, Knirsch W, Latal B, Scheer I, Wetterling K, Hahn A *et al.* Reduction of brain volumes after neonatal cardiopulmonary bypass surgery in single-ventricle congenital heart disease before Fontan completion. Pediatr Res 2018;83:63–70.
[635] Reich B, Heye KN, O'Gorman Tuura R, Beck I, Wetterling K, Hahn A *et al.* Interrelationship between hemodynamics, brain volumes, and outcome in hypoplastic left heart syndrome. Ann Thorac Surg 2019; 107:1838–44.
[636] Haller C, Caldarone CA. The evolution of therapeutic strategies: niche apportionment for hybrid palliation. Ann Thorac Surg 2018; 106:1873–80.
[637] Hehir DA, Ghanayem NS. Single-ventricle infant home monitoring programs: outcomes and impact. Curr Opin Cardiol 2013;28:97–102.
[638] Mahle WT, Spray TL, Gaynor JW, Clark BJ. Unexpected death after reconstructive surgery for hypoplastic left heart syndrome. Ann Thorac Surg 2001;71:61–5.
[639] Rudd NA, Frommelt MA, Tweddell JS, Hehir DA, Mussatto KA, Frontier KD *et al.* Improving interstage survival after Norwood operation: outcomes from 10 years of home monitoring. J Thorac Cardiovasc Surg 2014;148:1540–7.
[640] Anderson JB, Beekman RH, Kugler JD, Rosenthal GL, Jenkins KJ, Klitzner TS *et al.* Improvement in interstage survival in a national pediatric cardiology learning network. Circ Cardiovasc Qual Outcomes 2015; 8:428–36.
[641] Siehr SL, Norris JK, Bushnell JA, Ramamoorthy C, Reddy VM, Hanley FL *et al.* Home monitoring program reduces interstage mortality after the modified Norwood procedure. J Thorac Cardiovasc Surg 2014; 147:718–23.e1.
[642] Hansen JH, Furck AK, Petko C, Buchholz-Berdau R, Voges I, Scheewe J *et al.* Use of surveillance criteria reduces interstage mortality after the Norwood operation for hypoplastic left heart syndrome. Eur J Cardiothorac Surg 2012;41:1013–18.
[643] Ghanayem NS, Allen KR, Tabbutt S, Atz AM, Clabby ML, Cooper DS *et al.* Interstage mortality after the Norwood procedure: results of the multicenter Single Ventricle Reconstruction trial. J Thorac Cardiovasc Surg 2012;144:896–906.
[644] De Oliveira NC, Van Arsdell GS. Practical use of alpha blockade strategy in the management of hypoplastic left heart syndrome following stage one palliation with a Blalock-Taussig shunt. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 2004;7:11–15.
[645] Anderson JB, Beekman RH, Border WL, Kalkwarf HJ, Khoury PR, Uzark K *et al.* Lower weight-for-age z score adversely affects hospital length of stay after the bidirectional Glenn procedure in 100 infants with a single ventricle. J Thorac Cardiovasc Surg 2009;138:397–404.e1.
[646] Anderson JB, Iyer SB, Schidlow DN, Williams R, Varadarajan K, Horsley M *et al.* Variation in growth of infants with a single ventricle. J Pediatr 2012;161:16–21.e1; quiz 21.e2–3.
[647] Hehir DA, Rudd N, Slicker J, Mussatto KA, Simpson P, Li S-H *et al.* Normal interstage growth after the Norwood operation associated with interstage home monitoring. Pediatr Cardiol 2012;33:1315–22.
[648] Evans CF, Sorkin JD, Abraham DS, Wehman B, Kaushal S, Rosenthal GL. Interstage weight gain is associated with survival after first-stage single-ventricle palliation. Ann Thorac Surg 2017;104:674–80.
[649] Rüffer A, Arndt F, Potapov S, Mir TS, Weil J, Cesnjevar RA. Early stage 2 palliation is crucial in patients with a right-ventricle-to-pulmonary-artery conduit. Ann Thorac Surg 2011;91:816–22.
[650] Wilder TJ, McCrindle BW, Phillips AB, Blackstone EH, Rajeswaran J, Williams WG *et al.* Survival and right ventricular performance for matched children after stage-1 Norwood: modified Blalock-Taussig shunt versus right-ventricle-to-pulmonary-artery conduit. J Thorac Cardiovasc Surg 2015;150:1440–50, 1452.e1–8; discussion 1450–2.
