GUIDELINE

The International Society for Heart and Lung Transplantation Guidelines for the Management of Pediatric Heart Failure (Update From 2014)

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Pediatric heart failure (HF) secondary to cardiomyopathies, acquired heart disease, and congenital heart disease is associated with significant morbidity and mortality. These guidelines represent an update from the International Society for Heart and Lung Transplantation guidelines for the management of pediatric HF that were published in 2014 and incorporate interval advancements in medical therapies and new approaches in the evaluation and management of children with HF.

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1. INTRODUCTION

Pediatric heart failure (HF) secondary to cardiomyopathies, acquired heart disease, and congenital heart disease (CHD) remains associated with significant morbidity and mortality. These guidelines represent an update from the International Society for Heart and Lung Transplantation guidelines for the management of pediatric HF that were published in 2014.[1] The purpose of this update is to incorporate advancements in pharmacologic therapies and new approaches in the evaluation and management of children with HF since the prior guideline publication. These guidelines are not intended for use in the management of HF related to left to right shunts and are primarily focused on the population of children with HF due to dysfunction of the myocardium. Because the indications for heart transplantation in children, selection and management of ventricular assist devices in children and patients with CHD, management of cardiovascular implantable electronic devices in children, the diagnosis and treatment of hypertrophic cardiomyopathy (HCM), and the diagnosis and management of cardiac complications of muscular dystrophies are covered by existing consensus statements or guidelines, they are largely not included in this document.[2-6]

The strength and level of evidence were determined based on the standard approach for International Society for Heart and Lung Transplantation guidelines as shown in the table below. However, due to limited evidence and the paucity of clinical trials in children with HF, most of the guidelines are based on consensus and therefore classified as Level C. Additionally, in some areas of HF management, there is a complete lack of information so no recommendations were made. These challenges highlight opportunities for future research to better inform the care of children with HF.

Class and Levels of Evidence
Class I
Evidence and/or general agreement that a given treatment, procedure, or technique is beneficial, useful and effective as applied to patients, clinicians, or researchers
Class II
Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment, procedure, or technique
Class IIa
Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb
Usefulness/efficacy is less well established by evidence/opinion
Class III
Evidence or general agreement that the treatment, procedure, or technique is not useful or effective and in some cases may be harmful
Level of Evidence A
Data derived from multiple, high-quality randomized clinical trials, meta-analyses of high-quality RCTs, or one or more RCTs corroborated by high-quality registry studies
Level of Evidence B
Data derived from a single or multiple moderate-quality randomized clinical trial(s), meta-analyses of moderate-quality RCTs, or large nonrandomized studies
B1 Data derived from a single or multiple moderate-quality randomized clinical trial(s), meta-analyses of moderate-quality RCT
B2 Data derived from one or more high-quality nonrandomized, observational, or registry studies
Level of Evidence C
Consensus of expert opinion
C1 Expert opinion supported by small, observational studies, retrospective studies, meta-analyses of such studies, or physiologic/mechanistic studies
C2 Expert opinion alone or with group communications/questionnaires

Abbreviation: RCT, randomized controlled trial.

2. DEFINITION AND CLASSIFICATION OF PEDIATRIC HEART FAILURE

HF in children is a complex clinical syndrome resulting from impaired ventricular function (ejection or relaxation), volume or pressure overload, either alone or in combination.[1,7] There are numerous etiologies that require a synthesis of clinical, hemodynamic, and neurohumoral data. There is no universal approach to diagnosing HF as each case may weigh different elements of medical history, cardiac imaging, cardiac catheterization, or increasingly biomarkers. Signs and symptoms can also be diverse based on pathophysiology and age. Traditional symptoms include poor growth, feeding difficulties, respiratory distress, fatigue, and exercise intolerance.

2.1. Staging and Classification

The American College of Cardiology (ACC)/American Heart Association (AHA) Staging of HF has been previously adopted within pediatric HF guidelines.[1,7] This staging system has the advantage of identifying patients at risk (Stage A) and those with early cardiac disease (Stage B) prior to the onset of HF symptoms (Stage C) or advanced HF (Stage D). This staging strategy also provides a longitudinal assessment that discriminates between current and past HF symptoms.

Progression and advanced stages of HF have been associated with reduced survival in adult HF[8] and have guided therapeutic interventions. The most recent iteration of the ACC/AHA staging from adult HF guidelines addresses the evolving role of biomarkers and structural changes for recognition of patients at risk of developing HF and can be adopted in pediatrics with minor revisions[9] (Table 1). This iterative change remains important as new therapeutic interventions target early disease as highlighted in a recent AHA Statement focused on treatment strategies for pediatric cardiomyopathy.[10]

2.1.1. New York Heart Association Classification

The New York Heart Association (NYHA) classification is a simple ordinal scale (I-IV, Table 2) used by adult providers to characterize functional capacity of patients with symptomatic (Stage C) HF or advanced HF (Stage D). The assessment is subjective, can change at each encounter, and is often utilized to determine eligibility and

Table 1 ACC/AHA Stages of HF

Stages	Definition and criteria
Stage A: At risk for HF	At risk for HF but without symptoms, structural heart disease, or cardiac biomarkers of stretch or injury (e.g., previous exposure to cardiotoxic agents, family history of heritable cardiomyopathy, univentricular heart, congenitally corrected transposition of the great arteries)
Stage B: Pre-HF	No symptoms or signs of HF and evidence of 1 of the following:
	Structural heart disease Reduced left or right ventricular systolic function Reduced ejection fraction Reduced strain Ventricular hypertrophy Chamber enlargement Wall motion abnormalities Valvular heart disease *Evidence for increased filling pressures* By invasive hemodynamic measurements By noninvasive imaging suggesting elevated filling pressures (e.g., Doppler echocardiography)
	Patients with risk factors and increased levels of BNPs or persistently elevated cardiac troponin in the absence of competing diagnoses resulting in such biomarker elevations, such as acute coronary syndrome, chronic kidney disease, pulmonary embolus, or myopericarditis
Stage C: Symptomatic HF	Structural heart disease with current or previous symptoms of HF
Stage D: Advanced HF	Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize guideline–directed medical therapy

Abbreviations: AHA, American Heart Association; BNP, B-type natriuretic peptide; HF, heart failure.

Table 2 Ross and NYHA Classification

Class	Ross	NYHA
I	Asymptomatic	Asymptomatic
II	Mild tachypnea or diaphoresis with feeding in infants. Dyspnea on exertion in older children.	Slight limitation of physical activity. Ordinary physical activity results in mild symptoms, such as fatigue, shortness of breath and angina.
III	Marked tachypnea or diaphoresis with feeding in infants. Prolonged feeding times with growth failure due to heart failure. In older children, marked dyspnea on exertion.	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms.
IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest.	Severely limited. Experiences symptoms at rest.

Abbreviation: NYHA, New York Heart Association.

response to treatment interventions. Its application in pediatrics is limited as symptoms differ in young children and infants.

2.1.2. Ross Classification

In lieu of NYHA classification, the Ross Classification was developed for grading HF in infants and young children[11] (Table 2). It preserves the simplicity of the NYHA classification while also integrating common symptoms of HF in younger patients.

2.1.3. Other Scoring Systems

There have been other attempts to classify or score HF. One proposed system is the New York University Pediatric Heart Failure Index.[12] In this tool, points are assigned based on signs and symptoms, the patient's medical regimen, and the ventricular anatomy to derive a total score between 0 and 30 and showed initial promise of grading pediatric HF; however, the index is influenced by practice variation, has not been validated in larger trials, or achieved wider adoption. The recently concluded PANORMA-HF trial comparing sacubitril/valsartan to enalapril within pediatric left ventricular systolic dysfunction utilized a novel global rank end-point derived by ranking patients based on clinical events, NYHA/Ross classification and patient–reported HF symptoms[13]; however, the trial results have not been published and the applicability of the global rank outside of a trial remain unclear.

RECOMMENDATION

Documentation of HF severity and staging is recommended to facilitate monitoring of disease progression and patient management (Class I, Level of Evidence C).

2.2. Classification by Ejection Fraction

The 2022 Adult Heart Failure guidelines proposed a new mechanism for classifying HF by left ventricular ejection fraction (EF). This was sought because of differing prognosis and response to treatments and because most adult clinical trials select patients based on EF. It is also recognized that EF in isolation does not differentiate the complex etiologies and trajectories of adult HF patients. The guideline harmonized recent adult randomized controlled trials (RCTs) to identify 4 distinct categories[9]: HF with reduced EF (HFrEF), HF with improved EF (HFimpEF), HF with mildly reduced EF (HFmrEF), and HF with preserved EF (HFpEF).

While various algorithms have been investigated in adults for the diagnosis of HFpEF, it is not clear how these may translate to the pediatric or congenital population.[14-16] Diagnosis of HFpEF in children should include a thorough history (e.g., orthopnea, exertional dyspnea, fatigue, exercise intolerance, feeding intolerance), physical exam (e.g., hepatomegaly, jugular venous distention, peripheral edema, S3 gallop, pulmonary crackles or rales), electrocardiogram, and an echocardiogram.[17-23] Assessment of natriuretic peptides, exercise stress testing, cardiac magnetic resonance imaging (MRI), and right heart catheterization can be helpful adjunctive diagnostic tools. The most common etiologies of HFpEF in children include CHD and cardiomyopathies.[24]

Table 3 Proposed Classification of HF by EF for Children

Proposed classification of HF according to systemic ventricle EF	Criteria
HFrEF (HF with reduced EF)	EF ≤ 40%
HFmrEF (HF with mildly reduced EF)	EF 41%-49%
HFpEF (HF with preserved EF)	EF ≥ 50% Evidence of spontaneous or provokable increased systemic ventricular filling pressures (e.g., elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

Abbreviations: EF, ejection fraction; HF, heart failure.

Pediatrics does not have similar data from RCTs displaying differing prognosis or response to treatment, and there is not the same dilemma of differentiating a large volume of HFpEF patients; however, there may be benefits in extrapolating some aspects of this adult–based classification strategy into the pediatric population. Children with systolic dysfunction often only manifest HF symptoms once decompensated which has challenged enrollment in clinical trials that require Stage C HF. Defining HFmrEF in children could contribute to the identification of a consistent cohort to enroll in trials to assess response to therapy and could be inclusive of Stage B patients. The proposed approach to an EF–based classification system in children with HF, inclusive of patients with CHD, is shown in Table 3. In comparison to the adult classification system, HF with improved EF has been removed and left ventricular ejection fraction (LVEF) has been changed to EF given the variable morphology of systemic ventricles in patients with CHD. However, further study is required to determine if this proposed classification scheme is valid.

RECOMMENDATION

Classification of HF based on systemic ventricle EF may be useful for serial monitoring and for assessing treatment response (Class IIb, Level of Evidence C).

3. DIAGNOSIS

The basic diagnostic approach in children with suspected HF involves clinical evaluation (history and physical examination), 12-lead electrocardiogram, chest X-ray, and echocardiogram. Genetic testing and laboratory evaluations, such as serum B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), have utility in the diagnosis and prognosis of disease.

3.1. Genetic Testing

Genetic testing in pediatric patients with cardiomyopathy is a rapidly evolving field and the recommendations have been updated to reflect the latest data.[25-27] Testing can include a targeted panel, a comprehensive panel, exome sequencing, and/or genome sequencing. Genetic testing can establish a molecular diagnosis which may aid in management and prognostication. Moreover, when a pathogenic/likely pathogenic variant is found, cascade genetic testing can be offered to first–degree family members to identify those who are gene positive and at risk to develop disease. There are some special circumstances where exome or genome sequencing may be the most appropriate first step. Mitochondrial sequencing is a separate test that should be considered in cases where there is a high suspicion for a mitochondrial disorder.

RECOMMENDATION

1. Comprehensive or targeted panel genetic testing is recommended for pediatric patients affected with any subtype of cardiomyopathy (Class I, Level of Evidence C).
2. Variant–specific genetic testing is recommended for first–degree family members after the identification of a causative pathogenic/likely pathogenic variant in the index case (Class I, Level of Evidence C).
3. Exome or genome sequencing can be useful in patients with severe and/or complex cardiomyopathy after inconclusive panel gene testing (Class IIa, Level of Evidence C).

4. Mitochondrial gene sequencing can be useful in patients with multisystemic disease and/or high lactate levels that are out of proportion to the cardiac status (Class IIa, Level of Evidence C).
5. Whole exome testing may be useful as the initial step in genetic testing in certain instances (e.g., for infantile, syndromic, metabolic, and nonisolated cardiomyopathy (Class IIb, Level of Evidence C).

3.2. Laboratory Testing

As there is general consensus that BNP/NT-proBNP testing should be performed as part of the initial evaluation and is recommended for monitoring and to assess response to therapy this recommendation was updated to Class I.[28] Testing for underlying metabolic or mitochondrial causes of cardiomyopathy may be indicated during the initial presentation and if there is suspicion of a multisystem disease.[29,30]

RECOMMENDATION

1. BNP/NT-proBNP is recommended in the integrated evaluation and monitoring of patients with known HF to further define disease severity, disease progression, and response to therapy (Class I, Level of Evidence B).
2. BNP/NT-proBNP is recommended as an adjunctive marker, not a stand-alone test, to aid in the diagnosis of new HF in symptomatic patients (Class I, Level of Evidence B).
3. Laboratory evaluation for metabolic disorders, including lactate, pyruvate, ammonia, plasma amino acids, urine organic acids, free/total carnitine, and acylcarnitine profile, is reasonable in patients with cardiomyopathy (Class IIa, Level of Evidence C).

3.3. Cardiac Imaging—Echocardiography

Echocardiogram is the initial imaging tool in establishing HF phenotype. There is growing experience with the use of three-dimensional echocardiography, strain, and tissue Doppler imaging (TDI) to assess cardiac function in pediatric patient.[18,31,32] Use of these modalities is reasonable in the assessment of children with HF, but evidence for their utility remains limited.

RECOMMENDATION

1. Standard two-dimensional (2D) imaging to evaluate cavity dimensions, wall thickness, left ventricle (LV) mass, and LV function is recommended in all children with cardiomyopathy or HF to aid in diagnosis, assess response to therapy, track disease progression, or assess for LV remodeling (Class I, Level of Evidence B).
2. Diastolic function, including mitral inflow patterns, mitral annular TDI, and pulmonary venous Doppler flow patterns by echocardiography, can be useful in children with cardiomyopathy or HF (Class IIa, Level of Evidence C).
3. Three-dimensional imaging, measurement of strain, and TDI can be useful for the evaluation of children with cardiomyopathy or HF (Class IIa, Level of Evidence C).
4. Doppler-derived estimations of right heart pressures (right ventricular systolic pressure and pulmonary artery pressures) can be useful to monitor response to treatment and progression of disease (Class IIa, Level of Evidence C).
5. Fractional area change from the apical 4-chamber view and tricuspid annular planar systolic excursion are reasonable for the quantitative assessment of right ventricle (RV) function by two-dimensional echocardiography (Class IIa, Level of Evidence C).
6. TDI assessment of tricuspid annular motion can be useful for the assessment of RV longitudinal function (Class IIa, Level of Evidence C).
7. Doppler echocardiography may be useful for the assessment of RV diastolic function (Class IIb, Level of Evidence C).
8. Quantitative techniques, such as fractional area change, EF, annular excursion, and TDI, may be considered for serial follow-up of children with single ventricle heart disease (Class IIb, Level of Evidence C).

