Heart Failure in Children and Adolescents: An Update on Diagnostic Approaches and Management

Abstract

Cardiac failure is a clinical syndrome that may develop in children due to cardiac dysfunction or underlying structural heart diseases. Considering the differences in the diagnostic and therapeutic approaches of pediatric heart failure (PHF) and adult HF, we aimed to review the current literature on PHF. Relevant studies were extracted from Medline/PubMed, Google Scholar, and Clinical Trial Registries using the terms "Paediatric heart failure" or “heart failure in children” and “management” or "decongestive therapy". Recent advances in diagnostic approaches such as cardiac magnetic resonance, speckle-tracking echocardiography, tissue Doppler imaging, and molecular diagnostic techniques have increased our understanding of PHF. It is imperative to evaluate miscellaneous interrelated factors responsible for the development of PHF including myocardial function, pulmonary and systemic blood flow, heart rhythm, valve function, and nutrition. Although the recent advances show established results of many new drugs in adult HF trials, conclusions cannot be drawn that these drugs will show similar efficacy in children considering the heterogeneous nature of underlying mechanisms and variable pharmacodynamics and pharmacokinetics. Therefore, the underlying pathophysiology of PHF and the mechanism of action of different drugs should be considered to choose an appropriate therapy. Further trials are needed to establish these drugs’ efficacy and safety, and a combined multidisciplinary strategy will help enhance the outcome of PHF.

Keywords: Heart failure- Child- Paediatrics- Tachycardia- Heart diseases
Key message:

➢ Heart failure in children is not a discrete pathological diagnosis but rather a clinical syndrome characterized by various symptoms (e.g., shortness of breath, ankle swelling, fatigue) and signs (e.g., pulmonary crackles, and peripheral edema).

➢ Structural heart diseases; especially, congenital heart diseases are the commonest underlying etiology of PHF while myocarditis and primary cardiomyopathies are the common causes in children with structurally normal hearts.

➢ The pathophysiology of PHF is complex and multifactorial and varies according to the underlying etiology and age of the child.

➢ The principles of PHF management include decongestive therapy, treatment of underlying causes, prevention of further progression, and management of pulmonary or systemic obstruction.

➢ The appropriate drugs should be chosen based on their pharmacodynamics as well as patient characteristics such as clinical manifestations, hemodynamic state, and renal function.

Introduction:

Low cardiac output was identified as the clinical syndrome that led to heart failure (HF) in the 1950s. In recent years, researchers have been more interested in identifying the role of neurohormonal and molecular mechanisms affecting cardiac function in failing hearts. Paediatric HF (PHF) may develop secondary to structural problems, e.g., congenital heart disease (CHD) and cardiomyopathies, or cardiac dysfunction due to infectious and inflammatory diseases, metabolic syndromes, malnutrition, malignancies, and renal failure.
Despite being a well-recognized entity, data on the prevalence and incidence of PHF are rather limited. Although HF has a low incidence (0.9-7.4 cases per 100,000 children), morbidity and mortality are still high with a 7-26% in-hospital mortality.\(^5,6\) In patients aged less than 18 years, infants comprise most HF admissions (64%).\(^4\) In a systematic review of 83 studies, Shabby et al found a wide variation in the reported incidence of PHF ranging from 0.87 per 100,000 in the UK and Ireland to as high as 83.3 per 100,000 in Spain.\(^6\)

The development of various non-invasive, minimally invasive, modern radiological methods and pharmacological advances has aided in the better management of PHF. Drugs such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and more recently, angiotensin receptor neprilysin inhibitors (ARNI), and sodium-glucose cotransporter-2 (SGLT-2) inhibitors have completely transformed the management of HF. Although the efficacy of these drugs has been well documented in adult HF trials, similar pediatric trials are lacking to conclude that these drugs will show similar efficacy in children considering the heterogeneous mechanisms of PHF and variable pharmacodynamics and pharmacokinetics. Therefore, we aimed to provide an up-to-date review of the current developments in the diagnostic approaches and management of PHF.

**Review:**

We retrieve the relevant information from the studies focusing on PHF and its treatment by performing an extensive literature search using Medline/PubMed, and Google Scholar. The following search terms were used: "Paediatric heart failure" or “heart failure in children” and “management” or "decongestive therapy". The reference list of all the collected studies was checked to retrieve any additional relevant studies.

**Definitions:**
Heart Failure: According to the recommendations made by the European Society of Cardiology (ESC) in 2021, HF is not a discrete pathological diagnosis but rather a clinical syndrome characterized by the collection of symptoms (e.g., shortness of breath, ankle swelling, fatigue) and occasionally accompanying signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema).  

Acute Heart Failure: Heart failure is called "acute" when signs and symptoms of malperfusion and congestion, such as tachycardia, tachypnoea, respiratory distress, and hypotension, appear suddenly (within minutes to hours), and usually because of some anatomical or functional changes in the heart.

Chronic Heart Failure: Chronic HF is a progressive condition that may have both cardiac and non-cardiac causes. Respiratory distress, pedal edema, exercise intolerance, and growth failure are some symptoms indicative of underlying neurohormonal, circulatory, and molecular abnormalities.

Chronic HF is classified as either HF with preserved ejection fraction (HFpEF) or HF with reduced ejection fraction (HFrEF). HFrEF is characterized by symptomatic HF with a dilated left ventricle (LV), LVEF of <50%, and is most often caused by LV systolic dysfunction. HFpEF refers to symptomatic HF with preserved EF and normal or nearly normal LV systolic function. It is usually caused by severe LV diastolic dysfunction, also known as diastolic HF.