[651] Jean-St-Michel E, Meza JM, Maguire J, Coles J, McCrindle BW. Survival to stage II with ventricular dysfunction: secondary analysis of the single ventricle reconstruction trial. Pediatr Cardiol 2018;39:955–66.
[652] Rogers L, Pagel C, Sullivan ID, Mustafa M, Tsang V, Utley M *et al.* Interventions and outcomes in children with hypoplastic left heart syndrome born in England and Wales between 2000 and 2015 based on the national congenital heart disease audit. Circulation 2017; 136:1765–7.
[653] Taylor LC, Burke B, Donohue JE, Yu S, Hirsch-Romano JC, Ohye RG *et al.* Risk factors for interstage mortality following the Norwood procedure: impact of sociodemographic factors. Pediatr Cardiol 2016;37:68–75.
[654] Crowe S, Ridout DA, Knowles R, Tregay J, Wray J, Barron DJ *et al.* Death and emergency readmission of infants discharged after interventions for congenital heart disease: a national study of 7643 infants to inform service improvement. J Am Heart Assoc 2016;5:e003369.
[655] Knirsch W, Bertholdt S, Stoffel G, Stiasny B, Weber R, Dave H *et al.* Clinical course and interstage monitoring after the Norwood and hybrid

procedures for hypoplastic left heart syndrome. Pediatr Cardiol 2014; 35:851–6.
[656] Simsic JM, Phelps C, Kirchner K, Carpenito KR, Allen R, Miller-Tate H *et al.* Interstage outcomes in single ventricle patients undergoing hybrid stage 1 palliation. Congenit Heart Dis 2018;13:757–63.
[657] Hsu DT, Zak V, Mahony L, Sleeper LA, Atz AM, Levine JC *et al.*; Pediatric Heart Network Investigators. Enalapril in infants with single ventricle: results of a multicenter randomized trial. Circulation 2010; 122:333–40.
[658] Brown DW, Mangeot C, Anderson JB, Peterson LE, King EC, Lihn SL *et al.* Digoxin use is associated with reduced interstage mortality in patients with no history of arrhythmia after stage i palliation for single ventricle heart disease. J Am Heart Assoc 2016;5:e002376.
[659] Truong DT, Menon SC, Lambert LM, Burch PT, Sheng X, Minich LL *et al.* Digoxin use in infants with single ventricle physiology: secondary analysis of the pediatric heart network infant single ventricle trial public use dataset. Pediatr Cardiol 2018;39:1200–9.
[660] Crowe S, Knowles R, Wray J, Tregay J, Ridout DA, Utley M *et al.* Identifying improvements to complex pathways: evidence synthesis and stakeholder engagement in infant congenital heart disease. BMJ Open 2016;6:e010363.
[661] Elias ER, Murphy NA; Council on Children with Disabilities. Home care of children and youth with complex health care needs and technology dependencies. Pediatrics 2012;129:996–1005.
[662] Kogon B, Woodall K, Kanter K, Alsoufi B, Oster M. Reducing readmissions following paediatric cardiothoracic surgery: a quality improvement initiative. Cardiol Young 2015;25:935–40.
[663] Nieves JA, Uzark K, Rudd NA, Strawn J, Schmelzer A, Dobrolet N. Interstage home monitoring after newborn first-stage palliation for hypoplastic left heart syndrome: family education strategies. Crit Care Nurse 2017;37:72–88.
[664] Carlo WF, Cnota JF, Dabal RJ, Anderson JB. Practice trends over time in the care of infants with hypoplastic left heart syndrome: a report from the National Pediatric Cardiology Quality Improvement Collaborative. Congenit Heart Dis 2017;12:315–21.
[665] Hehir DA, Cooper DS, Walters EM, Ghanayem NS. Feeding, growth, nutrition, and optimal interstage surveillance for infants with hypoplastic left heart syndrome. Cardiol Young 2011;21(Suppl 2):59–64.
[666] Shirali G, Erickson L, Apperson J, Goggin K, Williams D, Reid K *et al.* Harnessing teams and technology to improve outcomes in infants with single ventricle. Circ Cardiovasc Qual Outcomes 2016;9:303–11.
[667] Tregay J, Wray J, Crowe S, Knowles R, Daubeney P, Franklin R *et al.* Going home after infant cardiac surgery: a UK qualitative study. Arch Dis Child 2016;101:320–5.
[668] Tregay J, Wray J, Bull C, Franklin RC, Daubeney P, Barron DJ *et al.* Unexpected deaths and unplanned re-admissions in infants discharged home after cardiac surgery: a systematic review of potential risk factors. Cardiol Young 2015;25:839–52.
