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.
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) 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. 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, 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.

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, and less than 50% of children who present with symptomatic HF survive for 5 years without cardiac transplantation, 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 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 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. 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, but without secondary validation of the predictive value for clinical outcomes. An age-stratified modification of the Ross classification has been proposed, 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.

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

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important influence on our confidence in the estimate of effect and might change the estimate</td>
</tr>
<tr>
<td>Low</td>
<td>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</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain</td>
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**Table 2. Symptoms characteristic of heart failure in children**

<table>
<thead>
<tr>
<th>Commonly encountered</th>
<th>Less commonly encountered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants and young children</td>
<td>Tachypnea</td>
</tr>
<tr>
<td></td>
<td>Feeding difficulty (reflux, vomiting, feeding refusal)</td>
</tr>
<tr>
<td></td>
<td>Diaphoresis</td>
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<tr>
<td></td>
<td>Pallor</td>
</tr>
<tr>
<td>Old children and adolescents</td>
<td>Fatigue</td>
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<tr>
<td></td>
<td>Effort intolerance</td>
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<tr>
<td></td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td>Orthopnea</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
</tbody>
</table>
Hospitalization and immediate supportive care is typically required. 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. They manifest most commonly in the first year of life. 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.

**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, 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. 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 enzymeopathies, 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. 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. 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%). Outcomes for these patients are generally good in childhood: at least 66% recover, 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. (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. 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, and the severity of presenting illness appears to affect survival. 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. 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.

**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. There is emerging evidence that certain markers such as lymphocytopenia or hyponatremia might predict worsened outcomes, however, this is currently inconclusive.

**RECOMMENDATION**

E2. Assessment of electrolytes (Na⁺, K⁺, Cl⁻, Ca²⁺), 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, with the most common findings of sinus tachycardia, LV hypertrophy, ST-T changes, myocardial infarction patterns, and first degree atrioventricular block.
In idiopathic DCM, electrocardiography (ECG) findings of left bundle branch block and left atrial enlargement correlated with HF-related deaths.33

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.

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 ectopy on Holter monitoring, along with prolonged repolarization on ECG, were independent predictors of sudden death.35 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.

**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.37 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.38,39 LV systolic dysfunction in children is currently defined by an EF < 25% and/or an EF < 55%.40

Specific echocardiographic appearances of the CMs vary considerably, and the phenotype-genotype correlation is not always consistent. Stress echocardiography using pharmacologic41 or exercise stress might demonstrate segmental wall motion abnormalities42 and changes in LV thickness.43 These are becoming important to evaluate ventricular reserve capacity, which is of growing interest in the risk stratification of children with HF.44

**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,45 and to assess the response to therapy.

**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 or noncardiac disease.51-52 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.

Elevated BNP levels might be associated with worseoutcome in HF. In addition, a significant relationship between increased NT-proBNP and increased symptoms, decreased ventricular function, increased ventricular volume, and diastolic dysfunction has been demonstrated. NT-proBNP is highest in acute myocardial dysfunction, declines with treatment or recovery from disease, and shows less of a decline in patients who progress to mechanical circulatory support. In chemotherapy patients, higher NT-proBNP levels are associated with higher treatment doses of doxorubicin and abnormal echocardiographic parameters including ventricular dysfunction. 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. Troponin T is likely to be more elevated in HF resulting from acute myocarditis but does not correlate with outcome.

**Other biomarkers.** Other biomarkers that have been investigated in pediatric HF are the circulating hormones arginine vasopressin, epinephrine, and norepinephrine, the interleukins, and C-reactive protein 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. Some disorders 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. 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
children, previously 1 of the main reasons for obtaining biopsy
use of immunosuppressive or immune-modulating therapy in
myocarditis, myocardial edema on T2-weighted CMRI can
diseases like myocarditis. In patients with biopsy-proven
potential in diseases including the primary CMs and acquired
Cardiac MRI
nasopharyngeal samples as appropriate.
parvovirus, hepatitis C, and the herpes group viruses (EBV,
myocarditis: typical viral pathogen screening using polymerase
isolate a viral pathogen to support a clinical diagnosis of
increase yield,79,83 but also the hazards of the procedure. EMB
The addition of LV biopsy or MRI-guided biopsy might
previously being considered. 79,80 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, vari-
ation in pathological interpretation, and sampling errors. 80-82
The addition of LV biopsy or MRI-guided biopsy might increase yield, 79,83 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. 83 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. 19 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. 15 The
sensitivity of these changes is increased by simultaneous
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. 85-87 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. 88 This technique offers insight into the pathophysi-
ology 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. 89
CMRI criteria for the diagnosis of myocarditis have been
proposed with several alternative tissue-characterization tech-
niques. 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

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 unex-
plained 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).

RECOMMENDATION

E14. A diagnosis of acute myocarditis should be consid-
ered in all children, regardless of age, who present
with new onset HF without a history of decreased
functional capacity, and specifically if echocardiog-
graphic 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 recom-
mended 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 con-
firmation via biopsy, except in specific cases as outlined in
Recommendation E15. The trade-off is diagnostic
confirmation for increased safety.

RECOMMENDATION

E16. CMRI might assist in the clinical diagnosis of
myocarditis, and might provide additional infor-
mation 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.90 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.91

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.92 No survival benefit has been demonstrated with the use of these agents93 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.94,95

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.96,97 In infants and children, milrinone can prevent low cardiac output syndrome after cardiac surgery.98 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.99 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 β1-adrenergic receptors, might be considered as an alternative choice, but higher doses might be required in patients who are already taking β-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
for this particular drug. There is very limited evidence 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. 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. There is very limited evidence to support the use of this drug in children.

**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. Some retrospective data have demonstrated a survival benefit for children with CM and HF, however, other data have failed to show any survival benefit. 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, but in contrast, ACEi therapy has appeared to be only marginally effective in anthracycline-induced CM. Angiotensin receptor blocker 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.

**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.

**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. 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.

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**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. 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. 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. These findings are supported by uncontrolled small-scale retrospective analyses. 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...
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 β-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 β-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. 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. ACEi, angiotensin-converting enzyme; IV, intravenous; NYHA, New York Heart Association.

Aldosterone antagonist therapy

Therapy with drugs that block the effects of aldosterone is well established in adults with systolic HF, in reducing mortality in selected patients with HF. 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 β-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.126
- Male gynaecomasia 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. In the setting of chronic congestive HF in adults, digoxin use decreased the rate of hospitalization and improved quality of life, but not survival. 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.129

**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. 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.131

**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. Prospective studies are, however, limited to a single small randomized controlled trial comparing 3 different immunosuppressive treatment strategies including a “steroid only” arm. 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. Additional data from a large registry series identified no effect of treatment strategy on patient survival in clinically diagnosed or biopsy-confirmed myocarditis.134

**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. There have been no randomized controlled trials of this therapy in children. 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. Recent registry data and national patient information dataset reviews also do not suggest a difference in outcome in pediatric myocarditis treated with IVIG.130,134

### 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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**Supplementary Material**

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at [www.onlinecjc.ca](http://www.onlinecjc.ca) and at [http://dx.doi.org/10.1016/j.cjca.2013.08.008](http://dx.doi.org/10.1016/j.cjca.2013.08.008).