Etiology:

The etiology of HF varies widely between adults and children. Ischemic heart disease (IHD), a common underlying cause of HF in adults, rarely causes HF in children. On the contrary, structural heart diseases; especially, CHDs are the commonest underlying etiology of PHF.
while children with structurally normal hearts are most often affected by myocarditis and primary cardiomyopathies.\(^3,4\) The most common morphological phenotypes of cardiomyopathy are dilated (60% cases) and hypertrophic cardiomyopathy (25% cases). In developed countries, the primary causes of PHF include CHDs or cardiomyopathy while rheumatic heart disease and infective endocarditis remain the common causes in developing countries. Table 1 highlights the various aetiologies of PHF. The common causes of HF at birth include fetal cardiomyopathies and extracardiac disorders (e.g., sepsis, hypoglycemia, and hypocalcemia) while ductus-dependent lesions lead to HF in the first week of birth such as coarctation of the aorta and hypoplastic left heart syndrome (HLHS). In the first month of life, left to right shunts, such as ventricular septal defect (VSD), patent ductus arteriosus (PDA), and aortopulmonary windows, are the main causes of PHF.\(^3,4\)

**Pathophysiology:**

The pathophysiology of HF in children is complex and multifactorial and varies according to the underlying etiology and age of the child. In CHDs, HF occurs due to the alteration in blood flow and hemodynamic overload, leading to ventricular remodeling and dysfunction. Chronic pressure overload results in myocardial hypertrophy which increases myocardial demand and oxygen consumption. The increased cardiac workload also leads to progressive dilatation of the ventricles, worsening heart function, and eventual HF. Cardiomyopathies are characterized by myocyte hypertrophy, apoptosis, and fibrosis resulting in impaired myocardial contractility and relaxation which manifest as HF. Acquired heart diseases such as Kawasaki disease, myocarditis, endocarditis, and rheumatic fever result in HF through inflammation and myocardial injury, leading to valvular dysfunction, decreased myocardial contractility, and cardiac output. In valvular heart diseases, regurgitation or stenosis causes
volume overload and pressure overload, respectively, resulting in ventricular remodeling and dysfunction.\(^9,^{10}\)

Regardless of the etiology, HF symptoms result from the inadequate cardiac output. The body tries to maintain the cardiac output through the activation of compensatory mechanisms involving the renin-angiotensin-aldosterone system (RASS), the sympathetic nervous system (SNS), and the secretion of natriuretic peptides. The SNS releases catecholamines and increases heart rate, systemic vascular resistance, and myocardial contractility while RAAS activation releases angiotensin II and aldosterone causing sodium and water retention, and leading to increased preload and ventricular dilation. Atrial natriuretic peptide and B-type natriuretic peptide (BNP), promote natriuresis and diuresis and inhibit renin secretion of aldosterone production. These molecules also inhibit cardiac remodeling, apoptosis, and fibrosis. Over time, these compensatory mechanisms become maladaptive, leading to progressive ventricular dysfunction and worsening HF through adverse cardiac remodeling. The release of pro-inflammatory cytokines and chemokines also contributes to myocardial damage and inflammation.\(^9,^{10}\)

**Clinical Presentations:**

The clinical presentation of HF in children can be diverse and vary widely depending on the age of the child, underlying etiology, and severity of the condition. PHF commonly presents with respiratory symptoms such as dyspnea, tachypnea, and respiratory distress which may exacerbate by physical activity or feeding. Circulatory symptoms include peripheral edema, hepatomegaly, and pleural effusions. Growth retardation and failure to thrive can occur in infants with HF due to increased metabolic demands while older children may experience palpitations, chest pain, and syncope due to decreased cardiac output and arrhythmias. These
children may experience signs of cerebral hypoperfusion, such as irritability, altered mental status, and lethargy. Peripheral cyanosis and pallor can also be present. \(^3,4,9,10\)

**Diagnostic Methods**

Non-invasive clinical examinations were done initially to diagnose PHF; however, early diagnosis is difficult due to the lack of sensitivity and specificity. A few of the commonly used non-invasive methods are enlisted below.

**Chest radiograph:**

A chest radiograph is advised for children with suspected HF to determine the size and shape of the heart and to look for signs such as pulmonary edema, septal lines (also known as Kerley B lines), and pleural effusions. \(^5\)

**Echocardiography:**

Due to its widespread availability in most centers, an echocardiogram is the most widely used and economically advantageous test to confirm the diagnosis of HF. It evaluates myocardial wall thickness, diameters, and volume of cardiac chambers, as well as ventricular systolic/diastolic function and pulmonary pressure. \(^2\) It also aids to determine the underlying cause of HF by capturing the anatomy and morphology of the heart, valves, major arteries, and surrounding tissues. \(^2\) M-mode, two-dimensional echocardiography (2D echo), and traditional Doppler are examples of typical echocardiographic procedures.