[669] Sames-Dolzer E, Gierlinger G, Kreuzer M, Schrempf J, Gitter R, Prandstetter C *et al.* Unplanned cardiac reoperations and interventions during long-term follow-up after the Norwood procedure. Eur J Cardiothorac Surg 2017;51:1044–50.
[670] Evans WN, Acherman RJ, Mayman GA, Rothman A. B-natriuretic peptide: a helpful clinical marker after Norwood I. Pediatr Cardiol 2008; 29:214–16.
[671] Eagam M, Loomba RS, Pelech AN, Tweddell JS, Kirkpatrick E. Predicting the need for neoaortic arch intervention in infants with hypoplastic left heart syndrome through the Glenn procedure. Pediatr Cardiol 2017; 38:70–6.
[672] Lowenthal A, Camacho BV, Lowenthal S, Natal-Hernandez L, Liszewski W, Hills NK *et al.* Usefulness of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide as biomarkers for heart failure in young children with single ventricle congenital heart disease. Am J Cardiol 2012;109:866–72.
[673] Butts RJ, Zak V, Hsu D, Cnota J, Colan SD, Hehir D *et al.* Factors associated with serum B-type natriuretic peptide in infants with single ventricles. Pediatr Cardiol 2014;35:879–87.
[674] Harahsheh AS, Hom LA, Clauss SB, Cross RR, Curtis AR, Steury RD *et al.* The impact of a designated cardiology team involving telemedicine home monitoring on the care of children with single-ventricle physiology after Norwood palliation. Pediatr Cardiol 2016;37:899–912.
[675] Cross R, Steury R, Randall A, Fuska M, Sable C. Single-ventricle palliation for high-risk neonates: examining the feasibility of an automated home monitoring system after stage I palliation. Future Cardiol 2012;8: 227–35.
[676] Tadphale SD, Tang X, ElHassan NO, Beam B, Prodhan P. Cavopulmonary anastomosis during same hospitalization as stage 1 Norwood/hybrid palliative surgery. Ann Thorac Surg 2017;103:1285–91.
[677] Petit CJ, Fraser CD, Mattamal R, Slesnick TC, Cephus CE, Ocampo EC. The impact of a dedicated single-ventricle home-monitoring program on interstage somatic growth, interstage attrition, and 1-year survival. J Thorac Cardiovasc Surg 2011;142:1358–66.
[678] Ghanayem NS, Tweddell JS, Hoffman GM, Mussatto K, Jaquiss R. Optimal timing of the second stage of palliation for hypoplastic left heart syndrome facilitated through home monitoring, and the results of early cavopulmonary anastomosis. Cardiol Young 2006;16:61–6.
[679] Meza JM, Jaquiss RDB, Anderson BR, Moga M-A, Kirklin JK, Sarris G *et al.* Current practices in the timing of stage 2 palliation. World J Pediatr Congenit Heart Surg 2017;8:135–41.
[680] Hill GD, Rudd NA, Ghanayem NS, Hehir DA, Bartz PJ. Center variability in timing of stage 2 palliation and association with interstage mortality: a report from the national pediatric cardiology quality improvement collaborative. Pediatr Cardiol 2016;37:1516–24.
[681] Davis D, Davis S, Cotman K, Worley S, Londrico D, Kenny D *et al.* Feeding difficulties and growth delay in children with hypoplastic left heart syndrome versus d-transposition of the great arteries. Pediatr Cardiol 2008;29:328–33.
[682] Kelleher DK, Laussen P, Teixeira-Pinto A, Duggan C. Growth and correlates of nutritional status among infants with hypoplastic left heart syndrome (HLHS) after stage 1 Norwood procedure. Nutrition 2006; 22:237–44.
[683] Vogt KN, Manlhiot C, Van Arsdell G, Russell JL, Mital S, McCrindle BW. Somatic growth in children with single ventricle physiology impact of physiologic state. J Am Coll Cardiol 2007;50:1876–83.
[684] Medoff-Cooper B, Irving SY, Marino BS, García-España JF, Ravishankar C, Bird GL *et al.* Weight change in infants with a functionally univentricular heart: from surgical intervention to hospital discharge. Cardiol Young 2011;21:136–44.
[685] Srinivasan C, Jaquiss RDB, Morrow WR, Frazier EA, Martin D, Imamura M *et al.* Impact of staged palliation on somatic growth in patients with hypoplastic left heart syndrome. Congenit Heart Dis 2010;5:546–51.