3.4. Cardiac Cross-Sectional Imaging

Cardiac MRI can be used in patients with HF for assessment of fibrosis, edema, or inflammation, to define the phenotype of cardiomyopathy (arrhythmogenic cardiomyopathy, left ventricular noncompaction, sarcoidosis, or

amyloidosis), or in the evaluation of LV size and function if echo images are inadequate or limited.[33-37] Additionally, there is a growing body of experience utilizing cardiac MRI in children and adults with single ventricle physiology, which can be useful in the assessment of cardiac function.[38] Cardiac computerized tomography angiograms can be useful to delineate the origin and anatomy of the coronary arteries if the echocardiogram is equivocal, especially in infants presenting with HF and a dilated cardiomyopathy (DCM).[39]

RECOMMENDATION

1. MRI is recommended in the diagnostic evaluation of arrhythmogenic ventricular cardiomyopathy in older children who do not require sedation or anesthesia (Class I, Level of Evidence C).
2. Cardiac MRI is reasonable to assess LV function, LV remodeling, and for the phenotyping of cardiomyopathy in children if echo imaging windows are limited (Class IIa, Level of Evidence C).
3. In children with RV failure, MRI is reasonable to assess RV size and EF (Class IIa, Level of Evidence C).
4. MRI is reasonable for the assessment of fibrosis, edema, or inflammation in unexplained cardiomyopathy or myocarditis if noninvasive testing does not yield a diagnosis (Class IIa, Level of Evidence B).
5. Cardiac MRI can be useful for volumetric and functional analysis of a single ventricle (Class IIa, Level of Evidence B).
6. Cardiac computerized tomography angiogram is reasonable to define coronary artery origins and anatomy if the echocardiogram is equivocal (Class IIa, Level of Evidence C).

3.5. Exercise and Physical Activity

3.5.1. Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) is an important component of the diagnostic and prognostic evaluation of pediatric HF. Giardini[40] evaluated the association of peak oxygen consumption with clinical outcomes in 82 children with DCM and found, in an adjusted analysis, that a peak VO_2 of < 62% predicted was associated with a significantly higher likelihood of death or heart transplant within 2 years (50.6% vs 4.4%, $p = 0.003$, HR = 10.78). Similar findings were noted by Lytrivi and colleagues,[41] who evaluated 50 children followed at a single center undergoing heart transplant evaluation, and found that those with biventricular circulation and a peak VO_2 < 50% predicted ($p < 0.001$, HR 4.7) and/or a VE/VCO_2 slope ≥34 ($p < 0.001$ HR 2.7) were more likely to reach the composite outcome (death prior to heart transplant, initiation of mechanical circulatory support [MCS], or heart transplant at highest urgency status). Furthermore, the AHA scientific statement published in 2007 proposes that heart transplant is indicated for children with Stage C HF and severe limitation of activity, defined as a peak oxygen consumption < 50% predicted if measurable.[2]

3.5.2. Six-Minute Walk Test

The 6-minute walk test (6MWT) is a standardized measure of physical endurance that can be performed in most children ≥6 years old and does not require the same level of equipment or specialized staff as a CPET, while still offering valuable information. den Boer and colleagues prospectively studied the association of 6MWT distance in 49 children with DCM ≥6 years old and found that subjects with a 6MWT distance < 63% predicted had a 2-year transplant-free survival of 73%, in contrast to 92% in patients with distance ≥63% predicted ($p = 0.003$).[42]

RECOMMENDATION

1. CPET with measurement of peak VO_2 consumption is reasonable for assessment and prognosis of children with HF (Class IIa, Level of Evidence B).
2. A 6MWT as part of the assessment and risk stratification of patients with HF may be considered if CPET is not feasible (Class IIa, Level of Evidence C).

3.6. Cardiac Catheterization

Cardiac catheterization and the use of endomyocardial biopsy to make a diagnosis and guide management in new onset HF should only be considered in a minority of children due to the risk of morbidity and mortality from the procedure. Biopsies may be most useful and associated with the lowest risk of adverse events when performed in children with suspected myocarditis, with a relatively low yield and higher risk of complications in children with presumed cardiomyopathy.[36,43,44] Evaluation of hemodynamics by cardiac catheterization can be safe and

effective in optimizing ventricular assist device (VAD) support and medical management.[45] Additionally, while there is no consensus on the threshold for pretransplant elevation in pulmonary vascular resistance that would preclude heart transplant, evaluation of hemodynamics by cardiac catheterization in children with HF may be useful to identify those that could benefit from optimizing pulmonary hemodynamics before transplant, for post-transplant management, and for wait-list mortality risk stratification.[46,47]

RECOMMENDATION

1. Coronary angiography to confirm coronary artery anatomy may be useful in patients with unexplained HF if noninvasive imaging is not definitive (Class IIb, Level of Evidence C).
2. Cardiac catheterization to assess hemodynamics may be useful to guide management and for risk stratification of children with HF or cardiomyopathy (Class IIb, Level of Evidence C).
3. Endomyocardial biopsy may be useful in pediatric patients presenting with HF when the results of the biopsy would inform prognosis or influence therapy, but risks of morbidity and mortality must be considered (Class IIb, Level of Evidence C).

3.7. Sleep Evaluation

Sleep disordered breathing (SDB), including central sleep apnea (CSA) and Cheyne-Stokes respiration, is prevalent in adults with HF, and their occurrence is associated with HF severity and the risk of mortality, likely due to neurohumoral and hemodynamic responses that are caustic to the failing heart. Furthermore, treatment of these conditions with noninvasive ventilation is associated with increased LVEF and improved survival. Less is known about the prevalence and consequence of CSA in pediatric HF. den Boer and colleagues completed a prospective observational study of 37 children with DCM; CSA was found in 19% of subjects, and there was no demonstrated association with severity of HF.[48] Similarly, Wheeler and colleagues[49] found no correlation between LVEF and CSA in children. That said, the lack of associations may be secondary to sample size, or that children in these cohorts had not experienced CSA for a duration long enough to have a phenotypic impact. Given the known long-term impact of SDB on cardiovascular health, it is reasonable to evaluate SDB in children with HF and a history consistent with sleep apnea.

RECOMMENDATION

Children with HF and a history consistent with sleep apnea should undergo evaluation for SDB (Class I, Level of Evidence C).

3.8. Remote Monitoring and Wearable Devices

Pulmonary congestion secondary to elevated LV filling pressures is a frequent cause for HF-related symptoms and hospital admissions. The COMPASS-HF[50] and CHAMPION studies showed that implantable hemodynamic monitors could detect volume overload and guide pharmacologic therapy in adults with HF. Using an invasively implanted pressure sensor in children comes with challenges, including smaller vessel size and a higher threshold for performing invasive procedures. Small studies[51,52] have demonstrated the feasibility of using the CardioMEMS device in children, and the Advanced Cardiac Therapies Improving Outcomes Network (ACTION) CardioMEMS database is developing a cohort of pediatric patients with implantable pulmonary artery pressure monitors to determine safety and efficacy in children. However, further evaluation is needed before any formal recommendation can be made.

Meta-analyses comparing home–based cardiac rehabilitation programs using wearable technology to in-hospital rehabilitation showed similar effects in adults with HF.[53] Additionally, a randomized trial using a wearable sensor showed that remote cardiac rehabilitation was associated with less sedentary time and was more cost-effective, suggesting wearable devices may offer more affordable cardiac rehabilitation options than facility–based supervised programs.[54] Given the importance of social determinants of health in children with heart disease, measures that increase equitable access to physical activity or cardiac rehabilitation programs for pediatric HF patients are critically important. While wearable devices and remote monitoring are being rapidly incorporated into the care of adult HF, more evidence is needed to determine the role of wearables, such as smart watches, rings, patches, etc., in assessing heart rate variability, activity levels, sleep, and fluid status in children with cardiomyopathy and HF.

RECOMMENDATION

Including wearable technology in cardiac rehabilitation and physical activity programs may be considered to increase access and effectiveness of these therapies in children with HF (Class IIb, Level of Evidence C).

4. PHARMACOLOGIC TREATMENT OF HEART FAILURE WITH REDUCED EF WITH A BIVENTRICULAR CIRCULATION AND A SYSTEMIC LV

Treatment for the child with HFrEF is largely extrapolated from guideline–directed medical therapy (GDMT) demonstrated to be efficacious in the adult population. There is limited evidence to support GDMT in children with HF so as was the case in the 2014 guidelines, the majority of recommendations remain Level of Evidence C. However, new medical therapies and studies have emerged and were used to inform these updated recommendations.

As outlined in the adult HF guidelines, while there remains significant practice variation, it is reasonable to develop a systematic approach regarding which medications to start first, the initial dose, a plan for uptitration, a defined target dose, and a strategy for adding additional therapies.[9] The same GDMT premises recommended in adults with HF could be extrapolated to children and include: (1) prioritize the GDMT believed to be the most beneficial for the individual patient, while considering etiology of HF and social determinants of health that could impact access, (2) uptitration should prioritize tolerance over achieving target dosing, (3) consider patient–related outcome measures in the decision-making process, and (4) when possible engage multidisciplinary team–based care. The pediatric HF learning network, ACTION, has developed provider education materials to work toward harmonizing the approach to GDMT at the time of discharge for children with HF.[55,56]

4.1. Diuretics

Diuretics inhibit sodium reabsorption in the kidneys, thereby promoting urinary salt and free water excretion[57] and are widely used to treat the symptoms of congestion in HF.

Adult data from the OPTIMIZE-HF registry showed that in elderly patients hospitalized for HF, those who were discharged home on loop diuretic therapy had significantly lower 30 day mortality and lower risk of HF readmission.[58] Diuretic therapy has class 1b recommendation for adults with fluid retention in American and European professional consensus HF guidelines.[9,59]

In children, diuretic therapy is used for symptomatic management of fluid retention despite lack of trials showing survival advantage or reduced hospitalizations.[60,61]

RECOMMENDATION

In children with fluid retention and ventricular dysfunction (HF stage C), diuretic therapy is recommended to achieve a euvolemic state (Class I, Level of Evidence C).

4.2. Renin-Angiotensin Aldosterone System

Medications that inhibit the renin-angiotensin-aldosterone system form part of the core therapies recommended for all adult HF patients with HFrEF. These recommendations are based on multiple RCTs that have demonstrated the use of these medications being associated with significantly improved morbidity and mortality.[9] While there have been no RCTs of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or aldosterone antagonists in pediatric HF patients, the recommendation for their use is based on extrapolation for adult studies given the limited pediatric data available.[62-64]

RECOMMENDATION

1. In children with left ventricular systolic dysfunction, ACE inhibitors should be routinely used unless there is a specific contraindication (Class I, Level of Evidence B).
2. In children with systemic ventricular dysfunction, ARB are a reasonable alternative for those who are intolerant of ACE inhibitors (Class IIa, Level of Evidence C).
3. In children with symptomatic systemic left ventricular dysfunction, treatment with aldosterone antagonists is reasonable (Class IIa, Level of Evidence C).

4.3. Angiotensin Receptor Neprilysin Inhibitors

Angiotensin receptor neprilysin inhibitors (ARNI) combine an ARB with a neprilysin inhibitor. Neprilysin catalyzes the degradation of natriuretic peptides and inhibiting it can lead to improved natriuresis, reduced sympathetic tone, and reduced aldosterone levels.[65] The first in-class ARNI, sacubitril-valsartan, combines the ARB, valsartan,

with the neprilysin inhibitor, sacubitril. The landmark PARADIGM-HF trial enrolled over 8,000 adults with HFrEF and randomized them to enalapril or sacubitril-valsartan. The trial was stopped after 27 months due to the significant improvement in mortality, HF hospitalizations, and HF symptoms.[66] ARNIs are now recommended as a Class 1, Level of Evidence A for adults with HFrEF.[9] The PANORAMA-HF trial enrolled 375 pediatric HF patients with systemic left ventricular systolic dysfunction in a Phase II/III study that randomized in the Phase III study to sacubitril-valsartan or enalapril for 52 weeks.[67] Based on an interim analysis that demonstrated improved natriuretic peptides at 12 weeks after randomization, sacubitril-valsartan was approved by the Food and Drug Administration (FDA) and the European Medicines Agency for use in children over the age of 1 year with symptomatic left ventricular systolic dysfunction. However, at the conclusion of the study, while both treatments showed clinical improvements in the study participants, there was no superiority of sacubitril-valsartan over enalapril.[68]

RECOMMENDATION

In children with symptomatic systemic left ventricular systolic dysfunction, ARNI in the place of an ACE inhibitor or ARB is reasonable (Class IIa, Level of Evidence B).

4.4. β-Receptor Antagonists

β-Adrenergic receptor antagonists (beta-blockers) are also part of the core medications recommended for adult patients with HFrEF,[9] based on multiple RCTs demonstrating improved outcomes, including survival and hospitalization. While a multicenter, prospective RCT in children did not demonstrate improved outcomes associated with this use of carvedilol over placebo in children with HF from diverse etiologies, the use of these medications is widespread among pediatric HF specialists.[69] While there is differential beta-receptor remodeling in pre–pubertal pediatric failing hearts and animal model data that suggest β_1-selective blockers could be beneficial compared to nonselective blockade in younger children, there is inadequate associated clinical evidence to support that level of specificity in the recommendation.[70,71] As such, based on extrapolation from studies in adult patients and the limited published pediatric experience, beta-blockers are recommended for children with HFrEF with a systemic left ventricle.

RECOMMENDATION

In children with systemic LV systolic dysfunction, use of β-blockers is reasonable (Class IIa, Level of Evidence C).

4.5. Cardiac Glycosides

While digitalis has been used for hundreds of years to treat cardiac disorders, there is a paucity of pediatric data to support its use in HFrEF. Among adult patients with symptomatic HFrEF, a large RCT found that digoxin use was not associated with improved survival, but was associated with fewer hospitalizations. Importantly, more adverse events were seen in patients with higher serum concentrations of digoxin.[72,73] Based on extrapolation from studies in adult patients, digoxin at low serum concentrations may be considered to relieve symptoms in children with HFrEF who remain symptomatic despite adequate neurohormonal blockade.

RECOMMENDATION

In children with symptomatic HFrEF, digoxin (at lower serum digoxin levels, e.g., 0.5-0.9 ng/ml) may be considered to relieve symptoms (Class IIb, Level of Evidence C).

