# Update on pediatric heart failure

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**Purpose of review**
This review highlights recent advances in the diagnosis and management of children with heart failure. We emphasize the clinical approach to patient care in the areas of acute decompensated heart failure, chronic heart failure, and failure of the patient with single ventricle physiology.

**Recent findings**
Important guidelines regarding the recognition and management of heart failure in children have been proposed and adopted, providing guidance for early recognition and ongoing management. Early diuresis, and avoidance of excessive inotropic agent use, in favor of milrinone as an inotropic-vasodilator agent, are emphasized. Close monitoring of airway pressures to improve ventricular filling, and extubation to positive pressure or high-flow nasal cannula therapy are also important. Chronic heart failure therapy requires combination treatment with diuretics, and the three major classes of drugs. Management of the failing Fontan requires attention to the hepatic, pulmonary and lymphatic circulations.

**Summary**
Improved outcomes in children with heart failure are possible. Inherent in this success is the engagement of an interdisciplinary team-based approach to care, with early recognition and escalation of care for specific patients who are not improving as predicted.

**Keywords**
angiotensin-converting enzyme, congestive heart failure, Fontan, inotropic agents, pediatric

## INTRODUCTION

Pediatric acute heart failure may result from a variety of structural or functional alterations of the heart, because of congenital or acquired diseases. Surgical palliation of structural congenital heart disease (CHD) has been enormously successful in recent decades, but has delayed, rather than removed the occurrence of heart failure in this group of patients [1]. Myocardial abnormalities may result in heart failure presenting in infancy, because of syndromic or sarcomeric gene abnormalities [2]. In infancy and childhood, acquired inflammatory diseases, such as myocarditis may cause acute heart failure, and later on, prior exposure to chemotherapeutic agents may present with heart failure. In this review, we will provide an update on the approach to clinical management of both acute, and chronic heart failure, as well as heart failure in patients with single ventricle physiology.

## ACUTE HEART FAILURE IN THE CRITICAL CARE SETTING

The management of acute heart failure stems from understanding the pathophysiology and hemodynamic profile of the patient prior to selecting the appropriate medication treatment intervention. It is vital when approaching a patient with heart failure, to determine whether the primary problem is that of abnormal preload (typically volume overload), ventricular dysfunction, or abnormal afterload (systemic vascular resistance, SVR) [3]. Often, patients with advanced heart failure, have disturbances of all three of these are and each of them will need to be addressed in sequence.

## ABNORMAL PRELOAD

Venous congestion, and total body fluid are increased in heart failure syndrome at any age, and must be addressed promptly and effectively with medical therapy. Although over 90% of children with acute decompensated heart failure are

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**Curr Opin Pediatr** 2019, 31:598–603
DOI:10.1097/MOP.0000000000000807

## KEY POINTS

- The survival of children with heart failure depends on early recognition, and aggressive early management in an intensive care setting.
- Guidelines are available for chronic heart failure care in children.
- Palliated congenital heart disease and the Fontan circulation in particular are subject to chronic deterioration in several ways.

prescribed diuretics, it may be delayed in infants and young children, in whom vomiting is common, and acute weight loss may be present [4,5]. Recent guidelines have emphasized the need to establish whether a patient has, or does not have evidence of both volume overload and arterial underperfusion [6]. The presence of cardiomegaly, hepatomegaly, tachypnea and a gallop rhythm are all consistent with volume overload, and loop diuretics are essential first-line therapy in this situation [7▪▪]. Fluid weight loss, and a decrease in B-type natriuretic peptide (BNP) levels may occur more quickly with continuous infusion therapy, but this may not alter length of hospitalization or outcome as reported in a recent meta-analysis [8▪]. Diuretic resistance may occur in children, and requires an additive approach using combination diuretic therapy, typically with a loop diuretic and a thiazide diuretic [9▪].

## VENTRICULAR DYSFUNCTION

Although diuresis is in progress, a clinical assessment of cardiac output (CO) must occur. In order to generate a higher stroke volume, it is often necessary to improve myocardial contractility. Catecholamine analogues are the primary inotropic agents used to generate this effect. Historically, the most commonly used agents have been dopamine and dobutamine, which are indirect beta-1 and beta-2 receptor agonists: whereas these will increase myocardial shortening, and therefore, stroke volume and CO [5]. However, they also increase heart rate and myocardial oxygen consumption, which is disadvantageous [10▪▪]. Moreover, dopamine, which has an alpha agonist effect will also increase pulmonary capillary wedge pressure (PCWP), at higher doses (>5 μg/kg/min), and many institutions now favor initiation of epinephrine over dopamine for acute heart failure management.

