

## Society Guidelines

# Presentation, Diagnosis, and Medical Management of Heart Failure in Children: Canadian Cardiovascular Society Guidelines

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## ABSTRACT

Pediatric heart failure (HF) is an important cause of morbidity and mortality in childhood. This article presents guidelines for the recognition, diagnosis, and early medical management of HF in infancy, childhood, and adolescence. The guidelines are intended to assist

## RÉSUMÉ

L'insuffisance cardiaque (IC) chez l'enfant est une cause importante de morbidité et de mortalité durant l'enfance. Cet article présente les lignes directrices sur le dépistage, le diagnostic et la prise en charge médicale précoce de l'IC en bas âge, durant l'enfance et l'adolescence.

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of

multidisciplinary experts on this topic with a mandate to formulate disease-specific Recommendations. These Recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these Recommendations will not necessarily produce successful outcomes in every case.

practitioners in office-based or emergency room practice, who encounter children with undiagnosed heart disease and symptoms of possible HF, rather than those who have already received surgical palliation. The guidelines have been developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, and are accompanied by practical Recommendations for their application in the clinical setting, supplemented by online material. This work does not include Recommendations for advanced management involving ventricular assist devices, or other device therapies.

## A. Introduction

Heart failure (HF) in children may present at birth (because of fetal disease<sup>1</sup>) or can develop at any stage of childhood. HF has multiple causes: predominant among these in developed countries are the primary cardiomyopathies (CMs), which account for 60% of children requiring a cardiac transplant, and the congenital heart diseases.<sup>2</sup> The incidence of primary CM in developed countries is reported to be between 0.8 and 1.3 cases per 100,000 children in the 0-18 year age group,<sup>3,4</sup> but is 10 times higher in the 0- to 1-year-old age group. The incidence of congenital heart disease is relatively high, occurring in 0.8% of live births. However, only a small percentage of these defects are severe enough to result in HF during childhood. In addition, certain systemic processes such as inflammatory diseases, metabolic disorders, endocrine derangements, and kidney disease result in an unknown number of cases. Recent data from the United States indicates that 10,000-14,000 children are hospitalized every year with HF as 1 of their diagnoses, and of those approximately 27% (approximately 3000) have abnormalities of the heart muscle (including irregular heart rhythm) as an underlying cause.<sup>5</sup>

On a global scale, parasitic infection, nutritional deficit, and rheumatic heart disease are the likely predominant causes of HF in childhood.

Because pediatric HF is a relatively uncommon condition, most practitioners in primary care or emergency departments have little practical experience with its presentation or management in children. The clinical manifestations might be dissimilar to those of adults, and quite variable. Because 87% of cases of new-onset HF only reach a diagnosis when the patient is in a state of severe decompensation,<sup>4</sup> and less than 50% of children who present with symptomatic HF survive for 5 years without cardiac transplantation,<sup>6,7</sup> early diagnosis and effective treatment remain significant challenges which should be addressed.

## B. Scope of the Guidelines

These guidelines cover the clinical symptoms and signs of HF in children (section I), the accepted diagnostic testing approach to HF in children (section II), and the accepted approach to medical therapy of HF in children (section III), and are constructed to assist primary care physicians, cardiologists, and other health care practitioners in the evaluation, diagnosis, and medical management of children with HF. Because the evidence base in children is weighted heavily to

Les lignes directrices visent à aider les praticiens qui rencontrent dans leur exercice en cabinet ou à la salle des urgences des enfants ayant une cardiopathie non diagnostiquée et des symptômes d'IC probable, plutôt que ceux qui ont déjà subi une chirurgie palliative. Les lignes directrices ont été établies en utilisant la méthodologie GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) et sont accompagnées de recommandations pratiques en vue de leur application en milieu clinique, en plus d'être complétées par un contenu en ligne. Ces travaux n'incluent pas les recommandations sur la prise en charge avancée concernant les dispositifs d'assistance ventriculaire ou les autres traitements à l'aide de dispositifs.

systolic HF, our treatment guidelines reflect this reality. Diastolic HF is an important but as yet poorly elucidated topic in the pediatric literature, and we have not addressed the treatment of isolated diastolic HF in this document. These guidelines do not deal with advanced interventions or device therapies for HF in children, nor do they offer recommendations for treatment of all underlying disease etiologies. Background information is provided for context, but is not intended to be exhaustive. Important practice points and figures which will be of assistance are provided for illustration.

Specific Recommendations are listed, which have been peer-reviewed and should be adopted. Appendices with greater detail with regard to diagnostic testing and drug dosages are also provided. This document is intended to enhance, but not replace, expert physician judgement in individual scenarios. Finally, the authors acknowledge that the content of these guidelines reflects a literature and clinical experience that borrows much from that of adult medicine. It is hoped that further research in pediatric HF, particularly in the area of congenital heart diseases, will result in refinement of these guidelines.

## C. Methods

### Development process

Our development process, including evidence inclusion criteria, search methods, consensus-building procedure, and evidence appraisal is available in [Supplemental Appendix S1](#).

### Grading of evidence and practice Recommendations

The quality of evidence supporting these Recommendations was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method<sup>8</sup> which rates quality on 4 levels ([Table 1](#)).

Although the evidentiary base determined the strength of our Recommendations, we recognize that the treatment-related values and preferences of patients and families also play a role in clinical decision-making. We have therefore made the values and preferences of our team explicit, as they pertain to each group of Recommendations. We have indicated the strength of Recommendations and also categorized the evidence quality.

## D. Presentation and Detection of HF in Children

### Definition

HF in children (aged 0-18 years) can be defined broadly as the failure of the heart to supply blood to either systemic or pulmonary circulation at an appropriate rate of flow, or to receive venous return at an appropriate filling pressure, resulting in adverse effects on the heart, the circulation, and the patient. This definition is not different to that applied to adult patients. Symptoms of HF in children are superficially similar regardless of the underlying etiology, but physical signs might be more specific. Systemic manifestations are mediated by sympathetic and central neurologic pathways, activated in response to pulmonary congestion and/or decreased systemic perfusion.<sup>9,10</sup> Clinical features of HF unique to children are:

1. Possible coexistence of structural congenital heart lesions, with simultaneous pulmonary overcirculation and systemic underperfusion (when the 2 circulations are linked in parallel by an intracardiac shunt or a patent arterial duct).
2. A change in symptom complexes over time from infancy through adolescence. In infants and young children, these are primarily respiratory and feeding difficulties (which are similar to the metabolic demands of physical exertion seen in older children).

### Symptom severity and recognition

Table 2 lists the typical features of HF in children, categorized as common and less common. The New York Heart Association (NYHA) classification of functional class is best suited to quantify changes in functional capacity in patients with established chronic HF. The Ross classification (Table 3), has been applied to younger children for the same purpose. Additional modifications and composite scales of severity have been proposed for children,<sup>11,12</sup> but without secondary validation of the predictive value for clinical outcomes. An age-stratified modification of the Ross classification has been proposed,<sup>13</sup> which also awaits validation. For children, there is therefore an empirical tool for grading the severity of acute decompensated HF symptoms, but not for predicting mortality based on status at presentation.

#### RECOMMENDATION

D1. The NYHA/Ross classification is a suitable basis for symptom stratification of patients with established chronic HF, but is not essential to establishing the diagnosis, or determining the prognosis of HF in children (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This Recommendation places high value on the need for the development of reliable and valid prognostic indicators for pediatric HF.

**Table 1.** Strength of Recommendations and quality of evidence classifications used in this guideline

| Quality of evidence | Interpretation   |
|---------------------|--|
| High                | Further research is very unlikely to change our confidence in the estimate of effect   |
| Moderate            | Further research is likely to have an important influence on our confidence in the estimate of effect and might change the estimate                              |
| Low                 | Further research is very likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate                  |
| Very low            | Any estimate of effect is very uncertain   |
| Recommendation      | Interpretation   |
| Strong              | The desirable effects clearly outweigh the undesirable effects, or clearly do not  |
| Conditional         | The trade-offs are less certain, either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced |

### Failure to thrive and nutritional deficiency conditions

Feeding difficulties (and therefore growth failure) are commonly recognized as presenting symptoms of congestive HF in infants and young toddlers (age 0-2 years).<sup>14-16</sup> The characteristic findings range from prolonged feeding time (> 20 minutes) with decreased volume intake to frank intolerance and vomiting after feeds. Irritability with feeding, sweating, and even refusal of feeds are also commonly reported. When HF is established in infants and toddlers for more than 1 month in duration, poor weight gain becomes evident, and in the longer term, failure in linear growth can also result. This “failure to thrive” is a classical finding in many forms of undiagnosed heart disease, and might also coexist with noncardiac diseases, which must be excluded. Persistent growth failure after diagnosis and treatment of HF in infants suggests inadequate response to therapy, and portends an ominous outcome.<sup>16</sup>

In the setting of primary nutritional deficit (calorie intake deficiency, protein deficiency, and in some cases, trace element deficiency), cardiac dysfunction might also occur. Children and adolescents with nutritional deficiency resulting

**Table 2.** Symptoms characteristic of heart failure in children

|                                | Commonly encountered  | Less commonly encountered   |
|--------------------------------|---|---|
| Infants and young children     | <ul style="list-style-type: none"> <li>• Tachypnea</li> <li>• Feeding difficulty (reflux, vomiting, feeding refusal)</li> <li>• Diaphoresis</li> <li>• Pallor</li> </ul>                          | <ul style="list-style-type: none"> <li>• Cyanosis</li> <li>• Palpitations</li> <li>• Syncope</li> <li>• Facial edema</li> <li>• Dependent edema</li> <li>• Ascites</li> </ul> |
| Older children and adolescents | <ul style="list-style-type: none"> <li>• Fatigue</li> <li>• Effort intolerance</li> <li>• Dyspnea</li> <li>• Orthopnea</li> <li>• Abdominal pain</li> <li>• Nausea</li> <li>• Vomiting</li> </ul> | <ul style="list-style-type: none"> <li>• Palpitations</li> <li>• Chest pain</li> <li>• Dependent edema</li> <li>• Ascites</li> </ul>  |

**Table 3. Classification of symptomatic severity in pediatric heart failure**

| Class of symptoms | Symptoms noted on history  |
|-------------------|--|
| I                 | Asymptomatic   |
| II                | Infants: mild tachypnea or diaphoresis with feeding; no growth failure<br>Older children: dyspnea on moderate exertion       |
| III               | Infants: marked tachypnea or diaphoresis with feeding; growth failure<br>Older children: dyspnea on mild or minimal exertion |
| IV                | Tachypnea, diaphoresis or respiratory distress at rest   |

Infants refers to age 0-1 year. Older children refers to age 1-10 years.

in hospitalization should therefore also be evaluated for underlying secondary cardiac effects of calorie and/or protein malnutrition.