4.6. Ivabradine

Resting heart rate is an independent predictor of outcome in adults with systolic HF.[74-76] Elevated heart rate increases myocardial oxygen requirement and reduces diastolic filling, cardiac output, and coronary perfusion. Ivabradine is a specific inhibitor of I_f channels in sinoatrial tissue. It slows phase 4 depolarization thereby reducing heart rate independent of the sympathetic nervous system.[77]

Ivabradine is recommended for selected adults with systolic HF in American and European professional consensus guidelines.[9,59] In adults, the SHIFT study showed that isolated heart rate reduction with ivabradine significantly reduced the composite end-point of cardiovascular death or hospitalization due to HF for patients in

sinus rhythm with heart rate > 70 beats/min and LVEF < 35%.[78] A number of posthoc analyses of the SHIFT study have shown that ivabradine improved quality of life, exercise tolerance, and patient-reported outcomes[79]; and the effect of ivabradine was preserved irrespective of systolic blood pressure,[80] comorbidities,[81,82] and high–risk HF status.[83] Posthoc analysis of the SHIFT study showed coadministration of ivabradine with carvedilol was safe and may confer additional benefit.[84] Early initiation of ivabradine is possible in adults[85,86] though this should be balanced against achieving maximum tolerated beta blocker dose. Ivabradine also improves NT-proBNP profiles in adults with HF.[87,88]

In children with cardiomyopathy, an observational study showed that elevated heart rate was independently associated with greater risk of death or transplantation.[89] A multicenter, double-blind RCT of ivabradine vs placebo in children aged > 6 months with DCM, a history of symptomatic class II to IV HF and LVEF < 45% on stable medications, showed significant benefit for the primary outcome of heart rate reduction. Ivabradine also showed a significant benefit in LVEF at 12 months compared to placebo. There were greater improvements with ivabradine in both NYHA functional class and Quality of Life measures compared to placebo though these did not reach significance. NT-proBNP was reduced in both groups. Adverse effects were comparable with the placebo group except for bradycardia which was reported with higher frequency in the ivabradine group.[90] The pharmacokinetic profile of ivabradine and its active metabolite have been described in children, and used to establish effective dose strategies in 4 different age groups.[91,92] Ivabradine tablets and oral liquid have FDA approval for children aged > 6 months with symptomatic chronic HF.

RECOMMENDATIONS

In children with stable HF, ivabradine is reasonable when heart rate reduction is desirable (Class IIa, Level of Evidence B).

4.7. Sodium-Glucose Cotransporter 2 Inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors work on the renal tubules and result in glucosuria and reduced sodium absorption. This last mechanism has been suggested to be both cardio- and renoprotective, though the precise mechanism of these medications in HF patients has yet to be elucidated. Nonetheless, multiple RCTs in adult patients with HF have demonstrated a consistent improvement in mortality and HF in patients with and without diabetes.[93,94] As a result, SGLT2 inhibitors are now recommended in adults with symptomatic HFrEF to decrease hospitalizations and cardiovascular mortality.[9]

There are no RCTs and limited data on the use of SGLT2 inhibitors in pediatric HF.[95,96] A recent meta-analysis focused on the use of SGLT2 inhibitors in children reported use in those 3 months to 24 years.[97] Use occurred in those with type 2 diabetes, type 1 diabetes, chronic kidney disease, and 1 study in children with HF. The pediatric study was a prospective observational study in 38 nondiabetic patients aged 3 months to 21 years already on GDMT treated with dapagliflozin. There were improvements in BNP levels with 4 patients experiencing acute kidney injury and 6 with a symptomatic urinary tract infection.

RECOMMENDATION

In children with symptomatic HFrEF, SGLT2 inhibitors may be considered, although their safety and effectiveness in children have not been systematically studied (Class IIb, Level of Evidence C).

4.8. Soluble Guanylate Cyclase

The nitric oxide (NO)—soluble guanylate cyclase (sGC)—cyclic guanosine monophosphate (cGMP) pathway plays an important role in regulating the cardiovascular system. Under normal physiological conditions, NO is produced by endothelial cells, diffuses to neighboring cells, and binds to sGC. sGC, an intracellular protein, cleaves guanosine triphosphate to cGMP. As a secondary messenger, cGMP can regulate vascular tone, cardiac remodeling and myocardial contractility directly, or by acting on other downstream targets, such as protein kinase G or phosphodiesterases.

sGC stimulators enhance endogenous NO binding to sGC and likely produce a more physiological effect on blood pressure. Riociguat, the first oral sGC stimulator, has not progressed for HF therapy due to its short half-life and fluctuating levels of drug and tissue cGMP.[98,99] Modifications to the riociguat molecule to increase half-life and reduce clearance led to the discovery of vericiguat which has shown important benefits in adult systolic HF studies.[99]

The phase III VICTORIA study investigated oral vericiguat vs placebo in adults with high-risk HF. This multi–center randomized controlled study included those on optimal medical therapy with a recent history of worsening HF requiring hospital admission within 3 to 6 months or intravenous diuretics within the previous 3 months. In addition, patients also had to be NYHA functional class II to IV, have an LVEF < 45% at baseline and elevated circulating NT-proBNP within 1 month before randomization. At 10.8 months, the incidence of the primary end-point of cardiovascular death or first hospitalization due to HF was significantly lower in the vericiguat group. Vericiguat is now Class 2b recommendation for adults with HFrEF with elevated natriuretic peptide levels and a recent HF hospitalization or use of intravenous diuretics.[9]

There are no published reports of the use of vericiguat in children with systolic HF. A phase II/III randomized clinical trial (VALOR study) to investigate efficacy, safety, and the pharmacokinetic profile of vericiguat in children with stable systolic HF is currently in progress. The primary outcome measure is change from baseline in NT-proBNP at week 16. Secondary outcomes include time to first cardiovascular event, hospitalization or clinical worsening, adverse effects and pharmacokinetic parameters for tablet and oral liquid formulations.[100]

RECOMMENDATION

In children with worsening of HF despite dose–optimized beta blocker, angiotensin converting enzyme inhibitor (ACEI), or ARNI, and aldosterone receptor antagonist, vericiguat may be considered as add-on therapy (Class IIb, Level of Evidence C).

4.9. Positive Inotropic Agents

Milrinone is commonly used for weeks to months as a bridge to transplant for children with HF. Improvements in left ventricular systolic function, cardiac output, and mitigation of underperfusion of end-organs have been demonstrated in small studies.[101,102] Additionally, milrinone is used for children with end-stage HF as a palliative measure or in the setting of hospice care to improve symptoms.[103] Section IX includes a comprehensive discussion and recommendations specific to the use of inotropic agents in the management of acute HF.

RECOMMENDATION

1. Chronic inotropic therapy with milrinone can be used as a bridge to transplant (Class IIa, Level of Evidence C).
2. Inotropic therapy may be considered for symptomatic relief in the palliative setting (Class IIa, Level of Evidence C).

4.10. Anticoagulation

Studies support the use of anticoagulation for adult patients with HF who are in atrial fibrillation, but the efficacy for adult patients with HF who are in sinus rhythm has never been proven.[104] While there is no data specific to the pediatric population, there have been attempts to develop consensus approaches for indications for anticoagulation for children with heart disease.[105,106] As newer agents emerge, treatment options have expanded and a phase 2 open-label clinical study of apixaban demonstrated safety and efficacy in children with heart disease, suggesting direct oral anticoagulants (DOACs) are a reasonable treatment option for children.[107] Despite the lack of data, prophylactic anticoagulation is sometimes used for children in HF with indwelling catheters in the intensive care setting. Based on the absence of supportive data in adults, there is no proven utility of anticoagulation in children with HF outside the intensive care unit who do not have a history of a prior thrombus and are in sinus rhythm.

RECOMMENDATION

1. Patients with intracardiac thrombus should receive anticoagulation (Class I, Level of Evidence B).
2. In children with low EF and persistent or uncontrolled paroxysmal atrial fibrillation or flutter, systemic anticoagulation is reasonable (Class IIa, Level of Evidence C).
3. For patients with a history of thrombus or a thromboembolic event who have an EF < 25% (fractional shortening < 15%), systemic anticoagulation is reasonable (Class IIa, Level of Evidence C).
4. In children with a history of thrombus or thromboembolic event who have an EF < 25%, DOACs may be considered (Class IIb, Level of Evidence C).
5. For patients with severe cardiac dysfunction in the intensive care setting or who have indwelling intravascular catheters, prophylactic anticoagulation may be considered (Class IIb, Level of Evidence C).

5. PHARMACOLOGIC TREATMENT OF HEART FAILURE WITH PRESERVED EF WITH BIVENTRICULAR CIRCULATION AND A SYSTEMIC LV

Similar to HFrEF, pharmacologic treatment of HFpEF in children is without a significant evidence basis and recommendations are largely derived from expert consensus and extrapolation of findings from adult clinical trials. Most RCTs in adults for the treatment of HFpEF have been neutral. As a result, renin-angiotensin antagonists, mineralocorticoid receptor antagonists, and ARNIs, phosphodiesterase-5 inhibitors, calcium channel blockers, digoxin, intravenous beta-agonists, prostaglandins, and endothelin receptor antagonists are not recommended for the routine treatment of HFpEF.[108-111]

5.1. Diuretics

Diuretics are a Class I recommendation for the treatment of congestive symptoms in adults with HFpEF and are recommended to achieve euvolemia in children as well.[112] However, careful titration is recommended due to preload dependence and risk of relative volume depletion which could result in decreased cardiac output.

RECOMMENDATION

In children with HFpEF, diuretics to establish a clinically euvolemic state are recommended, although uptitration of doses should be done cautiously to avoid volume depletion (Class I, Level of Evidence C).

5.2. Sodium-Glucose Cotransporter 2 Inhibitors

The most recent addition to the adult HF guidelines for treatment of HFpEF is the Class IIa recommendation for the use of SGLT2 inhibitors.[113] While this class of medications was initially developed for the treatment of diabetes, as described in the previous section, they were found to be effective in improving outcomes of adults with HFrEF who did not have diabetes.[93,114] The EMPEROR trial of empagliflozin in adults with HFpEF and an EF > 40% demonstrated a reduced risk of cardiovascular death or HF hospitalizations, independent of an underlying diagnosis of diabetes. There are a couple of small uncontrolled studies of the use of SGLT2 inhibitors in children with HF, but no systematic study has been performed in the pediatric population.[95,96] Acknowledging the lack of evidence and absence of pharmacokinetic data in children, given the high mortality of HFpEF in the pediatric population, it is reasonable to consider use of SGLT2 inhibitors for children with symptomatic HFpEF. However, a systematic study of this class of medications is needed in the pediatric and CHD HF populations to better inform our approach and assess safety and adverse effects of these medications, including acute kidney injury and genitourinary tract infections.

RECOMMENDATION

In children with symptomatic HFpEF, SGLT2 inhibitors may be considered (Class IIb, Level of Evidence C).

6. PHARMACOLOGIC TREATMENT OF SPECIAL POPULATIONS

In general, it is reasonable to apply the GDMT for HFrEF (Section 4) and HFpEF (Section 5) as described in this document for children with a biventricular circulation and a systemic LV regardless of the underlying etiology of their HF. In this section, we describe additional therapies that exist for some specific populations impacted by cardiomyopathy and HF.

6.1. Congenital Heart Disease Associated Heart Failure

Patients with single ventricle physiology or biventricular physiology with a systemic RV may respond differently to GDMT, suggesting caution in the extrapolation of adult clinical trial data to this patient population. For example, the pediatric carvedilol trial demonstrated that the cohort of patients with single ventricle physiology or a systemic RV tended to do worse with carvedilol compared to placebo.[69] Based on this study, caution should be used when considering a β-blocker for the treatment of HF in patients with this anatomy. Due to the impact of ventricular morphology in the carvedilol trial, patients with single ventricles or systemic RVs have been excluded from

subsequent pediatric HF clinical trials, further contributing to the paucity of data specific to these patient populations. While there have been no RCTs for the treatment of single ventricle or systemic RV HF, there was a small uncontrolled observational study of ARNI in **adults** with a failing systemic RV in a biventricular circulation that demonstrated some efficacy.[115] Despite the lack of data, the use of ACEI in the treatment of children with single ventricle or systemic RV systolic failure or in those with atrioventricular valve regurgitation is common. As a consequence of the limited treatment options available for these patients, early referral to an advanced HF/transplant specialist should be considered for patients with pulmonary hypertension associated with their underlying CHD, single ventricle physiology with symptomatic systemic ventricular dysfunction, and those with a biventricular circulation and a systemic RV.[116,117]

RECOMMENDATION

1. Referral to an advanced HF/transplant specialist is reasonable for patients with single ventricle physiology or a systemic RV and symptomatic systemic ventricular dysfunction (Class IIa, Level of evidence B).
2. ACEI/ARB therapy may be considered in patients with single ventricle physiology or a systemic RV and ventricular dysfunction (Class IIb, Level of evidence C).

6.2. Cardio-Oncology

The recommendations included in this document are specific to the long-term or late effects of cardiotoxic cancer therapies. Patients who have undergone cancer treatment that includes potentially cardiotoxic therapies should be considered ACC/AHA Stage A based on the National Comprehensive Cancer Network (www.nccn.org). The Childhood Cancer Guideline Harmonization Group has provided specific recommendations stating that patients who have received anthracyclines (≥100 mg/m^2) and/or radiation therapy should have screening of left ventricular function with an echocardiogram as the preferred method no later than 2 years after the completion of therapy and screening should continue with repeat electrocardiogram (ECG) and echocardiogram every 2 years thereafter unless otherwise dictated by clinical status.[118] There is insufficient evidence to recommend medical HF therapies to prevent the development of cardiomyopathy or HF for patients who have been exposed to anthracycline and/or radiation therapy.[118] Dexrazoxane should be considered to prevent cardiomyopathy associated with anthracycline if there is an anticipated lifetime cumulative dose > 150 mg/m^2.[118-122] Dexrazoxane has been noted to be safe with no effect on secondary malignancy or decreased efficacy when used in conjunction with appropriate anthracycline therapy against primary cancer. Patients who are experiencing HF secondary to oncology treatment should be treated with the HFrEF and HFpEF guidelines as previously described.

RECOMMENDATION

1. Patients who have undergone cancer treatment with potential for cardiotoxicity should be considered ACC/AHA Stage A (Class I, Level of evidence C).
2. Dexrazoxane is reasonable to prevent cardiomyopathy associated with anthracycline if there is an anticipated lifetime cumulative dose > 150 mg/m^2 (Class IIa, Level of evidence B).

6.3. RASopathies, Storage Diseases, and Other Disorders of Metabolism

Patients with genetic, metabolic, or mitochondrial disorders resulting in HFrEF or HFpEF should be treated based on the guidelines previously described. However, there are some specific targeted therapies that can influence the natural history of some of these disease processes. For example, for patients with infantile-onset Pompe disease, enzyme replacement therapy (alglucosidase alfa) has been effective in normalizing left ventricular hypertrophy and systolic function (global longitudinal strain, EF). Similarly, enzyme replacement therapy (idursulfase) in patients with mucopolysaccharidoses II is effective in reducing or stabilizing left ventricular mass and septal hypertrophy, although it does not alter valvar pathology. Based on the putative downstream effects of the specific gene mutation in pediatric patients with RASopathy-associated HCM, MEK1 inhibitors (trametinib) may be effective in decreasing cardiac hypertrophy.[123]

RECOMMENDATION

Enzyme replacement therapy is recommended in classic infantile-onset Pompe disease and mucopolysaccharidoses II (Class I, Level of evidence B).

6.4. Dystrophinopathies

There is a wide range of neuromuscular disorders associated with cardiomyopathies and HF, the most prevalent being those associated with dystrophinopathies. There have been working group and scientific statements describing management of HF in this population which will therefore not be repeated here.[5,124] In brief, given the difficulty in establishing HF symptoms in this population, initiation of oral HF therapies may be considered with any of the following: (1) asymptomatic LV dysfunction, (2) persistent BNP elevation, (3) significant or progressive fibrofatty replacement of cardiomyocytes on cardiac MRI, (4) age > 10 years. Gene therapy and other targeted treatment options are evolving for these patients.