Epinephrine has the benefit of a range of effects at different doses. Lower doses (<0.05 to 0.1 μg/kg/min) reduce SVR through beta-2 stimulation. Doses higher than 0.1 μg//kg/min result in an increase in SVR. The beta-1 agonist effect of epinephrine is present throughout all dose ranges and serves to better augment myocardial contractility than dopamine or dobutamine [11,12▪]. Caution must be taken with the use of any inotropic agent during the management of a patient in acute heart failure, as the myocardium can be prone to arrhythmias, and each of these proarrhythmic agents must be carefully titrated to effect [12▪]. Although inotropes are a useful tool in the short-term management of acute heart failure, chronic administration is associated with higher mortality in adult heart failure patients, and will also decrease adrenoreceptor responsiveness over time. Alternatives, such as mechanical circulatory support should be considered if the clinical condition has not improved after short-term therapy, and patients are not able to tolerate transition to oral therapy.

Levosimendan is a calcium-sensitizing agent developed as an inotropic therapy, which has been in use in many European countries, but is not approved by the Food and Drug Administration for use in the United States. A recent Swiss study evaluated the effects of levosimendan as a rescue therapy in postoperative pediatric cardiac patients in a low CO state within the first 48 h of cardiopulmonary bypass, and found it stabilized and improved CO parameters including lactate, mixed venous oxygen saturation and diuresis, while decreasing the vasoactive inotrope score and possibly mitigating the need for mechanical cardiac support [13].

## AFTERLOAD REDUCTION

Over the last few decades, milrinone has come into favor as a replacement for dobutamine [5]. As a phosphodiesterase III inhibitor, it results in an increase in myocardial contractility while also decreasing pulmonary and systemic vascular resistance, with a greater reduction in PCWP than dobutamine, an added benefit in acute heart failure [14]. Also, because of its mechanism of action, milrinone is not affected by adrenergic receptor downregulation.

For patients in acute heart failure and a significant volume load on the heart because of mitral valve regurgitation, either nitroprusside or nitroglycerin have been found to significantly improve stroke volume and CO with a decrease in PCWP, without increasing myocardial oxygen demand and consumption [10▪▪]. Care must be taken to ensure that an adequate ventricular filling pressure is maintained for appropriate stroke volume and CO: therefore, the vasodilators may be useful in conjunction with an inotropic agent, such as epinephrine.

## VASOPRESSOR DRUGS

Medications that increase afterload, such as norepinephrine and vasopressin, increase the workload of the heart and decrease cardiac output. Because of this, they have limited use in acute heart failure and are better suited to specific patient populations, such as those in warm septic shock, where there is a physiologic combination of high cardiac output and systemic vasoplegia. Neither is used as a first line therapy for heart failure, but rather as an adjunctive medication to help wean patients from other inotropic agents [15].

## DIASTOLIC HEART FAILURE

Diastolic heart failure in children results from primary cardiomyopathies (hypertrophic and restrictive), chronic ventricular pressure overload, and as a result of the preload limitation of Fontan physiology. None of these will benefit directly from inotropic therapy. Milrinone, which has a lusitropic effect, may improve diastolic filling time. Care must be taken to find a balance in ventricular preload and afterload, to avoid left venricular (LV) outflow tract obstruction. Beta blockers are useful for heart rate control in diastolic heart failure, but are better suited to introduction after the patient has been stabilized, and is euvolemic.

## VENTILATORY SUPPORT

An important goal in the early management of acute heart failure is to reduce LV afterload. Positive pressure ventilation, and in particular, an increase in end-expiratory pressure (PEEP), has been demonstrated to improve CO. This is likely achieved by a decrease in LV transmural pressure, and therefore, a reduction in ventricular wall stress during systole. An additional benefit is a reduction in left ventricular afterload, which also occurs. However, care must be taken to ensure adequate right ventricular (RV) filling during positive pressure ventilation, as excessive PEEP may compromise this, by reducing systemic venous return [16,17▪]. Maintaining a tidal volume range of 6–10 ml/kg and increasing expiration time will usually prevent lung overdistention and improve ventricular filling.

Once extubated, high-flow nasal cannula at 2 l/kg/minute of flow, or nasal/mask bilevel-positive airway pressure can ameliorate the immediate increase in LV afterload. Reduction of pulmonary vascular resistance using inhaled nitric oxide, oxygen therapy, and maintaining alkalosis through increased minute ventilation are also important to bridge patients to spontaneous ventilation.

