REVIEW

Clinical practice

Heart failure in children. Part I: clinical evaluation, diagnostic testing, and initial medical management

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Abstract Current evidence suggests that almost half of all children with cardiomyopathy and symptomatic heart failure will die or require a cardiac transplant within 5 years of diagnosis. The recognition, diagnostic assessment, and treatment of heart failure in children are therefore challenging undertakings, to say the least. It involves an assessment of cardiac appearance and function, adaptation of the child as a whole, and a diagnostic approach that evaluates many possible root causes. This review is intended to assist the practicing pediatrician and cardiologist by providing a framework for this diagnostic assessment and to give an overview of the treatment options available for children with heart failure. In this first part, we will focus on clinical evaluation, diagnostic testing, and initial medical management. In the second part of this series, the maintenance treatment and treatment options applicable when medical treatment is insufficient will be addressed.

Keywords Heart failure · Cardiomyopathy · Treatment · Children

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Introduction

Heart failure occurs in children as a consequence of congenital or acquired disorders, either systemic or involving only the cardiovascular system. Herein, we review an approach to the diagnosis and assessment of heart failure as a clinical syndrome in children. Acute-phase stabilization and medical treatment are discussed. Later, in part 2 of this series, we will review the maintenance treatment and intervention options for advanced heart failure, such as device therapy and heart transplantation. We will deal with heart failure arising both in infancy and in childhood due to either structural congenital or primarily cardiomyopathic disease.

Heart failure due to congenital structural heart disease typically presents early in life [3], resulting from abnormal cardiac chamber morphology, valvular function, or circulatory connections. Genetically determined diseases of the myocardium (cardiomyopathies, CM) may occasionally be apparent at birth but more frequently manifest later in infancy, childhood, or indeed during adult life. In CM, the basis for heart failure is usually reduced systolic function of the left ventricle (LV), although associated diastolic dysfunction is increasingly recognized as an important contributing factor in the pathophysiology of heart failure in children [38]. The function of the right ventricle (RV), previously overlooked, has also come under scrutiny, as a potential predictor of adverse outcome in patients with heart failure [13, 38].

Disorders affecting the myocardium are diverse and may arise from genetic abnormalities often involving sarcomeric and structural proteins or can be secondary to an acquired disease (like myocarditis) or toxic exposure (anthracycline toxicity). It is important to note that all known diagnoses

account for only around 35% of patients in most pediatric series [5, 11, 62] with the remainder being idiopathic.

Epidemiology

Congenital defects of the heart (CHD) have a population-based incidence which varies depending on inclusion criteria and mode of detection [10]. Moderate to severe CHD occurs in less than 0.6% of live births [24]. Heart failure associated with CHD occurs in approximately 20% of all patients. CM occur in only approximately eight per 100,000 infants [33] and even more infrequently in older children. Approximately 70% of cases of CHD are diagnosed in the first year of life [3], while the timing of the diagnosis of CM varies, with age-related peaks described [33].

The outcome of heart failure related to CHD has changed dramatically. In the "preinfant cardiac surgery" era, 20% of cardiac diagnoses in a tertiary-care setting develop clinical heart failure [26]. In that era, the annual crude mortality rate of symptomatic heart failure was in excess of 80% whereas overall mortality for surgically correctable lesions has now decreased to around 1–2%. The incidence of symptomatic heart failure has also declined, with Massin et al. [36] now reporting that only 10% of their patients in a tertiary-care pediatric cardiology care setting developed symptomatic heart failure. In the latter series, congenital anomalies still account for over 50% of the cases, and most patients (70%) are under 12 months of age at diagnosis, regardless of etiology. The outcome of children with CM however remains poor, with a 5-year risk for death or cardiac transplantation of around 50% for patients with dilated CM commonly cited [62]: there is likely an even greater hazard for those who present with symptomatic heart failure.

Clinical heart failure syndromes in children

John D. Keith wrote from this institution some 50 years ago [26] that heart failure was in essence "an inability of the heart to empty itself adequately, with the result that there is a high venous filling pressure and a decrease in the effective work done by the heart muscle." While this is a helpful (if cardiocentric) definition, we now understand that the problems of cardiac filling and emptying also reflect abnormalities of vascular function [50], systemic and metabolic responses [43], and abnormalities of other organs such as the kidney [54]. A simplistic alternative definition which captures the systemic nature of heart failure syndrome could be "the failure of cardiac function to maintain appropriate pulmonary and systemic circulation,

with resulting secondary consequences." This failure of cardiac function has a tendency to manifest with one of two common stereotypical syndromes in infants and children.