RECOMMENDATION

1. Periodic evaluation of treatment options should be performed at a center with expertise in comprehensive treatment of dystrophinopathies due to the rapid rate of development of novel therapies (Class I, Level of evidence C).
2. Adult female carriers of a dystrophinopathy should undergo periodic evaluation of cardiac function (Class I, Level of evidence C).
3. BNP and cardiac MRI, to assess global function and the presence of fibrofatty replacement of cardiomyocytes with late gadolinium enhancement, are reasonable in the surveillance of patients with dystrophinopathy (Class IIa, Level of evidence C).

7. LIFESTYLE MODIFICATIONS

Behavior that promotes a healthy diet, exercise, and sleep in addition to management of comorbidities that can be a consequence of obesity and a sedentary lifestyle, such as hypertension, is important in the comprehensive care of children with HF. Kamsheh and colleagues performed a single–center retrospective cohort study and identified 34 children with systolic dysfunction attributed to systemic hypertension. Most patients (81%), including 92% of infants, had resolution of their systolic dysfunction with treatment, demonstrating the importance of identification and treatment of hypertension–associated pediatric HF.[125] Treatment of systemic hypertension should be in accordance with the American Academy of Pediatrics Clinical Practice Guidelines.[126] When treating systemic hypertension in HFpEF, careful monitoring of hemodynamics and renal function is indicated due to the enhanced risk of hypotension and renal toxicity.

7.1. Exercise Training and Activity

A hallmark of symptomatic HF is exercise intolerance, namely fatigue and dyspnea with exertion. To maximize functional status in pediatric patients with HF, physician and parental physical activity restrictions should not be imposed unless there is a substantiated concern for an adverse event or progression of disease with exercise. Exercise testing may be helpful in identifying cardiac limitations to exercise in HF patients and an exercise training or cardiac rehabilitation program may be beneficial. It is reasonable to include aerobic and resistance training in an individualized exercise prescription, which can specify frequency, intensity, time, type, volume, and progression. Once an exercise regimen is established, home exercise training programs with individualized goals and reinforcement may be beneficial in improving functional capacity and quality of life.[127,128] These recommendations are distinct from those put forth in the 2015 AHA/ACC Scientific Statement which addresses participation in competitive sports.[129,130]

RECOMMENDATION

1. In children at risk for adverse events during exercise, pre–participation health screening and risk stratification should be performed prior to initiating an exercise training program and to inform appropriate guidance around exercise intensity and content (Class I, Level of Evidence C).
2. Detection of children at risk for sudden death, identification of medical contraindications to a training program, and appropriate recommendations for a defibrillator as primary or secondary intervention should be performed before initiating an exercise program or increasing frequency, intensity, or duration of the current program (Class I, Level of Evidence C).
3. Exercise training in a supervised setting should be prescribed, if deemed safe, as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF. The training program should be individualized to the patient's ability, resources, and the patient's response to exercise with an emphasis on safety (Class I, Level of Evidence C).

4. For pediatric patients with HF thought to be at increased risk of a having a cardiac event during physical activity, CPET is reasonable before shared decision-making regarding exercise training or competitive sports to determine exercise capacity, assess risk for adverse events, and determine suitability for the desired physical activities (Class IIa, Level of Evidence C).
5. Restriction from intense sports activity is reasonable for pediatric patients with arrhythmogenic cardiomyopathy based on the current Task force criteria[34,131] to minimize disease progression (Class IIa, Level of Evidence C).

8. ELECTROPHYSIOLOGY ASSESSMENT AND INTERVENTIONAL THERAPIES

Electrophysiological pathologies are both a complication and a potentially correctable cause of pediatric HF. Note that the HF-specific recommendations for electrophysiological interventional therapies are intended to be interpreted in addition to, rather than superseding, the 2 recent cardiac implantable electronic device guidelines. These are the 2021 PACES expert consensus on pacemakers and implantable cardioverter-defibrillators (ICDs) and the 2023 HRS/APHRS/LAHRS Guideline on Cardiac Physiologic Pacing.[132,133]

8.1. Ambulatory ECG Monitoring and Electrophysiology Testing and Treatment

Tachyarrhythmias can be a causative etiology of HF in children and electromechanical dyssynchrony contributes to deterioration in cardiac function and may be secondary to iatrogenic or congenital factors. The clinician should be cognizant of markers of electrical dyssynchrony (most obviously quantified on the surface ECG via the QRS duration) and mechanical dyssynchrony (which is observed qualitatively on echocardiogram and other multiphase imaging). Causes of electromechanical dyssynchrony include not only bundle branch block, but also ventricular pacing, pre-excitation via an accessory pathway, and frequent beats of ventricular origin: all of these may be targets for physiologic pacing or ablation.[134-136]

RECOMMENDATION

1. In a pediatric patient with HF who presents with palpitations or suspected cardiac syncope, ambulatory monitoring is recommended (Class I, Level of Evidence C).
2. Evaluation for tachycardia-induced cardiomyopathy is recommended in any patient presenting with DCM (Class I, Level of Evidence B).
3. In the pediatric patient with tachycardia-induced cardiomyopathy, ablation therapy is recommended when medical therapy fails or is associated with intolerable side effects (Class I, Level of Evidence B).
4. Ablation is recommended for frequent ventricular ectopy or tachycardia, predominantly from a single focus thought to be causing ventricular dysfunction, when medical therapy is either not effective or is associated with intolerable adverse effects (Class I, Level of Evidence B).
5. In pediatric patients with HF and a high risk of developing atrial or ventricular arrhythmias, or heart block, regular ambulatory monitoring is reasonable (Class IIa, Level of Evidence C).
6. In pediatric patients with presyncope or syncope with at least moderately impaired LV function, electrophysiology testing or long-term monitoring can be useful (Class IIa, Level of Evidence C).
7. Ablation therapy is reasonable as first-line therapy in larger pediatric patients (generally > 15-30 kg) with tachycardia-induced myopathies or frequent ventricular ectopy or tachycardia, predominantly from a single focus thought to be causing ventricular dysfunction (Class IIa, Level of Evidence B).
8. Ablation of the accessory pathway is reasonable in those with Woff-Parkinson-White pattern and ventricular dysfunction presumed secondary to dyssynchrony(Class IIa, Level of Evidence B).

8.2. Pacemaker and Resynchronization Therapy

Cardiac physiologic pacing is a relatively new umbrella term that is defined as any form of cardiac pacing intended to restore or preserve ventricular synchrony.[134] Traditionally, this was achieved via multisite cardiac resynchronization therapy, but in recent years there has been a rapid transition to conduction system pacing

(CSP) in adults. CSP involves engaging the pacing lead in the His bundle or, increasingly, the larger left bundle branch area. For children, the data for CSP are currently highly limited but are expected to evolve over the lifetime of these guidelines.[137] The 2023 HRS/APHRS/LAHRS Guideline on Cardiac Physiologic Pacing generally endorses multisite cardiac resynchronization therapy for adults with HF symptoms on GDMT with a systemic LV, LVEF < 45%, and ventricular dyssynchrony (defined as QRS duration z-score ≥3 or ventricular pacing > 40%); this indication has been reinforced by more recent multisite data.[133,134] The failing subpulmonary RV may also be a target for resynchronization via fusion-based pacing in selected cases.[134,138] Comprehensive data for CSP in pediatrics are likely to take many more years to collate, particularly regarding lead extraction, but may currently be considered in the pediatric population on a case by case basis, dependent upon operator experience.[134] Regardless, initial pacing implant for all pediatric patients should take into account the potentially deleterious impact of chronic ventricular pacing.[132,139] There are established guidelines for pacemaker implantation in pediatrics and these should also be applied to the pediatric HF patient population.[132]

RECOMMENDATION

1. In patients undergoing single ventricular site epicardial pacemaker placement, targeting of the apical LV is reasonable in preference to the RV epicardial position (Class IIa, Level of Evidence B).
2. In patients undergoing standard (nonphysiological pacing) transvenous pacemaker placement, targeting of the RV mid-septal inflow or outflow tract is reasonable in preference to the RV apical endocardial site (Class IIa, Level of Evidence B).
3. CSP may be considered based on operator experience and patient–specific risk factors (Class IIb, Level of Evidence C).
4. In pediatric patients with CHD requiring ventricular pacing, and with pre-existing HF symptoms with myocardial dysfunction, CSP may be considered (Class IIb, Level of Evidence B).

8.3. Implantable Cardioverter-Defibrillators

In addition, the pediatric HF population is at a poorly quantified risk of malignant arrhythmias, which may result in sudden cardiac arrest (SCA). The role of an ICD for secondary prevention is well-established, but more detailed guidelines for primary prevention ICD implantation in the pediatric population subgroups (including arrhythmogenic cardiomyopathy, HCM, CHD, and DCM) have been published in the "2021 PACES expert consensus statement on the indications and management of cardiovascular implantable electronic devices in pediatric patients."[132] It should be highlighted that in contrast to some studies of adult patients with nonischemic DCM and LVEF ≤35%, there is no clear evidence that ICDs implanted for primary prevention in pediatric patients with nonischemic DCM improve survival.[132] There are also SCA risk score calculators for pediatric HCM and ACHD: these should be interpreted and extrapolated with caution, but may assist in guiding the clinician in some of the more challenging cases, noting that some are likely to be further refined in the future by including specific genetic variant data.[140-142]

RECOMMENDATION

ICD therapy may be considered in children with CHD and HF where extrapolation of established adult CHD SCA risk scores suggests a high risk of SCA (Class IIb, Level of Evidence C).

9. MANAGEMENT OF COMORBIDITIES

Comorbidities are frequent in children with HF: one-third of pediatric patients present with acute onset HF, while two-thirds present with a chronic HF condition. These comorbidities have an impact on morbidity and mortality and a careful evaluation is required.[143]

9.1. Anemia

Anemia occurs in children with HF, especially those hospitalized for acute HF. It is associated with an increased risk of transplantation, MCS, and in-hospital mortality.[144] More than 50% of pediatric patients with HF have iron deficiency,[144-146] defined as ≥2 of the following: serum iron < 50 μg/dl, serum ferritin < 20 ng/ml, transferrin > 300

ng/ml, or transferrin saturation < 15%.[145,147] In adults, RCTs have shown that intravenous iron supplementation is safe and improves symptoms, exercise capacity, and quality of life in patients with HFrEF and iron deficiency,[148] but these data are lacking in the pediatric population.

RECOMMENDATION

1. Screening for anemia at the time of diagnosis of HF in children and at ongoing regular intervals is recommended (Class I, Level of Evidence C).
2. Screening for iron deficiency in children with HF is recommended (Class I, Level of Evidence B).
3. Intravenous iron supplementation is reasonable for the treatment of iron deficiency in pediatric patients with HF (Class IIa, Level of evidence B).
4. Erythropoiesis-stimulating agents to treat anemia in pediatric patients with HF is reasonable if anemia persists once iron stores are replete (Class IIa, Level of Evidence C).

9.2. Renal Dysfunction

Cardiorenal syndrome, coexisting heart and kidney dysfunction, is common in children with HF and represents an independent risk factor for increased morbidity and mortality.[143,149,150] Management includes diuresis and augmentation of cardiac output through afterload reduction.[151] In cases of renal failure associated with fluid overload and electrolyte derangement, renal replacement therapy with dialysis or extracorporeal fluid removal may be required.[152,153] Severe renal impairment in children with HF also carries a higher risk of death on the waiting list and a lower transplantation rate.[154-158] Timely and appropriate support with a VAD could also promote renal recovery and should be considered when renal dysfunction persists or worsens on medical therapy.

RECOMMENDATION

1. The presence and severity of renal dysfunction should be determined at the time of HF diagnosis and at ongoing regular intervals, including after changes in medical therapy (Class I, Level of Evidence B).
2. Management of acute kidney injury should include strict recording of fluid balance, daily weight measurements, and monitoring renal function (Class I, Level of Evidence C).
3. A review and adjustment of medications should be performed in children with HF and worsening renal function (Class I, Level of Evidence C).

9.3. Airway and Parenchymal Respiratory Disorders

Respiratory distress and sleep disordered breathing (SDB) are common presenting HF symptoms among children.[159,160] Pulmonary function testing with spirometry and polysomnography are useful studies to identify restrictive lung disease, obstructive breathing patterns, and to evaluate the etiology of SDB in children with HF. This testing can identify the most appropriate acute and chronic form of respiratory support (e.g., non–invasive positive pressure ventilation, nasal cannula, and heated high flow) that improves symptoms and alleviates reversible upper airway obstruction without causing harmful hemodynamic effects.[161]

RECOMMENDATION

1. In the pediatric patient with HF who presents with new or worsening respiratory symptoms, chest X-ray imaging should be obtained to evaluate for treatable pulmonary complications (Class I, Level of Evidence C).
2. Pulmonary function testing and polysomnography should be used in patients with signs and symptoms of sleep–related breathing disorders, especially when pulmonary hypertension is present (Class I, Level of Evidence C).
3. Pulmonary function testing should be used for detection and assessment of reversibility of obstructive–related breathing disorders as well as for the diagnosis of restrictive lung disease, especially when pulmonary hypertension is present (Class I, Level of Evidence C).

9.4. Malnutrition

Malnutrition is common in pediatric HF and is associated with increased mortality and unfavorable clinical outcomes compared to those with normal weight.[162] The etiology is multifactorial and is due to a combination of decreased food intake due to fatigue and anorexia combined with increased nutritional requirements,

inflammation, hypermetabolism and malabsorption. In these patients, a comprehensive nutritional assessment should be performed that includes a food and nutrition history, anthropometric measurements, biochemical data, medical tests and procedures, nutrition–related physical findings, and medical history, as no single parameter is a comprehensive indicator of nutritional status.

Several data have shown that vitamin D deficiency has a negative impact on ventricular function in children, can be a reversible cause of DCM (especially in infants), and should be investigated during nutritional screening.[163-166] The effects on mortality have not been well studied in RCTs in either adults or children. This hormone plays an important role in hemostasis and its effects also include boosting innate immunity and reducing chronic inflammation, making vitamin D a suitable supplement for left ventricular assist device patients.[167]

In a retrospective cohort study of over 4,000 pediatric patients listed for heart transplant, Davies et al found that underweight patients had increased risk adjusted wait-list mortality (operating room 1.4, 95% cardiac index 1.0-2.2). Similarly, Castleberry and colleagues found that hypoalbuminemia and poor growth were both independently associated with mortality in children listed for heart transplant (p = 0.020 and 0.008).[168,169]

The American Society of Parenteral and Enteral Nutrition details the factors that define a child as nutritionally compromised. Knowledge of appropriate anthropometric measurements and alternatives is critical and should be done by an experienced professional, given the challenges in assessing and interpreting nutritional state in the pediatric population.[170]

RECOMMENDATION

1. A weight-for-height z-score, which is below −2 standard deviation of the World Health Organization median standard curve in a child with HF represents malnutrition and requires further assessment and intervention (Class I, Level of Evidence C).
2. Enteral tube feeds, high calorie formulas/supplements, or intravenous nutrition may be necessary to correct nutritional deficiencies, and to improve nutritional status and growth (Class IIb, Level of Evidence C).

9.5. Frailty

End-stage HF carries an increased risk of frailty and sarcopenia, impaired growth, reduced physical performance, and altered metabolism can occur as a result of HF.[171] In the adult population, frailty has been associated with longer duration of hospitalization. Frailty is defined by an increased susceptibility to adverse events due to age-related or physiologic decline and can be determined using various instruments.[171] Fried's physical frailty phenotype classification (used in the adult population) requires the presence of 3 of the following 5 items to determine frailty: (1) slow walking speed, (2) impaired grip strength, (3) declining physical activity levels, (4) exhaustion/fatigue/no sense of fullness of energy, and (5) unintentional weight loss. The presence of 2 of the 5 items defines prefrailty. Treatment of frailty includes nutritional support and physical rehabilitation.[171] The practical assessment of frailty in young children is evolving with attempts being made to translate the adult paradigm into the pediatric and CHD population.[172] The impact of optimizing nutrition and physical rehabilitation in children with HF and associated frailty deserves further investigation.