## MECHANICAL CIRCULATORY SUPPORT

When conventional therapies for acute heart failure are not successful, other methods of supporting the myocardium should be considered, including extracorporeal membrane oxygenation or a left ventricular assist device. The latter, in particular has become a vital part of managing advanced heart failure in children over the last decade, and is dealt with in detail elsewhere [18].

## CHRONIC BIVENTRICULAR HEART FAILURE

Chronic heart failure with reduced ejection fraction (HFrEF) in children is most commonly because of a cardiomyopathy, usually involving the LV, occasionally both ventricles. Although the evidence-base for the management of LV HFrEF in children is not well developed, it is much better developed than the evidence-base for the management of HFrEF in patients with a systemic right ventricle, or single ventricle physiology. The most recent pediatric heart failure societal guidelines, one from Canada and one International, have made recommendations for the management of heart failure in children [6,19▪]. Both guidelines, emphasize the use of diuretics for fluid overload, and furosemide is the diuretic whose dosing and effects are most clearly delineated in children and most frequently used. Other recommendations include introducing angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (in those intolerant to ACE inhibitors), in addition to beta-blockers and mineralocorticoid receptor antagonists in children with systemic LV HFrEF. One should also consider ACE inhibitors and/or beta blockers in asymptomatic children with LV dysfunction. In chronic heart failure, many care providers institute ACE inhibitors first, and beta blockers next, although the order of initiation is probably less important than using combined therapy. There are many ACE inhibitors available for use in pediatric heart failure; commonly used ACE inhibitors include, captopril, enalapril, and lisinopril. Dosing and timing of uptitration is provider-specific and generally well tolerated [20]. Three beta-blockers have been approved for use in heart failure in adults: metoprolol, carvedilol, and bisoprolol. Metoprolol and carvedilol have been most commonly reported in the management of asymptomatic and symptomatic LV dysfunction in children. Two mineralocorticoid receptor antagonists are used in children: spironolactone and eplerenone. There is extensive experience with spironolactone in children, mainly with regard to its use as a potassium-sparing diuretic. Its

safety is well established. Eplerenone is less well characterized in pediatrics, but provides the additional benefit of avoiding possible gynaecomastia, a troublesome side effect, occasionally seen in male patients taking spironolactone. Recommended dosing of all of these medications is widely available for children.

The indication for digoxin in HFrEF is more controversial. In adults, it is currently a Class IIa indication for reducing hospitalization in adults with HFrEF [21]. The optimal indications for, and dosing of digoxin in children with HFrEF are not well defined. Similarly, the optimal timing, type and dosing of anticoagulation in HFrEF in children is generally institution-specific. No guidelines have been proposed to date.

Up until recently, all medications that were proven to be effective for the treatment of HFrEF in adults came from inhibition of the renin–angiotensin–aldosterone pathway. Two new drugs that have effects independent of this pathway have been shown to be effective in improving outcomes in HFrEF. Ivabridine, which inhibits the intracellular portion of the $I_f$ (or funny current) receptor of the sinoatrial node and slows heart rate by slowing diastolic depolarization is now available for adults: in the landmark SHIFT trial, ivabradine showed a significant reduction whenever compared with placebo, in the primary composite endpoint of cardiovascular death or hospital admission for worsening heart failure in adults with HFrEF [22]. Subsequently, a multicentre randomized controlled trial comparing ivabradine to placebo in children with dilated cardiomyopathy and stable HFrEF was completed. In this study, ivabradine safely lowered heart rate in children with heart failure [23▪]. In addition, an improvement in LV ejection fraction (LVEF) of 13.5 ejection fraction units was demonstrated in patients who received ivabradine compared with placebo (6.9 ejection fraction units), which was statistically significant.

Another new first-in-class medication, sacubritil/valsartan, combines a neprilysin inhibitor, sacubritil, with an angiotensin receptor blocker, valsartan. Sacubritil has multiple effects throughout many organs in the body, with its primary cardiovascular effect being to inhibit neprilysin, an enzyme that breaks down natriuretic peptides. In the PARADIGM-HF trial, over 8000 adults with HFrEF were randomized to either sacubritil/valsartan or enalapril over a 5-year period [24]. In those patients who received sacubritil/valsartan, there was a significant improvement in the primary endpoint of death from cardiovascular causes or hospitalization for heart failure when compared with enalapril. On the basis of this, a pediatric multicenter randomized trial is currently being conducted comparing sacubritil/valsartan to enalapril in children with LV HFrEF [25]. An important aspect of chronic heart failure therapy is the improvement of nutrition, attendance to medication compliance and frequent follow-up, all of which are best accomplished by an interdisciplinary outpatient clinic [26].