(a) Increased systolic output with pulmonary overcirculation

This syndrome is frequently (though not exclusively) seen in infants and young children, and therefore it is the manifestation most frequently recognized by general pediatricians. It occurs in various congenital lesions with increased pulmonary blood flow as a common denominator. In this setting, ventricular systolic function is typically preserved or even hyperdynamic with an increased LV chamber dimension. The most common causes are: a large ventricular septal defect [27] (typically greater than 4-mm size in infancy [40]), a moderate to large patent arterial duct (PDA) or persistent aortopulmonary connections as seen in an aortopulmonary window, or a common arterial trunk. Clinical features include hyperdynamic pulses, sweating, pallor, and, most importantly, tachypnea. Although pulmonary vascular congestion is common and rales may be noted, frank pulmonary edema is infrequent [40]. Auscultation is notable for a characteristic heart murmur and a gallop rhythm. Hepatomegaly is invariably present, and peripheral edema is invariably absent except in the terminal phase [40]. The typical age of presentation is between 2 weeks and 6 months, although some children are overlooked for some time, despite progressive growth failure and other signs and symptoms. In some cases, congestive heart failure is moderated by the presence of persistently elevated pulmonary vascular resistance. The timing of surgical intervention in infants with a shunt lesion should be determined by the balance of symptom severity and surgical feasibility. The presence of a pressure-restrictive shunt lesion may support a strategy of watchful waiting [28], even if left ventricular dilatation and remodeling is present.

(b) Low cardiac output

A frequent presentation in infancy is that of decreased systemic circulatory output. Pediatric patients usually present when cardiac output has declined beyond moderate impairment, with symptoms in part reflecting the underlying anatomic cause. If the problem is mechanical obstruction to aortic outflow (hypoplastic left heart, critical aortic stenosis, or severe coarctation of the aorta), the infant will present with decreased pulses, pallor, and frank circulatory collapse between 2 and 14 days of life [26]. Tachypnea is a frequent feature too, either due to excessive pulmonary blood flow, elevated pulmonary venous pressure, or hypoxemia with acidosis. This is distinguished from the lack of compensatory overventilation which is seen in patients with hypoxemia from birth due to cyanotic heart disease [7].

Primary or acquired diseases of the myocardium (such as dilated CM or acute myocarditis) can mimic some features of the above clinical appearance: however, the presence of a displaced or diffuse cardiac apex, a gallop rhythm, soft heart sounds, and a murmur of mitral regurgitation raises suspicion that a dilated hypocontractile LV, rather than a primarily obstructed outflow tract or aorta is the true underlying cause.

Commonly overlooked congenital lesions

Unfortunately, the absence of an obvious heart murmur does not exclude an important heart defect. When pulmonary arterial pressures are elevated, certain lesions become more occult. These include a persistent PDA and large ventricular septal defects which may escape clinical detection in early infancy. Coarctation of the aorta can progress during infancy and may result in precipitous heart failure when the PDA closes or progressive hypertension and LV dysfunction which are initially overlooked. Anomalous origin of the left coronary artery from the pulmonary artery or Bland–White–Garland syndrome most frequently presents between 2 and 6 months of age with a dilated LV, mitral regurgitation, and a fairly typical electrocardiographic pattern of an anterior infarct, with q waves in aVL [16]. Timely recognition of this well-described complex allows corrective reimplantation of the

Table 1 Common acquired disorders resulting in heart failure in infancy and childhood

	Etiology	Age Demographic	Clinical Features	Specific Therapy
Rheumatic heart disease.	Group A β hemolytic streptococcus.	School aged children	Fever, arthralgia, rash, systolic murmur.	Penicillin, ASA/corticosteroids Later surgical management of valvular disease, antibiotic prophylaxis.
Acute myocarditis.	Usually viral Coxackie B Adenovirus, Parvovirus B19 HHV others.	Any age, including intrauterine.	Acute cardiovascular collapse in some, indolent course in others. Chest pain, arrhythmias. Elevated troponin T.	Supportive therapy. corticosteroids and cyclosporine/azothioprine are controversial. IV IgG is controversial. Recent data to support Interferon β in specific etiologies.
Incessant supraventricular tachycardia.	Typically atrial ectopic tachycardia. Occasionally PJRT, Atrial flutter with AV block.	Early childhood to adolescence.	Fatigue, dyspnea, pallor. Tachycardia is disproportionate to symptoms.	Rate control with digoxin +/- amiodarone. Anticoagulation if thrombus is noted. RF ablation of ectopic focus.
Anti-neoplastic drugs.	daunorobicin, doxorubicin, rarely cyclophosphamide.	Usually manifesting in late childhood, to adolescence.	48 hrs. – 4 weeks post exposure, although acute severe response is rare. Individual variance to dosage exposure noted.	Preventive- dexrazoxane, chelating agents, mitochondrial stabilizing therapy are all unproven as yet.
Nutritional cardiomyopathy.	Feeding intolerance, caloric deficiency, eating disorders.	Infancy (unusual dietary preferences) or adolescence (eating disorders).	Evidence of protein or trace element deficiency, dermatitis, edema, pallor.	Careful graduated refeeding. Vitamin and trace element supplementation.

