Heart Failure in Children with Congenital Heart Disease

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Background: Heart failure (HF) is a complex clinical syndrome resulting from diverse primary and secondary causes and shared pathways of disease progression, correlating with substantial mortality, morbidity, and cost. HF in children is most commonly attributable to coexistent congenital heart disease, with different risks depending on the specific type of malformation. Current management and therapy for HF in children are extrapolated from treatment approaches in adults. This review discusses the causes, epidemiology, and manifestations of HF in children with congenital heart disease and presents the clinical, genetic, and molecular characteristics.

Keywords: CHD, HF

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Introduction

Congenital Heart Diseases (CHD)

Acongenital heart defect (CHD), also known as a congenital heart anomaly and congenital heart disease, is a defect in the structure of the heart or great vessels that is present at birth. Signs and symptoms depend on the specific type of defect. Symptoms can vary from none to life-threatening. When present, symptoms may include rapid breathing, bluish skin (cyanosis), poor weight gain, and feeling tired. CHD does not cause chest pain. Most congenital heart defects are not associated with other diseases. A complication of CHD is heart failure ***(Sharon et al., 2017)***.

Heart defects are among the most common birth defect, occurring in 1% of live births (2-3% including bicuspid aortic valve). In 2013, 34.3 million people had CHD. In 2010, they resulted in 223,000 deaths, down from 278,000 deaths in 1990 ***(Vos et al., 2015)***.

For congenital heart defects that arise without a family history (de novo), the recurrence risk in offspring is 3-5%. This risk is higher in left ventricular outflow tract obstructions, heterotaxy, and atrioventricular septal defects ***(Canobbio et al., 2017)***.

Causes:

The cause of congenital heart disease may be genetic, environmental, or a combination of both. Genetic mutations, often sporadic, represent the largest known cause of congenital heart defects. The genes regulating the complex developmental sequence have only been partly elucidated. Some genes are associated with specific defects. A number of genes have been associated with cardiac manifestations. Mutations of a heart muscle protein, α-myosin heavy chain (MYH6) are associated with atrial septal defects ***(Razmara et al., 2018)***

Several proteins that interact with MYH6 are also associated with cardiac defects. The transcription factor GATA4 forms a complex with the TBX5 which interacts with MYH6. Another factor, the homeobox (developmental) gene, NKX2-5 also interacts with MYH6. Mutations of all these proteins are associated with both atrial and ventricular septal defects; In addition, NKX2-5 is associated with defects in the electrical conduction of the heart and TBX5 is related to

the Holt-Oram syndrome which includes electrical conduction defects and abnormalities of the upper limb ***(Cantù et al., 2018)***.

The Wnt signaling co-factors BCL9, BCL9L and PYGO might be part of this molecular pathways, as when their genes are mutated, this causes phenotypes similar to the features present in Holt-Oram syndrome. Another T-box gene, TBX1, is involved in velo-cardio-facial syndrome DiGeorge syndrome, the most common deletion which has extensive symptoms including defects of the cardiac outflow tract including tetralogy of Fallot ***(Cantù et al., 2018).*** The notch signaling pathway, a regulatory mechanism for cell growth and differentiation, plays broad roles in several aspects of cardiac development. Notch elements are involved in determination of the right and left sides of the body plan, so the directional folding of the heart tube can be impacted. Notch signaling is involved early in the formation of the endocardial cushions and continues to be active as the develop into the septa and valves. It is also involved in the development of the ventricular wall and the connection of the outflow tract to the great vessels ***(Razmara et al., 2018)***.

Mutations in the gene for one of the notch ligands, Jagged1, are identified in the majority of examined cases of arteriohepatic dysplasia (Alagille syndrome), characterized by defects of the great vessels (pulmonary artery stenosis), heart (tetralogy of Fallot in 13% of cases), liver, eyes, face, and bones. Though less than 1% of all cases, where no defects are found in the Jagged1 gene, defects are found in Notch2 gene. In 10% of cases, no mutation is found in either gene. For another member of the gene family, mutations in the Notch1 gene are associated with bicuspid aortic valve, a valve with two leaflets instead of three. Notch1 is also associated with calcification of the aortic valve, the third most common cause of heart disease in adults ***(Spinner et al., 2013)***.

Mutations of a cell regulatory mechanism, the Ras/MAPK pathway are responsible for a variety of syndromes, including Noonan syndrome, LEOPARD syndrome, Costello syndrome and cardiofaciocutaneous syndrome in which there is cardiac involvement. While the conditions listed are known genetic causes, there are likely many other genes which are more subtle. It is known that the risk for congenital heart defects is higher when there is a close relative with one ***(Razmara et al., 2018)***.

Known environmental factors include certain infections during pregnancy such as rubella, drugs (alcohol, hydantoin, lithium and thalidomide) and maternal illness (diabetes mellitus, phenylketonuria, and systemic lupus erythematosus). Alcohol exposure in the father also appears to increase the risk of congenital heart defects ***(Zhang et al., 2020)***.

Being overweight or obese increases the risk of congenital heart disease. Additionally, as maternal obesity increases, the risk of heart defects also increases. A distinct physiological mechanism has not been identified to explain the link between maternal obesity and CHD, but both prepregnancy folate deficiency and diabetes have been implicated in some studies ***(Howards et al., 2015)*** **Signs and symptoms:**

General signs of congenital heart disease can include a blue tinge to the skin (cyanosis), rapid breathing, rapid heartbeat, swelling in the legs, tummy and around the eyes, shortness of breath in babies during feeding (making it hard for them to gain weight) and in older children and adults during exercise, extreme tiredness, and fatigue, fainting during exercise, swelling in the hands, ankles, or feet. In more severe cases, these problems may develop shortly after birth. The general signs of this disease include: excessive sweating, extreme tiredness, fatigue, poor feeding, rapid heartbeat, shortness of breath, chest pain, blue tinge to the skin (cyanosis), and clubbed fingernails. The congenital heart disease develops shortly after birth and the symptoms do not develop until early childhood or teenage years ***(Choices et al., 2014).*** However, some complications may develop during adulthood such as problem with growth and development of heart and body, the infections of respiratory tract, throat, lungs and sinuses, heart infection, endocarditis, pulmonary hypertension, high blood pressure, and the heart being unable to pump enough blood which can cause a heart failure. However, symptoms sometimes don't develop until the teenage years or early adulthood ***(Sun et al., 2015).***