Several challenges unique to pediatric echo include complicated anatomy and difficulty in the evaluation of cardiac functions in ventricles with varying morphologies. More recent advancements in pediatric echo include non-Doppler-based (2D) stress and strain rate imaging, 3D-echo, functional imaging, and imaging of cardiac deformation. High spatial and
temporal resolution imaging is made possible by modern ultrasound technology; especially in pediatric probes, and provides a useful window into the myocardium's mechanics and function.\textsuperscript{11) }

In a 2D picture, one can analyze motion by observing speckles (natural acoustic markers). A change in each speckle's geometry reflects the motion of adjacent tissue.\textsuperscript{12) } The velocity of speckles may be computed from the change in location after the frame rate has been established and this motion pattern of speckles reflects the motion pattern of cardiac tissue. Consequently, by seeing these speckles, it is feasible to calculate the stress and strain rate.\textsuperscript{13) }

The connection of the echocardiographic speckle tracking approach with the well-known optical imaging modality of particle image velocimetry (PIV) has enabled the creation of a novel technique for observing the LV flow pattern. The velocity vector field in LV may be sufficiently reconstructed using this angle-independent contrast echo-based approach.\textsuperscript{13) }

However, echo is less reliable for determining the etiology of HF; particularly, in children. Owing to its dynamic nature, the strain echo may be beneficial in determining the absence of ischemia in uncertain situations involving hypertrophic cardiomyopathy or mitral regurgitation (MR). With the use of 3D echo, the precise pathophysiology of several underlying valvulopathies, such as mitral valve prolapse (MVP), may also be explained. Additionally, 3D-echo and functional echo may help identify complicated anatomy and functional changes and choose appropriate treatments.\textsuperscript{14) } Many studies have compared 2D and 3D-echo (2DE and 3DE) with a "reference" standard like cardiac magnetic resonance (CMR). A recent meta-analysis of all 3DE studies evaluating LV volumes and EF revealed that 3DE often underestimated volumes, but not as much as 2DE.\textsuperscript{14) }

\textit{Troponin:}
Cardiac troponins (cTn) are the primary biomarkers to detect ischemia or myocardial infarction (MI), as well as the etiology of acute HF. Increased blood Troponin I (TnI) and T (TnT) levels suggest severe cardiac damage; particularly, acutely decompensated chronic HF as both proteins are present in the contractile apparatus of myocytes. However, cTn levels are higher in healthy neonates and infants than in adolescents, and males usually have higher values than females. In a study by Dionne et al, the optimum troponin cut-off value to differentiate between a cardiac and noncardiac diagnosis of HF was greater in children under 3 months (0.045 ng/mL) than in older infants (0.005 ng/mL). In previous research, children with myocarditis had considerably greater TnT levels than children with dilated cardiomyopathy (DCM) or HF caused by massive left-to-right shunts. However, normal troponin levels do not rule out the potential of myocarditis.

**B-type natriuretic peptide (BNP):**

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are produced by myocardium in response to cardiac strain and children with CHD, cardiomyopathy, or rejection of heart transplant have significantly elevated BNP and NT-proBNP levels. Although there is a lack of substantial randomized trials to prove its efficacy in normal clinical practice, NTproBNP is a commonly accepted biomarker for HF diagnosis and treatment monitoring and risk stratification. A recent meta-analysis suggested that BNP testing might be an effective screening tool for PHF. Lin CW et al. found that a combination of modified Ross criteria score (≥4) and NT-proBNP (≥598 ng/l) can be used to make a diagnosis of PHF with 95% accuracy.

**Cardiac catheterization:**

Non-interventional pediatric cardiac catheterization is an important tool in accurately assessing the hemodynamic condition in children with CHD. Although it is not indicated for
the diagnosis of PHF, diagnostic catheterization may give important information about anatomy and pathophysiology in certain cases of PHF to manage these children better.\(^{23}\) Additionally, in patients with unexplained pulmonary hypertension, right cardiac catheterization helps to confirm the diagnosis, assess if high vascular resistance is reversible, and rule out other treatable reasons. Although imaging studies such as echo and cardiac MRI are becoming important tools for hemodynamic evaluation, they provide only indirect evidence while catheterization can provide direct evidence of LV diastolic dysfunction.\(^{24}\)

*Endomyocardial biopsy (EMB):*

Due to its invaluable information on myocardial histology, immunohistochemistry, and molecular structure, the EMB is utilized to ascertain the origin of various cardiac disorders, improve patient stratification, and guide treatment choices. EMB is helpful for managing patients with unexplained acute HF, hemodynamic compromise, ventricular arrhythmias/conduction problems with unclear causes, and tracking heart transplant rejection status. Considering the evolution of cutting-edge imaging technology, it is necessary to rethink the EMB’s current role in the study and therapy of cardiovascular illnesses.\(^{25}\)

Although it is considered the gold standard for myocarditis diagnosis, the real indication in children is still up for debate. Considering the high hazards of this invasive procedure should be restricted to patients where the confirmation of the diagnosis of myocarditis is helpful to optimize the therapeutic approaches.\(^{26}\) The common complications include pericardial effusion, deep venous thrombosis, third-degree atrioventricular block, and vascular problems.\(^{27}\) The present guidelines are mainly based on case-control studies and expert opinion due to the lack of prospective studies evaluating the efficacy of EMB in children.\(^{26}\)

**Recent Advances in Diagnostic Techniques**
Cardiac Imaging

Evaluation of CHD as the underlying cause of PHF has shown improved accuracy when a CT scan was used in addition to catheter angiography and echo. In most cases, extracardiac vascular systems are implicated, making CT a better tool for diagnosing complicated CHDs than echo.\textsuperscript{2,3} CT angiography offers a non-invasive alternative to catheter-based angiography for visualizing vascular architecture.\textsuperscript{2,3} Skepticism has been raised about the safety of CT scans for children; however, modern multidetector and dual-source CT has enhanced temporal resolution, leading to quicker scans and lower radiation exposure.