RECOMMENDATION

Evaluation and management of frailty in children with HF is reasonable based on (1) slowness: 6MWT; (2) weakness: handgrip strength; (3) Fatigue PedsQL Multi-dimensional Fatigue Scale; (4) body composition: triceps skinfold thickness; and (5) Physical activity questionnaire (Class IIa, Level of Evidence B).

9.6. Obesity and Metabolic Syndrome

The impact of obesity on outcomes in children and adolescents with HF has been studied in a large cohort.[162] Castleberry et al[162] found that event-free survival is reduced in obese children with pediatric cardiomyopathy, including symptomatic and asymptomatic individuals. Obesity is closely associated with some risk factors for HF, such as metabolic syndrome as well as diabetes, dyslipidemia, and hypertension. Controlling obesity can delay the onset of these comorbidities.[173] The glucagon-like peptide 1 receptor agonists have recently shown a beneficial effect in the adult population in preventing serious cardiovascular events and HF,[174,175] and have been used in combination with SGLT2 inhibitors.[176] These data are not yet available for the pediatric population. However, aggressive early measures to address obesity in the child with HF is important and should include

lifestyle modifications that promote weight loss. The utility of SGLT2 inhibitors and glucagon-like peptide 1 receptor agonists for treatment of HF in children with metabolic syndrome is deserving of further study.

RECOMMENDATION

1. Evaluation for metabolic syndrome and all other cardiovascular risk factors, including hypertension, dyslipidemia, insulin resistance, and liver disease should be performed in obese children with HF (Class I, Level of Evidence C).
2. In pediatric patients with HF and metabolic syndrome, an intensive, multidisciplinary weight-reduction program and management of other identifiable risk factors should be initiated (Class I, Level of Evidence B).
3. In children with HF and associated obesity or metabolic syndrome, it is reasonable to perform exercise testing to determine suitability for enrollment in an exercise training program (Class IIa, Level of Evidence C).

9.7. Mental Health

Children and teens with HF are at risk for impaired mental health, which has the potential to impact HF presentation and course, treatment adherence, candidacy for advanced cardiac therapies, and overall emotional and physical wellbeing. While large-scale, multisite prospective and randomized mental health-focused studies are lacking, expert consensus and literature to date underscore the significance of screening for and intervening upon the mental health care needs of this patient population. Psychiatric diagnoses are observed in 30% of 11- to 17-year-olds and in 25% of 6- to 10-year-olds with HF.[177] Notably, there was a significant increase in the prevalence of psychiatric diagnoses observed across eras (1999-2009 vs 2010-2016). In a single-center experience of children 8 to 17 years of age awaiting heart or heart-lung transplant, 24% endorsed symptoms indicative of a depressive diagnosis.[178] Certainly, HF requiring advanced cardiac therapies, such as VAD and transplant, has important implications for mental health, including uncertain prognosis and survival, need for hospitalization and invasive interventions, and impact on physical functioning. Studies demonstrate that children with HF supported by a VAD, suffer from procedural anxiety, sadness, limitations in activities (i.e., play, school) and sleep disturbances.[179-183] Further study to understand the impact of positive psychological wellbeing, including resilience and optimism, is warranted in children with HF.

RECOMMENDATION

1. Annual screening for emotional and behavioral conditions, including anxiety, depression, adjustment, attention and sleep disorders, is recommended for children with HF (Class I, Level of Evidence B).
2. Mental health intervention and psychologic support is recommended when indicated for children with HF and in those undergoing ICD and/or VAD implantation (Class I, Level of Evidence B).

9.8. Neurodevelopment

Although a great deal of research has focused on neurodevelopment in CHD, considerably less is known specific to pediatric HF.[184-187] Single-center and case-based studies provide additional evidence for the importance of screening for neurodevelopmental needs in children with HF. In a small study of 7 children with advanced HF in the context of cardiomyopathy, MRI detected gray matter loss similar to that observed in adult HF.[188] In children with HF who go on to receive heart transplantation, relative deficits in attention, executive functioning, visual-spatial skills, motor, academic and adaptive skills have been reported.[189] While these small studies have mostly reported general intelligence scores to be in the low average range for pediatric heart transplant recipients, considerable heterogeneity in diagnoses and the course leading to HF greatly impact neurodevelopment. In addition to risk factors outlined specific to CHD, the presence of social determinants of health, earlier age at organ failure onset, disease severity (e.g., longer hospital stays, time away from education/learning, malnutrition), and neurological complications (e.g., stroke) can also contribute to neurodevelopmental risks[189] in pediatric HF.

RECOMMENDATION

1. Early intervention, developmental supports, and school-based accommodations should be provided for children with HF demonstrating any concerns in these domains (Class I, Level of Evidence B).
2. Screening for neurodevelopmental assessment/reassessment annually in children with HF and in accord with established guidelines for those with CHD is reasonable (Class IIa, Level of Evidence B).
3. Brain imaging is reasonable in patients with HF, particularly those with VAD therapy or those supported by extracorporeal membrane oxygenation (ECMO) (Class IIa, Level of Evidence B).

10. MANAGEMENT OF ACUTE DECOMPENSATED HEART FAILURE

The initial presentation of HF in children is often acute and of sudden onset and prompt assessment and early management can influence outcomes.

10.1. Diagnosis and Monitoring

The diagnosis of acute HF should be based on signs and symptoms combined with supportive evidence from chest X-rays (e.g., cardiomegaly, pulmonary plethora, pleural effusions), ECGs (looking for the presence of sinus rhythm or arrhythmias, abnormal Q waves, ST or T wave abnormalities suggesting a strain pattern or abnormal repolarization and low voltages) with echocardiography often confirming the diagnosis. Laboratory investigations, including natriuretic peptide levels, liver and renal function (to assess for end-organ dysfunction), blood gas analysis, inflammatory markers and viral serology, complete blood count, and other tests looking for possible underlying causes such as metabolic diseases and thyroid function, should be performed early. Symptoms of HF in children and adolescents are often nonspecific and typical symptoms such as dyspnea and cough or respiratory distress and exercise intolerance may develop late in the course of the disease which may already be advanced at presentation. Respiratory symptoms are common in all age groups whereas adolescents more commonly present with symptoms such as abdominal pain, nausea, vomiting, anorexia, and weight loss.[190] Chest pain, cardiac arrest, and cardiogenic shock are relatively rare presentations.

An assessment should be made of the severity of HF, the patient's volume status as evidenced by the degree of fluid retention/congestion (the "wet vs dry" patient) and the adequacy of perfusion (the "cold vs warm" patient) as initial treatment may be slightly different depending on the hemodynamic presentation. These descriptions or profiles also correlate with patient outcomes with "cold and wet" patients having the highest mortality in adult studies.[191] Reversible causes need to be looked for so that appropriate treatment can be started early.

The initial evaluation should aim to identify patients at risk of rapid deterioration, those requiring enhanced levels of monitoring, and those with evidence of poor perfusion or hemodynamic instability who should be managed in an intensive care unit. Continuous ECG monitoring should be used routinely to assess for arrhythmias, and early transfer to a center with pediatric HF specialists and the facilities for mechanical support or transplant evaluation should be considered. Judicious use of central venous catheters to allow for measurement of central venous pressure and mixed venous saturations and provide secure access for administration of medications and fluids is reasonable. Placement of an arterial catheter for continuous blood pressure monitoring is often employed in those requiring inotropic support. Pulmonary artery catheters ("Swan-Ganz catheters") allow for direct measurement of right atrial, right ventricular, pulmonary arterial, and pulmonary wedge pressures and are used commonly in adult practice but are not recommended for routine use in pediatrics as there are no data demonstrating improved outcomes and the risk of complications, including bleeding, thromboembolism, cardiac perforation, and infection in children, is significant, particularly in small children or in those with an intracardiac shunt.[192] Near-infrared tissue spectroscopy may be helpful in providing trends in cerebral and somatic oxygen saturation and can be used as a proxy of oxygen extraction.

Cardiac catheterization is not routinely used for diagnosis of HF, but can be helpful to identify coronary abnormalities when noninvasive imaging has not documented normal coronary flow, in patients with CHD to clarify potential structural causes of deterioration, and to provide hemodynamic measurements to aid in management.

RECOMMENDATION

1. The diagnosis of acute HF should be based on signs and symptoms of HF combined with supportive evidence from chest X-ray imaging, ECG, echocardiography, and laboratory evaluations, including natriuretic peptide levels (Class I, Level of Evidence B).
2. The severity of HF should be assessed based on the degree of congestion and adequacy of perfusion (Class I, Level of Evidence C).
3. In patients with severe acute HF, it is reasonable to initiate transfer to a center with pediatric HF specialists who have the expertise and ability to optimize medical therapy, evaluate for heart transplantation, and provide mechanical support (Class IIa, Level of Evidence C).
4. For patients with acute HF, serial testing to monitor for electrolyte abnormalities, hemoglobin levels, end-organ perfusion, and response to therapy is indicated (Class I, Level of Evidence C).
5. In children hospitalized with acute HF, evaluation and monitoring for arrhythmias with continuous ECG monitoring/telemetry is warranted (Class I, Level of Evidence C).

6. In children with decompensated HF, central venous catheters are reasonable for administration of medications and to measure central venous pressure and mixed venous saturation (Class IIa, Level of Evidence C).
7. In children with acute decompensated HF, it is reasonable to place an arterial catheter for continuous blood pressure measurement (Class IIa, Level of Evidence C).
8. In decompensated patients with acute HF, trends in cerebral or somatic regional oxygen saturation and venous oxygen saturations levels may be helpful (Class IIb, Level of Evidence C).
9. In patients with palliated or repaired CHD who present with acute HF, cardiac catheterization is indicated if a noninvasive evaluation fails to establish a definitive diagnosis or if invasive hemodynamic measurements are needed for management decisions (Class I, Level of Evidence C).

10.2. Fluid Management and Diuretics

The mainstays of management in the initial stabilization of the child with acute HF are diuresis, inotropic agents, vasodilators, and respiratory support with the initial treatment choice dependent on the clinical presentation and evaluation of fluid status.

Patients who are well perfused but with signs of congestion/volume overload (e.g., tachypnea, hepatomegaly) may benefit from diuresis. Loop diuretics are commonly used as first-line therapy either with intermittent dosing or as a continuous infusion.[193] Edema of the gastroenterology tract can present as feeding intolerance in infants or abdominal pain in older children, making consideration of intravenous diuretics necessary. Continuous infusions of loop diuretics may be of increased benefit in neonates and children with HF who are critically ill by increasing the likelihood of achieving a negative fluid balance and mitigating rapid fluid shifts.[194]

While a low sodium diet and fluid restriction are often considered, especially in older children with HF, there are no data (even in adults) to support this practice.[195-197]

RECOMMENDATION

1. An initial and ongoing assessment of fluid status should be performed in all patients admitted to the hospital with acute HF (Class I, Level of Evidence C).
2. Diuretics are the first-line therapy for patients with acute HF with evidence of fluid overload (Class I, Level of Evidence C).
3. Careful monitoring for side effects of anticongestive therapies, including renal function, electrolytes, and hypotension, should be performed in all patients with acute HF (Class I, Level of Evidence C).

10.3. Inotropic Agents

In patients with evidence of low cardiac output and compromised systemic and end-organ perfusion, such as those with hypotension and cardiogenic shock, there is a Class I indication for the use of intravenous inotropic support. This is generally considered a short-term strategy, as failure to improve with inotropic support should result in consideration for mechanical support. The choice of inotropic agent will depend on the clinical presentation with milrinone and/or dobutamine generally used as first-line agents in children. If there is hypotension and ongoing poor end-organ perfusion, then epinephrine is often added.

Dobutamine is a catecholaminergic agent acting primarily on the myocardial beta-1 receptors which has a quick onset of action, increases heart rate, stroke volume, and cardiac output, and also causes venous and arterial vasodilatation resulting in reduced pulmonary capillary wedge pressure which is of benefit in patients with pulmonary edema.[198] It does, however, cause an overall increase in myocardial oxygen consumption which limits its use to short–term rescue therapy. Dobutamine should be used with caution in patients who are on beta-blockers as an unbalanced alpha-1 effect in these patients may result in peripheral vasoconstriction.

Milrinone is a phosphodiesterase-3 inhibitor which increases intracellular cyclic adenosine monophosphate and has both inotropic and vasodilator properties resulting in a decrease in both systemic and pulmonary arterial resistances. It delivers more effective afterload reduction and improved coronary perfusion pressure compared to dobutamine with less effect on heart rate and myocardial oxygen demand[199] and plays a central role in acute HF management in pediatrics. Milrinone can also be used for longer term management than dobutamine but it does have a long half-life and due to its clearance by the kidneys dosing needs to be adjusted in patients with renal impairment.

Epinephrine is a catecholamine that activates myocardial beta-1 adrenergic receptors causing inotropy and at lower doses it activates beta-2 receptors resulting in reduced systemic vascular resistance whereas at higher doses it results in increased systemic vascular resistance through its effect on the peripheral alpha-adrenergic receptors. It has rapid effects in patients with hypotension and poor perfusion but can increase the risk of arrhythmias and causes increased myocardial oxygen consumption and reduced distal perfusion with longer term use.

RECOMMENDATION

1. Intravenous inotropic support should be used in patients with acute HF presenting as cardiogenic shock or low cardiac output with poor systemic and end-organ perfusion (Class I, Level of Evidence C).
2. Milrinone or dobutamine is reasonable as a first-line rescue therapy, with epinephrine playing a role in the face of refractory hypotension and poor end-organ perfusion in children with acute HF (Class IIa, Level of Evidence C).

10.4. Vasodilators

In patients with acute HF who do not have evidence of hypotension, especially in those with pulmonary edema or significant volume load, such as valvar regurgitation, vasodilators such as nitroprusside, may be used, often in combination with diuretics. Vasodilators may improve stroke volume and cardiac output and reduce pulmonary capillary wedge pressure but may impair ventricular preload and therefore concurrent use of an inotropic agent is usually needed.[200] Vasodilators should be used with caution in patients with HCM or left-sided obstructive lesions as they can lead to reduced coronary perfusion and may exacerbate left ventricular outflow tract obstruction.

RECOMMENDATION

In pediatric patients with acute HF, vasodilators may be used in the absence of hypotension and in combination with diuretics for symptomatic relief (Class IIb, Level of Evidence C).

10.5. Calcium Sensitizing Agent

Levosimendan is a calcium sensitizing agent which binds to cardiac troponin C causing a change in the configuration of tropomyosin resulting in increased inotropy without increased myocardial oxygen consumption. Afterload reduction occurs through peripheral vasodilatation. Although side effects in pediatric patients are few, the impact of levosimendan on major clinical outcomes remains undetermined and the quality of evidence for its use is low.[201] Where available, it may be considered in children with acute HF who are unresponsive to traditional inotropic therapy.

RECOMMENDATION

Levosimendan may be considered in children with acute HF unresponsive to traditional inotropic therapy (Class IIb, Level of Evidence C).