Complications:

Children and adults with congenital heart disease can also develop a range of further problems, such as problems with growth and development, repeated respiratory tract infections (RTIs), heart infection (endocarditis), pulmonary hypertension, heart failure where the heart is unable to efficiently pump enough blood around the body ***(Poterucha et al., 2019).***

Clinical picture of HF:

In a patient with appropriate symptoms and a number of physical signs, including a displaced apex beat, elevated venous pressure, oedema, and a third heart sound, the clinical diagnosis of heart failure may be made with some confidence. However, the clinical suspicion of heart failure should also be confirmed with objective investigations and the demonstration of cardiac dysfunction at rest. It is important to note that, in some patients, exercise-induced myocardial

ischaemia may lead to a rise in ventricular filling pressures and a fall in cardiac output, leading to symptoms of heart failure during exertion ***(Gohar et al., 2019).***

European Society of Cardiology's guidelines for diagnosis of heart failure (2018):

Essential features

Symptoms of heart failure (for example, breathlessness, fatigue, ankle swelling) and Objective evidence of cardiac dysfunction (at rest) **Non-essential features**

Response to treatment directed towards heart failure (in cases where the diagnosis is in doubt) ***(Crespo-Leiro et al., 2018).***

Echocardiography:

Echocardiography is the preferred examination in CHF. Two-dimensional and Doppler echocardiography may be used to determine systolic and diastolic LV performance, the cardiac output (ejection fraction), and pulmonary artery and ventricular filling pressures ***(Guazzi et al., 2015).***

The chest x-ray in congenital heart disease:

Ebstein's anomaly showing the classic appearance of cardiomegaly, small aortic knuckle, small pulmonary arteries giving the appearance of underfilled lungs, dilated inferior vena cava and huge right atrium. The right ventricular outflow is prominent and pushed to the left by the dilated right atrium, which is dilated due to tricuspid regurgitation ***(Sadeghpour and Hashemi et al., 2014).***

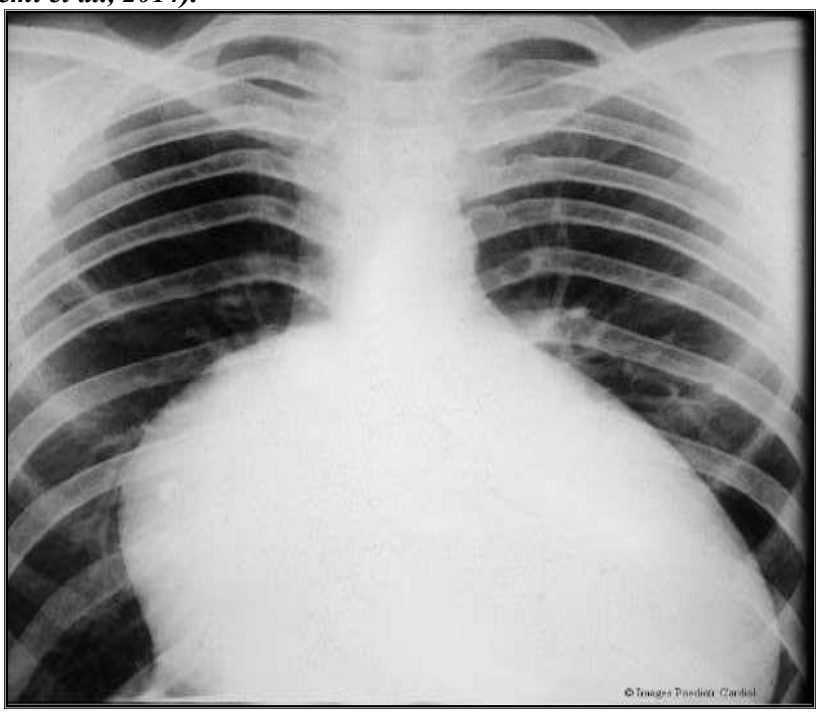


Fig. (1): Ebstien's anomaly ***(Yuan et al., 2017).*** **Diagnosis of CHD**

The first step in the diagnostic approach to pediatric HF is history and physical examination ***(Hinton et al., 2017).*** Many congenital heart defects can be diagnosed prenatally by fetal echocardiography. This is a test which can be done during the second trimester of pregnancy, when the woman is about 18–24 weeks pregnant. It can be an abdominal ultrasound or transvaginal ultrasound ***(Sun et al., 2015).***

The test and diagnosis of congenital heart disease in children or adults can be performed by taking blood pressure and electrocardiogram (ECG) or X-ray of heart patients (Tests and diagnosis). When blood does not flow normally through vessels, there is a sound of heart murmur in heart beat which is measured by stethoscope to examine the heart defects. Following tests are used to diagnose congenital heart disease ***(Robinson et al., 2014).***

If a baby is born with cyanotic heart disease, the diagnosis is usually made shortly after birth due to the blue color of their skin (called cyanosis). If a baby is born with a septal defect or an obstruction defect, often their symptoms are only noticeable after several months or sometimes even after many years. ***(Sun et al., 2015)*** **Electrocardiogram:** Electrocardiogram is used to rule out arrhythmia/ischemia/left bundle branch block Sinus tachycardia is common in acute HF. In chronic HF, an abnormal electrocardiogram increases the likelihood of decompensated HF ***(Masarone et al., 2017)***

Chest radiography:

Chest radiography is indicated in all children with suspected HF to assess heart size and to check for other signs of HF such as pulmonary edema, septal lines (or Kerley B lines), and pleural effusions ***(Masarone et al., 2017)***