PJRT permanent junctional reciprocating tachycardia

Table 2 Commonly recognized disorders and mutations associated with cardiomyopathy and heart failure in childhood

Diagnosis	Typical features	Gene/Gene product	Inheritance (Gene locus)	Cardiac phenotype
A. Skeletal myopathy with cardiac involvement				
Becker MD. Duchenne MD.	Pre-adolescent males: myopathic with cardiac dysfunction noted later in adolescence. Female carriers rarely symptomatic.	Dystrophin	XR (Xq21)	DC
Barth syndrome.	Males, early childhood: Typical facies, short stature, skeletal myopathy, neutropaenia, low cholesterol, organic aciduria.	Taffazin	XR (Xq28)	DC LVNC EFE Also implicated in X-linked EFE, fatal infantile DC.
Emery Dreifuss MD.	Males with slowly developing humeroperoneal myopathy and contractures. Male or Female, similar features.	Emerin Lamin A/C	XR (Xq28) AD (1q11-23)	Sinus node dysfunction Atrial fibrillation/flutter AV block
Fascioscapulohumeral MD.	Facial, shoulder girdle involvement.	Tandem repeat deletions	AD (4q35)	Typically minor conduction system changes. Heart failure very rare.
Limb Girdle muscular dystrophies (several distinct types).	Proximal limb myopathy, other features. Clinically Genetically heterogeneous.	Lamin A/C (laminopathies have several other phenotypes) Abnormalities of dystrophin associated membrane protein complex.	AD (1q11-23) (several other alleles)	DC, variable severity. AV block or conduction system disease also seen.
Myotonic dystrophy. Type 1 Type 2	Myotonia, diffuse weakness, wasting. Similar, less severe phenotype.	CTG repeats on Serine-threonine kinase ZF9gene	AD (19q13.3) AD (3q21)	Conduction system problems (AV block, QTc prolongation) occasional DC Virtually any form of rhythm disturbance including VT.
B. Metabolic, Neurologic, Skeletal and Cardiac Involvement				
Fatty acid oxidation disorders (several distinct disorders). Carnitine uptake (primary carnitine def.) CarnitineTranslocase VLCAD	Variable severity features of: hepatopathy, skeletal muscle weakness and cardiomyopathy.	OCTN2 CACT Acyl coA dehydrogenase	AR (5q31) AR (3p21.31) Unknown (17p)	DC or HCM, arrhythmias, sudden death. Neonatal DC or HCM arrhythmias, sudden death. Arrhythmias, myalgia, occasional rhabdomyolysis.
Glycogen strorage disorders. (11 types) Type IIa Type IIb	Pompe disease Danon disease: Males with weakness, mental retardation and hypertrophic cardiomyopathy.	Acid α-glucosidase LAMP-2	AR (17q23) XD (Xq25)	Severe HCM, heart failure. sudden death. HCM, decreased function, occasionally WPW.
Mitochondrial and respiratory chain disorders	Early infancy to early childhood. Metabolic acidosis. Neurologic abnormalities, strokes, seizures, skeletal myopathy.	Multiple mitochondrial and nuclear mutations implicated. Typically affecting any one of complexes I, II, IV, or V, coenzyme Q, or of the pyruvate dehydrogenase complex.	AR or Mt. inheritence	HCM or DC Arrhythmias Sudden death

AD autosomal dominant, *AR* autosomal recessive, *AV* atrioventricular, *DC* dilated cardiomyopathy, *EFE* endocardial fibroelastosis, *HCM* hypertrophic cardiomyopathy, *LVNC* left ventricular noncompaction, *MD* muscular dystrophy, *Mt.* mitochondrial, *VLCAD* very-long-chain acyl-CoA dehydrogenase, *XR* X-linked recessive

Table 2 (continued)

Diagnosis	Typical features	Gene/Gene product	Inheritance (Gene locus)	Cardiac phenotype
C. Primarily Cardiac involvement				
Hypertrophic cardiomyopathy	Isolated cardiac involvement. Any age, either sex. Family history common.	β-Myosin heavy chain (β-MHC) Myosin binding protein (cMYBPC) Troponin T (TNNT2) Troponin I (TNNI3) α-Tropomyosin (α-TM) and others	AD (40% sporadic) 14q1 (30-40% of cases) 11p11 (30% of cases) 1q3 (10-15% of cases) 19q13 15q2	Typically assymmetric septal hypertrophy, occasionally apical hypertrophy. Arrhythmic sudden death in young adults, but rare in children.
Dilated cardiomyopathy	Isolated cardiac involvement. Any age, either sex.	Multiple genes implicated, including:Lamin A/C (the most commonly genotyped defect) TNNT2, TNNI3, α-TM, β-MHC, cMYBPC, and others including: Titin Troponin C Δ-Sarcoglycan Thymopoeitin Cardiac Actin (ACTC) Telethonin	50% are inherited as AD. Penetrance varies markedly Only about 10% of cases can be genotyped. 2q31 3p21 5p33 12q22 15q14 17q2	DC with variable RV involvement, conduction system disease and risk for sudden arrhythmic death. 50% risk of death or transplantation within 5 years.
Restrictive cardiomyopathy	Isolated cardiac involvement. Any age, either sex.	Troponin I (TNNI3) most common, TNNT2, β-MHC, and ACTC also described.	19q3	Massively enlarged atria, restrictive diastolic filling. 50% 2-year mortality once symptoms noted. Sudden arrhythmic death frequent. Thromboembolism risk.
LV noncompaction cardiomyopathy	Isolated cardiac involvement. Any age, either sex.	Multiple genes implicated (including β-MHC, α-cardiac actin, TNNT2) Familial cases Cypher/Zasp (LDB3) α-dystrobrevin (DTNA) Taffazin-G4.5	Most commonly sporadic, Minority genotyped. AD (incomplete penetrance) 10q22-23 18q12 XR (Xq28) in Barth syndrome.	Apical/posterior lateral wall trabecular /compacted zone >2:1 ratio Risk of thrombus, primary arrhythmia. Severe newborn form recognized. Assocaiton with Ebstein's malformation, in some kindreds.
Arrhythmogenic RV cardiomyopathy	Isolated cardiac involvement. Typically emerges in teenagers, young adults.	Most implicated genes encode for abnormalities of the desmosome (plakoglobin, desmoplakin and plakophilin).	AD for most cases AR for Naxos disease (17q1), and related variants. Complex genetic heterogeneity. Familial in up to 50% (penetrance as low as 30%).	Fibrofatty infiltrate of the RV on MRI/biopsy. Unusually high propensity for ventricular arrhythmia and sudden death in the absence of LV dilatation or dysfunction.