10.6. Adrenal Insufficiency

Adrenal insufficiency may contribute to the hemodynamic instability seen in critically ill patients with a low cardiac output and therefore treatment with stress dose steroid regimens could be considered if indicated.

RECOMMENDATION

In patients with hemodynamic compromise secondary to acute HF, evaluation and treatment of adrenal insufficiency may be considered (Class IIb, Level of Evidence C).

10.7. Antiarrhythmic Treatment

Although prophylactic antiarrhythmic treatment is not recommended for children with acute HF, potential precipitating factors for arrhythmias (e.g., electrolyte disturbance) should be evaluated and corrected as appropriate.

RECOMMENDATION

In patients hospitalized with acute HF, potential precipitating factors for arrhythmias (e.g., electrolyte abnormalities) should be corrected to prevent arrhythmias (Class I, Level of Evidence C).

10.8. Thyroid Disorders

Thyroid disease, both hypo- and hyperthyroidism, can contribute to or be the precipitating cause of HF.[202] Screening of thyroid function is recommended in all children with HF. Treatment of thyroid disorders should be based on general endocrine guidelines.

RECOMMENDATION.

In critically ill children with acute HF, evaluation of thyroid homeostasis is reasonable, and if hypothyroidism is identified, thyroid replacement is reasonable (Class IIa, Level of Evidence C).

10.9. Respiratory Support

Children with acute HF often require respiratory support to improve oxygenation and reduce respiratory distress. Non–invasive positive pressure ventilation, such as continuous positive airway pressure, can have positive benefits of improved oxygenation and reduced work of breathing by increasing the alveolar distending pressure thereby redistributing pulmonary edema and reducing lung and airway resistance. Noninvasive ventilation may be considered as an adjunct to other medical therapies in patients with increased respiratory effort and acute HF. The subsequent reduced work of breathing then has favorable impacts on the balance of oxygen demand and delivery.[203] Positive pressure ventilation also reduces left ventricular afterload and improves cardiac output in patients but if respiratory failure progresses in the setting of low cardiac output or pulmonary edema, intubation and mechanical ventilation may be necessary.

RECOMMENDATION

1. Invasive ventilation is recommended for children with acute HF and respiratory failure (Class I, Level of Evidence C).
2. Noninvasive ventilation is reasonable for the treatment of children with acute HF, pulmonary edema, and significantly increased work of breathing (in the presence or absence of pulmonary edema) as an adjunct to other medical therapies (Class IIa, Level of Evidence C).

10.10. Acute Right Heart Failure

Acute right HF can present most commonly following surgical repair of CHD but can also be seen in the setting of sepsis, acute myocarditis, and in pulmonary hypertension. It is also rarely seen following blunt chest trauma. Low cardiac output in these patients is associated with high right-sided filling pressures, subsequent reduced left ventricular filling, and venous and lymphatic congestion. It is reasonable to use milrinone as an inotrope and pulmonary vasodilator in this setting and dobutamine, dopamine, or low dose epinephrine may be required. Loop diuretics are also often used in this context.

RECOMMENDATION

1. Low dose epinephrine, dobutamine, or dopamine is reasonable in the setting of acute right HF (Class IIa, Level of Evidence C).
2. Use of milrinone as an inotrope and pulmonary vasodilator is reasonable in the setting of acute right HF (Class IIa, Level of Evidence C).

10.11. Perioperative Acute Heart Failure

In the postoperative CHD patient with a low cardiac output state, early evaluation for hemodynamically significant residual lesions should be performed. Milrinone reduces the risk of a low cardiac output state following congenital cardiac surgery[204] and other inotropic agents may be needed. In children unable to be weaned from cardiopulmonary bypass, ECMO support is often instituted early with transition to more durable forms of mechanical support required in patients who do not recover quickly.

RECOMMENDATION

1. Prompt evaluation and treatment of residual hemodynamically significant lesions should be performed for those with early postoperative HF (Class I, Level of Evidence C).
2. Milrinone therapy after cardiac surgery in infants and children to reduce the risk of low cardiac output syndrome is reasonable (Class IIa, Level of Evidence B).

3. In infants and children unable to wean from cardiopulmonary bypass or with refractory low cardiac output syndrome after cardiac surgery, MCS (ECMO or VAD) is reasonable to use as a bridge to recovery or transplant (Class IIa, Level of Evidence C).

11. ANESTHETIC CONSIDERATIONS

Children with HF frequently present for diagnostic, surgical, or catheter-based interventions requiring anesthesia care. Although anesthesia for children is safe, it is well documented and accepted that children with heart disease undergoing noncardiac procedures have an increased risk of cardiac arrest, significant complications, and mortality.[205-207] Among children with heart disease, patients with ventricular dysfunction requiring medication are classified as having severe heart disease as defined by the American College of Surgeons National Surgical Quality Improvement Program based on residual lesion burden and functional status, and incur the highest mortality (operating room 7.32).[207] Hypotension requiring inotropic support under anesthesia is a common complication.[208] Consequently, in children with impaired heart function, the need for general anesthesia, even for short, minimally invasive procedures, remains a considerable risk.

Comprehensive perioperative planning with multidisciplinary input is essential in managing patients with HF and preventing significant morbidity and mortality. Preoperatively, this should include risk assessment, evaluation of medical and surgical history, optimization of cardiac functional status, medication, and fasting management, review of pertinent cardiac imaging studies and laboratory results, identification of specific surgical/procedural concerns, location and timing of the procedure, and team composition.[209,210] Intraoperative anesthetic management should be individualized based on the preoperative assessment to maintain hemodynamic stability, end-organ perfusion, and prevent cardiovascular collapse. Before proceeding, a clear understanding of the likely impact of the anesthetic agents, ventilation strategies, and operative technique on the failing cardiovascular system is essential and should be communicated to the operative team. Intraoperative considerations include appropriate monitoring with potential for invasive lines; adequate venous access; use of induction and maintenance agents that maintain hemodynamic stability with minimal effect on myocardial contractility, rate, and rhythm, and support the balance between systemic and pulmonary resistances; anticipate the effects of positive pressure ventilation; fluid management, including the possibility of blood transfusion; need for vasoactive agents; arrhythmia management; and rescue strategies in the event of cardiovascular collapse or cardiac arrest.[211-216] Given the risk of cardiac arrest, thorough perioperative discussion must include appropriateness and availability for MCS. This discussion should include the timing of MCS (backup vs elective vs emergent), cannulation and device strategies, location logistics, and procedure being performed.[217] Postoperative care is an extension of the above considerations, including the location and availability of expertise to manage these patients successfully.

RECOMMENDATION

1. In children with HF requiring anesthesia, a multidisciplinary team approach with meticulous perioperative planning is recommended to minimize the morbidity and mortality (Class I, Level of Evidence C).
2. Perioperative care of children with HF should be provided by, or in consultation with, an anesthesiologist with expertise in caring for children with heart disease (Class I, Level of Evidence C).
3. In the anesthetic management of children with HF, careful consideration should be given to location, timing of procedure, team composition, and availability of MCS (Class I, Level of Evidence C).

12. HEALTH CARE DELIVERY

For patients who are able to achieve medical stability, discharge planning is essential to prepare families for management at home and educate them regarding recognition of progression of HF. This effort aims to reduce hospitalizations or the severity of illness when patients return for care. Discharge criteria, such as outlined in Table 4, should be discussed with the family early during the hospitalization.

Ongoing follow-up is crucial for recognizing early signs of congestion and decompensation, monitoring end-organ function, and continually optimizing medical management. While traditionally, most monitoring in pediatrics has occurred in person, the COVID-19 pandemic allowed for the establishment of virtual options for monitoring and treatment. Virtual care has shown potential in pediatric HF to be a promising option for ongoing follow-up,

Table 4 Discharge Considerations for Children With HF

Medical stability	Hemodynamic stability with improvement of end-organ dysfunction Medical therapy initiated and tolerated Tolerance of nutrition with adequate calories Stable fluid and diuretic regimen
Education	Signs and symptoms of heart failure Review of medications Overview of activities and any limitations Review of high-risk behaviors in adolescents, including sexual activity (potential teratogenic effects of many of the medications used), effects of alcohol and drugs Diet/fluid/sodium goals
Access to care	Do they have a working phone? How to contact the team How to seek emergency help Ensure stable transportation for follow-up If living remotely from the pediatric HF specialty center discuss considerations of staying locally for a period of time
Follow-up	Local cardiology/primary care provider notified and appointments made Appointments made with HF specialist Bloodwork plan and medication uptitration regimen plan in place Community supports in place (homecare) Exercise rehab plan and appointments

medication titration, and education. Whether this care option and the use of home surveillance, such as daily weights, blood pressure, and heart rate monitoring, can impact outcomes in pediatric HF remains unknown.

When considering discharge, follow-up, and transition of care for children with HF, equity must be considered.[218] Equity aims to ensure that all patients, regardless of sex, race, or socio-economic or demographic background, have equal access to high–quality health care services and treatment options. In adult studies and presumed to be true in the pediatric population, disparities in HF care led to inequalities in patient outcomes. Each patient's social determinants of health must be considered when designing a care plan.

A structured transition program, commencing several years before the transfer of care from the pediatric to the adult team, should be an integral component of routine HF care. Such types of programs have been documented to be useful, by increasing medication compliance and attendance to follow-up appointment, in other forms of chronic disease.[219] This program should encompass ongoing education regarding the underlying diagnosis, medication education including adherence, potential interactions and possible adverse events, as well as addressing high-risk behaviors and future planning. Where feasible, collaborating with an adult program should also be a part of a structured transition program.

RECOMMENDATION

Transition preparation should begin in early adolescence with annual transition readiness assessment before transfer of care from the pediatric to the adult team (Class I, Level of Evidence B).

13. HEALTH EQUITY

Strategies are needed to simultaneously assess barriers and provide a comprehensive and multidisciplinary approach to address patient needs to mitigate health inequity in the child with HF.

13.1. Assessment of Barriers to Receiving Quality Care

Technological advances have helped in overcoming some barriers, including enhanced use of telemedicine when appropriate.[220] Additionally, patient portals can be effective in improving the quality and efficiency of patient engagement.[221]

RECOMMENDATION

1. For children with HF, treatment strategies should address barriers (e.g., case management, cost-reduction, and out-of-pocket cost limits) through a comprehensive and multidisciplinary approach (Class I, Level of Evidence C).
2. Telemedicine is a reasonable approach to enhance HF follow-up and communication (Class IIa, Level of Evidence C).
3. Telemedicine is reasonable to enhance transitions of care after hospital discharge improving patient engagement and adherence to medications (Class IIa, Level of Evidence C).
4. Interventions utilizing technology, such as patient portals, can be effective to improve the quality and efficiency of patient engagement with health care and help facilitate awareness of health care services and disease management (Class IIa, Level of Evidence C).

13.2. Assessment of Health Literacy of Patients and Caregivers

An assessment of the whole family's level of health literacy is important when providing counseling regarding HF management.[222] Particularly, for children, the parent's understanding of the illness and management can influence outcomes.[223] The teach-back method can be utilized to assess comprehension of the information where the patient is asked to explain back what they have just been instructed.[224] Printed materials should be written at the sixth–grade reading level or lower, and all medical terms should always be explained.[225] For patients who do not have proficiency in the health care center's official language, a trained medical interpreter should be used whenever possible. Virtual or phone interpreters are a reasonable alternative,[226] but in the absence of in-person or phone interpreters, electronic tools (apps) may be useful to bridge the language gap in health care.[227]

RECOMMENDATION

1. The medical team should assess the whole family's level of health literacy as they provide counseling regarding HF management (Class I, Level of Evidence C).
2. The medical team should provide easily understandable and accessible information to all patients, regardless of their education levels (Class I, Level of Evidence C).
3. A trained interpreter should be used to improve communication, clinical outcomes, and satisfaction with care in patients who do not speak the native language (Class I, Level of Evidence C).
4. When a bilingual clinician or a professional interpreter is not available, virtual or phone interpretation services are a reasonable alternative (Class IIa, Level of Evidence C).
5. In the absence of in-person or virtual or phone interpreters, electronic tools (apps) may be useful to bridge the language gap in health care (Class IIb, Level of Evidence A).

14. GOALS OF CARE

Despite notable advancements in medical management and advanced cardiac therapies, morbidity and mortality remain high in pediatric HF. Advanced heart disease has been defined as complex or severe CHD or acquired heart disease with a high possibility of serious adverse events or mortality in the next 2 years.[228,229]

14.1. Palliative Care

Palliative care, provided by both primary cardiology teams as well as subspecialty palliative care teams, focuses on reducing distress and improving quality of life in patients with serious illnesses through symptom management interventions, goals of care and decision-making support, and psychosocial interventions for patients and families.[230]

There is growing literature in adult HF for the utility of early palliative care interventions in improving outcomes in patients with advanced heart disease.[231] Several guideline documents are helpful[9,232,233] in summarizing the current support. These guidelines agree on the importance of early integration of palliative care across all stages of HF. These guidelines outline the details of symptom management, decision-making, and communication of prognosis and life-sustaining therapies, as well as advance care planning.

The recent AHA Statement on palliative care in pediatric heart disease[232] provides a more detailed approach to this topic. Parents of children who die of advanced heart disease, including HF, report high symptom burden at their child's end of life. Breathing difficulties, feeding intolerance, poor sleep, and fatigue were some of the most distressing symptoms as perceived by parents. Two-thirds describe their child's quality of life in the month before death to be fair to poor.[234] Among children who die of advanced heart disease, most deaths occur in intensive care settings with invasive interventions common at end of life.[235,236] Multicenter research specific to pediatric VAD has also shown high symptom burden, specifically in the domains of procedural distress, limitations in activity, postoperative pain, sadness, and fatigue.[179] Similar to the more heterogeneous advanced heart disease cohort, the majority of pediatric patients on VAD die in the hospital setting with interventions, such as mechanical intervention common at end of life.[237] Ethical frameworks[238] and standardized pediatric VAD deactivation checklists have been developed to facilitate compassionate care at end of life.[239,240] Taken together, these single-center and registry-based studies highlight the important need for multidisciplinary palliative care for pediatric patients with end-stage HF and those receiving ECMO, VAD support, or listed for transplantation.

Beyond symptom management and goals of care discussions, pediatric HF research has also underscored the need for assessing communication preferences specific to prognosis, outcome, clinical trajectory, and goals of care at least yearly. Research has demonstrated discrepancies in parent/physician agreement of child functional class, symptom burden, life expectancy, and impact on activities of daily living in pediatric advanced heart disease.[241,242] Moreover, research has demonstrated that the majority of adolescents and young adults living with HF desire communication and decision-making involvement regarding their prognosis, treatment options, and advance care planning.[243,244] Lastly, efforts to enhance palliative care training for trainees and HF cardiologists and care teams are critical.

RECOMMENDATION

1. Pediatric palliative care should be incorporated into the care of all patients with advanced heart disease, including patients with end-stage HF and those receiving ECMO, VAD support, and patients listed for transplantation (Class I, Level of Evidence B).
2. Standard communication by pediatric cardiology or palliative care teams with parents or guardians, adolescents, and young adults with HF about prognosis, outcome, clinical trajectory, and goals of care is reasonable at least yearly, and with each hospitalization or procedure (Class IIa, Level of Evidence C).