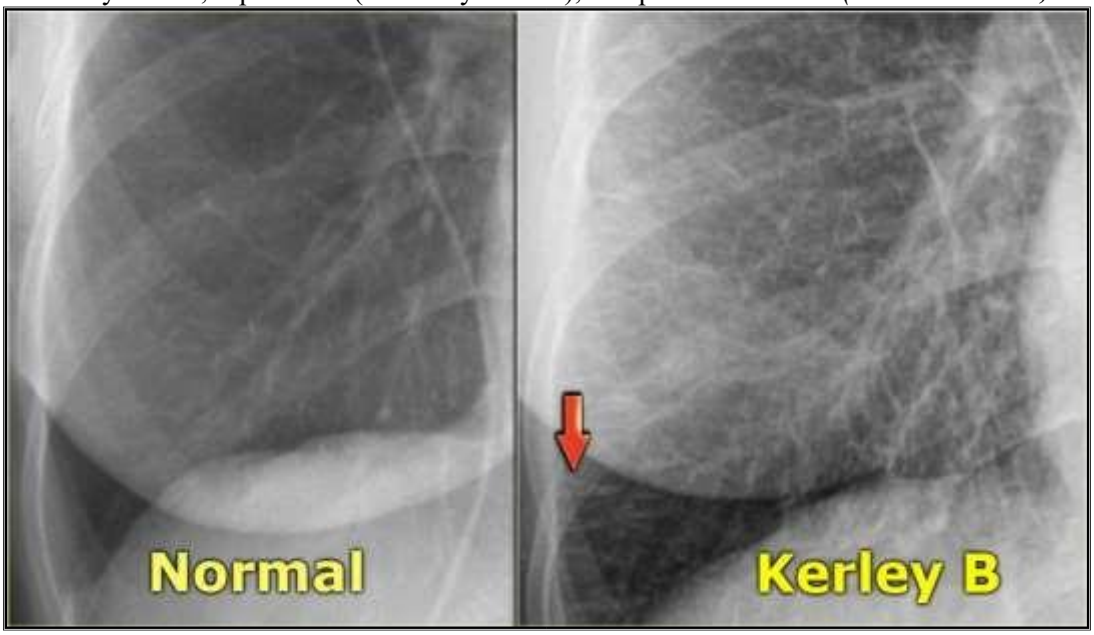


Fig. (2): Kerley-B lines are seen as peripheral short 1-2 cm horizontal lines near the costophrenic angles.

Echocardiography:

The echocardiogram is the most useful, widely available, and low-cost test for patients with PHF. Echocardiography provides immediate data on cardiac morphology and structure, chamber volumes/diameters, wall thickness, ventricular systolic/diastolic function, and pulmonary pressure. These data are crucial to make the correct diagnosis and to guide appropriate treatment ***(Kantor et al., 2013)***.

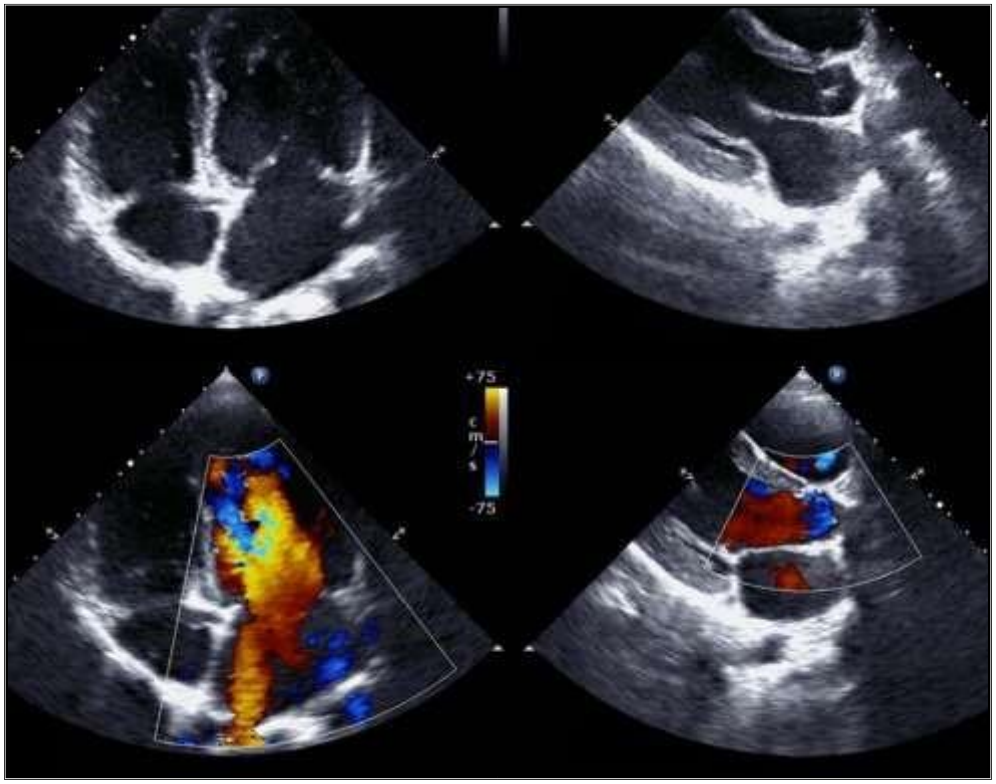


Fig. (3): Echocardiography show pulmonary hypertension in infants.

Laboratory investigations:

Laboratory investigations should include complete blood count to assess anemia and rule out infections, arterial blood gas, and electrolytes to evaluate hyponatremia, hyperkalemia, hypoxemia and acidosis, renal/hepatic function, and lactate to evaluate end-organ function, natriuretic peptides (NT-pro-BNP/BNP) to evaluate cardiac function and LV filling pressure, troponin to rule out any inflammatory or ischemic cardiomyopathy ***(Kantor et al., 2013).***

Cardiac catheterization:

Despite advances in noninvasive diagnostic techniques, cardiac catheterization is presently indicated for accurate evaluation of pressure gradients in patients with complex valve diseases and also evaluation of hemodynamic parameters (pulmonary and systemic vascular resistance, cardiac output, and cardiac index) in Fontan patients or during pre-transplant screening ***(Hinton et al., 2017)***