MRI provides a radiation-free, non-invasive option for gaining insight into a patient's internal structure and functioning. Compared to traditional contrast agents like gadolinium, ferumoxytol may be a safer and more practical option for people with renal impairment.\textsuperscript{28} Younger children need to be sedated with the related danger of sedation as cardiac MRI may take up to 1-2 hours depending on the anatomy. Cardiac MRI may aid in the diagnosis, preoperative evaluation, risk assessment, and treatment of certain cardiac conditions, such as cardiomyopathies and complicated CHDs, via tissue characterization and evaluation.\textsuperscript{29}

Multidirectional vascular flow patterns and hemodynamics may be detected by using MRI 4D-flow evaluation. Jacobs et al showed that 4D-flow evaluation augmented by Gadobenate dimeglumine is more accurate than 2D flow. Right ventricular volumes in children with rTOF were measured with great reproducibility and accuracy, with just a little overestimation compared to 2D imaging.\textsuperscript{30}

Molecular Diagnostic Techniques

Genetic testing for CHDs has progressed from evaluating a small number of loci to examining the whole genome, owing to recent developments in bioinformatics, DNA
sequencing technology, and the computational infrastructure required to handle genomic data. Sanger sequencing, fluorescence in situ hybridization (FISH), karyotyping, and multiplex ligation-dependent probe amplification are some of the time-honored methods of genetic investigation. Whole-exome sequencing (WES), chromosomal microarray (CMA), and whole-genome sequencing (WGS) are all examples of high-throughput genomic testing. By using probes with known sequences, FISH can recognize macromolecules with high specificity. Current commercially available FISH probes for CHD mostly target aneuploidy and the 22q11 deletion.

**Management of PHF:**

The principles of PHF management include decongestive therapy, treatment of underlying causes, prevention of further progression, and management of pulmonary or systemic obstruction. The appropriate drugs should be chosen based on their pharmacodynamics as well as patient characteristics such as clinical manifestations, hemodynamic state, and renal function.

**Supportive management:**

Patients with chronic HF are more likely to have anemia and iron deficiency (ID), albeit both conditions may coexist. Anaemia and ID are both linked to severe symptoms and worse clinical outcomes. Furthermore, it is important to recognize that anemia may either be the root cause of HF or a factor associated with the development of HF and worsening clinical conditions. Even though ID may be quickly identified using two biomarkers (serum ferritin and transferrin saturation), it is still underdiagnosed in PHF patients. Due to low oral absorption in these patients, oral iron supplementation is inadequate for treating ID anemia in children with HF.
Furthermore, it has been shown that anemia and poor long-term clinical outcomes in HF patients are related to low erythropoietin levels. Studies have shown an increase in functional ability and a decrease in hospitalization in HF patients with anemia treated with erythropoietin-stimulating drugs. In a meta-analysis by Montero et al., 24 of 25 investigations showed a lower Erythropoietin (Epo) ratio in HF patients with anemia than normal reference values or non-anemic HF patients. Also, circulating Epo was higher irrespective of Hb levels in HF patients compared with healthy controls. 35)

Lifestyle factors such as poor food quality, obesity, inactivity, and increased emotional stress levels are implicated in the changing epidemiology of HF. Children with CHD are strongly encouraged by the European Association for Cardiovascular Prevention and Rehabilitation to participate in light to moderate levels of physical activity, including recreational sports and fitness training. Clinical improvement from PHF therapy and management may also be influenced by a patient's commitment to a healthy lifestyle via practices like yoga and meditation. 36)

**Acute Decompensated Heart Failure (ADHF)**

Vasoactive medications, diuretics, and inotropic medicines are the current standard of care for the management of ADHF in children. Details of the drugs used for the management of ADHF are summarized in Table 2.

**Diuretics:**

Loop diuretics like furosemide and bumetanide are still the first line of treatment. The recent ISHLT guidelines for the management of PHF recommend the initiation of diuretics in patients having fluid retention with ventricular dysfunction and these should be continued until the euvoema is achieved. 32-33) Although studies failed to demonstrate survival benefits
in PHF patients, diuretics were very effective in reducing systemic, pulmonary, and venous congestion with a good safety profile. Continuous infusion of furosemide may be better and safer in acute HF and in the postoperative setting.

**Inotropes and Vasoactive drugs:**

Inotropes are used as rescue therapy in ADHF patients to prevent end-organ failure by increasing perfusion pressure and allowing diuresis to occur. These drugs improve myocardial contractility and increase cardiac output. Digoxin remained the main drug for PHF management for many years before an increased understanding of HF pathophysiology gave preference to neurohormonal control over inotropic therapy. Nowadays, other inotropes such as milrinone, dobutamine, dopamine, and epinephrine are utilized more with milrinone and/or dobutamine being used as first-line inotrope while epinephrine can be used in cases with refractory hypotension and poor end-organ perfusion.

The ISHLT guidelines recommended the use of temporary inotropic support in children presenting with cardiogenic shock, and low cardiac output with poor end-organ perfusion. However, these drugs should be used as a short-term measure for initial stabilization and as a bridge to transplant or mechanical circulatory support. After stabilization, oral HF maintenance medication should be started to reduce the risk of recurrence and alleviate chronic HF symptoms.