14.2. Hospice Care

Hospice care emphasizes comfort-based, quality of life focused care in the final months of life. In the United States, children do not need to stop all life-sustaining treatment to be eligible for hospice care. Pediatric patients with HF can receive concurrent care, which can include home-based inotropes or VAD support, in addition to hospice care. It is important to understand patient and family goals of care so that timely and appropriate referrals to hospice can be made when indicated.

RECOMMENDATION

Development of standardized and ethical approaches to withdrawal of life-sustaining therapies, including ventilators, ICDs, and MCS, is reasonable to guide care at end of life in pediatric patients with HF (Class IIa, Level of Evidence C).

15. QUALITY METRICS AND REPORTING

HF in children is classified as a rare disease, as per the definition suggested by the Genetic and Rare Diseases Information Center in the NIH of a prevalence of less than 60 cases/100,000 population, equivalent to 200,000 cases in the United States (https://rarediseases.info.nih.gov/about). Rare diseases pose unique challenges for patients and clinicians alike, some of which can be mitigated by implementing specific features of care. According to the National Academy of Medicine, use of routinely collected data for continuous learning in a learning health system should be considered as a means to improve outcomes in all diseases.[245] This is even more pressing for rare diseases, in which other forms of medical information such as clinical trials data are more likely to be deficient. While a true learning health system extends far beyond a clinical registry, there is little doubt that systematic aggregation of multicenter data is a key driver of the effectiveness of learning health systems. A

critical aspect of learning health systems in driving improved outcomes is that data must not only be collected but also shared.[246] Within pediatric HF, the ACTION has promoted practices of both multi–center data collection and data sharing in support of generating real-world evidence. Other networks in pediatric cardiology such as the Pediatric Cardiac Critical Care Consortium and the Pediatric Acute Care Cardiology Collaborative have also promoted similar goals, with a focus more on congenital heart surgery and structural heart disease rather than on HF.[247-249] Linkage of these data sources, also in accordance with recommendations from the National Academy of Medicine, offers further potential to improve outcomes for children with HF, some of whom also have structural heart disease.

In 2001, the Institute of Medicine issued a seminal report on the US health system, evaluating opportunities to improve quality across the system.[250] Among the key recommendations in this report was the need for patient-centered care, which is characterized as "care that is respectful of and responsive to individual patient preferences, needs, and values." To achieve this goal, one important step is the collection of patient-reported outcomes to inform clinicians of key preferences. Although this is not yet a routine component of clinical care delivery, it is gaining wider acceptance, and was the topic of detailed FDA guidance in 2009 on integration of patient-reported outcomes data into clinical trial end-points (https://www.fda.gov/media/77832/download). While there is as yet, no clearly preferred system of patient-reported outcomes for pediatric HF, there are circumstances in which these data have been systematically collected and it is timely to acknowledge the value of such data in helping to promote high–quality clinical care in pediatric HF, to match the progress that has been made in adult HF care through systems, such as Kansas City Cardiomyopathy Questionnaire and Minnesota Living with Heart Failure.[179,251,252]

RECOMMENDATION

1. Participation in multi–center data collection to facilitate clinical care improvement is reasonable for centers that treat children with HF (Class IIa, Level of Evidence C).
2. Incorporating one or more patient–entered data elements/outcomes (e.g., assessments of quality of life, anxiety, or depression) into the comprehensive care of children with HF may be considered (Class IIb, Level of Evidence C).

APPENDIX 1 SUMMARY OF RECOMMENDATIONS

SECTION 2: DEFINITION AND CLASSIFICATION OF PEDIATRIC HEART FAILURE	
2.1 Staging and Classification	
Class I	Documentation of HF severity and staging is recommended to facilitate monitoring of disease progression and patient management. **Level of Evidence C**
2.2 Classification by Ejection Fraction	
Class IIb	Classification of HF based on systemic ventricle ejection fraction may be useful for serial monitoring and for assessing treatment response. **Level of Evidence C**
SECTION 3: DIAGNOSIS	
3.1 Genetic Testing	
Class I	Comprehensive or targeted panel genetic testing is recommended for pediatric patients affected with any subtype of cardiomyopathy. **Level of Evidence C** Variant–specific genetic testing is recommended for first–degree family members after the identification of a causative pathogenic/likely pathogenic variant in the index case. **Level of Evidence C**

Continued

Class IIa	Exome or genome sequencing can be useful in patients with severe and/or complex cardiomyopathy after inconclusive panel gene testing. **Level of Evidence C** Mitochondrial gene sequencing can be useful in patients with multisystemic disease and/or high lactate levels that are out of proportion to the cardiac status. **Level of Evidence C**
Class IIb	Whole exome testing may be useful as the initial step in genetic testing in certain instances (e.g., for infantile, syndromic, metabolic, and nonisolated cardiomyopathy). **Level of Evidence C**
3.2 Laboratory Testing	
Class I	BNP/NT-proBNP is recommended in the integrated evaluation and monitoring of patients with known HF to further define disease severity, disease progression, and response to therapy. **Level of Evidence B** BNP/NT-proBNP is recommended as an adjunctive marker, not a stand-alone test, to aid in the diagnosis of new HF in symptomatic patients. **Level of Evidence B**
Class IIa	Laboratory evaluation for metabolic disorders, including lactate, pyruvate, ammonia, plasma amino acids, urine organic acids, free/total carnitine, and acylcarnitine profile, is reasonable in patients with cardiomyopathy. **Level of Evidence C**
3.3 Cardiac Imaging—Echocardiography	
Class I	Standard two-dimensional imaging to evaluate cavity dimensions, wall thickness, LV mass, and LV function is recommended in all children with cardiomyopathy or HF to aid in diagnosis, assess response to therapy, track disease progression, or assess for LV remodeling. **Level of Evidence B**
Class IIa	Diastolic function, including mitral inflow patterns, mitral annular tissue Doppler imaging (TDI) and pulmonary venous Doppler flow patterns by echocardiography can be useful in children with cardiomyopathy or HF. **Level of Evidence C** Three-dimensional imaging, measurement of strain, and TDI can be useful for the evaluation of children with cardiomyopathy or HF. **Level of Evidence C** Doppler-derived estimations of right heart pressures (right ventricular systolic pressure and pulmonary artery pressures) can be useful to monitor response to treatment and progression of disease. **Level of Evidence C** Fractional area change from the apical 4-chamber view and tricuspid annular planar systolic excursion are reasonable for the quantitative assessment of RV function. **Level of Evidence C** TDI assessment of tricuspid annular motion can be useful for the assessment of RV longitudinal function. **Level of Evidence C**
Class IIb	Doppler echocardiography may be useful for the assessment of RV diastolic function. **Level of Evidence C** Quantitative techniques, such as fractional area of change, EF, annular excursion, and TDI, may be considered for serial follow-up of children with single ventricle heart disease. **Level of Evidence C**
3.4 Cardiac Cross-Sectional Imaging	
Class I	MRI is recommended in the diagnostic evaluation of arrhythmogenic ventricular cardiomyopathy in older children who do not require sedation or anesthesia. **Level of Evidence C**
Class IIa	Cardiac MRI is reasonable to assess LV function, LV remodeling, and for the phenotyping of cardiomyopathy in children if echo imaging windows are limited. **Level of Evidence C** In children with RV failure, MRI is reasonable to assess RV size and EF. **Level of Evidence C** MRI is reasonable for the assessment of fibrosis, edema, or inflammation in unexplained cardiomyopathy or myocarditis if noninvasive testing does not yield a diagnosis. **Level of Evidence B** Cardiac MRI can be useful for volumetric and functional analysis of a single ventricle. **Level of Evidence B** Cardiac CT angiogram is reasonable to define coronary artery origins and anatomy if the echocardiogram is equivocal. **Level of Evidence C**

Continued

3.5 Exercise and Physical Activity	
Class IIa	Cardiopulmonary exercise testing with measurement of peak VO_2 consumption is reasonable for assessment and prognosis of children with HF. **Level of Evidence B** A 6-min walk test as part of the assessment and risk stratification of patients with HF may be considered if cardiopulmonary exercise testing is not feasible. **Level of Evidence C**
3.6 Cardiac Catheterization	
Class IIb	Coronary angiography to confirm coronary anatomy may be useful in patients with unexplained HF if noninvasive imaging is not definitive. **Level of Evidence C** Cardiac catheterization to assess hemodynamics may be useful to guide management and for risk stratification of children with HF or cardiomyopathy. **Level of Evidence C** Endomyocardial biopsy may be useful in pediatric patients presenting with HF when the results of the biopsy would inform prognosis or influence therapy, but risks of morbidity and mortality must be considered. **Level of Evidence C**
3.7 Sleep Evaluation	
Class I	Children with HF and a history consistent with sleep apnea should undergo evaluation for sleep disordered breathing. **Level of Evidence C**
3.8 Remote Monitoring and Wearables	
Class IIb	Including wearable technology in cardiac rehabilitation and physical activity programs may be considered to increase access and effectiveness of these therapies in children with HF. **Level of Evidence C**
SECTION 4: PHARMACOLOGIC TREATMENT OF HEART FAILURE WITH REDUCED EF WITH A BIVENTRICULAR CIRCULATION AND A SYSTEMIC LV	
4.1 Diuretics	
Class I	In children with fluid retention and ventricular dysfunction (HF stage C), diuretic therapy is recommended to achieve a euvolemic state. **Level of Evidence C**
4.2 Renin-Angiotensin Aldosterone System	
Class I	In children with left ventricular systolic dysfunction, ACE inhibitors should be routinely used unless there is a specific contraindication. **Level of Evidence B**
Class IIa	In children with systemic ventricular dysfunction, angiotensin receptor blockers (ARB) are a reasonable alternative for who are intolerant of ACE inhibitors. **Level of Evidence C** In children with symptomatic systemic left ventricular dysfunction, treatment with aldosterone antagonists is reasonable. **Level of Evidence C**
4.3 Angiotensin Receptor Neprilysin Inhibitors	
Class IIa	In children with symptomatic systemic left ventricular systolic dysfunction, angiotensin receptor neprilysin inhibitors in the place of an ACE inhibitor or ARB are reasonable. **Level of Evidence B**
4.4 β-Receptor Antagonists	
Class IIa	In children with systemic LV systolic dysfunction, use of β-blockers is reasonable. **Level of Evidence C**
4.5 Cardiac Glycosides	
Class IIb	In children with symptomatic HFrEF, digoxin (at lower serum digoxin levels, e.g., 0.5-0.9 ng/ml) may be considered to relieve symptoms. **Level of Evidence C**
4.6 Ivabradine	
Class IIa	In children with stable HF, ivabradine is reasonable when heart rate reduction is desirable. **Level of Evidence B**

Continued

4.7 Sodium-Glucose Cotransporter 2 Inhibitors	
Class IIb	In children with symptomatic HFrEF, SGLT2 inhibitors may be considered, although their safety and effectiveness in children have not been systematically studied. **Level of Evidence C**
4.8 Soluble Guanylate Cyclase	
Class IIb	In children with worsening of HF despite dose optimized beta-blocker, ACEI or ARNI, and aldosterone receptor antagonist, vericiguat may be considered as add-on therapy. **Level of Evidence C**
4.9 Positive Inotropic Agents	
Class IIa	Chronic inotropic therapy with milrinone can be used as a bridge to transplant. **Level of Evidence C.** Inotropic therapy may be considered for symptomatic relief in the palliative setting. **Level of Evidence C**
4.10 Anticoagulation	
Class I	Patients with intracardiac thrombus should receive anticoagulation. **Level of Evidence B**
Class IIa	In children with low EF and persistent or uncontrolled paroxysmal atrial fibrillation or flutter, systemic anticoagulation is reasonable. **Level of Evidence C** For patients with a history of thrombus or a thromboembolic event who have an EF $<25\%$ (fractional shortening $<15\%$), systemic anticoagulation is reasonable. **Level of Evidence C**
Class IIb	In children with a history of thrombus or thromboembolic event who have an EF $<25\%$, direct oral anticoagulants may be considered. **Level of Evidence C** For patients with severe cardiac dysfunction in the intensive care setting or who have indwelling intravascular catheters, prophylactic anticoagulation may be considered. **Level of Evidence C**
SECTION 5: PHARMACOLOGIC TREATMENT OF HEART FAILURE WITH PRESERVED EF WITH BIVENTRICULAR CIRCULATION AND A SYSTEMIC LV	
Class I	In children with HFpEF, diuretics to establish a clinically euvolemic state are recommended, although uptitration of doses should be done cautiously to avoid volume depletion. **Level of Evidence C**
Class IIb	In children with symptomatic HFpEF, SGLT2 inhibitors may be considered. **Level of Evidence C**
SECTION 6: PHARMACOLOGIC TREATMENT OF SPECIAL POPULATIONS	
6.1 Congenital Heart Disease Associated Heart Failure	
Class IIa	Referral to an advanced HF/transplant specialist is reasonable for patients with single ventricle physiology or a systemic RV and symptomatic systemic ventricular dysfunction. **Level of Evidence B**
Class IIb	ACEI/ARB therapy may be considered in patients with single ventricle physiology or a systemic RV and ventricular dysfunction. **Level of Evidence C**
6.2 Cardio-oncology	
Class I	Patients who have undergone cancer treatment with potential for cardiotoxicity should be considered ACC/AHA Stage A. **Level of Evidence C**
Class IIa	Dexrazoxane is reasonable to prevent cardiomyopathy associated with anthracycline if there is an anticipated life-time cumulative dose >150 mg/m^2. **Level of Evidence B**
6.3 RASopathies, Storage Diseases, and Other Disorders of Metabolism	
Class I	Enzyme replacement therapy is recommended in classic infantile-onset Pompe disease and mucopolysaccharidoses II. **Level of Evidence B**

Continued

6.4 Dystrophinopathies	
Class I	Periodic evaluation of treatment options should be performed at a center with expertise in comprehensive treatment of dystrophinopathies due to the rapid rate of development of novel therapies. **Level of Evidence C** Adult female carriers of a dystrophinopathy should undergo periodic evaluation of cardiac function. **Level of Evidence C**
Class IIa	BNP and cardiac MRI are reasonable in the surveillance of patients with dystrophinopathy. **Level of Evidence C**
SECTION 7: LIFESTYLE MODIFICATIONS	
7.1 Exercise Training and Activity	
Class I	In children at risk for adverse events during exercise, pre–participation health screening and risk stratification should be performed before initiating an exercise training program and to inform appropriate guidance around exercise intensity and content. **Level of Evidence C** Detection of children at risk for sudden death, identification of medical contraindications to a training program, and appropriate recommendations for a defibrillator as primary or secondary intervention should be performed before initiating an exercise program or increasing frequency, intensity, or duration of the current program. **Level of Evidence C** Exercise training in a supervised setting should be prescribed, if deemed safe, should be prescribed as an adjunctive approach to improve clinical status in ambulatory patients with current or prior symptoms of HF. The training program should be individualized to the patient's ability, resources, and the patient's response to exercise with an emphasis on safety. **Level of Evidence C**
Class IIa	For pediatric patients with HF thought to be at increased risk of a having a cardiac event during physical activity, cardiopulmonary exercise testing is reasonable before shared decision-making regarding exercise training or competitive sports to determine exercise capacity, assess risk for adverse events and determine suitability for the desired physical activities. **Level of Evidence C** Restriction from intense sports activity is reasonable for pediatric patients with arrhythmogenic cardiomyopathy based on the current Task force criteria[34,131] to minimize disease progression. **Level of Evidence C**
SECTION 8: ELECTROPHYSIOLOGY ASSESSMENT AND INTERVENTIONAL THERAPIES	
8.1 Ambulatory ECG Monitoring and Electrophysiology Testing and Treatment	
Class I	In a pediatric patient with HF who presents with palpitations or suspected cardiac syncope, ambulatory monitoring is recommended. **Level of Evidence C** Evaluation for tachycardia-induced cardiomyopathy is recommended in any patient presenting with DCM. **Level of Evidence B** In the pediatric patient with tachycardia-induced cardiomyopathy, ablation therapy is recommended when medical therapy fails or is associated with intolerable side effects. **Level of Evidence B** Ablation is recommended for frequent ventricular ectopy or tachycardia, predominantly from a single focus thought to be causing ventricular dysfunction, when medical therapy is either not effective or is associated with intolerable adverse effects. **Level of Evidence B**
Class IIa	In pediatric patients with HF patients and a high risk of developing atrial or ventricular arrhythmias, or heart block, regular ambulatory monitoring is reasonable. **Level of Evidence C** In pediatric patients with HF and a high risk of developing atrial or ventricular arrhythmias, or heart block, regular ambulatory monitoring is reasonable. **Level of Evidence C** Ablation therapy is reasonable as first-line therapy in larger pediatric patients (generally >15-30 kg) with tachycardia-induced myopathies or frequent ventricular ectopy or tachycardia, predominantly from a single focus thought to be causing ventricular dysfunction. **Level of Evidence B** Ablation of the accessory pathway is reasonable in those with WPW pattern and ventricular dysfunction presumed secondary to dyssynchrony. **Level of Evidence B**