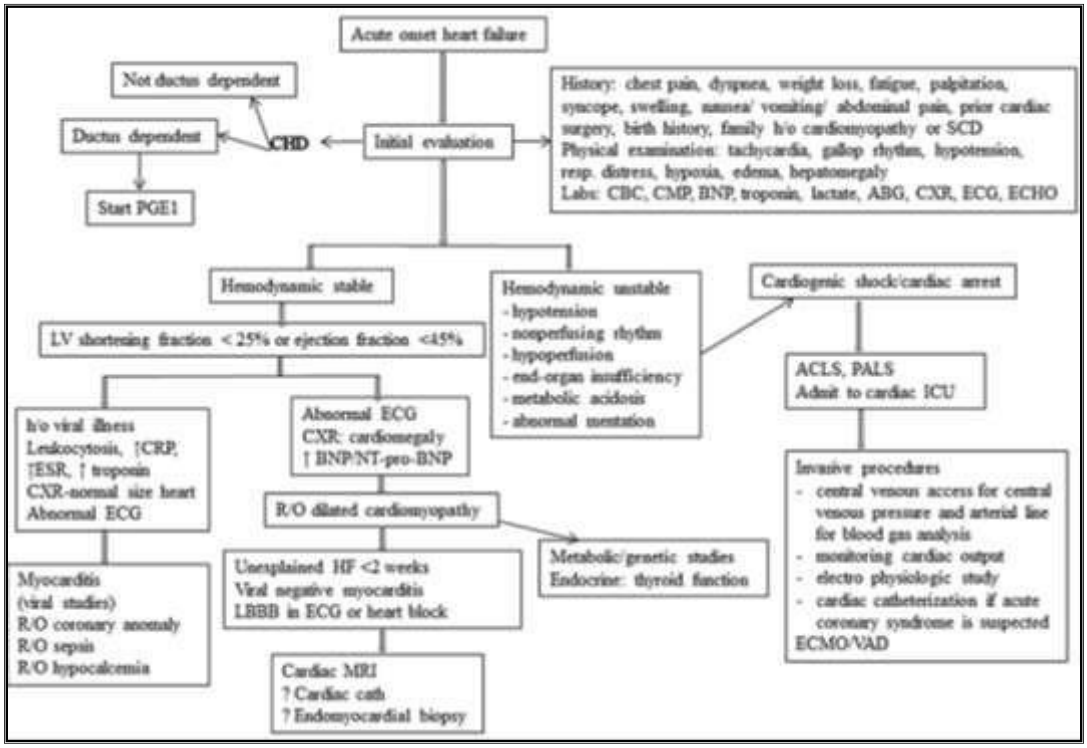


Fig. (4): Diagnosis and management of acute heart failure in children ***(kantor et al., 2013).*** Pediatric Heart Failure (PHF)

AHF in children with CHD in uncommon but increasing and is associated with significant morbidity, mortality and resource utilization. Approximately 1 in 5 children do not survive to hospital discharge. Many risk factors for mortality may not be modifiable, and further study is needed to identify modifiable risk factors and improve care for this complex population ***(Burstein et al., 2019).***

Heart failure (HF) is an important healthcare issue in both adults and children because of its high mortality, morbidity, and cost of care. By 2030, more than 8 million people in the Unites States (US) (1 in every 33) will have HF, and the projected cost estimates of treating patients will be $160 billion in direct costs as forecasted by American Heart Association (AHA) ***(Heidenreich et al., 2017).*** **Definition of PHF:**

As per the American College of Cardiology (ACC)/AHA task force on practice guidelines, the term "heart failure" is preferred over the older term "congestive heart failure". Heart failure in children is a clinical and pathophysiological syndrome that results from ventricular dysfunction, volume, or pressure overload, either alone or in combination. As a complex clinical syndrome, HF is characterized by typical symptoms and signs associated with specific circulatory, neurohormonal, and molecular abnormalities ***(Kirk et al., 2014)***.

The term "acute HF" generally describes a structural or functional alteration in the heart that occurs in minutes to hours followed by congestion, malperfusion, tachycardia, and hypotension. Acute HF is not synonymous with "worsening HF", as usually the patient has worsened either mechanically (as in the case of acute aortic or mitral insufficiency) or functionally (as a result of arrhythmia or myocardial ischemia) in pre-existing heart disease ***(Packer et al., 2018)***.

Often in patients with a diagnosis of HF, the disease progresses due to sub-optimal treatment or a lack of adherence to medical therapy, and presents with clinical decompensation, and the term "acute on chronic HF" may be used. "Chronic HF" in children is a progressive clinical and pathophysiological syndrome caused by cardiovascular and non-cardiovascular abnormalities that result in characteristic signs and symptoms, including edema, respiratory distress, growth failure, exercise intolerance, and is accompanied by circulatory, neurohormonal, and molecular derangement ***(Anderson et al., 2019).***

"Advanced HF" patients are those with clinically significant circulatory compromise who require special care, including consideration for continuous inotropic therapy, mechanical circulatory support, or heart transplantation. "End-stage HF" is the final common pathway of all forms of heart disease and may lead to therapies such as orthotopic heart, lung, or heart-lung transplantation ***(Anderson et al., 2019).***

It is important to distinguish "right HF" and "left HF" as the clinical management is different. There are also other nomenclatures, and HF may be described as "compensated HF" or "decompensated HF" depending upon whether end-organ perfusion is maintained. Heart failure can also be described as "systolic HF" with reduced ejection fraction, HF with preserved systolic function, which is synonymous with "diastolic HF", and combined systolic and diastolic HF. The term "high output HF" is often used to describe cardiac or extra-cardiovascular conditions leading to volume overload and congestion. In general, a commonly accepted definition of HF has been challenging ***(Kirk et al., 2014)***.
The International Society for Heart and Lung Transplantation (ISHLT) stratified pediatric HF into four stages (Stages A–D), which is useful to identify those at risk for HF and who are currently asymptomatic (Stage A) versus those on the other end of the spectrum (Stage D), who have advanced HF and, thus, would require therapeutic interventions for maintenance of end-organ function ***(Kirk et al., 2014).*** **Table (1):** Heart Failure Severity Classifications:

Class	NYHA	Ross
I	No limitations of physical activity	No limitations of physical activity
II	May experience fatigue, palpitations, dyspnea, or angina during moderate exercise but not during rest	Mild tachypnea or diaphoresis with feeding
III	Symptoms with minimal exertion that interfere with normal daily activity	Infants with growth failure and marked tachypnea or diaphoresis with feedings, older children with marked dyspnea on exertion
Iv	Unable to carry out any physical activity because they typically have symptoms of HF at rest that worsens with any exertion	Symptoms at rest such as tachypnea, retractions, grunting, or diaphoresis

Causes of PHF:

For example, outflow tract obstruction (pressure overload) or pulmonary over-circulation (volume overload) may be confusing because ventricular dysfunction may be associated with poor contractility (systolic dysfunction) or poor relaxation (diastolic dysfunction), with or without the clinical presence of HF. There is an overlapping relationship of HF, CHD, and cardiomyopathy. Of note, patients with CHD and HF, especially with single ventricle physiology, make up a significant proportion of the heart transplantation population, over 50% in infants. ***(Hinton et al., 2017)***. PHF has numerous causes that are a consequence of cardiac and noncardiac disorders, either congenital or acquired. In the pediatric population, rheumatic fever was the most common cause of HF in children in the United States in the 1950s and continues to be a common cause of pediatric HF in developing countries ***(Sibetcheu et al., 2018).***
Traditionally, HF has been synonymous with cardiomyopathy in the literature of pediatric heart disease, but over time, it became clear that cardiomyopathy is but one cause of HF. Although the proportion of CHD patients with HF is lower than the proportion with rhythm disturbances or cardiomyopathy, CHD is a much more common disease and therefore contributes a greater number of cases to the overall HF count ***(Hinton et al., 2017)***.
Nearly 60% of HF cases in pediatric patients occurred within the first year of life, but in these studies, the overall mortality was lower in the CHD population than in patients with HF from other causes. The fact that the risk of HF varied depending on the underlying cause raises the fundamental question of whether HF is the same disease process across the spectrum of age ranges and precipitating causes ***(Sibetcheu et al., 2018)***.
In addition, it suggests that there may be the potential for risk stratification and customization of therapy. HF is a common morbidity identified in the adult CHD population, an age range complicated by additional factors and not covered in many pediatric studies. HF is known to occur in ≈25% of adult CHD patients by the age of 30, and the incidence increases with age ***(Jin et al., 2021).***
Tracking the natural history of specific CHD types or specific genetic causes and comparing the similarities and differences of HF in children and adults, promises to provide insight into the risk of HF at the time of diagnosis in childhood. Taken together, these data indicate that HF is an important cause of morbidity and mortality in pediatric and adult CHD, and HF in this population is heterogeneous with regard to underlying cause and outcome ***(Jin et al., 2021)***.
The issues emerging in the management of the growing adult CHD mutations in developmental signaling pathways long known to be associated with CHD such as the Notch pathway and noncanonical WNT signaling also cause LVNC in animal models and humans. Given the developmental importance of these signaling pathways for cardiogenesis, future research investigating the shared developmental mechanisms leading to both CHD and cardiomyopathy from disruption in these pathways will likely be informative ***(Chen et al., 2013).***

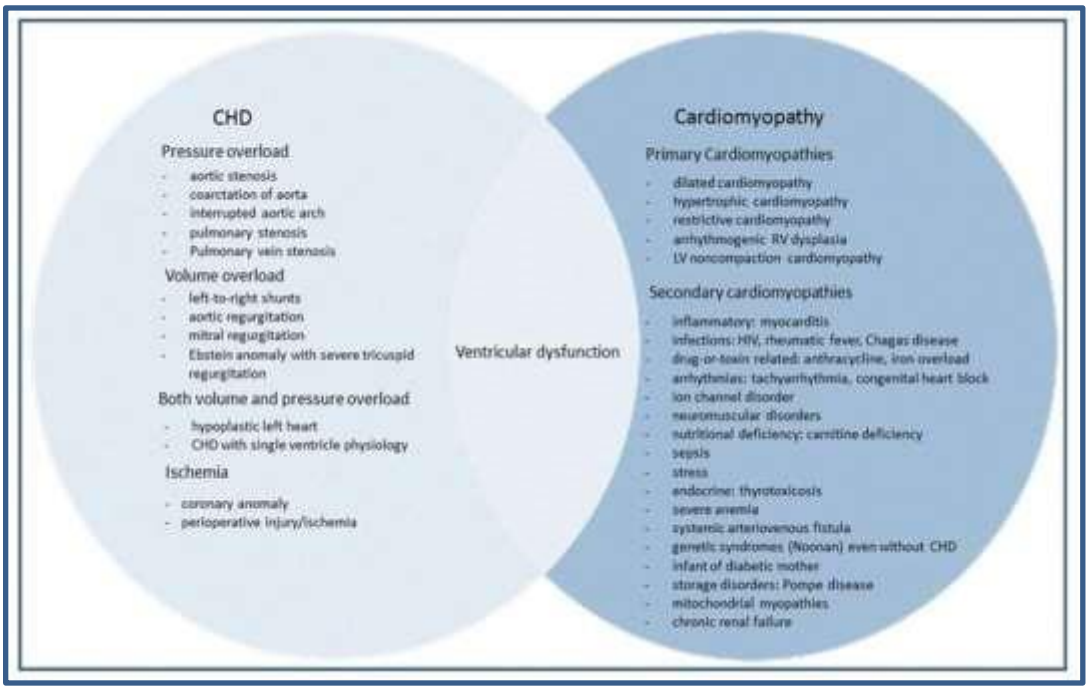


Fig. (5): Common causes of heart failure in children ***(Hinton et al., 2017).***