### RECOMMENDATION

D2. Underlying cardiac disease should be considered and excluded in younger infants with feeding difficulties and growth failure when primary gastrointestinal and other common causes have been ruled out, and in infants, toddlers, and children with chronic calorie, protein, or trace element deficiency (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This Recommendation places a high value on early diagnosis of underlying HF in situations of ambiguous clinical symptoms and signs, or when uncertainty is present. Early and repeated cardiovascular examination of infants is mandated as the most valuable screening tool available. Expert evaluation is considered preferable in situations of uncertainty, notwithstanding the potential for unnecessary referral: the trade-off of missed diagnosis at an earlier stage of disease being of such significant consequence to the patient and family.

### Presentation of CMs in children

CMs are uncommon in general practice, but nonetheless important causes of HF in children. They have multiple causes; genetic and acquired. Although the presenting symptoms of HF are similar to those arising from other causes, the major phenotypes of the CMs do have some noteworthy features, as outlined in the following sections.

**Dilated CMs.** Dilated CMs (DCMs) are the most common phenotypic pattern of CM in childhood, and are frequently encountered for the first time as acute decompensated HF.<sup>4</sup> They manifest most commonly in the first year of life.<sup>3</sup> Irritability, abdominal distress, and feeding intolerance are typical symptoms, with sudden or aborted sudden death occurring less commonly. Signs of hypoperfusion and respiratory distress frequently herald an impending collapse. Hospitalization and immediate supportive care is typically required.<sup>9</sup>

**Noncompaction CM.** Noncompaction CM, commonly referred to as 'left ventricular [LV] noncompaction' might actually involve either or both ventricles; this is a genetic CM with a characteristic hypertrabeculated or "spongy" LV endomyocardial layer, within an outer thin-walled compacted layer of muscle. HF is the presenting complaint in a third of patients with this phenotype,<sup>13</sup> although in other patients, syndromal or chromosomal abnormalities and metabolic disease are the primary presenting features.

**Restrictive CM.** Restrictive CM is primarily a genetic disorder of 1 of several sarcomeric proteins in children, is characterized by symptoms of diastolic HF, which in children presents as orthopnea, cough (and sometimes a presumed diagnosis of asthma), chest pain, or syncope.<sup>17</sup> Sudden death is common in this disease, and later progression to signs and symptoms of congestive HF might also occur. Signs of right ventricular (RV) failure, with hepatic venous congestion or ascites because of long-standing left atrial and pulmonary hypertension might eventually be noted.

**Hypertrophic CM.** Hypertrophic CM (HCM) in infancy and early childhood has many causes, including syndromal abnormalities, myocardial glycogen or lysosomal enzymopathies, abnormalities of oxidative phosphorylation, and also the sarcomeric mutations commonly recognized in young adult patients. Children might present with symptoms related to the underlying metabolic disorder, and later develop systolic HF. Those with severe hypertrophy might also demonstrate symptoms of diastolic HF. Syncope related to LV outflow tract obstruction or to ventricular arrhythmias is well described in school-aged children and adolescents with HCM.

**Arrhythmogenic RV CM.** Arrhythmogenic RV CM is an important group of diseases of the desmosomal complex, which result in fibro-fatty myocardial infiltration of either ventricle, and ventricular arrhythmias in adolescence and young adulthood. These patients rarely present with HF classical symptoms in childhood, because of severe biventricular systolic dysfunction.

Because numerous genetic and metabolic disorders are associated with CM, affected patients with these diagnoses might present with HF symptoms as a primary complaint. The more commonly encountered conditions are detailed in [Supplemental Table S1](#). In the case of the skeletal muscular dystrophies, these symptoms can be difficult to identify because of muscle weakness limiting activity.<sup>18</sup> There is no correlation between the severity of the skeletal myopathy and the degree of cardiac involvement.

### Myocarditis in children

Myocarditis can occur from fetal to adult life, with viral infections being the most commonly defined cause.<sup>19</sup> Clinical symptoms at presentation in a reported series of childhood myocarditis are defined as respiratory (56%); decreased activity (17%); chest pain mimicking a coronary syndrome or pericarditis (7%); syncope (5%); and nonspecific (14%).<sup>20</sup> Outcomes for these patients are generally good in childhood: at least 66% recover,<sup>19,21</sup> with 10% showing

incomplete recovery and 24% of registry cases progressing to death or cardiac transplantation.

### RECOMMENDATION

- D3. A high index of suspicion for CM with acute decompensated HF is necessary in emergency and primary care settings, when evaluating infants with weakness, lethargy, abdominal pain, unexplained or disproportionate tachycardia, and tachypnea<sup>22</sup> (Strong Recommendation, Low-Quality Evidence).
- D4. In suspected muscular dystrophies, symptoms and signs of congestive HF might be concealed because of reduced physical activity. Careful evaluation of myocardial function (via serial echocardiography or magnetic resonance imaging [MRI]) beginning in midchildhood is recommended (Strong Recommendation, Moderate-Quality Evidence).
- D5. Myocarditis should always be considered in the differential diagnosis of children who present with a viral prodrome and nonspecific respiratory or abdominal symptoms associated with tachycardia, hypotension, or cardiac rhythm abnormalities, even in the absence of cardiomegaly on chest x-ray (CXR) (Strong Recommendation, Low-Quality Evidence).

**Values and preferences.** These Recommendations place a high value on a comprehensive approach to history-taking, examination, and differential diagnosis for children with suspected genetic or acquired CM and on a comprehensive approach to ongoing evaluation in suspected cases.

### Methods in practice

- Signs and symptoms of congestive left and right HF might also occur in primary restrictive CM. These include tachypnea, dyspnea (with or without exertion), orthopnea, diaphoresis, hepatomegaly, jugular venous distension, and edema.
- Myocarditis might present with ectopic ventricular rhythm, and limited classical symptoms of acute HF.<sup>23</sup> It might also progress to a fulminant state within a short time, characterized by the evolution of cardiac findings to those of circulatory shock within hours. Most deaths appear to occur early in the disease progression,<sup>24</sup> and the severity of presenting illness appears to affect survival.<sup>25</sup> Therefore, caution and close follow-up is required for patients who are believed to have myocarditis, and appear only mildly affected on first assessment.
- Cardiomegaly is not usually prominent in acute myocarditis, and therefore a CXR can be misleading. It is important to have a high index of suspicion, and to include myocarditis early in the differential diagnosis of children who present with gastrointestinal (abdominal pain and vomiting) or flu-like symptoms, because the differentiation from noncardiac illnesses is difficult at symptom onset.

### Evaluating the need for treatment

Diagnostic testing is always indicated in children with suspected HF. [Figure 1](#) illustrates a useful construct to assist

the clinician in their evaluation, based on the presence of abnormal perfusion and increased fluid congestion.

### E. Diagnosis of HF in Children

The child presenting with symptoms and signs of HF requires urgent assessment to establish the diagnosis, rapidly determine their hemodynamic status, and identify any reversible causes of HF.

#### Chest radiography

Cardiomegaly on pediatric CXR is highly predictive of ventricular dilation on echocardiography, with high specificity and negative predictive value. However, the sensitivity and positive predictive value are low.<sup>26</sup> The incidental finding of cardiomegaly on CXR should prompt review of the patient for additional signs or symptoms suggestive of cardiac disease, and might warrant further investigation with an echocardiogram. Cardiomegaly on CXR has been found to be of prognostic value in children with DCM.<sup>27</sup>

### RECOMMENDATION

- E1. Chest radiography is indicated as a first-line investigation in children with suspected HF (Strong Recommendation, Moderate-Quality Evidence).

#### Biochemical and routine laboratory testing

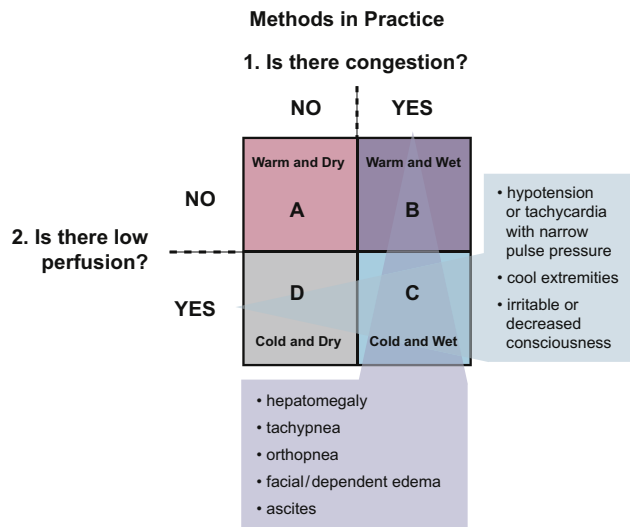
Symptomatic HF in children might be associated with perturbations of electrolyte and fluid balance, acid-base status, renal function, liver function, thyroid function, and complete blood count. Therefore, a preliminary survey of these systems is useful, and might reveal information regarding an associated underlying diagnosis.<sup>28</sup> There is emerging evidence that certain markers such as lymphocytopenia or hyponatremia might predict worsened outcomes, however, this is currently inconclusive.<sup>29</sup>

### RECOMMENDATION

- E2. Assessment of electrolytes (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, Ca<sup>2+</sup>), glucose, acid-base status, urea and creatinine, hepatic transaminases, thyroid hormone levels, and a complete blood count should be performed at initial presentation of HF and repeated as needed to assess ongoing clinical status (Strong Recommendation, Low-Quality Evidence).

#### Electrocardiography

**Electrocardiography and cardiac rhythm assessment.** The electrocardiogram is nonspecific but frequently abnormal in pediatric HF patients,<sup>30-32</sup> with the most common findings of sinus tachycardia, LV hypertrophy, ST-T changes, myocardial infarction patterns, and first degree atrioventricular block.



**Figure 1.** Patterns of presentation recognized in acute decompensated heart failure.

In idiopathic DCM, electrocardiography (ECG) findings of left bundle branch block and left atrial enlargement correlated with HF-related deaths.<sup>33</sup>

A specific etiology for HF might be strongly suggested by some ECG abnormalities, such as inferolateral Q waves (anomalous left coronary artery from the pulmonary artery) or biatrial enlargement (restrictive CM).