coronary artery into the aorta, with excellent long-term results.

Cardiomyopathy

Acquired diseases of the myocardium (Table 1) or primary genetically determined CM (Table 2, electronic supplement) can be detected at any age from fetal life onward. In many cases, the evolution is gradual, allowing for compensation of hemodynamic disturbance until an advanced stage of systolic heart failure, and LV dilatation is reached. The morphologic appearance of CM hearts varies dramatically and has led to the widely recognized WHO classification based on the dominant phenotypic pattern [48]. Classical phenotypic patterns include dilated, hypertrophic, restrictive, and arrhythmogenic RV CM. This approach has recently been modified to incorporate the entity of primary left ventricular noncompaction [35] and to reflect the fact that some CM are really systemic diseases, while others affect primarily the heart.

Infants with CM may or may not develop heart failure. If they do, they will present with low output symptoms and failure to thrive, while in teenagers, pallor, fatigue, syncopal events, or unexplained tachycardia are commonly noted. Abdominal pain and nausea/vomiting is commonly noted in our experience of children with acute decompensated heart failure (ADHF) [17]. Certain populations

must always be considered at risk for CM and therefore developing heart failure: children with a history (or family history) of myopathy or muscular dystrophy [41], those suspected of having an underlying metabolic disease (glycogen storage, fatty acid oxidation disorders, or other mitochondrial diseases [20]), certain syndromal disorders (the mucopolysaccharidoses, Barth syndrome [19, 55], Costello syndrome [53]), those exposed to cardiotoxic drugs (particularly in the anthracycline group [64]), children with chronic or multisystem diseases, including renal failure of any cause [8], systemic lupus erythematosus [21, 22], hematologic disorders [66], hyperthyroidism [18], eating disorders [44], or even inflammatory dermatologic diseases like epidermolysis bullosa [51]. Echocardiographic screening has been adopted for many of these problems in current practice.

Assessment and initiation of therapy

Focusing on heart failure as a syndrome in the absence of a structural congenital or primary rhythm abnormality allows us to develop a simple construct for patient assessment (Fig. 1). This concept was originally proposed by Warner-Stevenson and colleagues [57] and is a useful starting point in the emergency setting. As illustrated, patients fall into one of four groups by virtue of the presence or absence of

congestion and underperfusion. These patterns of presentation are not immutable, and with the initiation of rational treatment, patients can and should retrace their steps from groups C to B to A. Patients in group D may stabilize transiently on inotropic support but will not usually be able to sustain this and have a high mortality. The latter need urgent consideration for mechanical circulatory support and transplant listing, if their status does not improve in the presence of a normal central venous filling pressure. Below we detail the emergent approach to dealing with heart failure syndrome.

(a) Emergency management of ADHF

The initial approach to any patient with impending circulatory collapse is similar: oxygen, ventilatory assistance, and vascular access are paramount, although we do not encourage attempted endotracheal intubation of patients with heart failure unless there is a cardiac arrest. The necessary sedation and vagal effects of endotracheal intubation are extremely hazardous in this setting, and our experience has been that high FiO_2 bag and mask assistance initially, with noninvasive positive pressure ventilation to follow, is well tolerated with significantly less morbidity. This has been validated by the experience in adult patients [59] and has become our method of choice for initial ventilatory support in distressed children, where there is