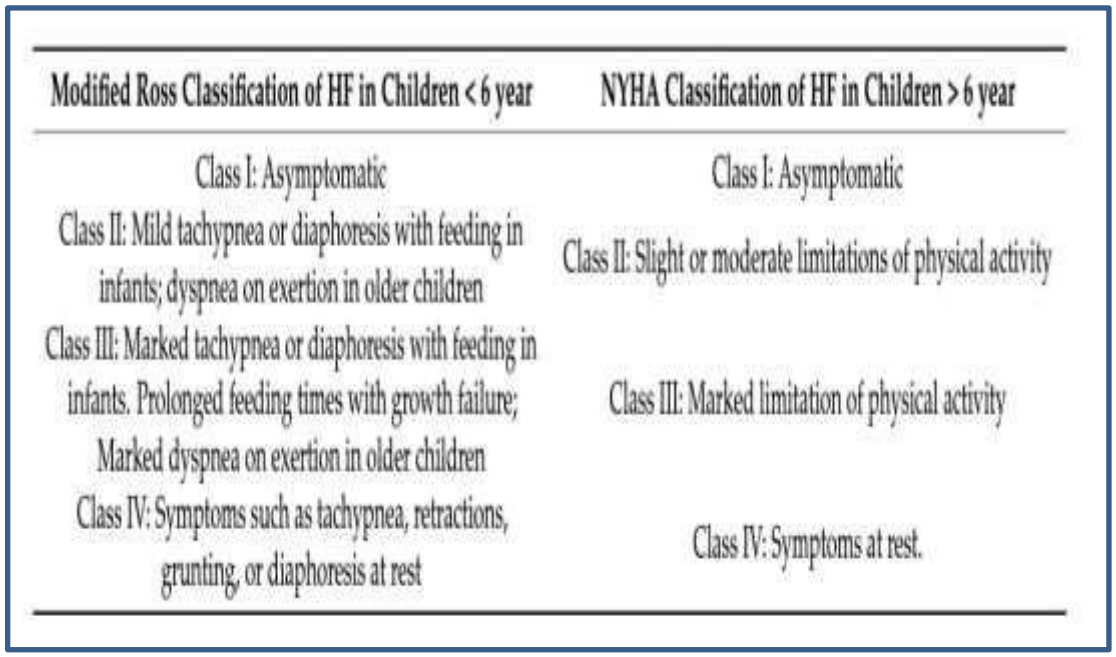
Clinical picture of PHF:

The clinical picture of HF is directly related to age. In general, the symptoms of HF depend upon whether there is congestion due to chronic right HF or hypo-perfusion due to acute left HF. Signs and symptoms of chronic right HF include elevated jugular venous pressure, pleural effusion, ascites, pedal edema, abdominal discomfort, and hepatomegaly. Signs and symptoms of acute left HF include dyspnea, orthopnea, rales on auscultation due to pulmonary edema, dizziness, fatigability, nausea, vomiting, abdominal pain, and feeding intolerance ***(Kantor et al., 2013).***

When right HF is acute it can present with hypo-perfusion, tachycardia, and hypotension. Similarly, when left HF is chronic it can present with signs and symptoms of chronic congestion. Right HF associated with left HF and is a predictor of increased morbidity and mortality. The well-known New York Heart Association (NYHA) HF classification does not apply to young children on a practical level and is thought to lack the sensitivity needed to assess and capture the progression of HF severity in children ***(Kantor et al., 2013)***.

For this reason, the modified Ross HF classification is used for the assessment of children younger than six years with HF. If a patient presents with symptoms of HF, further classification into perfusion (warm vs. cold) and congestion (filling pressure) status (dry vs. wet) provides a current clinical context with the ultimate goal being warm and dry (well perfused with normal filling pressure) ***(Ross et al., 2012)***

Recently, an analysis from the Pediatric Heart Transplant Society database described that (I) congestion is more common than low cardiac output/hypoperfusion in children with end-stage HF and correlates with NYHA/Ross classification and end-organ dysfunction; (II) the severity of HF symptoms based on NYHA/Ross classification correlates best with elevations in pulmonary capillary wedge pressure (defined as >15 mmHg); (III) end-organ function correlates best with elevation in right atrial pressure; and (IV) death or deterioration while waiting for heart transplant is highest among children with both congestion and low cardiac output ***(Chen et al., 2017)***.



Modified Ross Classification of HF in Children < 6 year	NYHA Classification of HF in Children > 6 year
Class I: Asymptomatic	Class I: Asymptomatic
Class II: Mild tachypnea or diaphoresis with feeding in infants; dyspnea on exertion in older children	Class II: Slight or moderate limitations of physical activity
Class III: Marked tachypnea or diaphoresis with feeding in infants. Prolonged feeding times with growth failure; Marked dyspnea on exertion in older children	Class III: Marked limitation of physical activity
Class IV: Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest	Class IV: Symptoms at rest.

Fig. (6): NYHA and modified Ross classification of heart failure in children ***(Ross et al., 2012)***

It is also suggested that there is a primary role of congestion in the pathophysiology of end-organ dysfunction occurring in the setting of chronic left HF. Children with both congestion and hypoperfusion (wet/cold) have the highest risk of death or clinical deterioration ***(Chen et al., 2017)***.

Management of PHF:

General treatment:

In infants, in addition to rest, the nutritional support must ensure a caloric intake about of 150 kcal/kg/d. This is achieved using dietary supplements, preferring small and frequent meals that are better tolerated. In children and adolescents, current recommendations suggest that 25–30 kcal/kg/d is a reasonable target for most patients ***(Masarone et al., 2017).*** Carbohydrates should not exceed 6 g/kg/d and lipids should not exceed 2.5 g/kg/d. The provision of essential amino acids is necessary in the critically ill. Evidence suggests that 1.2–1.5 g/kg/d of protein is needed. Nutritional supplementation is required in HF secondary to metabolic and mitochondrial diseases (such as carnitine and ubiquinone) ***(Tang et al., 2019).***

In acyanotic CHD patients or in patients with cardiomyopathies, ventilatory support with oxygen must be initiated when SaO2 < 90%. On the contrary, in patients with cyanotic CHD, oxygen has little effect in raising SaO2 and is not indicated. However, in some cases with chronic left to right shunting, irreversible pulmonary vascular disease can develop and cause right to left shunting (Eisenmenger syndrome) ***(Tang et al., 2019).***

In the early stages, the resulting pulmonary hypertension may be responsive to oxygen; hence, this is indicated while the child is waiting for cardiac transplantation or for palliation surgery. Rest and reduction of salt intake are recommended in all patients with edemas and fluid retention. Restriction of fluids is indicated in patients with edemas unresponsive to diuretic therapy or hyponatremia ***(Masarone et al., 2017)***.