In addition, a specific arrhythmic cause of HF might be identified, such as incessant tachycardia (usually ectopic atrial tachycardia), atrioventricular block, or ventricular pre-excitation.<sup>34</sup>

**Ambulatory ECG/Holter monitoring.** Ambulatory ECG monitoring appears to have some value in risk stratification of sudden death in HF resulting from primary CM. In an observational cohort study of pediatric and adult patients (ages 14-68 years) with idiopathic DCM, high grade ventricular

#### RECOMMENDATION

- E3. All patients should have 12-lead ECG performed at the time of presentation with HF, to exclude features of congenital or ischemic heart disease, arrhythmia and pre-excitation (Strong Recommendation, Moderate-Quality Evidence).
- E4. Holter/ambulatory ECG monitoring is not indicated as a primary diagnostic test in HF, unless HCM, arrhythmogenic RV CM, or tachycardia-induced CM is the suspected cause (Conditional Recommendation, Low-Quality Evidence).
- E5. Holter/ambulatory ECG monitoring might be indicated during chronic follow-up, particularly in higher arrhythmia risk groups, including patients with primary restrictive CM or HCM, with tachycardia-induced CM, or those who are taking anti-arrhythmic therapy (Conditional Recommendation, Low-Quality Evidence).

ectopy on Holter monitoring, along with prolonged repolarization on ECG, were independent predictors of sudden death.<sup>33</sup> In patients with Duchenne or Becker muscular dystrophy, ventricular ectopy was common and suspected to be associated with ventricular dysfunction and the risk of sudden cardiac death.<sup>35,36</sup>

#### Echocardiography

**Patients with initial presentation of HF.** Transthoracic echocardiography is an indispensable part of the initial diagnostic evaluation of pediatric HF to exclude possible structural disease. Therefore, echocardiography should be prioritized, because delayed recognition results in delayed surgical repair, and progression of ventricular failure.<sup>37</sup> Initial echocardiography will also establish a baseline for future comparison. It should include the evaluation of LV measurements (using 2-dimensional or M-mode), including shortening fraction (SF), and measurement of ejection fraction (EF) using volume estimation (Simpson's method of disks, area-length method, or automated 3-D algorithm), and the assessment of diastolic function. These data are instructive for short-term management and long-term prognosis.<sup>38,39</sup> LV systolic dysfunction in children is currently defined by an SF < 25% and/or an EF < 55%.<sup>40</sup>

Specific echocardiographic appearances of the CMs vary considerably, and the phenotype-genotype correlation is not always consistent. Stress echocardiography using pharmacologic<sup>41</sup> or exercise stress might demonstrate segmental wall motion abnormalities<sup>42</sup> and changes in LV thickness.<sup>43</sup> These are becoming important to evaluate ventricular reserve capacity, which is of growing interest in the risk stratification of children with HF.<sup>44</sup>

**Screening of patients at risk.** Patients with underlying primary diseases (including oncology patients currently or previously treated with anthracycline chemotherapy, patients with metabolic disorders, neuromuscular diseases, and others) who are therefore at increased risk for HF will benefit from periodic echocardiographic re-evaluation regardless of the presence or absence of symptoms. This applies to first-degree relatives of patients with all forms of CM which is considered to be potentially genetic in origin (see Recommendation 2 in the following 'Recommendations' box),

**Serial echocardiography in HF follow-up.** Periodic follow-up echocardiography is considered useful for surveillance of disease progression,<sup>45</sup> and to assess the response to therapy.<sup>46-49</sup>

#### Biomarkers

**Natriuretic peptide biomarkers.** The natriuretic peptides (brain natriuretic peptide [BNP] or amino terminal [NT]-proBNP) are established as a valuable aid to the identification of HF in adults in the emergency room setting, and have shown some utility in children in identifying cardiac disease in patients presenting with nonspecific respiratory symptoms<sup>50</sup> or noncardiac disease.<sup>51,52</sup> NT-proBNP correlates well with BNP and might advantageous in children, because it has a longer half-life (70 minutes vs 15 minutes), is less unstable

## RECOMMENDATION

- E6. All patients with symptoms consistent with HF should undergo transthoracic echocardiography in a pediatric cardiology facility at, or as soon as possible after, initial presentation. This initial echocardiographic study should include as a minimum (Strong Recommendation, High-Quality Evidence):
- Ruling out congenital heart disease (with attention to coronary arteries);
  - Assessment of myocardial appearance for phenotypic patterns of CM;
  - Assessment of the systolic function parameters of the left ventricle by determining the SF and/or EF;
  - Measurement of the LV end diastolic dimension Z-score;
  - Determination of the presence of mitral regurgitation;
  - Quantitative or qualitative assessment of RV function and RV pressure;
  - Assessment of LV diastolic function;
  - Exclusion of intracardiac thrombus.
- E7. Populations at increased risk for ventricular dysfunction should undergo routine periodic screening echocardiography even in the absence of cardiac symptoms (Strong Recommendation, Moderate-Quality Evidence).
- E8. All patients with HF should undergo periodic follow-up echocardiography to reassess ventricular function with respect to response to medical therapy and to assess further progression of ventricular dysfunction. Follow-up echocardiography should also be repeated if there is a significant change in the clinical status of the patient, either in terms of improvement or deterioration (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** These Recommendations place a high value on the diagnostic accuracy of expert pediatric echocardiography done in a qualified facility, for primary evaluation and for follow-up assessment of at risk or affected patients. The trade-off of inconvenient access to such a facility is considered acceptable considering the benefits of early accurate diagnosis.

*in vitro*, and can be collected in standard tubes used for other biochemical tests.<sup>53,54</sup>

Elevated BNP levels might be associated with worse outcome in HF.<sup>55</sup> In addition, a significant relationship between increased NT-proBNP and increased symptoms, decreased ventricular function, increased ventricular volume,<sup>56,57</sup> and diastolic dysfunction has been demonstrated.<sup>58</sup> NT-proBNP is highest in acute myocardial dysfunction, declines with treatment or recovery from disease,<sup>59-61</sup> and shows less of a decline in patients who progress to mechanical circulatory support.<sup>62</sup> In chemotherapy patients, higher NT-proBNP levels are associated with higher treatment doses of doxorubicin and abnormal echocardiographic parameters including ventricular dysfunction.<sup>63,64</sup> Taken together, there is compelling precedent for

the use of natriuretic peptides in augmenting clinical diagnosis, and in selected cases, to guide therapeutic decisions for children with HF. The use of serial BNP or NT-proBNP measurements in children to guide therapeutic intervention or to monitor HF status shows some promise. The evidence for or against a benefit from this “BNP-guided therapy” strategy in pediatric HF is still insufficient to allow a formal Recommendation.

**Cardiac troponins.** Normal pediatric values for the cardiac troponin isoforms have been variably reported and their specificity to HF is limited. In neonates there is pronounced variability in “normal” troponin levels and their utility is likely very limited. Troponin I can be elevated in CM with increasing levels correlating with severity, but no threshold levels have yet been identified to predict disease progression or mortality.<sup>65-68</sup> Troponin T is likely to be more elevated in HF resulting from acute myocarditis but does not correlate with outcome.<sup>67</sup>

**Other biomarkers.** Other biomarkers that have been investigated in pediatric HF are the circulating hormones arginine vasopressin,<sup>69</sup> epinephrine, and norepinephrine,<sup>9,70</sup> the interleukins,<sup>71-73</sup> and C-reactive protein<sup>74</sup> as markers of inflammation. These biomarkers have variable sensitivity and specificity to severity and cause of HF.

## RECOMMENDATION

- E9. BNP or NT-proBNP levels are useful in distinguishing HF from respiratory or other noncardiac disease and should be used as a confirmatory test in the acute evaluation of pediatric HF (Strong Recommendation, Moderate-Quality Evidence).

## Metabolic and genetic testing

Recent reports suggest a genetic cause for more than 50% of patients with dilated CM.<sup>75,76</sup> Some disorders<sup>77,78</sup> with cardiac involvement are associated with high mortality rates. Conversely, early and accurate identification of a metabolic or genetic cause for HF might allow for lifesaving disease-specific management, might identify family members at risk, and might provide guidance for reproductive counselling. Although the evaluation for genetic and metabolic disease might be complex, and involve several specialties, Recommendations are provided for the essential components; in [Supplemental Table S1](#) the primary and secondary tests to be pursued are listed.

## Endomyocardial biopsy for acute myocarditis

Acute myocarditis presents a diagnostic challenge in adults and children.<sup>19</sup> The prognosis in pediatric myocarditis is significantly better than for DCM (which is often the primary differential diagnosis) with a higher probability of recovery in children, and only approximately 10% of cases being listed for transplant. With a confirmed diagnosis of myocarditis, the likelihood of spontaneous recovery increases, and the

**RECOMMENDATION**

- E10. All pediatric patients presenting with HF require a thorough personal health history and a family history including a 3-generation pedigree (Strong Recommendation, High-Quality Evidence).
- E11. Metabolic laboratory testing in children with unexplained CM (of hypertrophic, dilated, or non-compaction phenotype) should be based on clinical presentation and assisted by specialist consultation: virtually all undiagnosed patients, whether there is a familial pattern or not, require primary screening tests, including serum amino acids, organic acids, total and free carnitine levels, lactate, and urine testing for ketones, mucopolysaccharides, and oligosaccharides (Strong Recommendation, High-Quality Evidence).
- E12. Specialty consultation with genetic and/or metabolic services is recommended to guide further testing such as muscle biopsy or specific gene screening, molecular, or cytogenetic testing. Excluding familial CM is crucial, especially when the presentation is in the fetus or newborn (Strong Recommendation, High-Quality Evidence).
- E13. At-risk family members might require secondary diagnostic screening, including genetic testing, echocardiography, or other relevant modalities of screening, depending on the etiology identified (Conditional Recommendation, Low-Quality Evidence).

treatment plan might change, especially if transplantation was previously being considered.<sup>79,80</sup> However, the diagnostic accuracy of RV endomyocardial biopsy (EMB) for suspected myocarditis tends to be low, and is affected by the length of time from presentation of symptoms to time of biopsy, variation in pathological interpretation, and sampling errors.<sup>80-82</sup> The addition of LV biopsy or MRI-guided biopsy might increase yield,<sup>79,83</sup> but also the hazards of the procedure. EMB is associated with an increased risk of adverse events in children with suspected myocarditis who are using inotropic support.<sup>84</sup> In addition, there is limited evidence to support the use of immunosuppressive or immune-modulating therapy in children, previously 1 of the main reasons for obtaining biopsy confirmation of myocarditis.<sup>19</sup> Attempts should be made to isolate a viral pathogen to support a clinical diagnosis of myocarditis: typical viral pathogen screening using polymerase chain reaction should include: enterovirus, adenovirus, parvovirus, hepatitis C, and the herpes group viruses (EBV, CMV, HSV, HHV6/7, VZV) from blood, stool, and/or nasopharyngeal samples as appropriate.