Fig. 1 Patterns of presentation recognized in ADHF, as represented by a 2×2 contingency diagram: the clinical assessment should answer the two questions posed and attempt to assign the patient to one of four categories as indicated by the appropriate physical findings. Patients who are well compensated (group A) may become volume-overloaded, with signs of systemic or pulmonary venous congestion, moving to group B. Following on this, signs of decreased cardiac output may develop (group C). With diuretics and reduction in systemic vascular resistance, most patients in C and B return back to group A. However, some will remain underperfused despite restoration of normovolemia (group D). In this group, there is an increased likelihood of continued inotropic support and or mechanical support being required (redrawn and modified from Stevenson et al. [35]). ACEi angiotensin converting enzyme inhibitor
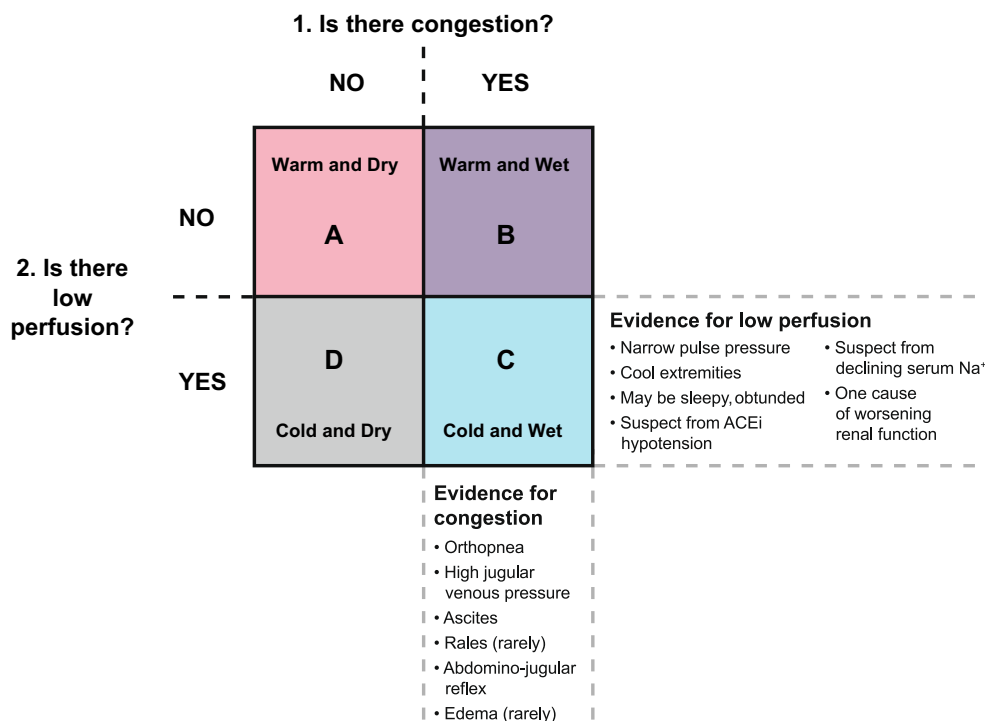
known cardiac compromise. If necessary, endotracheal intubation can be performed later on in a setting where extracorporeal membrane oxygenation is available on standby, or avoided altogether.

Volume overload is virtually universal, and diuretic therapy is widely used to manage CHF, but there have been only two randomized trials in adults to guide their precise dosing and usage [23]. Diuretic therapy with a loop diuretic agent (furosemide, torsemide, bumetamide, or ethacrynic acid) will result in the decrease of tubular reabsorption of sodium and water and a fairly predictable drop in venous filling pressure by 3–6 mmHg. Although early use of intravenous loop diuretics is effective in virtually all patients with ADHF, there are numerous adverse effects of diuretic usage, including sodium and potassium depletion, ototoxicity, and of course renal insufficiency which is a mortality risk in heart failure [37]. Therefore, diuretic usage should not be indiscriminate or excessive. Infusion at a lower dosage or oral therapy is preferable to high-dose intravenous bolus usage [58]. Patients with advanced pulmonary hypertension, RV failure or restrictive LV physiology, or pulmonary venous obstruction present a unique challenge and may worsen in the face of rapid reductions in LV stroke volume which might occur through overzealous diuresis.

What is the role of inotropic support for the failing heart? While an increase in cardiac output is desirable, sustained use of inotropic agents is controversial [60]: several studies have found an increased hospital and medium-term mortality following their intermittent use in adult patients with heart failure [6, 58]. Dopamine (a catecholamine-like precursor of norepinephrine, which also promotes norepinephrine release) acts as an adrenergic agonist on the heart and promotes peripheral vasoconstriction: effectively, it will raise blood pressure and systemic vascular resistance and increase heart rate. Dobutamine (a synthetic analog of dopamine, with more prominent β_1 and β_2 than α-agonist effects) will increase myocardial oxygen consumption, with variable effects on blood pressure. While episodic inotropic support is to be avoided if at all possible in chronic heart failure, this may reflect a problem more relevant to the adult population with coexisting ischemic myocardial disease [15]. Many cases of acute cardiovascular collapse in childhood however result from reversible disease states, including acute severe myocarditis. In this context, beta adrenergic agonists, including epinephrine, are a lifesaving temporary measure and are clearly indicated for 24–48 h if necessary. For routine use, the value of inotropic support in pediatric decompensated heart failure has not been prospectively verified, and therefore we reserve the use of epinephrine and dobutamine for those patients who have symptomatic low cardiac output despite optimization of other therapies.

Milrinone, a bipyridine derivative and a phosphodiesterase III inhibitor with moderate inotropic effects, increased relaxation velocity, and moderate vasodilator properties, offers several advantages: it results in a marked increase in cardiac index and a drop in pulmonary capillary wedge pressure and improved mixed venous oxygen saturations, increased coronary venous flow, and only minimal effects on mean arterial pressure [47]. The central hemodynamic benefits of this drug appear to be well maintained, and, importantly, its use in children has been proven to be effective in the setting of postoperative low cardiac output syndrome [25]. Milrinone has however also been associated with arrhythmias [12] and adverse hemodynamic effects [46], but we have found this to be the best first choice of therapy in patients with moderate to severe ventricular dysfunction with respiratory or underperfusion symptoms.