Medical Therapy:

The goals of acute HF management in children are to improve hemodynamics and prevent progression. Current management includes stabilization with intravenous inotropes/vasopressors, mechanical ventilation, treatment of arrhythmia, and progression to mechanical support, if needed. Should some recovery occur, the child is often left with chronic HF and the lingering diagnosis of dilated cardiomyopathy, with or without a genetically based or syndrome/systemic disease-based diagnosis ***(Rossano et al., 2014).***

The goal of clinical management of chronic HF in children is to maintain stability, prevent progression, and provide a reasonable milieu to allow somatic growth and optimal development. Despite the lack of sufficient randomized prospective studies, angiotensin-converting enzyme inhibitors (ACEi) are first-line, and β-receptor antagonists are second-line therapies in children. Following the adult guidelines, and without having data pertaining to the pediatric population, mineralocorticoids are also accepted in the treatment of pediatric HF, while diuretics should only be used to achieve a euvolemic status ***(Rossano et al., 2014).***

Current treatment for chronic HF includes some combination of ACEi (level of evidence B), β-blockers (level of evidence B), diuretics (level of evidence C), aldosterone antagonists (level of evidence C), and digoxin (level of evidence C). Diuretics are used to treat fluid retention associated with ventricular dysfunction, ACEi decrease afterload by antagonizing the renin-angiotensin aldosterone system, β-blockers antagonize the deleterious effects of chronic sympathetic myocardial activation and can reverse LV remodeling and, additionally, carvedilol has vasodilatory properties due to its additional α-blocking action, while ACEi and β-blockers can slow disease progression and prolong survival, titration and tolerability often present challenges ***(Kirk et al., 2014).***

Diuretics:

Diuretics therapy plays a crucial role in the treatment of pediatric patients with HF. The benefits of diuretic therapy include reduction of systemic, pulmonary, and venous congestion. Spironolactone may exert additional beneficial effects by attenuating the development of aldosterone-induced myocardial fibrosis and catecholamine release ***(Masarone et al., 2017)***.

Potential complications of diuretic therapy include electrolyte abnormalities (hyponatremia, hypo- or hyperkaliemia, and hypochloremia) and metabolic alkalosis. Electrolyte balance should be carefully monitored, especially during aggressive diuretic therapy, as the failing myocardium is more sensitive to arrhythmias induced by electrolyte imbalance ***(Masarone et al., 2017)***.

ACE inhibitors:

ACE inhibitors prevent, attenuate, or possibly reverse the pathophysiological myocardial remodeling. In addition, they decrease afterload by antagonizing the rennin–angiotensin aldosterone system ***(Kirk et al., 2014)***.

According to recent guidelines of The International Society of Heart and Lung Transplantation on the management of pediatric HF, ACE inhibitors are recommended in all patients with HF and left ventricular systolic dysfunction. Therapy with ACE inhibitors should be started at low doses with a subsequent up-titration to the target dose with careful monitoring of blood pressure, renal function, and serum potassium ***(Kirk et al., 2014)***.

β blockers: β blockers are now an accepted therapy in the pediatric population. β blockers antagonize the deleterious effects of chronic sympathetic myocardial activation and can reverse left ventricular remodeling and improve systolic function. Recent reports seem to show that the addition of β blockers to the standard therapy may be useful in patients with left ventricular systolic dysfunction ***(Schranz et al., 2019)***.

In addition, a recent Cochrane Database of Systematic Reviews on β blockers for children with congestive HF was published. Seven studies with a total of 420 children were included in the review and the authors conclude that the current available data suggest that children with HF might benefit from β-blocker treatment. Low-dose therapy should be started in stable patients with a progressive up-titration to the target dose ***(Singh et al., 2019)***.

Inotropes:

Digoxin is the main oral inotropic drug used in PHF and is indicated in symptomatic patients with left and/or right ventricular systolic dysfunction. The use of intravenous inotropes should be reserved for patients with a severe reduction of cardiac output resulting in compromised vital organ perfusion (hypotensive acute/decompensated HF) ***(Schranz et al., 2019)***.

Although increased inotropy results in improved cardiac output and blood pressure, the final result is increased myocardial oxygen consumption and demand. The failing myocardium has a limited contractile reserve and hemodynamic collapse can occur with high-dose inotropic support in this setting ***(Schranz et al., 2019)***.

Sympathomimetic amines:

Dopamine and dobutamine have been shown to be effective inotropes and vasopressors in neonates, infants, and children with circulatory failure. These drugs increase cardiac output and decrease systemic and pulmonary vascular resistance; however, they can induce tachycardia/tachyarrhythmia with a mismatch between myocardial oxygen delivery and the requirement. Therefore, we reserve the use of these drugs only for patients with low cardiac output despite other therapies ***(Singh et al., 2019).***

Phosphodiesterase type III inhibitors:

This class of drugs incorporates amrinone, enoximone, milrinone, and olprinone, of which milrinone, the strongest and shortest acting with the best control, is the most commonly used in pediatric intensive care ***(Kirk et al., 2014)***. Phosphodiesterase type III inhibitors have vasodilatory and inotropic actions and improve diastolic ventricular relaxation. Despite the pro-arrhythmic effects of milrinone, it represents the first choice of therapy in patients with moderate/severe ventricular dysfunction with hypoperfusion symptoms ***(Masarone et al., 2017)***.

Calcium sensitizer:

Levosimendan exerts strong inotropic and vasodilating effects, possibly stronger than dobutamine, with less potential for myocardial ischemia. The absence of pro-arrhythmic effects and the ability to reverse the effects of β blockade make levosimendan a potential drug of choice in the context of postoperative low-cardiac output syndrome rather than in acute HF in children ***(Singh et al., 2019)***.

Vasodilators:

Vasodilators administered intravenously (nitroglycerin and nitroprusside) or orally (hydralazine and nifedipine) are indicated only in cases of hypertensive acute HF refractory to treatment (β blockers and ACE inhibitors) or severe valve regurgitations in patients intolerant to ACE inhibitors ***(Masarone et al., 2017)***.

References

Anderson, B. R., Dragan, K., Glied, S., Woo, J., LaPar, D., and Billings, J. (2019): Building capacity to assess longitudinal outcomes and health expenditures for children with congenital heart disease. Journal of the American College of Cardiology, 73(9S1), 649-649.

Burstein, D. S., Shamszad, P., Dai, D., Almond, C. S., Price, J. F., Lin, K. Y., and Rossano, J. W. (2019): Significant mortality, morbidity and resource utilization associated with advanced heart failure in congenital heart disease in children and young adults. American heart journal, 209, 919.

Cantù, C., Felker, A., Zimmerli, D., Prummel, K. D., Cabello, E. M., Chiavacci, E., and Mosimann, C. (2018): Mutations in Bcl9 and Pygo genes cause congenital heart defects by tissuespecific perturbation of Wnt/β-catenin signaling. Genes and development, 32(21-22), 1443-1458.

