

Clinical Updates and Guidelines

Canadian Cardiovascular Society/Canadian Pediatric Cardiology Association Focused Guidelines on Acute Heart Failure in Children

Primary Panel: Aamir Jeewa, MB, BCh (Co-chair),^a Ivan D. Florez, MD, MSc, PhD,^{b,c,d} Carlos Cuello-Garcia, MD, PhD,^b Nassiba Alami, MD,^e Luis Altamirano-Diaz, MD,^{f,g} Kathryn Armstrong, MB, MCh,^h Jenna Ashkanase, MD,ⁱ Chentel Cunningham, PhD, NP,^j Santokh Dhillon, MD,^k Anne Dipchand, MD,^a Linda Fazari, NP-Paeds,^a Lars Grosse-Wortmann, MD,^l Paula Holinski, MD,^j Michael Khoury, MD,^j Kimberly Y. Lin, MD,^m Joseph Rossano, MD, MS,^m Simon Urschel, MD,^j Laura Zahavich, MSc, CGC,ⁿ Paul F. Kantor, MB, BCh, MSc,^o and Jennifer Conway, MD, MSc (Co-chair),^j

Review Panel: Joseph Atallah, MD, CM, MSc,^j Holger Bucholz, MD, RN,^j Catherine Chant-Gambacourt, MN, NP,ⁱ Frédéric Dallaire, MD, PhD,^p Adrian Dancea, MD,^q Anne Fournier, MD,^e Kristen George, NP,^a Steven Greenway, MSc, MBA, MD,^{r,s} Derek G. Human, MA, BM, BCh,^h Jane Loughheed, BA, MD,^t Allison Mejilla, BSc, BScPharm, ACRP,^u Jack F. Price, MD,^v S. Lucy Roche, MB, ChB,^w and Lindsay Ryerson, MD^j

^a Division of Cardiology, The Hospital for Sick Children, Toronto, Ontario, Canada; ^b Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada; ^c Department of Pediatrics, University of Antioquia, Medellín, Colombia; ^d Pediatric Intensive Care Unit, Clinica Las Americas-AUNA, Medellín, Colombia; ^e Division of Pediatric Cardiology, Sainte-Justine University Hospital Center, University of Montreal, Montreal, Quebec, Canada; ^f Division of Children's Health & Therapeutics, Children's Health Research Institute, London Health Sciences Centre, London, Ontario, Canada; ^g Division of Pediatric Cardiology, Western University, London, Ontario, Canada; ^h Division of Pediatric Cardiology, British Columbia Children's Hospital, Vancouver, British Columbia, Canada; ⁱ Division of Cardiology, McMaster Children's Hospital, McMaster University, Hamilton, Ontario, Canada; ^j Division of Pediatric Cardiology, Stollery Children's Hospital, Edmonton, Alberta, Canada; ^k Division of Cardiology, Department of Pediatrics, Izaak Walton Killam Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada; ^l Division of Cardiology, Department of Pediatrics, Doernbecher Children's Hospital, Oregon Health and Science University, Portland, Oregon, USA; ^m Division of Cardiology, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania, USA; ⁿ Division of Clinical & Metabolic Genetics, The Hospital for Sick Children, Toronto, Ontario, Canada; ^o Division of Cardiology, Department of Pediatrics, Keck School of Medicine of the University of Southern California, Children's Hospital Los Angeles, Los Angeles, California, USA; ^p Department of Pediatrics, Université de Sherbrooke, and Centre de recherche du Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec, Canada; ^q Division of Pediatric Cardiology, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada; ^r Department of Pediatrics and Cardiac Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; ^s University of Calgary, Cumming School of Medicine, Calgary, Alberta, Canada; ^t Division of Pediatric Cardiology, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada; ^u Pharmacy Services, University of Alberta Hospital, Alberta Health Services, Edmonton, Alberta, Canada; ^v Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA; ^w Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada

Keywords: Pediatrics; acute heart failure; guidelines; myocarditis; mechanical circulatory support

Corresponding author: Dr Aamir Jeewa, Labatt Family Heart Centre, 555 University Ave, Toronto, Ontario M5G 1X8, Canada. Tel.: +1-416-813-7654.