Although milrinone is widely used for the treatment of ADHF in children, only a few pediatric studies are available to conclude its effectiveness. Administering milrinone to children with ADHF before CHD surgery improved end-organ perfusion and cardiac output; however, this improvement seemed to be short-lived in the PRIMACORP study. Extended-release milrinone improved the quality of life and functional ability in Phase I/II clinical study in adult patients with advanced HF, and it was well tolerated at 30 days.
**Vasodilators:**

Vasodilators such as nitroprusside or nitroglycerin are indicated in selected cases of ADHF who present with significant cardiac volume overload (e.g., valvar regurgitation) in the absence of hypotension. These drugs significantly improve stroke volume and cardiac output without increasing myocardial oxygen demand. Nitroglycerine is a prodrug and nitroprusside exert a greater effect on peripheral arteriolar dilatation than nitroglycerine.\(^{32-33}\)

**Calcium sensitizer (Levosimendan):**

Intravenous Levosimendan, a vasoactive drug, improves cardiac contractility and decreases afterload. Activation of sarcolemmal potassium channels in peripheral vascular smooth muscles causes vasodilation and decreases afterload, whereas sensitization of troponin C to calcium mediates its inotropic action. Additionally, it protects the heart by activating potassium channels in the cardiomyocyte mitochondria.\(^{39}\)

Available small randomized controlled trials (RCTs) have shown improved hemodynamic conditions in pediatric cardiac surgery patients treated with levosimendan. However, preventive use of levosimendan did not result in a decrease in mortality, duration of ICU, or overall hospital stay.\(^{40}\) Therefore, levosimendan should be used in selected children with ADHF not responding to standard vasoactive medications.

**Mechanical circulatory support:**

Extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs) are two examples of cutting-edge technology useful in the management of PHF.

**Extracorporeal membrane oxygenation (ECMO):**
Over the last several decades, individuals with CHD who have undergone surgical repair have increasingly been treated with ECMO for cardiopulmonary failure. However, ECMO should be considered only when all other medical options have been exhausted. Rapid ECMO deployment, often known as "E-cardiopulmonary resuscitation" (E-CPR), has been developed in recent years as an emergency life support for patients in cardiac arrest who are unresponsive to standard CPR (CPR). Despite major advancements in ECMO technology and management, in-hospital mortality associated with ECMO continues to be high as well as other serious risks including cerebral bleeding, sepsis, and kidney failure.41-42

**Ventricular assist device (VAD):**

VAD has a crucial role in the management of selected patients with severe HF awaiting a heart transplant. VADs help to maintain adequate systemic pressure and output to allow end-organ perfusion and function while unloading the failing ventricle, lowering myocardial oxygen demand, and encouraging favorable remodeling (especially, in the brain, heart, and kidneys. 42) Although modern implanted VADs are widely available for adults, only a few devices are available for children. The timing of VAD implantation and patient selection is critical for a successful outcome. In a prospective clinical study of VAD implantation in children, the VAD support group had considerably higher survival rates than the ECMO control groups.42) The first pediatric VAD quality improvement network (Advanced Cardiac Therapies Improving Outcomes Network - ACTION) was created in 2007. Recent ACTION Network analysis showed excellent outcomes of VAD with 96% survival at 1 year while the most common adverse events were major bleeding and infection.43)

**Newer Drugs for ADHF**

Many other drugs have shown promising results in adult HF trials; however, similar evidence is not available currently to recommend or refute their uses in the management of PHF, such
as serelaxin, ularitide Recombinant human relaxin-2, or serelaxin, acts as a vasodilator and maintains end-organ perfusion. In the RELAX-AHF study, serelaxin showed a significant reduction in HF symptoms, and mortality in adults hospitalized with AHF.\textsuperscript{44}\) However, a similar pediatric trial (RELAX-PEDS-PK trial) was terminated early after getting disappointing findings from the RELAX-AHF-2 study in adults.\textsuperscript{45}\)

Isotonic acid (istanto) is the first synthetic medication having inotropic and lusitropic actions comparable to those of digitalis. HORIZON-HF trial demonstrated improved diastolic function and pulmonary capillary wedge pressure (PCWP) in adult HF patients but no such pediatric studies are available currently.\textsuperscript{46}\) Synthetic natriuretic peptides (ularitide) act by stimulating the guanylate cyclase/cyclic guanosine monophosphate (GC/cGMP) pathway, which results in increased natriuresis, diuresis, and vasodilation. Clinical studies of ularitide in adults with ADHF indicated a reduction in PCWP and a decrease in dyspnea\textsuperscript{47}; however, no studies are available on its safety or efficacy in children.

**Chronic Heart Failure (CHF)**

CHF in children should be managed appropriately to promote early recovery and prevent further progression as well as to correct the underlying causes such as CHD correction. In patients with HFrEF, ACE inhibitors, ARBs, diuretics, aldosterone antagonists, and β-blockers are commonly used in different combinations. No treatment has been shown to reduce mortality and morbidity in HFpEF; however, diuretics are frequently used to reduce congestion and associated symptoms. Although many adult trials have shown good safety and efficacy of these drugs, limited pediatric trials are available to demonstrate the safety and efficacy of these drugs in children. Current pharmacological management options are mainly guided by the results of adult studies (Table 3).

**Drugs for the management of chronic HF:**
Angiotensin-converting enzyme inhibitors (ACEI):

ACEIs have a Class 1 (level of evidence B) indication for individuals with LV dysfunction, whereas those with no symptoms have a Class IIa recommendation. Patients with HF benefit from ACEIs because they alleviate symptoms, decrease the progression of HF, lessen the need for hospitalization, and increase survival by inhibiting the activation of RAAS and adrenergic activity. In children, large-scale RCTs of these medications are not available.

Angiotensin receptor blockers (ARBs):

ARBs are used in children who are intolerant to ACEIs like they are used in adults. A prospective, randomized, placebo-controlled study including 5,000 adult patients with HF found that valsartan substantially improved EF, signs, and symptoms of HF, and the quality of life.