Chen, H., Zhang, W., Sun, X., Yoshimoto, M., Chen, Z., Zhu, W., and Shou, W. (2013): Fkbp1a controls ventricular myocardium trabeculation and compaction by regulating endocardial Notch1 activity. Development, 140(9), 1946-1957.

Chen, S., Dykes, J. C., McElhinney, D. B., Gajarski, R. J., Shin, A. Y., Hollander, S. A., and Almond, C. S. (2017): Haemodynamic profiles of children with end-stage heart failure. European heart journal, 38(38), 2900-2909.

Choices, N. H. S. (2014): Ingrown toenail.

Crespo-Leiro, M. G., Metra, M., Lund, L. H., Milicic, D., Costanzo, M. R., Filippatos, G., and Ruschitzka, F. (2018): Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. European journal of heart failure, 20(11), 1505-.1535

Gohar, A., Rutten, F. H., den Ruijter, H., Kelder, J. C., von Haehling, S., Anker, S. D., and Hoes, A. W. (2019): Mid-regional pro-atrial natriuretic peptide for the early detection of non-acute heart failure. European journal of heart failure, 21(10), 1219-1227.

Guazzi, M., Naeije, R., Arena, R., Corrà, U., Ghio, S., Forfia, P., and Temporelli, P. (2015): Echocardiography of right ventriculoarterial coupling combined with cardiopulmonary exercise testing to predict outcome in heart failure. Chest, 148(1), 226-234.

Heidenreich, P. A., Albert, N. M., Allen, L. A., Bluemke, D. A., Butler, J., Fonarow, G. C., and Trogdon, J. G. (2017): Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circulation: Heart Failure, 6(3), 606-619.

Hinton, R. B., and Ware, S. M. (2017): Heart failure in pediatric patients with congenital heart disease. Circulation research, 120(6), 978-994.

Howards, P. P., Johnson, C. Y., Honein, M. A., and Flanders, W. D. (2015): Adjusting for bias due to incomplete case ascertainment in case-control studies of birth defects. American journal of epidemiology, 181(8), 595-607.

Jin, X., Ni, W., Wang, G., Wu, Q., Zhang, J., Li, G., and Xing, Q. (2021): Incidence and risk factors of congenital heart disease in Qingdao: a prospective cohort study. BMC public health, 21(1), 1-10.

Kantor, P. F., et al., (2013): Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. Canadian journal of Cardiology, 29(12), 1535-1552.

Kirk, R., Dipchand, A. I., Rosenthal, D. N., Addonizio, L., Burch, M., Chrisant, M., and Weintraub, R. (2014): The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary. The Journal of Heart and Lung Transplantation, 33(9), 888-909.

Masarone, D., Valente, F., Rubino, M., Vastarella, R., Gravino, R., Rea, A., and Limongelli, G. (2017): Pediatric heart failure: a practical guide to diagnosis and management. Pediatrics and Neonatology, 58(4), 303-312.

Packer, M. (2018): Acute heart failure is an event rather than a disease: plea for a radical change in thinking and in therapeutic drug development. JACC: Heart Failure, 6(1), 73-75.

Poterucha, T. J., Kochav, J., O'Connor, D. S., and Rosner, G. F. (2019): Cardiac tumors; clinical presentation, diagnosis, and management. Current treatment options in oncology, 20, 1-15.

Razmara, E., and Garshasbi, M. (2018): Whole-exome sequencing identifies R1279X of MYH6 gene to be associated with congenital heart disease. BMC cardiovascular disorders, 18(1), 1-7.

Robinson, J. A., Driscoll, D. J., O'Leary, P. W., Burkhart, H. M., Dearani, J. A., Daly, R. C., and Johnson, J. N. (2014): Cardiac and multiorgan transplantation for end-stage congenital heart disease. In Mayo Clinic Proceedings (Vol. 89, No. 4, pp. 478-483). Elsevier.

Ross, R. D. (2012): The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. Pediatric cardiology, 33(8), 1295-1300.

Rossano, J. W., and Shaddy, R. E. (2014): Heart failure in children: etiology and treatment. The Journal of pediatrics, 165(2), 228-233.

Sadeghpour, A., and Hashemi, A. (2014): Chest radiography in congenital heart disease. In Comprehensive Approach to Adult Congenital Heart Disease (pp. 57-64). Springer, London.

Schranz, D. (2019): Pharmacological Heart Failure Therapy in Children: Focus on Inotropic Support. In Pediatric Pharmacotherapy (pp. 177-192). Springer, Cham.

Sharon, V. C., and Priya, V. V. (2017): Awareness of Congenital Cardiac Anomalies in South Indian Population-A Questionnaire Based Study. Journal of Pharmaceutical Sciences and Research, 9(2), 85.

Sibetcheu, A. T., Agbor, V. N., Nyaga, U. F., Bigna, J. J., and Noubiap, J. J. (2018): Epidemiology of heart failure in pediatric populations in low-and middle-income countries: a protocol for a systematic review. Systematic reviews, 7(1), 1-6.

Singh, R. K., and Singh, T. P. (2019): Heart failure in children: management. UpToDate, Waltham, MA. Accessed December, 11.

Spinner, N. B., Leonard, L. D., and Krantz, I. D. (2013): Alagille syndrome.

Sun, R., Liu, M., Lu, L., Zheng, Y., and Zhang, P. (2015): Congenital heart disease: causes, diagnosis, symptoms, and treatments. Cell biochemistry and biophysics, 72(3), 857-860.

Tang, W. W., Li, D. Y., and Hazen, S. L. (2019): Dietary metabolism, the gut microbiome, and heart failure. Nature Reviews Cardiology, 16(3), 137-154.

Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., and Dicker, D. (2015): Global Burden of Disease Study 2013 Collaborators Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet, 386(9995), 743-800.

Yuan, S. M. (2017): Ebstein's anomaly: genetics, clinical manifestations, and management. Pediatrics and Neonatology, 58(3), 211-215.

Zhang, S., Wang, L., Yang, T., Chen, L., Zhao, L., Wang, T., and Qin, J. (2020): Parental alcohol consumption and the risk of congenital heart diseases in offspring: An updated systematic review and meta-analysis. European journal of preventive cardiology, 27(4), 410-421.