**Cardiac MRI**

Cardiac MRI (CMRI) is showing increasing diagnostic potential in diseases including the primary CMs and acquired diseases like myocarditis. In patients with biopsy-proven myocarditis, myocardial edema on T2-weighted CMRI can be found in the LV subepicardial or intramural areas.<sup>83</sup> The sensitivity of these changes is increased by simultaneous

**RECOMMENDATION**

- E14. A diagnosis of acute myocarditis should be considered in all children, regardless of age, who present with new onset HF without a history of decreased functional capacity, and specifically if echocardiographic ventricular dilation is less than expected for the degree of systolic dysfunction and clinical severity (Strong Recommendation, Moderate-Quality Evidence).
- E15. EMB should only be performed if confirming the clinical diagnosis of myocarditis will have a clear effect on the patient treatment plan (for example, listing for transplantation). EMB is not recommended in infants weighing less than 10 kg, or in patients who are hemodynamically unstable (Strong Recommendation, Moderate-Quality Evidence).

**Values and Preferences.** These Recommendations place a higher emphasis on clinical diagnosis supported by noninvasive imaging, and a lower emphasis on confirmation via biopsy, except in specific cases as outlined in Recommendation E15. The trade-off is diagnostic confirmation for increased safety.

morphological and functional assessment. This modality might offer children a less invasive option to identify inflammation, with a lower risk of adverse events than EMB. The accuracy and reproducibility of CMRI is at least equal to echocardiography in the assessment of LV size and function and is likely superior in the assessment of RV size and function.<sup>85-87</sup> In patients with DCM, the prognostic value of MRI tissue characterization, and the characterization of scar tissue by late gadolinium enhancement is described in adults.<sup>88</sup> This technique offers insight into the pathophysiology of HF in children regardless of etiology, and might be useful to determine the prognosis and timing of treatment in children with slowly progressive ventricular dysfunction such as Duchenne's muscular dystrophy or anthracycline-related CM.<sup>89</sup>

CMRI criteria for the diagnosis of myocarditis have been proposed with several alternative tissue-characterization techniques. When available, CMRI offers a reasonable alternative to EMB, although the sensitivity and specificity for children with myocarditis is not known. The predictive value of CMRI findings in children with CM in general is also uncertain, and so at this point, CMRI is not recommended as a preliminary investigation in children with HF.

**RECOMMENDATION**

- E16. CMRI might assist in the clinical diagnosis of myocarditis, and might provide additional information in CMs by tissue and scar characterization. The prognostic value of CMRI findings is not yet known (Conditional Recommendation, Low-Quality Evidence).



## F. Medical Treatment of the Child With Acute HF

### Acute therapy for HF

As indicated in [Figure 1](#), patients can be thought of as having symptoms related to fluid overload, underperfusion, or both. The early management of children with HF should address these problems. It is important to note that indiscriminate administration of intravenous fluid resuscitation is contraindicated, and will worsen the condition of children with HF symptoms. The following approach is recommended.

**Diuretic agents.** Loop diuretic agents play a key role in the acute management of patients with symptomatic HF. Nevertheless, the current literature examining their relative efficacy and effect on survival in the pediatric HF population is very limited. A Cochrane review of diuretic therapy in adults with chronic HF confirms that use of diuretic agents effectively relieve symptoms, reduce episodes of worsening HF, increase exercise capacity, and potentially have some influence on survival.<sup>90</sup> These data, along with empirical evidence, is sufficient to justify their routine use in the emergency setting in children with HF. Thiazide diuretic agents will significantly enhance the effect of loop diuretic agents, and can be added in patients with limited response to loop diuretic agents.<sup>91</sup>

**Vasopressin antagonist agents (tolvaptan, conivaptan, and others).** These renal tubular V2 receptor antagonists promote diuresis and have demonstrated symptom reduction in combination with diuretic agents in adults with HF.<sup>92</sup> No survival benefit has been demonstrated with the use of these agents<sup>93</sup> and there are insufficient data to make a Recommendation regarding their use in children.

#### RECOMMENDATION

F1. A loop diuretic, such as furosemide, is recommended for patients with HF and signs and symptoms of congestion. An initial starting dose of 0.5-1 mg/kg intravenously or orally every 6-12 hours, is safe and effective (Strong Recommendation, Moderate-Quality Evidence).

### Methods in practice

- The goal of therapy is to return patients to a euvolemic state, over a period of days to weeks. Subsequently, gradual weaning to the lowest required dose of diuretic is appropriate. Blood pressure, electrolyte, and renal function indices should be monitored. Fluid intake restriction to 80% of basal metabolic requirements might be necessary in some patients, depending on their caloric status and needs. A reduction of free water and an increase in calorie-rich fluid intake is desirable in most settings.

- Patients who are unresponsive to loop diuretic agents alone might benefit from the addition of a thiazide agent. Metolazone is the most commonly used agent, but the benefit is probably a class effect. Hypokalemia or hyponatremia are commonly noted with this combination, and therefore electrolyte monitoring is important.

**Inotropic agents.** There are no controlled clinical trial data to guide the use of inotropic agents in the setting of acute HF because of myocardial disease in children. Even in adults, only a few randomized controlled studies have assessed the safety and efficacy of inotropic agents in advanced HF, and have not demonstrated a long-term survival benefit.

Nevertheless, these medications appear to improve end-organ perfusion in patients with low cardiac output, including in children with myocardial dysfunction after cardiopulmonary bypass, and also provide short-term symptomatic relief. However, the goal of therapy needs to be carefully considered: although there is good empirical evidence that inotropes can bridge patients to mechanical circulatory support or cardiac transplantation, their toxicities prohibit routine use and limit their utility to only the sickest patients, who genuinely require rescue from low cardiac output with organ dysfunction with metabolic acidosis. The requirement for inotropic support for more than 48 hours requires a plan for weaning of support, transition to a more viable means of circulatory support, and consideration of the need for cardiac transplantation.<sup>94,95</sup>

**Milrinone.** Children with decompensated HF who present with clinical evidence of low cardiac output syndrome (poor perfusion, decreased urine output, cool extremities) might return to an adequately perfused state when inotropes are added to standard diuretic therapy. Milrinone, an inotrope with vasodilatory properties, can increase cardiac index, reduce pulmonary capillary wedge pressure, and reduce systemic vascular resistance in adults with advanced HF.<sup>96,97</sup> In infants and children, milrinone can prevent low cardiac output syndrome after cardiac surgery.<sup>98</sup> Milrinone might cause peripheral dilation and should be used with caution in hypotensive patients. Dosing is indicated in [Supplemental Table S2](#).

**Catecholaminergic drugs.** Dopamine is a sympathomimetic agent that increases heart rate, stroke volume, and systemic vascular resistance in a dose-related fashion.<sup>99</sup> Epinephrine and norepinephrine have similar properties, but are more commonly associated with arrhythmias, compromised distal perfusion, and increased myocardial oxygen demand. Dobutamine, a catecholamine analogue that activates  $\beta_1$ -adrenergic receptors, might be considered as an alternative choice, but higher doses might be required in patients who are already taking  $\beta$ -blockers. Dosing is indicated in [Supplemental Table S2](#).

### Vasodilator agents

Systemic vasodilators are occasionally used in children in the setting of acute decompensated HF, to reduce afterload. Although commonly used in adults in whom hypertension is a frequent comorbidity, there is insufficient evidence of

**RECOMMENDATION**

- F2. Children presenting with HF because of reduced cardiac output with end-organ dysfunction are likely to benefit from inotropic therapy as a rescue strategy. In this setting, milrinone, dobutamine, and low dose epinephrine have all shown efficacy in children (Strong Recommendation, Low-Quality Evidence).
- F3. Inotropic therapy should be confined to patients with depressed systolic function and clinical evidence of low cardiac output syndrome who can be closely monitored for tachyarrhythmias and blood pressure lability (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** These Recommendations place a high priority on improving cardiac output in an emergency setting, and acknowledge the deleterious effect of sustained inotropic stimulation on myocardial survival.

efficacy to justify routine Recommendations as to their use in pediatric HF patients. They might have an adjunctive role in stabilizing patients with reduced systolic function and associated hypertension because of renal dysfunction or other causes. Specific drugs considered optional are as follows.

**Nitroprusside sodium.** Administered intravenously as a continuous infusion, nitroprusside is an effective dilator of arteriolar and smooth muscle cells. It can acutely improve cardiac index in children with acute HF.<sup>100</sup> Prolonged administration (> 72 hours), especially when associated with renal failure, can result in thiocyanate toxicity.

**Nitroglycerine.** Despite its common use in the adult with acute HF, nitroglycerin, predominantly a venodilator, is uncommonly used in the children because there is no evidence demonstrating a specific indication for its use in HF in children.

**Nesiritide.** This synthetic analogue of natriuretic peptide has vasodilatory and natriuretic effects. Nesiritide has been used for more than a decade in adults with acute HF, although the most recent data do not suggest a significant long-term benefit for this particular drug.<sup>101</sup> There is very limited evidence to support the use of this drug in children.<sup>102,103</sup>

### **Chronic therapy for HF: angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker therapy**

Randomized trials in adult patients have repeatedly shown that angiotensin-converting enzyme inhibitor (ACEi) therapy reduces symptoms and improves survival of HF patients at optimal doses. Studies in children have focused predominantly on hemodynamic markers.<sup>104-109</sup> Some retrospective data<sup>110</sup> have demonstrated a survival benefit for children with CM and HF,<sup>111</sup> however, other data have failed to show any survival benefit.<sup>7,112</sup> Although widely used, ACEi therapy remains unvalidated by any randomized controlled trial measuring survival in children with symptomatic HF. Recent data suggest that the use of a tissue-specific ACEi (perindopril)

in boys with Duchenne's muscular dystrophy can delay the progression of LV remodelling,<sup>113</sup> but in contrast, ACEi therapy has appeared to be only marginally effective in anthracycline-induced CM.<sup>114</sup> Angiotensin receptor blockade therapy in children with HF is untested, although in a small study, losartan was ineffective in reducing NT-proBNP levels or increasing exercise performance in young adults with systemic RV dysfunction.<sup>115</sup>