[686] Hong BJ, Moffett B, Payne W, Rich S, Ocampo EC, Petit CJ. Impact of postoperative nutrition on weight gain in infants with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2014;147:1319–25.
[687] Li Y, Huang Y. Early versus late parenteral nutrition in critically ill children. N Engl J Med 2016;375:384–5.
[688] Hill GD, Hehir DA, Bartz PJ, Rudd NA, Frommelt MA, Slicker J *et al.* Effect of feeding modality on interstage growth after stage I palliation: a report from the National Pediatric Cardiology Quality Improvement Collaborative. J Thorac Cardiovasc Surg 2014;148:1534–9.
[689] Hebson CL, Oster ME, Kirshbom PM, Clabby ML, Wulkan ML, Simsic JM. Association of feeding modality with interstage mortality after single-ventricle palliation. J Thorac Cardiovasc Surg 2012;144:173–7.
[690] Brown KL, Wray J, Knowles RL, Crowe S, Tregay J, Ridout D, *et al.* Infant Deaths in the UK Community Following Successful Cardiac Surgery: Building the Evidence Base for Optimal Surveillance, a Mixed-Methods Study. Southampton, UK: NIHR Journals Library, 2016 (Health Services and Delivery Research). http://www.ncbi.nlm.nih.gov/books/NBK363028/ (16 December 2019, date last accessed).
[691] Sarajuuri A, Lönnqvist T, Schmitt F, Almqvist F, Jokinen E. Patients with univentricular heart in early childhood: parenting stress and child behaviour. Acta Paediatr 2012;101:252–7.
[692] Stewart J, Dempster R, Allen R, Miller-Tate H, Dickson G, Fichtner S *et al.* Caregiver anxiety due to interstage feeding concerns. Congenit Heart Dis 2015;10:E98–106.
[693] Stoffel G, Spirig R, Stiasny B, Bernet V, Dave H, Knirsch W. Psychosocial impact on families with an infant with a hypoplastic left heart syndrome during and after the interstage monitoring period—a prospective mixed-method study. J Clin Nurs 2017;26:3363–70.
[694] Sood E, Karpyn A, Demianczyk AC, Ryan J, Delaplane EA, Neely T *et al.* Mothers and fathers experience stress of congenital heart disease differently: recommendations for pediatric critical care. Pediatr Crit Care Med 2018;19:626–34.
[695] Wray J, Tregay J, Bull C, Knowles RL, Crowe S, Brown K. Issues facing families of infants discharged after cardiac surgery: the perceptions of charity helpline staff. Acta Paediatr 2018;107:1418–26.
[696] Wray J, Brown K, Tregay J, Crowe S, Knowles R, Bull K *et al.* Parents' experiences of caring for their child at the time of discharge after cardiac surgery and during the postdischarge period: qualitative study using an online forum. J Med Internet Res 2018;20:e155.

[697] Jacobs JP, O'Brien SM, Pasquali SK, Jacobs ML, Lacour-Gayet FG, Tchervenkov CI *et al.* Variation in outcomes for benchmark operations: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. Ann Thorac Surg 2011;92:2184–91; discussion 2191–2.

[698] Jacobs JP, O'Brien SM, Pasquali SK, Jacobs ML, Lacour-Gayet FG, Tchervenkov CI *et al.* Variation in outcomes for risk-stratified pediatric cardiac surgical operations: an analysis of the STS Congenital Heart Surgery Database. Ann Thorac Surg 2012;94:564–71; discussion 571–2.

[699] Jacobs JP, Jacobs ML, Mavroudis C, Tchervenkov CI, Pasquali SK, Subramanyan RK *et al.* The Society of Thoracic Surgeons Congenital Heart Surgery Database—Twenty-Seventh Harvest (July 1, 2013–June 30, 2017). The Society of Thoracic Surgeons (STS) and Duke Clinical Research Institute (DCRI), Duke University Medical Center, Durham, NC, USA, Fall 2017 Harvest.

[700] Jacobs JP, Franklin RCG, Jacobs ML, Colan SD, Tchervenkov CI, Maruszewski B *et al.* Classification of the functionally univentricular heart: unity from mapped codes. Cardiol Young 2006;16:9–21.

[701] Jacobs JP, Jacobs ML, Austin EH, Mavroudis C, Pasquali SK, Lacour-Gayet FG *et al.* Quality measures for congenital and pediatric cardiac surgery. World J Pediatr Congenit Heart Surg 2012;3:32–47.