β-Blockers:

Beta-blockers have class IIa recommendations for the initiation in children with LV systolic failure who are experiencing symptoms. β-blockers act by inhibiting chronic activation of SNS in HF patients and reverse LV remodeling by decreasing LV dilation and improving LV systolic function. Improved coronary perfusion, cardiac output, and avoidance of arrhythmias are additional benefits of β-blockers. Although adult HF trials have shown survival benefits with the use of selective β-blockers, similar results could not be demonstrated in children. A multi-center RCT failed to show the benefits of carvedilol over placebo in children with HFrEF; however, it could be an underpowered study and a large placebo effect. A Cochrane review, including seven studies with a total of 420 children receiving β-blockers for HF, suggested a beneficial role of β-blockers in PHF management.

Diuretics
Diuretics are the preferred drug to treat HFP EF to achieve euvolemia with loop diuretics (e.g., furosemide) being the first choice but a combination of diuretics is commonly used to reduce the side effects. There is a Class I (level of evidence C) recommendation for the use of aldosterone antagonists in PHF associated with LV dysfunction.\textsuperscript{10,48}

**Digoxin**

Digoxin use in PHF was mostly empirical based on adult studies. Recent guidelines recommend against the use of digoxin in children with asymptomatic LV dysfunction as adult trials could not demonstrate survival benefits (Class I, level of evidence C). However, it can be used in symptomatic PHF patients (Class IIa, level of evidence C) at low levels. Digoxin is also helpful in children with severe HF intolerant to ACE inhibitors and β-blockers and in children with CHD and HF to reduce symptoms and hospitalization.\textsuperscript{4,10,48}

**Ivabradine:**

Ivabradine slows the heart rate by decreasing the rate of phase-4 depolarization in sinoatrial tissue, which is controlled by voltage. Ivabradine was shown to lower the occurrence of serious adverse events by reducing the heart rate in a retrospective analysis of patients with end-stage Duchenne cardiomyopathy.\textsuperscript{51} In a small trial, Ivabradine alleviated HF symptoms in children by lowering heart rate as a direct consequence of the termination or decrease of inappropriate tachycardia caused by atrial automatic tachycardias.\textsuperscript{52} Ivabradine has got Food and Drug Administration (FDA) approval for use in children older than 6 months with HF symptoms.\textsuperscript{35}

**Sacubitril-Valsartan:**

Sacubitril is the first medication that effectively blocks both angiotensin II and renin-angiotensin system activity. Neprilysin enzyme physiologically degrades natriuretic peptides
and hence plays a critical function in the cardiovascular system. Sacubitril/valsartan combination was shown to be more effective than enalapril in reducing mortality and length of hospital stay in adults with HFrEF in the landmark PARADIGM-HF trial.\textsuperscript{53} The relative risk of hospitalization or death due to major cardiac events was 18% lower in patients on sacubitril/valsartan compared to those taking enalapril. However, hypotension was more common with this combination than with enalapril, despite a decreased occurrence of increased creatinine or serum potassium.

**Newer Drugs for Chronic Heart Failure:**

Many new drugs have shown promising results in trials conducted on adult HF patients; however, these are not yet recommended for the management of PHF due to the lack of pediatric trials. Omecamtiv-mecarbil increases the activity of cardiac myosin ATPase while activating the cardiac myosin. The GALACTIC-HF study showed a decrease in HF events and death in participants receiving Omecamtiv-Mecarbil than those getting a placebo in adult symptomatic chronic HF patients.\textsuperscript{54} Vericiguat, a new oral soluble medication, has got approval for the treatment of adult patients with HFrEF by modulating endothelial activities in cardiac and vascular smooth muscles through activation of the GC enzyme. The VICTORIA study demonstrated significantly decreased overall mortality, cardiovascular mortality, and hospitalization due to HF in patients receiving Vericiguat.\textsuperscript{55} Sodium-Glucose Co-Transporter 2 (SGLT-2) inhibitors such as Dapagliflozin and Empagliflozin act on proximal renal tubules to treat type II diabetes mellitus in adults. Recently, McMurray et al. showed that dapagliflozin improves survival in adult patients hospitalized with HFrEF with or without diabetes mellitus.\textsuperscript{56}

**Cardiac Resynchronization Therapy**
Cardiac resynchronization therapy (CRT) is recommended in adults with HFrEF (LVEF <35%) not responding to optimal HF medicines with QRS duration >120 ms. CRT improves HF symptoms by improving cardiac motion, reducing the risk of sudden death, and improving the quality of life in these patients. The use of CRT is suggested in selected pediatric patients; especially, adolescents and young adults such as patients with systemic ventricles, and a history of severe LV dysfunction (LVEF <30%) with or without associated ventricular arrhythmias secondary to CHD (aortic or mitral stenosis). For CRT in children, the cut-off value of QRS duration is taken as the 98th percentile for age.\(^\text{10}\)

**Future Direction**

Despite their interpretative limits, recent data shows that cardiac biomarkers may be useful in diagnosing and prognosticating myocarditis, CHD, cardiac surgery, and HF, as well as assessing the severity and cardiac involvement in immune-related and other systemic illnesses. However, most studies discussing the connections between elevated cardiac biomarkers and clinical outcomes are retrospective in nature. Prospective trials are lacking to demonstrate the usefulness of biomarkers in improving clinical outcomes by choosing appropriate treatment and reducing hospitalizations. These studies are difficult to accomplish in the pediatric population due to low patient frequency, but they are urgently required to support evidence-based recommendations and appropriate clinical adoption of chosen cardiac biomarkers in the evaluation of cardiac and noncardiac diseases.\(^\text{15}\) Adult HF clinical studies may help design appealing drug trials in pediatric patients, but they are not alternatives. The underlying pathophysiology of HF and the pharmacological mechanisms of various drugs must be considered while choosing medicines for PHF. The industry has little motivation to develop children-specific HF treatments owing to low PHF cases. To accelerate pediatric HF drug and device studies, the governments could fund such trials and fill the knowledge gap in
the literature. Novel clinical trial designs that accelerate the development, evaluation, and review and connect Centres for Medicare and Medicaid Services funding to FDA marketing clearance may enable early market access. Device-based treatments for children may reduce medication adverse effects and enhance HF compliance and results.\textsuperscript{58)}