It is important to integrate the use of inotropic, vasodilator, and diuretic therapy in a fashion that suits a patient's hemodynamic needs. We adopt a general categorical approach as illustrated in Fig. 2 and begin complementing diuretic therapy with appropriate fluid and occasionally salt restriction once perfusion is established; renal function is considered secure, and inotropic therapy is weaning.

With established dilated CM presenting in the emergency room setting (but not in an "arrest" situation), we find the quadratic classification of heart failure syndrome proposed by Warner et al. helpful and leads to an algorithmic approach, as illustrated in Fig. 3. It should be borne in mind that pediatric patients rarely present with florid peripheral edema and that, when pulmonary edema is present, tachypnea and cough are the most commonly encountered symptoms. Similarly, in our experience, abdominal distress, pallor, and nausea are frequent signs of low cardiac output syndrome. For a distressed or underperfused patient, we will typically initiate therapy with an inotropic/vasodilator agent such as milrinone, using a loading and maintenance dose as indicated in Table 4 (electronic supplement).

Levosimendan has been licensed in Europe and Australasia but not in the USA or Canada. This agent belongs to class of calcium-sensitizing compounds, which sensitizes troponin C to calcium, increasing contractile force. It also opens vascular ATP-dependent K+ channels to achieve vasodilation. This drug had shown encouraging effects, suggesting a benefit over dobutamine or placebo in initial trials in adults with ADHF but has subsequently failed to show a mortality advantage in larger-scale trials [32]. Reports of the initial use of Levosimendan in children indicate its ability to facilitate the weaning of catecholamine support in children with heart failure [14, 42, 63]. A randomized trial in children is anticipated but will likely be performed in the context of postoperative low-cardiac-output syndrome rather than ADHF in children.

Nesiritide, a synthetic analog of endogenous brain natriuretic peptide (BNP), has been in use for some years and gains support for both its safety [52] and efficacy [34] in critical care units, although the published series are small to date. The drug mimics the effect of endogenous BNP on the vascular endothelium, by effecting an increase in cyclic guanine monophosphate in a manner analogous to the nitric oxide pathway. The adult experience with this drug has been mixed: emergency room (ER) patients in ADHF treated with nesiritide experienced better symptomatic relief than if treated with placebo over 8 h but with more hypotension and were more likely to return to the ER within 30 days, suggesting no advantage over conventional therapy [39]. A post hoc analysis of the three major trials to have used nesiritide in adults with ADHF suggested a near double risk of death in the short term [1]. However, retrospective data from >65,000 patients with ADHF who were enrolled in the Acute Decompensated Heart Failure National Registry showed a favorable propensity-adjusted risk for in-hospital mortality with nesiritide (or nitroglycerine) versus milrinone or dobutamine [2]. Given this uncertainty and concerns regarding deterioration of renal
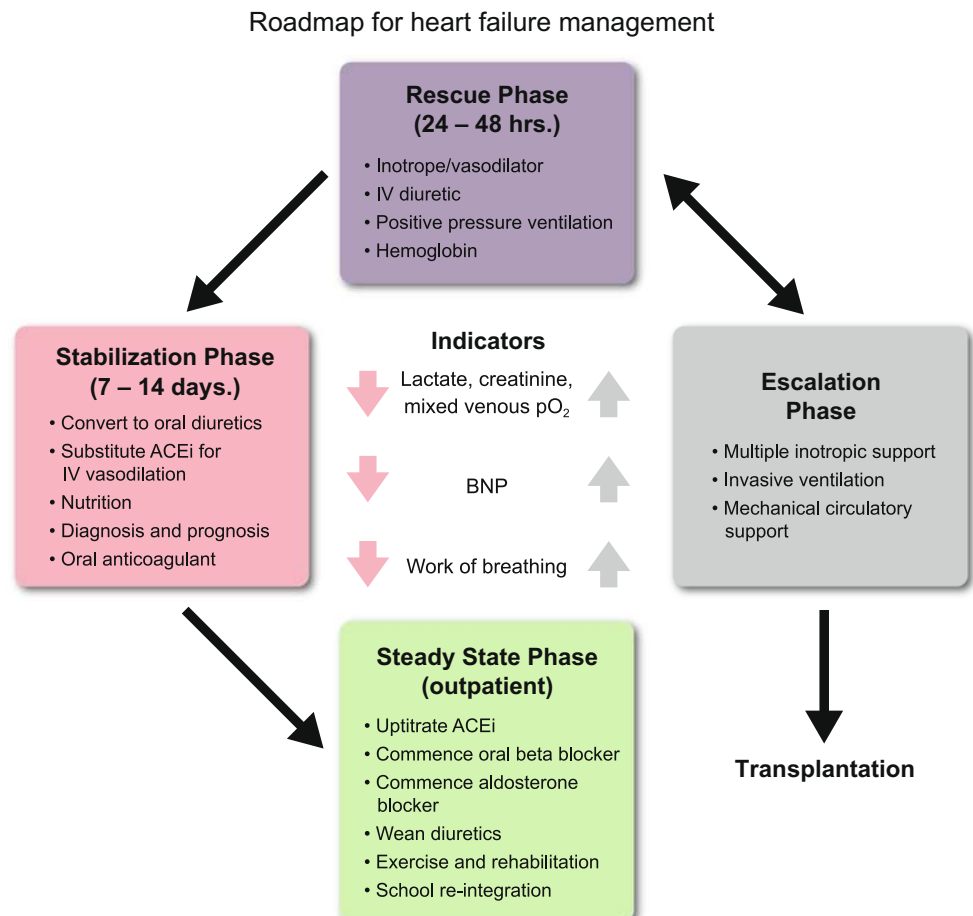
function with nesiritide, its use beyond the labeled indication (up to 48 h in ADHF) is not advised [61]. Our preferred approach is to await a randomized controlled trial evaluating the efficacy of this agent over those currently available for children. We would however consider using nesiritide in the context of failed diuretic or inodilator therapy.