**RECOMMENDATION**

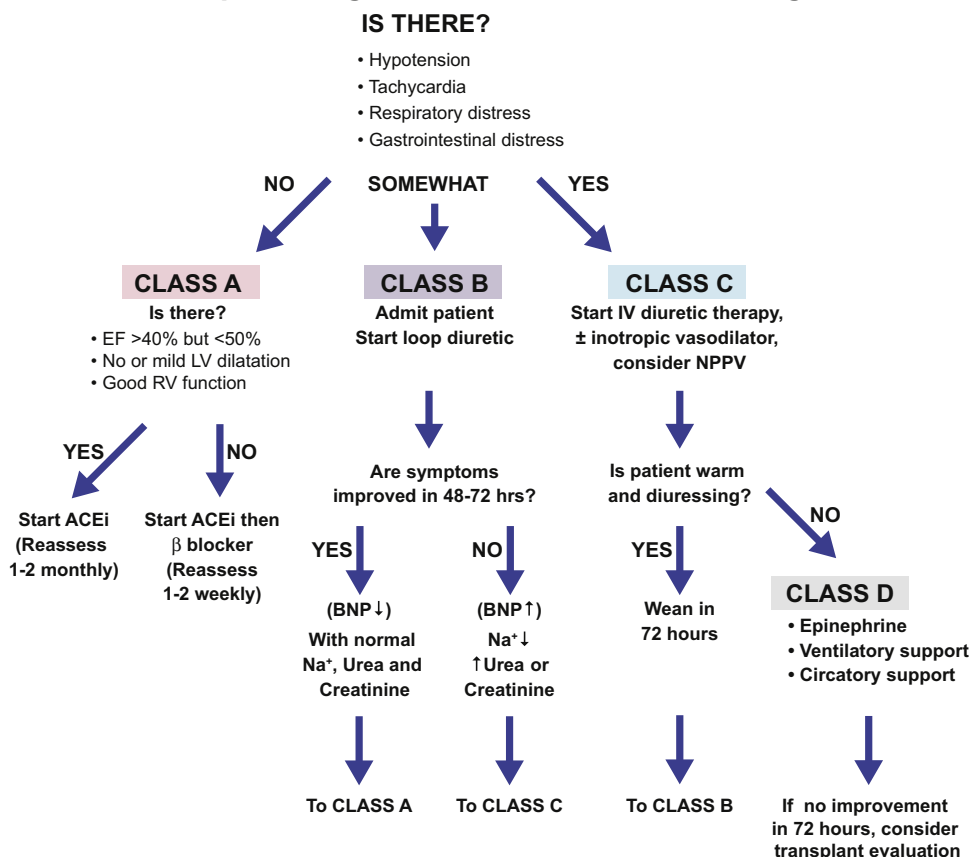
- F4. The use of ACEi therapy is indicated in children with HF because of primary heart muscle disease of the systemic left ventricle (Strong Recommendation, Moderate-Quality Evidence).

**Values and preferences.** The Recommendation favours commitment to a course of medical therapy, which, although of uncertain duration, is associated with symptom improvement, and possibly with survival benefit in certain patient groups.

**Methods in practice**

- In advanced HF, ACEi therapy introduction should occur after stabilization of HF symptoms with diuretic and simultaneous to inotropic support withdrawal. Uptitration can proceed safely over 3-10 days in most inpatients, and can be more gradual in outpatients.
- Captopril is the typical first choice for most infants and with enalapril being an appropriate choice for those older than the age of 2 years (see [Supplemental Table 2](#)). The use of a captopril tablet dissolved in a precise volume of water, and dosing a fraction of the suspension (dissolve and dose method) overcomes the problem of the short half-life of this medication in suspension form.
- In older children with stable hemodynamic status, longer-acting ACEi therapy, such as ramipril and perindopril, might be considered for use to enhance adherence.
- Caution is advised when these agents are used in the first 4 months of life, because renal dysfunction is more common,<sup>116</sup> and therefore uptitration must be carefully monitored. A small drop in systolic blood pressure is typically noted in patients who take an ACEi. This might occasionally exceed the expected 5%-10% drop in baseline values, necessitating observation for up to 2 hours after the first dose.<sup>117</sup> The magnitude of the effect has been reported to be greater in patients with high renin levels (who commonly also have hyponatremia).<sup>106,118</sup>
- A creatinine rise of greater than 50% over baseline value in any patient requires a reassessment of fluid balance and diuretic therapy, and consideration for a dosage reduction or withdrawal of ACEi therapy.<sup>116</sup>
- Adequate pregnancy avoidance measures are required in adolescent female patients who take an ACEi because of its teratogenic effects.

## Simplified algorithm for heart failure management



**Figure 2.** Simplified decision-making in symptomatic acute decompensated heart failure management. Groups A-D correspond to those designated in Figure 1. It is usual to admit all patients who are symptomatic at their initial presentation. Those with mild symptoms and no vomiting/gastrointestinal symptoms might respond to oral therapy, although IV diuretics are typically required. It is usual to reserve IV inotropic/vasodilator therapy for those who have underperfusion and volume overload. Most patients should be able to achieve oral maintenance therapy, at least on a temporary basis. ±, with or without; ACEi, angiotensin-converting enzyme inhibitor; BNP, brain natriuretic peptide; EF, ejection fraction; IV, intravenous; LV, left ventricular; NPPV, noninvasive positive pressure ventilation; RV, right ventricular.

### β-Adrenergic antagonists

β-Blockade is an established therapy in adults with congestive HF, with benefits attributed to the blunting of maladaptive sympathetic responses, heart rate slowing, and improved diastolic ventricular filling. The efficacy of this therapy in children, including those with a structurally normal heart, however, remains unclear. Carvedilol (a nonselective β-adrenoreceptor antagonist with α-adrenergic blocking activity) is commonly used in pediatric patients with HF. However, a multicentre, randomized, double-blind, placebo controlled study of 161 children and adolescents with symptomatic systolic HF did not show an improvement in their composite clinical status after 8 months of treatment with carvedilol, although improvements in EF were noted.<sup>119</sup> The study, however, was underpowered, and included children with a systemic right ventricle and single ventricle physiology, and this diversity might have compromised the ability to determine a benefit for patients with DCM. The dosing frequency of carvedilol might also not have been optimal for younger children.<sup>120</sup> In a smaller single centre study of children with severe LV systolic dysfunction, carvedilol was found to be effective in preventing death and transplantation and in improving clinical

and echocardiographic parameters.<sup>121</sup> These findings are supported by uncontrolled small-scale retrospective analyses.<sup>47,122</sup> The evidence to support the use of alternative β-adrenergic blockers such as metoprolol or bisoprolol is well established in adults, but can only be extrapolated to children with HF.

### RECOMMENDATION

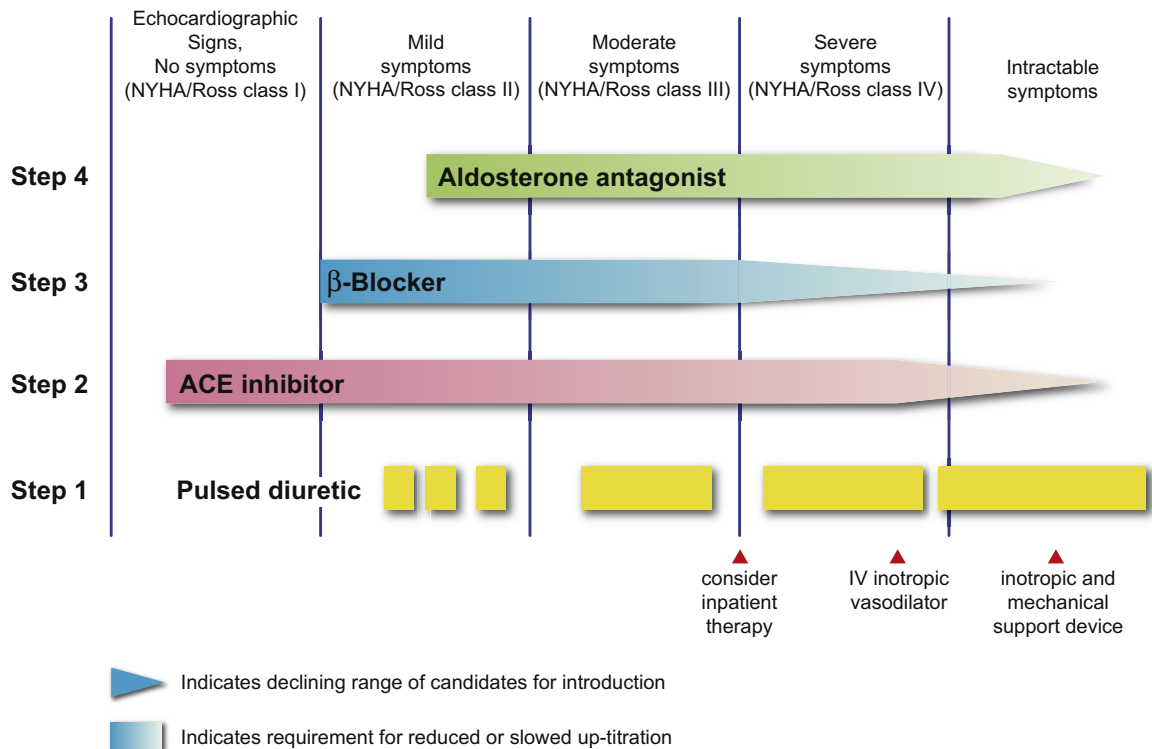
F5. Treatment with a β-adrenergic antagonist such as carvedilol, metoprolol, or bisoprolol might be initiated in the treatment of moderate to severe systolic dysfunction of a systemic left ventricle (Conditional Recommendation, Moderate-Quality Evidence).

**Values and preferences.** This Recommendation is based on the premise that patients are willing to accept a relatively low rate of side effects for potential clinical benefits in the absence of conclusive evidence for benefit.

### Methods in practice

- Dosing and uptitration instructions are provided in [Supplemental Table S2](#). In general, a starting dose of

## Stepwise introduction of medical therapy in heart failure



**Figure 3.** A symptom-based guide to the introduction of oral maintenance therapy for children with chronic heart failure (HF). The introduction of  $\beta$ -blocker therapy might be considered in patients already taking ACE inhibitor therapy with asymptomatic persistent moderate reduction in left ventricular ejection fraction (usually ejection fraction less than 40%), especially if the etiology is considered to be ischemic heart disease. **Lighter shading** for each drug indicates when the possibility of a lower target dose, or slower increment than usual is needed, because of advanced HF with severely compromised systolic function. Narrowing of the bars indicates the possibility that fewer patients will tolerate the introduction of that agent at that given symptomatic stage. Note the preferred use of pulsed diuretic therapy, which becomes more frequent as symptoms advance. **Red arrows** indicate the point at which admission to hospital and additional support therapies might be required. ACE, angiotensin-converting enzyme; IV, intravenous; NYHA, New York Heart Association.