Over the last several decades, PHF therapy has evolved to meet new standards of care and new problems. Newer treatment options are extending the lives of children with HF, but at a higher total cost, thus preventive measures and high-quality care are urgently needed. Due to its palliative nature and short life expectancy, heart transplantation is the only viable alternative for preserving lives. Assuming cardiac dysfunction and its treatment are not restricted to heart rate (rhythm), myocardial contractility, preload, and afterload, there are effective but underutilized therapeutic options. Modifying ventricular afterload by enhancing contra-lateral ventricular performance represents a paradigm change in the management of PHF. Therapeutic use of adverse ventricular-ventricular interactions (VVI) is possible. It is believed that functional recovery may be accomplished in over 80\% of newborns with DCM despite requirements for listing to orthotopic heart transplant when surgical implantation of a pulmonary artery banding (PAB) is used to restore heart function through VVI.\textsuperscript{58)}

**Conclusion**

Recent advances in the diagnostic and therapeutic approaches toward PHF have changed the outcome significantly. Newer diagnostic approaches such as cardiac magnetic resonance, speckle-tracking echo, tissue Doppler imaging, and molecular techniques have increased our understanding of PHF. Recent adult HF trials have suggested the possibility of the application of newer drugs such as ARNI and SGLT-2 inhibitors in the management of PHF. However, further pediatric trials are needed to establish the efficacy and safety of these drugs in children considering the underlying pathophysiology of PHF as well as the mechanism of
action of different drugs. The future outcomes for children with HF will improve with the implementation of a multidisciplinary approach.

**Funding:** Nil

**Conflict of Interest:** None

**Ethical approval:** NA

**Author contributor ship:**

**Dalwinder Janjua:** Conceptualization (Supporting); Data curation (Supporting); Formal analysis (Supporting); Writing – original draft (Lead). **Abdulrahman Ahmed Alsayed Ali Zeyada:** Data curation (Lead); Formal analysis (Equal); Writing – original draft (Supporting). **Ahmed Taher Elsheikh:** Data curation (Lead); Formal analysis (Equal); Writing – original draft (Supporting). **Amit Agrawal:** Conceptualization (Lead); Data curation (Supporting); Writing – original draft (supporting), Writing – Review and editing (Lead)

**References:**

1. Keith JD: Congestive Heart Failure. Pediatrics 1956;18:491–500. 10.1542/peds.18.3.491


42. Lawson WE, Koo M. Percutaneous Ventricular Assist Devices and ECMO in the Management of Acute Decompensated Heart Failure. Clin Med Insights Cardiol 2015;9s1:CMC.S19701. 10.4137/cmc.s19701


CD007037.


Table 2 - Commonly used drugs for the management of Acute heart failure in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Site of action</th>
<th>Action</th>
<th>Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics (HF with signs of fluid overload and ventricular dysfunction)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics (Furosemide)</td>
<td>Na+/K+/2Cl- cotransporter inhibition</td>
<td>Ascending limb of the loop of Henle</td>
<td>Excretion of Na+, K+, Cl- and free water</td>
<td>Oral: 1 mg/kg q 6-12h IV: 0.5-2 mg/kg Continuous infusion: 0.1 – 0.4 mg/kg/h</td>
<td>Hyponatremia, Hypokalemia, Metabolic acidosis</td>
</tr>
<tr>
<td>Thiazide diuretics (Hydrochlorothiazide)</td>
<td>Inhibition of Na+ reabsorption</td>
<td>DCT</td>
<td>Excretion of Na+, K+, Cl- and free water</td>
<td>1 – 2 mg/kg q 12h</td>
<td>Electrolyte imbalance</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists (Spironolactone)</td>
<td>Inhibition of binding of aldosterone to its receptor</td>
<td>DCT</td>
<td>Excretion of Na+ and sparing of K+</td>
<td>0.5 – 1.5 mg/kg q 12h</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Metolazone</td>
<td>Inhibition of Na+ reabsorption in both PCT and DCT</td>
<td></td>
<td>Excretion of Na+, K+, Cl- and free water</td>
<td>0.1 – 0.2 mg/kg q 12h</td>
<td>Electrolyte imbalance</td>
</tr>
<tr>
<td>Vasopressin antagonists (Tolvaptan, Conivaptan)</td>
<td>Vasopressin-2 channel antagonism (Aquaporin channels)</td>
<td>Renal collecting duct</td>
<td>Reduction of water absorption</td>
<td>0.1 mg/kg/d (not well established)</td>
<td>Hypernatremia</td>
</tr>
<tr>
<td><strong>Vasoactive and inotropic drugs (HF with cardiogenic shock, and low cardiac output with poor end-organ perfusion)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>Phosphodiesterase – III inhibitor</td>
<td>Myocardium, Peripheral vessels</td>
<td>↑inotropy, ↑lusitropy, ↓SVR, ↓PVR</td>
<td>0.25–1 μg/kg/min</td>
<td>Hypotension, Arrhythmias</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>β1 receptors; cAMP pathway activation</td>
<td>Myocardium</td>
<td>↑inotropy, ↑chronotropy</td>
<td>2.5–10 μg/kg/min</td>
<td>Hypotension, Tachycardia</td>
</tr>
<tr>
<td></td>
<td>β2 receptor</td>
<td>Peripheral vessels</td>
<td>Vasodilation</td>
<td>&lt;5 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Receptors</td>
<td>Vasoconstriction</td>
<td>Effect</td>
<td>Dose</td>
<td>Side Effects</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------</td>
<td>--------</td>
<td>------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>α1 receptors</td>
<td>Peripheral vessels</td>
<td>Vasoconstriction</td>
<td>&gt;10 μg/kg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>β1 receptors: cAMP pathway activation</td>
<td>Myocardium</td>
<td>↑ inotropy</td>
<td>0.01–0.1 μg/kg/min</td>
<td>Tachycardia, ↑ myocardial oxygen demand</td>
</tr>
<tr>
<td></td>
<td>β2 receptors</td>
<td>Peripheral vessels</td>
<td>Vasodilation</td>
<td>0.05 to 0.1 mg/kg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>α receptors</td>
<td>Peripheral vessels</td>
<td>Vasoconstriction</td>
<td>&gt;0.1 mg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>D1 receptors</td>
<td>Kidney</td>
<td>↑ renal perfusion</td>
<td>&lt;3 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β1 receptors: cAMP pathway activation</td>
<td>Myocardium</td>
<td>↑ inotropy, ↑ chronotropy</td>
<td>3–10 μg/kg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>α receptors</td>
<td>Peripheral vessels</td>
<td>Vasoconstriction</td>
<td>&gt;10 μg/kg/min</td>
<td></td>
</tr>
</tbody>
</table>