## THE FAILING FONTAN CIRCULATION

Heart failure in palliated congenital heart disease presents distinct challenges for the practitioner, and in the single ventricle patient with a Fontan circulation, these challenges are unique. The principal of Fontan's and Kreutzer's palliative operation was established in the early 1970s in young adult patients who had survived neonatal tricuspid atresia with chronic cyanosis, and was always recognized to be a palliation [27,28▪]. Over time, and because of improved fetal detection, improved operative staging and better surgical results for these infants and toddlers, survival has improved [29–31]. The consequence has been a dramatic rise in adolescents and young adults with Fontan physiology, but not without the accompanying problems that characterize failure of this circulation: these are mainly the venous hypertension of the porto-caval vascular bed, the loss of pulsatile flow to the pulmonary vascular bed, and acquired lymphatic dysfunction. Together these are co-conspirators in the development of Fontan failure, which should be considered a failure of this modified venous circulation, rather than of ventricular pump function (although the two may occur simultaneously) [32].

The problem of venous hypertension has been recognized to result in fibrosis of the liver in experimental models, and is considered likely in most if not all Fontan patients [33]. When fibrosis progresses, central-to-central vein or central-to-portal vein bridging occurs, with eventual progression to cirrhosis being possible. Improved monitoring and surveillance programs are now being established in concert with hepatologists, which have resulted in consensus for the assessment and management of Fontan-associated liver disease [34].

Improvement of the lung circulation might well be achieved by the use of pulmonary vasodilators. This is based on the observation that the pulmonary vascular resistance of many Fontan patients is elevated into a supra-physiologic range for the non-pulsatile flow. Initial reports of improvement in hypoxemia, and exercise duration with sildenafil have led to a randomized controlled trial of udenafil in Fontan recipients, which is nearing completion, and should report results in 2020 [35–37].

Finally, lymphatic disruption and dysfunction has now been recognized as a universal phenomenon in Fontan patients. It is occasionally severe enough to result in overt leakage of chyle into the pleural, bronchial, peritoneal or intestinal cavities, resulting in plastic bronchitis (where exudative cast formation obstructs the large and medium sized airways), chylous effusions, or debilitating protein losing enteropathy (PLE) with malnutrition, immune deficiency and ultimately, death [38]. The problem of PLE has been loosely defined in Fontan patients as a state of hypoalbuminemia (<3 g/dl) in the absence of synthetic hepatic dysfunction, together with evidence of increased intestinal protein loss (typically fecal alpha 1 antitrypsin levels are measured). Current thinking emphasizes the hypothesis that lymphatic rupture into focal areas of the small intestine is the most likely direct cause, and this has been nicely reviewed by Levitt and Levitt [39▪▪]. Previously it was felt that this condition was a direct indication for cardiac transplantation, as it carried a 50% mortality in a multicenter study from some 20 years ago [40]. However, more recent reports suggest an improvement in survival in the current era, with patients benefiting from treatment with budesonide, spironolactone, sildenafil, fenestration creation, and occasionally Fontan revision [41,42]. MRI-directed lymphangiography, and coil occlusion of culprit lymphatic channels has shown dramatic benefit for some patients in this situation [43▪▪]. This, however, does not address the underlying cause of the problem. When these measures are unsuccessful, patients should be considered for cardiac transplantation. In the current era, improved survival of single ventricle patients undergoing cardiac transplantation is evident, but timely referral remains crucial [44].

## CONCLUSION

Pediatric heart failure encompasses a wide variety of causes. The presentation is frequently in an acute decompensated state, which requires aggressive stabilization, often including rescue therapy with inotropic support. Chronic heart failure therapy is becoming better established, although the formal evidence base for treatments remains sparse. Fontan physiology is associated with several problems, which can lead to failure of the circulation. Early recognition of patients who are unresponsive to usual therapy is vital. Future research should emphasize the establishment of long-term follow-up registries in which nested case–control or randomized controlled studies can be conducted.

### Acknowledgements

*None.*

### Financial support and sponsorship

*None.*

### Conflicts of interest

*R.E.S. has received honoraria, and acts as a scientific consultant for Novartis. P.F.K. has received honoraria, and acted in a scientific advisory capacity for Novartis.*

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