(b) Special situations, combination therapy, and nondrug therapy

Having a standardized approach is helpful, but what is to be done when standard approaches fail? In our experience, complications can be anticipated in certain situations.

• *Patients with profound hypotension and poor systolic function*: a combination of parenteral inotropic drugs is sometimes given to temporarily escalate support in the hope of recruiting myocardial function. In our experience, the use of epinephrine (added to milrinone) for more than 48 h is a surrogate marker of the need for mechanical circulatory support. There is growing evidence that myocardial recovery is more likely with

Fig. 2 Overview of management strategy in ADHF: patients who present with volume overload (with or without hypoperfusion) will require rescue therapy to reestablish normovolemia and adequate perfusion. Much of this, with a large attendant decrease in BNP levels, occurs within the first 48 h of presentation, although some patients require up to a week of mainly parenteral therapy, depending mainly on the integrity of renal function and severity of cardiac compromise. The intent is to move to a stabilization phase, with priorities as noted. However, some patients will not respond to medical therapy and, as indicated by the directional *arrows*, may require consideration for device therapy and bridging to transplantation

Roadmap for heart failure management

Rescue Phase (24 – 48 hrs.)
• Inotrope/vasodilator
• IV diuretic
• Positive pressure ventilation
• Hemoglobin

Stabilization Phase (7 – 14 days.)
• Convert to oral diuretics
• Substitute ACEi for IV vasodilation
• Nutrition
• Diagnosis and prognosis
• Oral anticoagulant

Indicators
Lactate, creatinine, mixed venous pO$_2$
BNP
Work of breathing

Escalation Phase
• Multiple inotropic support
• Invasive ventilation
• Mechanical circulatory support

Steady State Phase (outpatient)
• Uptitrate ACEi
• Commence oral beta blocker
• Commence aldosterone blocker
• Wean diuretics
• Exercise and rehabilitation
• School re-integration

Transplantation

mechanical support (a bridge to recovery for some patients) than with "forced recruitment" of damaged myocardium, by adrenergic hyperstimulation.

- *Declining renal function in the presence of heart failure:* the cardiorenal syndrome has been described as the "Gordian Knot" of heart failure. This results when excessive diuresis and vasodilation in combination result in deteriorating renal function, diuretic resistance, and hypotension. A report by Price et al. suggested that renal function commonly worsens in children within the first week of treatment in those admitted with ADHF [45] but that the requirement for renal replacement therapy is infrequent (5%). Overall, an increase of serum creatinine of more than 0.3 mg/dl (26 mmol/l) resulted in a tenfold increase in the hazard ratio of the need for mechanical circulatory support.

Unfortunately, the use of nesiritide and low-dose dopamine was implicated as a risk factor for this problem, confirming previous observations in adults [65].