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8.2 Pacemaker and Resynchronization Therapy	
Class IIa	In patients undergoing single ventricular site epicardial pacemaker placement, targeting of the apical LV is reasonable in preference to the RV epicardial position. **Level of Evidence B** In patients undergoing standard (nonphysiological pacing) transvenous pacemaker placement, targeting of the RV mid-septal inflow or outflow tract is reasonable in preference to the RV apical endocardial site. **Level of Evidence B**
Class IIb	Conduction system pacing (CSP) may be considered based on operator experience and patient–specific risk factors. **Level of Evidence C** In pediatric patients with CHD requiring ventricular pacing, and with pre–existing HF symptoms with myocardial dysfunction, CSP may be considered. **Level of Evidence B**
8.3 Implantable Cardioverter-Defibrillators	
Class IIb	ICD therapy may be considered in children with CHD and HF where extrapolation of established adult congenital heart disease SCA risk scores suggests a high risk of SCA. **Level of Evidence C**
SECTION 9: MANAGEMENT OF COMORBIDITIES	
9.1 Anemia	
Class I	Screening for anemia at the time of diagnosis of HF in children and at ongoing regular intervals is recommended. **Level of Evidence C** Screening for iron deficiency in children with HF is recommended. **Level of Evidence B**
Class IIa	Intravenous iron supplementation is reasonable for the treatment of iron deficiency in pediatric patients with HF. **Level of Evidence B** Erythropoiesis stimulating agents to treat anemia in pediatric patients with HF is reasonable if anemia persists once iron stores are replete. **Level of Evidence C**
9.2 Renal Dysfunction	
Class I	The presence and severity of renal dysfunction should be determined at the time of the HF diagnosis and at ongoing regular intervals, including after changes in medical therapy. **Level of Evidence B** Management of acute kidney injury should include strict recording of fluid balance, daily weight measurements, and monitoring renal function. **Level of Evidence C** A review and adjustment of medications should be performed in children with HF and worsening renal function. **Level of Evidence C**
9.3 Airway and Parenchymal Respiratory Disorders	
Class I	In the pediatric patient with HF who presents with new or worsening respiratory symptoms, chest X-ray imaging should be obtained to evaluate for treatable pulmonary complications. **Level of Evidence C** Pulmonary function testing and polysomnography should be used in patients with signs and symptoms of sleep–related breathing disorders, especially when pulmonary hypertension is present. **Level of Evidence C** Pulmonary function testing should be used for detection and assessment of reversibility of obstructive–related breathing disorders as well as for the diagnosis of restrictive lung disease, especially when pulmonary hypertension is present. **Level of Evidence C**
9.4 Malnutrition	
Class I	A weight-for-height z-score, which is below –2 SD of the WHO median standard curve in a child with HF represents malnutrition and requires further assessment and intervention. **Level of Evidence C**
Class IIb	Enteral tube feeds, high calorie formulas/supplements, or intravenous nutrition may be necessary to correct nutritional deficiencies, and to improve nutritional status and growth. **Level of Evidence C**

Continued

9.5 Frailty	
Class IIa	Evaluation and management of frailty in children with HF is reasonable based on (1) slowness: 6-min walk test; (2) weakness: handgrip strength; (3) fatigue PedsQL Multi-dimensional Fatigue Scale; (4) body composition: triceps skinfold thickness; and (5) Physical activity questionnaire. **Level of Evidence B**
9.6 Obesity and Metabolic Syndrome	
Class I	Evaluation for metabolic syndrome and all other cardiovascular risk factors, including hypertension, dyslipidemia, insulin resistance, and liver disease should be performed in obese children with HF. **Level of Evidence C** In pediatric patients with HF and metabolic syndrome, an intensive, multidisciplinary weight-reduction program and management of other identifiable risk factors should be initiated in pediatric patients with HF and metabolic syndrome. **Level of Evidence B**
Class IIa	In children with HF and associated obesity or metabolic syndrome it is reasonable to perform exercise testing to determine suitability for enrolment in an exercise training program. **Level of Evidence C**
9.7 Mental Health	
Class I	Annual screening for emotional and behavioral conditions, including anxiety, depression, adjustment, attention and sleep disorders, is recommended for children with HF. **Level of Evidence B** Mental health intervention and psychologic support is recommended when indicated for children with HF and in those undergoing ICD and/or VAD implantation. **Level of Evidence B**
9.8 Neurodevelopment	
Class I	Early intervention, developmental supports, and school-based accommodations should be provided as needed for children with HF demonstrating any concerns in these domains. **Level of Evidence B**
Class IIa	Screening for neurodevelopmental assessment/reassessment annually in children with HF and in accord with established guidelines for those with CHD is reasonable. **Level of Evidence B** Brain imaging is reasonable in patients with HF, particularly those with VAD therapy or those supported by extracorporeal membrane oxygenation. **Level of Evidence B**
SECTION 10: MANAGEMENT OF ACUTE DECOMPENSATED HEART FAILURE	
10.1 Diagnosis and Monitoring	
Class I	The diagnosis of acute HF should be based on signs and symptoms of HF combined with supportive evidence from chest X-ray imaging, ECG, echocardiography, and laboratory evaluations, including natriuretic peptide levels. **Level of Evidence B** The severity of HF should be assessed based on the degree of congestion and adequacy of perfusion. **Level of Evidence C** In patients with palliated or repaired CHD who present with acute HF, cardiac catheterization is indicated if a noninvasive evaluation fails to establish a definitive diagnosis or if invasive hemodynamic measurements are needed for management decisions. **Level of Evidence C** For patients with acute HF, serial testing to monitor for electrolyte abnormalities, hemoglobin levels, end-organ perfusion, and response to therapy is indicated. **Level of Evidence C** In children hospitalized with acute HF, evaluation and monitoring for arrhythmias with continuous ECG monitoring/telemetry is warranted. **Level of Evidence C**

Continued

Class IIa	In patients with severe acute HF, it is reasonable to initiate transfer to a center with pediatric HF specialists who have the expertise and ability to optimize medical therapy, evaluate for heart transplantation, and provide mechanical support. **Level of Evidence C** In children with decompensated HF, central venous catheters are reasonable in decompensated HF for administration of medications and to measure central venous pressure and mixed venous saturation. **Level of Evidence C** In children with acute decompensated HF, it is reasonable to place an arterial catheter for continuous blood pressure measurement. **Level of Evidence C**
Class IIb	In decompensated patients with acute HF, trends in cerebral or somatic regional oxygen saturation or venous oxygen saturations levels may be helpful. **Level of Evidence C**
10.2 Fluid Management and Diuretics	
Class I	An initial and ongoing assessment of fluid status should be performed in all patients admitted to the hospital with acute HF. **Level of Evidence C** Diuretics are the first-line therapy for patients with acute HF with evidence of fluid overload. **Level of Evidence C** Careful monitoring for side effects of anticongestive therapies, including renal function, electrolytes, and hypotension, should be performed in all patients with acute HF. **Level of Evidence C**
10.3 Inotropic Agents	
Class I	Intravenous inotropic support should be used in patients with acute HF presenting as cardiogenic shock or low cardiac output with poor systemic and end-organ perfusion. **Level of Evidence C**
Class IIa	Milrinone or dobutamine is reasonable as a first–line rescue therapy, with epinephrine playing a role in the face of refractory hypotension and poor end-organ perfusion in children with acute HF. **Level of Evidence C**
10.4 Vasodilators	
Class IIb	In pediatric patients with acute HF, vasodilators may be used in the absence of hypotension and in combination with diuretics for symptomatic relief. **Level of Evidence C**
10.5 Calcium Sensitizing Agent	
Class IIb	Levosimendan may be considered in children with acute HF unresponsive to traditional inotropic therapy. **Level of Evidence C**
10.6 Adrenal Insufficiency	
Class IIb	In patients with hemodynamic compromise secondary to acute HF, evaluation and treatment of adrenal insufficiency may be considered. **Level of Evidence C**
10.7 Antiarrhythmic Treatment	
Class I	In patients hospitalized with acute HF, potential precipitating factors for arrhythmias (e.g., electrolyte abnormalities) should be corrected to prevent arrhythmias. **Level of Evidence C**
10.8 Thyroid Disorders	
Class IIa	In critically ill children with acute HF, evaluation of thyroid homeostasis is reasonable, and if hypothyroidism is identified, thyroid replacement is reasonable. **Level of Evidence C**
10.9 Respiratory Support	
Class I	Invasive ventilation is recommended for children with acute HF and respiratory failure. **Level of Evidence C**
Class IIa	Noninvasive ventilation is reasonable for the treatment of children with acute HF, pulmonary edema, and significantly increased work of breathing (in the presence or absence of pulmonary edema) as an adjunct to other medical therapies. **Level of Evidence C**

Continued

10.10 Acute Right Heart Failure	
Class IIa	Low-dose epinephrine, dobutamine, or dopamine is reasonable in the setting of acute right HF. **Level of Evidence C** Use of milrinone as an inotrope and pulmonary vasodilator is reasonable in the setting of acute right HF. **Level of Evidence C**
10.11 Perioperative Acute Heart Failure	
Class I	Prompt evaluation and treatment of residual hemodynamically significant lesions should be performed for those with early postoperative HF. **Level of Evidence C**
Class IIa	Milrinone therapy after cardiac surgery in infants and children to reduce the risk of low cardiac output syndrome is reasonable. **Level of Evidence B** In infants and children unable to wean from cardiopulmonary bypass or with refractory low cardiac output syndrome after cardiac surgery, mechanical circulatory support (ECMO or VAD) is reasonable to use as a bridge to recovery or transplant. **Level of Evidence C**
SECTION 11: ANESTHETIC CONSIDERATIONS	
Class I	In children with HF requiring anesthesia, a multidisciplinary team approach with meticulous perioperative planning is recommended to minimize the morbidity and mortality. **Level of Evidence C** Perioperative care of children with HF should be provided by, or in consultation with, an anesthesiologist with expertise in caring for children with heart disease. **Level of Evidence C** In the anesthetic management of children with HF, careful consideration should be given to location, timing of procedure, team composition, and availability of mechanical circulatory support. **Level of Evidence C**
SECTION 12: HEALTH CARE DELIVERY	
Class I	Transition preparation, should begin in early adolescence with annual transition readiness assessment before transfer of care from the pediatric to the adult team. **Level of Evidence B**
SECTION 13: HEALTH EQUITY	
13.1 Assessment of Barriers to Receiving Quality Care	
Class I	For children with HF, treatment strategies should address barriers (e.g., case management, cost-reduction, and out-of-pocket cost limits) through a comprehensive and multidisciplinary approach. **Level of Evidence C**
Class IIa	Telemedicine is a reasonable approach to enhance HF follow-up and communication. **Level of Evidence C** Telemedicine is reasonable to enhance transitions of care after hospital discharge improving patient engagement and adherence to medications. **Level of Evidence C** Interventions utilizing technology, such as patient portals, can be effective to improve the quality and efficiency of patient engagement with health care and help facilitate awareness of health care services and disease management. **Level of Evidence C**
13.2 Assessment of Health Literacy of Patients and Caregivers	
Class I	The medical team should assess the whole family's level of health literacy as they provide counseling regarding HF management. **Level of Evidence C** The medical team should provide easily understandable and accessible information to all patients, regardless of their education levels. **Level of Evidence C** A trained interpreter should be used to improve communication, clinical outcomes, and satisfaction with care in patients who do not speak the native language. **Level of Evidence C**
Class IIa	When a bilingual clinician or a professional interpreter is not available, virtual or phone interpretation services are a reasonable alternative. **Level of Evidence C**

Continued

Class IIb	In the absence of in-person or virtual or phone interpreters, electronic tools (apps) may be useful to bridge the language gap in health care. **Level of Evidence A**
SECTION 14: GOALS OF CARE	
14.1 Palliative care	
Class I	Pediatric palliative care should be incorporated into the care of all patients with advanced heart disease, including patients with end-stage HF and those receiving ECMO, VAD support, and patients listed for transplantation. **Level of Evidence B**
Class IIa	Standard communication by pediatric cardiology or palliative care teams with parents or guardians, adolescents, and young adults with HF about prognosis, outcome, clinical trajectory, and goals of care is reasonable, at least yearly, and with each hospitalization or procedure. **Level of Evidence C**
14.2 Hospice Care	
Class IIa	Development of standardized and ethical approaches to withdrawal of life-sustaining therapies, including ventilators, ICDs, and MCS is reasonable to guide care at end of life in pediatric patients with HF. **Level of Evidence C**
SECTION 15: QUALITY METRICS AND REPORTING	
Class IIa	Participation in multi–center data collection to facilitate clinical care improvement is reasonable for centers that treat children with HF. **Level of Evidence C**
Class IIb	Incorporating one or more patient–entered data elements/outcomes (e.g., assessments of quality of life, anxiety, or depression) into the comprehensive care of children with HF may be considered. **Level of Evidence C**

Abbreviations: ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; ACEI, angiotensin converting enzyme inhibitor; ARNI, angiotensin receptor neprilysin inhibitors; BNP, B-type natriuretic peptide; CHD, congenital heart disease; CT, computerized tomography; ECG, electrocardiogram; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricle; MCS, mechanical circulatory support; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricle; SD, standard deviation; SGLT2, Sodium-glucose cotransporter 2; TDI, tissue Doppler imaging; VAD, ventricular assist device; WHO, World Health Organization; WPW, Woff-Parkinson-White.

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Continued

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Continued

First name last name	Position and company of employment	Any relevant consultant work	Any relevant speakers bureau work	Any relevant ownership, partnership, or principal	Any relevant personal research	Any relevant institutional, organizational, or other financial benefit	Any relevant expert witness experience
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Abbreviations: NIH/NHLBI, National Institutes of Health/National Heart Lung and Blood Institute.

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