0.05 mg/kg every 12 hours is required, with pharmacokinetics in children younger than 4 years favouring dosing every 8 hours.

- The initiation of  $\beta$ -blocker therapy after inotropic support requires caution. There is limited evidence to guide practice, so Recommendations for decision-making are largely empirical, with a guide provided in Figure 2. It should be noted that initiation of  $\beta$ -blocker therapy might be considered in children who are asymptomatic but have a persistent moderate reduction in LV EF (usually less than 40%) despite being established while using optimal ACEi therapy, especially if the etiology is considered to be ischemic heart disease. The general approach to sequential addition of chronic medical therapy in pediatric HF patients is summarized in Figure 3.
- In older children with stable hemodynamic status, consideration might be given to starting a  $\beta$ -blocker as soon as ACEi dosing has been established.

### Aldosterone antagonist therapy

Therapy with drugs that block the effects of aldosterone is well established in adults with systolic HF,<sup>123</sup> in reducing

mortality in selected patients with HF.<sup>124,125</sup> Data regarding the role of spironolactone or related agents in the treatment of children with HF are very limited.

### RECOMMENDATION

F6. Aldosterone antagonist therapy is reasonable in children with chronic systolic HF, provided renal function is normal or only mildly impaired. Close monitoring of renal function and serum potassium is required when coadministering aldosterone antagonist therapy with ACEi therapy (Conditional Recommendation, Low-Quality Evidence).

### Methods in practice

- Spironolactone is the typical agent used, because experience with eplerenone in children is limited. Spironolactone is typically initiated for patients in whom therapy with an ACEi and  $\beta$ -blocker has not resulted in improved ventricular function or reversal of ventricular remodelling (as indicated in Fig. 3).

- Hyperkalemia might result in patients who receive spironolactone and an ACEi, especially if renal function is already compromised. Therefore, potassium levels and renal function indices should be checked before starting spironolactone, within 7-14 days after introduction, and periodically thereafter. Any potassium supplementation should be carefully re-evaluated.
- Dosing suggestions are provided in [Supplemental Table S2](#), with the usual starting dose of 1 mg/kg/d, and the target maximum of 2 mg/kg/d being tolerated by most patients.<sup>126</sup>
- Male gynecomastia is a nonreversible complication, and must be closely monitored.

## Digoxin

Digoxin has been studied extensively in adults with congestive HF, in whom there is some evidence of acute hemodynamic benefit.<sup>127</sup> In the setting of chronic congestive HF in adults, digoxin use decreased the rate of hospitalization and improved quality of life, but not survival.<sup>128</sup> In children, the addition of digoxin to diuretic therapy has traditionally occurred in infants with a large ventricular septal defect and pulmonary congestion because of overcirculation. However, digoxin is not reported to result in improved contractility, or improvement in clinical symptoms in this setting. There are no pediatric data supporting the use of digoxin in children with structurally normal hearts and systolic dysfunction, and therefore no Recommendation can be made for routine digoxin use in children with HF. If it is already being used in conjunction with carvedilol in children (for arrhythmic control for example), digoxin dosing might require reduction.<sup>129</sup>

## Medical management of myocarditis

The typical approach to therapy for myocarditis in children focuses on supportive care, and recognition of clinical deterioration which is a common occurrence.<sup>130</sup> Because of risks of hemodynamic instability and rhythm disturbances, patients should be admitted to an intensive care unit or ward with close monitoring, including cardiac monitoring. The role of the immune system in the pathogenesis of myocarditis has led to an ongoing interest in the role of immunomodulation and immunosuppression as therapeutic modalities. A demonstration of a beneficial effect for this approach in the pediatric age group has been difficult to achieve, because of a lack of robust, adequately designed and powered studies, and because of the frequent occurrence of spontaneous recovery. Results of a recent meta-analysis examining available studies in adults and children did not indicate any beneficial effect of immunosuppressive therapy on survival or LV remodelling in patients with myocarditis.<sup>131</sup>

**Corticosteroid therapy.** Small and predominantly retrospective cohort studies in children with acute myocarditis have suggested that steroids (alone or in combination with other immunosuppressive agents) might be beneficial to survival and symptomatic recovery.<sup>90,132</sup> Prospective studies are, however, limited to a single small randomized controlled trial comparing 3 different immunosuppressive treatment strategies

including a “steroid only” arm.<sup>69</sup> This study failed to show any hemodynamic or clinical improvement with steroid use alone, and some benefit in these parameters when steroids were combined with cyclosporine or azathioprine. A recent Cochrane review does not support a role for corticosteroids in the treatment of myocarditis.<sup>133</sup> Additional data from a large registry series identified no effect of treatment strategy on patient survival in clinically diagnosed or biopsy-confirmed myocarditis.<sup>134</sup>

**Intravenous immunoglobulin G.** Numerous case reports, and 1 retrospective study have suggested a potential benefit of intravenous immunoglobulin G (IVIG) in the treatment of myocarditis.<sup>135</sup> There have been no randomized controlled trials of this therapy in children.<sup>134</sup> A recent Cochrane review of this therapy for adult patients failed to show any difference between those who did or did not receive IVIG, with regard to mortality, the need for transplantation, or insertion of an LV assist device.<sup>134</sup> Recent registry data and national patient information dataset reviews also do not suggest a difference in outcome in pediatric myocarditis treated with IVIG.<sup>130,134</sup>

## RECOMMENDATION

- F7. A standard approach to HF management should be applied in patients with myocarditis including inotropic support and diuretic therapy (Strong Recommendation, Moderate-Quality Evidence).
- F8. For fulminant myocarditis, mechanical circulatory support should be considered. Invasive therapies are considered acceptable considering the prospect of spontaneous recovery (Strong Recommendation, Moderate-Quality Evidence).
- F9. Corticosteroids are not recommended as a routine treatment for myocarditis, particularly in the absence of robust randomized controlled trial evidence. Continued speculative use of immunosuppressive therapy in the absence of a prospective clinical trial will not contribute to the evidence base of management for this disorder (Conditional Recommendation, Low-Quality Evidence).
- F10. IVIG is not recommended as a routine treatment for myocarditis (Conditional Recommendation, Low-Quality Evidence).

**Values and preferences.** These Recommendations place a high priority on conservative management in an observed and monitored hospital setting when this disease is in evolution.

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## References

- Thakur V, Fouron JC, Mertens L, Jaeggi ET. Diagnosis and management of fetal heart failure. *Can J Cardiol* 2013;29:759-67.
- Kantor PF, Andelfinger G, Dancea A, Khairy P. Heart failure in congenital heart disease. *Can J Cardiol* 2013;29:753-4.
- Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. *New Engl J Med* 2003;348:1647-55.
- Andrews RE, Fenton MJ, Ridout DA, Burch M. New-onset heart failure due to heart muscle disease in childhood: a prospective study in the United Kingdom and Ireland. *Circulation* 2008;117:79-84.
- Rossano JW, Kim JJ, Decker JA, et al. Prevalence, morbidity, and mortality of heart failure-related hospitalizations in children in the United States: a population-based study. *J Card Fail* 2012;18:459-70.
- Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA* 2006;296:1867-76.
- Kantor PF, Abraham JR, Dipchand AI, Benson LN, Redington AN. The impact of changing medical therapy on transplantation-free survival in pediatric dilated cardiomyopathy. *J Am Coll Cardiol* 2010;55:1377-84.
- Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of Recommendations. *BMJ* 2008;336:924-6.
- Ross RD, Daniels SR, Schwartz DC. Plasma norepinephrine levels in infants and children with congestive heart failure. *Am J Cardiol* 1987;59:911-4.
- Wu JR, Chang HR, Huang TY, Chiang CH, Chen SS. Reduction in lymphocyte beta-adrenergic receptor density in infants and children with heart failure secondary to congenital heart disease. *Am J Cardiol* 1996;77:170-4.
- Laer S, Mir TS, Behn F, et al. Carvedilol therapy in pediatric patients with congestive heart failure: a study investigating clinical and pharmacokinetic parameters. *Am Heart J* 2002;143:916-22.
- Connolly D, Rutkowski M, Auslender M, Artman M. The New York University Pediatric Heart Failure Index: a new method of quantifying chronic heart failure severity in children. *J Pediatr* 2001;138:644-8.
- Ergul Y, Nisli K, Varkal MA, et al. Electrocardiographic findings at initial diagnosis in children with isolated left ventricular non-compaction. *Ann Noninvasive Electrocardiol* 2011;16:184-91.
- Nugent AW, Daubeney PE, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. *New Engl J Med* 2003;348:1639-46.
- Ross RD, Bollinger RO, Pinsky WW. Grading the severity of congestive heart failure in infants. *Pediatr Cardiol* 1992;13:72-5.
- Azevedo VM, Albanesi Filho FM, Santos MA, Castier MB, Tura BR. The impact of malnutrition on idiopathic dilated cardiomyopathy in children [in Portuguese]. *J Pediatr (Rio J)* 2004;80:211-6.
- Rivenes SM, Kearney DL, Smith EO, Towbin JA, Denfield SW. Sudden death and cardiovascular collapse in children with restrictive cardiomyopathy. *Circulation* 2000;102:876-82.
- Melacini P, Vianello A, Villanova C, et al. Cardiac and respiratory involvement in advanced stage Duchenne muscular dystrophy. *Neuromuscul Disord* 1996;6:367-76.
- Foerster SR, Canter CE, Cinar A, et al. Ventricular remodeling and survival are more favorable for myocarditis than for idiopathic dilated cardiomyopathy in childhood: an outcomes study from the Pediatric Cardiomyopathy Registry. *Circ Heart Fail* 2010;3:689-97.
- Kern J, Modi R, Atalay MK, Kochilas LK. Clinical myocarditis masquerading as acute coronary syndrome. *J Pediatr* 2009;154:612-5.
- English RF, Janosky JE, Ettedgui JA, Webber SA. Outcomes for children with acute myocarditis. *Cardiol Young* 2004;14:488-93.
- Narang A, Kumar P, Narang R, et al. Clinico-epidemiological profile and validation of symptoms and signs of severe illness in young infants (< 60 days) reporting to a district hospital. *Indian Pediatr* 2007;44:751-9.
- Camargo PR, Snitcowsky R, da Luz PL, et al. Favorable effects of immunosuppressive therapy in children with dilated cardiomyopathy and active myocarditis. *Pediatr Cardiol* 1995;16:61-8.
- Lee KJ, McCrindle BW, Bohn DJ, et al. Clinical outcomes of acute myocarditis in childhood. *Heart* 1999;82:226-33.
- Klugman D, Berger JT, Sable CA, He J, Khandelwal SG, Slonim AD. Pediatric patients hospitalized with myocarditis: a multi-institutional analysis. *Pediatr Cardiol* 2010;31:222-8.
- Satou GM, Lacro RV, Chung T, Gauvreau K, Jenkins KJ. Heart size on chest x-ray as a predictor of cardiac enlargement by echocardiography in children. *Pediatr Cardiol* 2001;22:218-22.
- Azevedo VM, Santos MA, Albanesi Filho FM, Castier MB, Tura BR, Amino JG. Outcome factors of idiopathic dilated cardiomyopathy in children - a long-term follow-up review. *Cardiol Young* 2007;17:175-84.
- Guo H, Lee JD, Ueda T, et al. Different clinical features, biochemical profiles, echocardiographic and electrocardiographic findings in older and younger patients with idiopathic dilated cardiomyopathy. *Acta Cardiol* 2005;60:27-31.
- Patel MS, Berg AM, Vincent RN, Mahle WT. Serum parameters and echocardiographic predictors of death or need for transplant in newborns, children, and young adults with heart failure. *Am J Cardiol* 2010;105:1798-801.