- *Patients with preserved systolic function*: some patients will present with symptomatic heart failure with primarily diastolic function impairment. Primary restrictive CM (sometimes with hypertrophy of the LV), acute myocarditis, pericardial tumors, and fibrosis are all potential causes. Symptomatic management of these patients who may depend on adequate preload for LV function requires gentle diuretic therapy and should avoid the use of inotropic vasodilatation if possible. While there is as yet no proven therapy that has any substantial impact on diastolic heart failure, cardioselective third-generation beta-blocker agents (such as
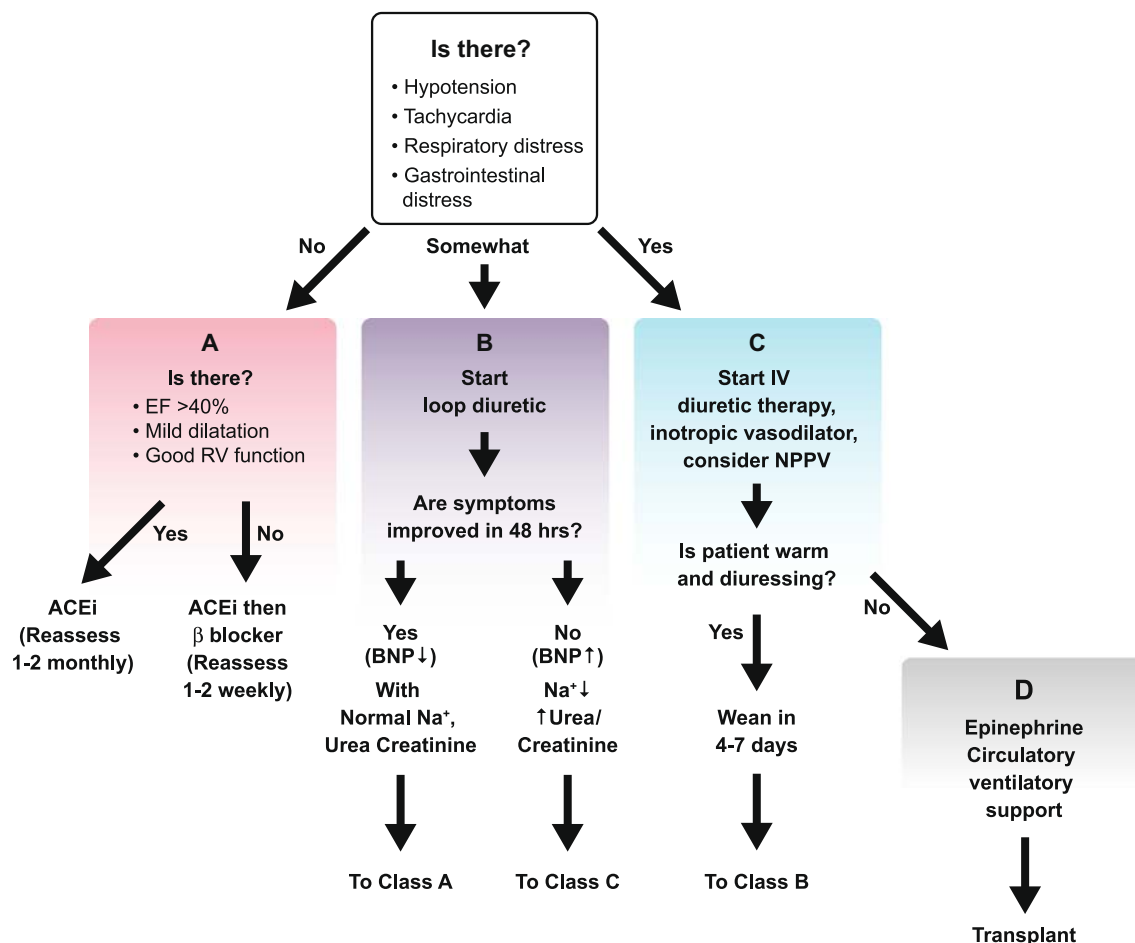
Fig. 3 Simplified decision making in symptomatic ADHF management. Groups A–D correspond to those designated in Fig. 1. Our institutional practice is to admit all patients who are symptomatic at their initial presentation. Those with mild symptoms and no vomiting/GI symptoms *may* respond to oral therapy, although i.v. diuretics are typically required. Our preference is to reserve i.v. inotropic/vasodilator therapy for those who have underperfusion as well as volume overload. Most patients should be able to achieve oral maintenance therapy, at least on a temporary basis. *NPPV* noninvasive positive-pressure ventilation

metoprolol) in low dosages have been useful in achieving cardiac rate control in our experience. Most patients with *symptomatic* restrictive CM however will require evaluation for a possible defibrillator device and cardiac transplantation listing due to the poor 2-year survival rate reported for these patients [49].

- *Acute myocarditis:* although a topic unto itself, myocarditis is important to consider for two reasons. First, it is a common source of concern as a differential diagnosis for emergency room physicians [17], and second there is no consensus as to whether medical therapy with either immunosuppressive or immunomodulatory therapy is of value [9]. In a majority of individuals, viral isolation is possible if searched for carefully [29]. Viral persistence in the heart following the acute phase is associated with a worse prognosis in adult subjects [31]. While acute fulminant myocarditis may result in rapid and severe acute heart failure, paradoxically, it is more often than not associated with survival [4] and to a large degree, recovery of function with time. All efforts to maintain circulatory output, including inodilators, supplementary inotropes, and if necessary mechanical circulatory support as a bridge to recovery, are used. There is no clear evidence to support one (or any) form of immunotherapy over another at this point. Interferon B has recently been reported to be effective for specific causal agents [30]. We advocate for endomyocardial biopsy and MRI assessment to confirm the diagnosis in hemodynamically stable patients over 10 kg in weight. Following the acute phase, we maintain standard maintenance heart failure therapy for as long as 2 years after apparent functional recovery because of the poorly defined [56] risk of continued late remodeling of the ventricle.

Summary

ADHF in childhood is a high-risk scenario which demands early recognition and effective treatment. In early infancy, previously undiagnosed congenital heart lesions are common, although acute myocarditis and dilated CM are increasingly recognized in toddlers and also in those under 1 year of age. Treatment is keyed to the anatomic diagnosis and the nature of the child's circulatory disturbance. Early intervention with diuretic therapy and inotropic vasodilator support has been proven effective in stabilizing the majority of patients, allowing time for a detailed diagnostic assessment of the underlying cause of disease. A second review detailing the therapy of chronic and advanced heart failure in children will follow to supplement this discussion.

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