**Vasodilators (Acute HF with significant volume overload in absence of hypotension)**

<table>
<thead>
<tr>
<th>Vasodilator</th>
<th>Release of Nitric Oxide</th>
<th>Vessels</th>
<th>Arteriolar Vasodilation</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroprusside</td>
<td>Release of nitric oxide</td>
<td>Peripheral vessels</td>
<td>Arteriolar Vasodilation</td>
<td>0.3–4 μg/kg/min 0.5-10 μg/kg/min</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Newer drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitization of Troponin C to Calcium</th>
<th>Myocardium</th>
<th>Improved Myocardial Contractility</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levosimendan</td>
<td>Sarcolemmal K+ channel activation</td>
<td>Vascular smooth muscles</td>
<td>Vasodilation, after load reduction</td>
<td>0.5-2 μg/kg/min</td>
<td>Hypotension, arrhythmias</td>
</tr>
</tbody>
</table>

HF – heart failure, DCT - distal convoluted tubules, PCT - proximal convoluted tubules, IV – intravenous, SVR – systemic vascular resistance, PVR – pulmonary vascular resistance, Na+ - Sodium, K+ - Potassium, Cl- - Chloride, cAMP – cyclic adenosine monophosphate
Table 3 - Commonly used drugs for the management of chronic heart failure in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Action</th>
<th>Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitors (All patients with HF and left ventricular systolic dysfunction)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>Inhibits activation of RAAS</td>
<td>Decreases after load, Prevents myocardial remodelling</td>
<td>0.1 mg/kg q 8h (max 2 mg/kg/dose)</td>
<td>Hypotension, Angioedema, Bradykinin-system-related cough, Hyperkalemia</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Inhibits sympathetic activity</td>
<td></td>
<td>0.1 mg/kg q 12h (max 0.5 mg/kg/day)</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td></td>
<td></td>
<td>0.05–2 mg/kg q 12-24h</td>
<td></td>
</tr>
<tr>
<td><strong>Angiotensin receptor blockers (Children not tolerating ACE inhibitors)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>Inhibits activation of RAAS</td>
<td>Decreases after load, Prevents myocardial remodelling</td>
<td>0.5 – 2 mg/kg/d</td>
<td>Hypotension, Angioedema, Hyperkalemia</td>
</tr>
<tr>
<td><strong>β blockers (HF with left ventricular systolic dysfunction)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Inhibits sympathetic activity</td>
<td>Improves systolic function, Prevents myocardial remodelling</td>
<td>0.1 – 0.2 mg/kg q 12h (max 1 mg/kg/dose)</td>
<td>Bronchospasm, Bradycardia, heart block, hypotension, hyperglycemia</td>
</tr>
<tr>
<td>Carvedilol</td>
<td></td>
<td></td>
<td>0.05 – 0.1 mg/kg q 12h (max 1 mg/kg/dose)</td>
<td></td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>Na+/K+/2Cl-/cotransporter inhibition</td>
<td>Excretion of Na+, K+, Cl- and free water</td>
<td>0.5 – 1 mg/kg q 6-12h</td>
<td>Hyponatremia, Hypokalemia, Metabolic acidosis</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Inhibition of Na+ reabsorption</td>
<td>Excretion of Na+, K+, Cl- and free water</td>
<td>0.5 – 1 mg/kg q 12h</td>
<td>Electrolyte imbalance</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Inhibition of binding of aldosterone to its receptor</td>
<td>Excretion of Na+ and sparing of K+</td>
<td>0.5 – 2 mg/kg q 12 h</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Inhibition of Na-K-ATPase pump</td>
<td>Increased inotropy, negative chronotropic effect</td>
<td>3 to 5 mcg/kg q 12h</td>
<td>Arrhythmia, hyperkalemia</td>
</tr>
</tbody>
</table>