30. Ciszewski A, Bilinska ZT, Lubiszewska B, et al. Dilated cardiomyopathy in children: clinical course and prognosis. *Pediatr Cardiol* 1994;15: 121-6.
31. Badertscher A, Bauersfeld U, Arbenz U, Baumgartner MR, Schinzel A, Balmer C. Cardiomyopathy in newborns and infants: a broad spectrum of aetiologies and poor prognosis. *Acta Paediatr* 2008;97:1523-8.
32. Taliercio CP, Seward JB, Driscoll DJ, Fisher LD, Gersh BJ, Tajik AJ. Idiopathic dilated cardiomyopathy in the young: clinical profile and natural history. *J Am Coll Cardiol* 1985;6:1126-31.
33. Cianfrocca C, Pelliccia F, Nigri A, Critelli G. Resting and ambulatory ECG predictors of mode of death in dilated cardiomyopathy. *J Electrocardiol* 1992;25:295-303.
34. Udink ten Cate FE, Kruessell MA, Wagner K, et al. Dilated cardiomyopathy in children with ventricular preexcitation: the location of the accessory pathway is predictive of this association. *J Electrocardiol* 2010;43:146-54.
35. Kirchmann C, Kececioglu D, Korinthenberg R, Dittrich S. Echocardiographic and electrocardiographic findings of cardiomyopathy in Duchenne and Becker-Kiener muscular dystrophies. *Pediatr Cardiol* 2005;26:66-72.
36. Chenard AA, Becane HM, Tertrain F, De Kermadec JM, Weiss YA. Ventricular arrhythmia in Duchenne muscular dystrophy: prevalence, significance and prognosis. *Neuromuscul Disord* 1993;3:201-6.
37. Chang RK, Alladarid V. Electrocardiographic and echocardiographic features that distinguish anomalous origin of the left coronary artery from pulmonary artery from idiopathic dilated cardiomyopathy. *Pediatr Cardiol* 2001;22:3-10.
38. Goldberg SJ, Valdes-Cruz LM, Sahn DJ, Allen HD. Two-dimensional echocardiographic evaluation of dilated cardiomyopathy in children. *Am J Cardiol* 1983;52:1244-8.
39. Weintraub RG, Nugent AW, Davis A, King I, Bharucha T, Daubeney PE. Presentation, echocardiographic findings and long-term outcomes in children with familial dilated cardiomyopathy. *Prog Pediatr Cardiol* 2011;31:119-22.
40. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.
41. Paraskevidis IA, Adamopoulos S, Tsiapras D, Karatzas D, Kremastinos DT. Prognostic usefulness of echocardiographic dobutamine in younger (14 to 25 years) and older (40 to 55 years) patients with idiopathic dilated cardiomyopathy. *Am J Cardiol* 2004;93:251-5.
42. Wallis DE, O'Connell JB, Henkin RE, Costanzo-Nordin MR, Scanlon PJ. Segmental wall motion abnormalities in dilated cardiomyopathy: a common finding and good prognostic sign. *J Am Coll Cardiol* 1984;4:674-9.
43. Fisher SD, Easley KA, Orav EJ, et al. Mild dilated cardiomyopathy and increased left ventricular mass predict mortality: the prospective P2C2 HIV Multicenter Study. *Am Heart J* 2005;150:439-47.
44. Roche SL, Vogel M, Pitkanen O, et al. Isovolumic acceleration at rest and during exercise in children normal values for the left ventricle and first noninvasive demonstration of exercise-induced force-frequency relationships. *J Am Coll Cardiol* 2011;57:1100-7.
45. Van der Hauwaert LG, Deneff B, Dumoulin M. Long-term echocardiographic assessment of dilated cardiomyopathy in children. *Am J Cardiol* 1983;52:1066-71.
46. Udink Ten Cate FE, Lorenz SR, Khalil M, Schmidt BE, Sreeram N. Does reversed apical or basal left ventricular rotation in children with dilated cardiomyopathy recover following medical therapy? A two-dimensional speckle tracking study. *Int J Cardiol* 2011;153:330-3.
47. Erdogan I, Ozer S, Karagoz T, Celiker A, Ozkutlu S, Alehan D. Treatment of dilated cardiomyopathy with carvedilol in children. *Turkish J Pediatr* 2009;51:354-60.
48. Yeoh T, Hayward C, Benson V, et al. A randomised, placebo-controlled trial of carvedilol in early familial dilated cardiomyopathy. *Heart Lung Circ* 2011;20:566-73.
49. Pahl E, Sleeper LA, Canter CE, et al. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. *J Am Coll Cardiol* 2012;59:607-15.
50. Ramachandra G, Shields L, Brown K, Ramnarayan P. The challenges of prompt identification and resuscitation in children with acute fulminant myocarditis: case series and review of the literature. *J Paediatr Child Health* 2010;46:579-82.
51. Hammerer-Lercher A, Geiger R, Mair J, et al. Utility of N-terminal pro-B-type natriuretic peptide to differentiate cardiac diseases from noncardiac diseases in young pediatric patients. *Clin Chem* 2006;52: 1415-9.
52. Auerbach SR, Richmond ME, Lamour JM, et al. BNP levels predict outcome in pediatric heart failure patients: post hoc analysis of the Pediatric Carvedilol Trial. *Circ Heart Fail* 2010;3:606-11.
53. Sugimoto M, Manabe H, Nakau K, et al. The role of N-terminal pro-B-type natriuretic peptide in the diagnosis of congestive heart failure in children. Correlation with the heart failure score and comparison with B-type natriuretic peptide. *Circ J* 2010;74:998-1005.
54. Sahin M, Portakal O, Karagoz T, Hascelik G, Ozkutlu S. Diagnostic performance of BNP and NT-ProBNP measurements in children with heart failure based on congenital heart defects and cardiomyopathies. *Clin Biochem* 2010;43:1278-81.
55. Deshpande SR. B-type natriuretic peptide at presentation of dilated cardiomyopathy in children predicts outcome. *Congenital Heart Disease* 2011;6:539-40.
56. Ratnasamy C, Kinnamon DD, Lipshultz SE, Rusconi P. Associations between neurohormonal and inflammatory activation and heart failure in children. *Am Heart J* 2008;155:527-33.
57. Rusconi P, Kinnamon DD, Ratnasamy C, Lipshultz Miller SE. Etiology-specific prognostic value of serial measurements of NT-proBNP in heart failure. *J Heart Lung Transplant* 2009;1:5300.
58. Kocharian A, Shabaniyan R, Rahimzadeh M, et al. N-terminal Pro-B-type natriuretic peptide and ventricular dysfunction in children and adolescents. *Cardiol Young* 2009;19:580-8.
59. Cimen O, Oran B, Cimen D, et al. Release of N-terminal pro-brain natriuretic peptide in children with acute rheumatic carditis. *Cardiol Young* 2010;20:297-301.
60. Fried I, Bar-Oz B, Perles Z, Rein AJ, Zonis Z, Nir A. N-terminal pro-B-type natriuretic peptide levels in acute versus chronic left ventricular dysfunction. *J Pediatr* 2006;149:28-31.
61. Nasser N, Perles Z, Rein AJ, Nir A. NT-proBNP as a marker for persistent cardiac disease in children with history of dilated cardiomyopathy and myocarditis. *Pediatr Cardiol* 2006;27:87-90.
62. Wong DT, George K, Wilson J, et al. Effectiveness of serial increases in amino-terminal pro-B-type natriuretic peptide levels to indicate the

- need for mechanical circulatory support in children with acute decompensated heart failure. *Am J Cardiol* 2011;107:573-8.
63. Hongkan W, Soongswang J, Veerakul G, et al. N-terminal pro brain natriuretic peptide and cardiac function in doxorubicin administered pediatric patients. *J Med Assoc Thai* 2009;92:1450-7.
  64. Soker M, Kervancioglu M. Plasma concentrations of NT-pro-BNP and cardiac troponin-I in relation to doxorubicin-induced cardiomyopathy and cardiac function in childhood malignancy. *Saudi Med J* 2005;26:1197-202.
  65. Al-Biltagi M, Issa M, Hagar HA, Abdel-Hafez M, Aziz NA. Circulating cardiac troponins levels and cardiac dysfunction in children with acute and fulminant viral myocarditis. *Acta Paediatr* 2010;99:1510-6.
  66. Bottio T, Vida V, Padalino M, Gerosa G, Stellan G. Early and long-term prognostic value of Troponin-I after cardiac surgery in newborns and children. *Eur J Cardiothorac Surg* 2006;30:250-5.
  67. Soongswang J, Durongpisitkul K, Nana A, et al. Cardiac troponin T: a marker in the diagnosis of acute myocarditis in children. *Pediatr Cardiol* 2005;26:45-9.
  68. Sugimoto M, Ota K, Kajihama A, Nakau K, Manabe H, Kajino H. Volume overload and pressure overload due to left-to-right shunt-induced myocardial injury. Evaluation using a highly sensitive cardiac Troponin-I assay in children with congenital heart disease. *Circ J* 2011;75:2213-9.
  69. Price JF, Towbin JA, Denfield SW, et al. Arginine vasopressin levels are elevated and correlate with functional status in infants and children with congestive heart failure. *Circulation* 2004;109:2550-3.
  70. Venugopalan P, Agarwal AK. Plasma catecholamine levels parallel severity of heart failure and have prognostic value in children with dilated cardiomyopathy. *Eur J Heart Fail* 2003;5:655-8.
  71. Nishii M, Inomata T, Takehana H, et al. Serum levels of interleukin-10 on admission as a prognostic predictor of human fulminant myocarditis. *J Am Coll Cardiol* 2004;44:1292-7.
  72. Tsutamoto T, Hisanaga T, Wada A, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 1998;31:391-8.
  73. Tsutamoto T, Wada A, Matsumoto T, et al. Relationship between tumor necrosis factor-alpha production and oxidative stress in the failing hearts of patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2001;37:2086-92.
  74. Habeeb NM, Al Hadidi IS. Ongoing inflammation in children with rheumatic heart disease. *Cardiol Young* 2011;21:334-9.
  75. Cox GF, Sleeper LA, Lowe AM, et al. Factors associated with establishing a causal diagnosis for children with cardiomyopathy. *Pediatrics* 2006;118:1519-31.
  76. Kindel SJ, Miller EM, Gupta R, et al. Pediatric cardiomyopathy: importance of genetic and metabolic evaluation. *J Card Fail* 2012;18:396-403.
  77. Sparkes R, Patton D, Bernier F. Cardiac features of a novel autosomal recessive dilated cardiomyopathic syndrome due to defective importation of mitochondrial protein. *Cardiol Young* 2007;17:215-7.
  78. Yaplitto-Lee J, Weintraub R, Jansen K, Chow CW, Thorburn DR, Boneh A. Cardiac manifestations in oxidative phosphorylation disorders of childhood. *J Pediatr* 2007;150:407-11.
  79. Cazes A, Van Huyen JP, Fornes P, et al. Mechanical ventricular assistance in heart failure: pathology of the cardiac apex removed during device implantation. *Cardiovasc Pathol* 2010;19:112-6.
  80. Webber SA, Boyle GJ, Jaffe R, Pickering RM, Beerman LB, Fricker FJ. Role of right ventricular endomyocardial biopsy in infants and children with suspected or possible myocarditis. *Br Heart J* 1994;72:360-3.
  81. Chow LC, Dittrich HC, Shabetai R. Endomyocardial biopsy in patients with unexplained congestive heart failure. *Ann Intern Med* 1988;109:535-9.
  82. Lewis AB, Neustein HB, Takahashi M, Lurie PR. Findings on endomyocardial biopsy in infants and children with dilated cardiomyopathy. *Am J Cardiol* 1985;55:143-5.
  83. Grun S, Schumm J, Greulich S, et al. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. *J Am Coll Cardiol* 2012;59:1604-15.
  84. Pophal SG, Sigfusson G, Booth KL, et al. Complications of endomyocardial biopsy in children. *J Am Coll Cardiol* 1999;34:2105-10.
  85. Lidegran M, Odhner L, Jacobsson LA, Greitz D, Lundell B. Magnetic resonance imaging and echocardiography in assessment of ventricular function in atrially corrected transposition of the great arteries. *Scand Cardiovasc J* 2000;34:384-9.
  86. Lai WW, Gauvreau K, Rivera ES, Saleeb S, Powell AJ, Geva T. Accuracy of guideline Recommendations for two-dimensional quantification of the right ventricle by echocardiography. *Int J Cardiovasc Imaging* 2008;24:691-8.
  87. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002;90:29-34.
  88. Assomull RG, Prasad SK, Lyne J, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol* 2006;48:1977-85.
  89. Silva MC, Meira ZM, Gurgel Giannetti J, et al. Myocardial delayed enhancement by magnetic resonance imaging in patients with muscular dystrophy. *J Am Coll Cardiol* 2007;49:1874-9.
  90. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane Database Syst Rev* 2012;2:CD003838.
  91. Channer KS, McLean KA, Lawson-Matthew P, Richardson M. Combination diuretic treatment in severe heart failure: a randomised controlled trial. *Br Heart J* 1994;71:146-50.
  92. Gheorghiadu M, Konstam MA, Burnett JC Jr, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA* 2007;297:1332-43.
  93. Konstam MA, Gheorghiadu M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;297:1319-31.
  94. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002;287:1541-7.
  95. O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1999;138:78-86.



96. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986;73:III168-74.
97. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. *Circulation* 1986;73:III175-83.
98. Hoffman TM, Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003;107:996-1002.
99. Beregovich J, Bianchi C, Rubler S, Lomnitz E, Cagin N, Levitt B. Dose-related hemodynamic and renal effects of dopamine in congestive heart failure. *Am Heart J* 1974;87:550-7.
100. Beekman RH, Rocchini AP, Dick M 2nd, Crowley DC, Rosenthal A. Vasodilator therapy in children: acute and chronic effects in children with left ventricular dysfunction or mitral regurgitation. *Pediatrics* 1984;73:43-51.
101. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011;365:32-43.
102. Jefferies JL, Denfield SW, Price JF, et al. A prospective evaluation of nesiritide in the treatment of pediatric heart failure. *Pediatr Cardiol* 2006;27:402-7.
103. Behera SK, Zuccaro JC, Wetzel GT, Alejos JC. Nesiritide improves hemodynamics in children with dilated cardiomyopathy: a pilot study. *Pediatr Cardiol* 2009;30:26-34.
104. Rheuban KS, Carpenter MA, Ayers CA, Gutgesell HP. Acute hemodynamic effects of converting enzyme inhibition in infants with congestive heart failure. *J Pediatr* 1990;117:668-70.
105. Montigny M, Davignon A, Fouron JC, Biron P, Fournier A, Elie R. Captopril in infants for congestive heart failure secondary to a large ventricular left-to-right shunt. *Am J Cardiol* 1989;63:631-3.
106. Scammell AM, Arnold R, Wilkinson JL. Captopril in treatment of infant heart failure: a preliminary report. *Int J Cardiol* 1987;16:295-301.
107. Shaddy RE, Teitel DF, Brett C. Short-term hemodynamic effects of captopril in infants with congestive heart failure. *Am J Dis Child* 1988;142:100-5.
108. Shaw NJ, Wilson N, Dickinson DF. Captopril in heart failure secondary to a left to right shunt. *Arch Dis Child* 1988;63:360-3.
109. Sluysmans T, Styns-Cailteux M, Tremouroux-Wattiez M, et al. Intravenous enalaprilat and oral enalapril in congestive heart failure secondary to ventricular septal defect in infancy. *Am J Cardiol* 1992;70:959-62.
110. Lewis AB, Chabot M. The effect of treatment with angiotensin-converting enzyme inhibitors on survival of pediatric patients with dilated cardiomyopathy. *Pediatr Cardiol* 1993;14:9-12.
111. Stern H, Weil J, Genz T, Vogt W, Buhlmeyer K. Captopril in children with dilated cardiomyopathy: acute and long-term effects in a prospective study of hemodynamic and hormonal effects. *Pediatr Cardiol* 1990;11:22-8.
112. Burch M, Siddiqi SA, Celermajer DS, Scott C, Bull C, Deanfield JE. Dilated cardiomyopathy in children: determinants of outcome. *Br Heart J* 1994;72:246-50.
113. Duboc D, Meune C, Pierre B, et al. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. *Am Heart J* 2007;154:596-602.
114. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. *J Clin Oncol* 2004;22:820-8.
115. Dore A, Houde C, Chan KL, et al. Angiotensin receptor blockade and exercise capacity in adults with systemic right ventricles: a multicenter, randomized, placebo-controlled clinical trial. *Circulation* 2005;112:2411-6.
116. Leversha AM, Wilson NJ, Clarkson PM, Calder AL, Ramage MC, Neutze JM. Efficacy and dosage of enalapril in congenital and acquired heart disease. *Arch Dis Child* 1994;70:35-9.
117. Scammell AM, Arnold R. The effect of the first dose of captopril on blood pressure in infants in heart failure. *Int J Cardiol* 1989;22:377-9.
118. Robinson B, Heise CT, Moore JW, Anella J, Sokolowski M, Eshaghpour E. Afterload reduction therapy in patients following intraatrial baffle operation for transposition of the great arteries. *Pediatr Cardiol* 2002;23:618-23.
119. Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA* 2007;298:1171-9.
120. Albers S, Meibohm B, Mir TS, Laer S. Population pharmacokinetics and dose simulation of carvedilol in paediatric patients with congestive heart failure. *Br J Clin Pharmacol* 2008;65:511-22.
121. Azeka E, Franchini Ramires JA, Valler C, Alcides Bocchi E. Delisting of infants and children from the heart transplantation waiting list after carvedilol treatment. *J Am Coll Cardiol* 2002;40:2034-8.
122. Nishiyama M, Park IS, Yoshikawa T, et al. Efficacy and safety of carvedilol for heart failure in children and patients with congenital heart disease. *Heart Vessels* 2009;24:187-92.
123. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol* 1996;78:902-7.
124. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-17.
125. Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005;46:425-31.
126. Buck ML. Clinical experience with spironolactone in pediatrics. *Ann Pharmacother* 2005;39:823-8.
127. Gheorghiadu M, St Clair J, St Clair C, Beller GA. Hemodynamic effects of intravenous digoxin in patients with severe heart failure initially treated with diuretics and vasodilators. *J Am Coll Cardiol* 1987;9:849-57.
128. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. *N Engl J Med* 1997;336:525-33.
129. Ratnapalan S, Griffiths K, Costei AM, Benson L, Koren G. Digoxin-carvedilol interactions in children. *J Pediatr* 2003;142:572-4.
130. Ghelani SJ, Spaeder MC, Pastor W, Spurney CF, Klugman D. Demographics, trends, and outcomes in pediatric acute myocarditis in

- the United States, 2006 to 2011. *Circ Cardiovasc Qual Outcomes* 2012;5:622-7.
131. Liu C, Chen J, Liu K. Immunosuppressive treatment for inflammatory cardiomyopathy: meta-analysis of randomized controlled trials. *Int Heart J* 2005;46:113-22.
132. Chan KY, Iwahara M, Benson LN, Wilson GJ, Freedom RM. Immunosuppressive therapy in the management of acute myocarditis in children: a clinical trial. *J Am Coll Cardiol* 1991;17:458-60.
133. Chen HS, Liu J, Yang M. Corticosteroids for viral myocarditis. *Cochrane Database Syst Rev* 2006;CD004471.
134. Robinson J, Hartling L, Vandermeer B, Crumley E, Klassen TP. Intravenous immunoglobulin for presumed viral myocarditis in children and adults. *Cochrane Database Syst Rev* 2005;CD004370.
135. Drucker NA, Colan SD, Lewis AB, et al. Gamma-globulin treatment of acute myocarditis in the pediatric population. *Circulation* 1994;89:252-7.

### Supplementary Material

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