E-mail: aamir.jeeva@sickkids.ca

 @JediJeewa

 @jediJeewa.bsky.social

Linkedin: <https://www.linkedin.com/in/aamir-jeeva-04074b27>

The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca. 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.

Received for publication October 14, 2025. Revised manuscript received December 15, 2025, Accepted December 19, 2025.

ABSTRACT

Acute heart failure in children is a complex clinical syndrome associated with significant morbidity and mortality, often requiring intensive care management and consideration of advanced therapies. The heterogeneity in presentation and limited pediatric-specific data have historically led to wide variations in care. The Canadian Cardiovascular Society/Canadian Pediatric Cardiology Association focused guidelines on acute heart failure in children provides updated, evidence-informed recommendations to guide clinicians in diagnostic evaluation and therapeutic interventions. This focused guideline addresses 10 prioritized clinical questions and offers recommendations on the following topics: (1) use of cardiac magnetic resonance imaging; (2) prognostic use of brain natriuretic peptides, and (3) genetic testing; (4) strategies for diuretic initiation and (5) guideline-directed medical therapy; (6) choice of inotropic and vasoactive agents for acute support; (7) monitoring strategies including the role of pulmonary artery catheters; (8) timing for initiating durable ventricular assist device support; (9) the use of temporary mechanical circulatory support; and (10) indications and timing for left atrial decompression in children supported with extracorporeal membrane oxygenation. These recommendations are on the basis of systematic evidence reviews, the evidence to decision framework, and expert consensus, with detailed methodology and supporting evidence provided in [Supplementary material S1-S11](#).

The Canadian Cardiovascular Society (CCS) first published national guidelines on the presentation, diagnosis, and management of heart failure (HF) in children in 2013.¹ To date, this seminal work is one of the most cited guidelines in pediatric HF literature. Since that time, advances in pediatric HF science, increased utilization of mechanical circulatory support (MCS), and the evolution of precision diagnostic tools have markedly reshaped clinical practice for pediatric HF. Although Canadian data on the prevalence of pediatric HF are limited, evidence from the United States shows that, compared with adults with HF, children experience higher mortality rates, increasing hospital admissions, and greater resource utilization.²⁻⁹ These developments have necessitated an updated guideline that reflects current evidence and supports the provision of high-quality, evidence-informed care to this vulnerable population.

This *CCS/Canadian Pediatric Cardiology Association Pediatric Acute Heart Failure Guideline* provides focused, updated recommendations to guide clinicians in the acute management of pediatric acute HF (AHF), defined by the new onset or acute presentation of symptomatic HF necessitating hospital care whether that be in the emergency room or intensive care unit. Unlike the broader scope of the 2013 CCS guidelines, this update is intentionally narrowed and structured to include 10 rigorously developed questions around patients and/or population of interest (P), intervention (I), comparator (C), and outcomes (O) (PICO), emphasizing evidence in areas where practice variation and knowledge gaps remain. The writing group was cognizant of the paucity of

RÉSUMÉ

L'insuffisance cardiaque (IC) aiguë chez l'enfant est un syndrome clinique complexe associé à une morbidité et à une mortalité significatives, qui nécessite souvent une prise en charge en soins intensifs et un traitement avancé. L'hétérogénéité du tableau clinique et les données limitées spécifiques à l'enfant font qu'à ce jour, les soins varient beaucoup. Les lignes directrices de la Société cardiovasculaire du Canada/l'Association canadienne de cardiologie pédiatrique spécifiques à l'IC aiguë chez l'enfant fournissent des recommandations actualisées fondées sur des données probantes pour orienter les cliniciens lors de l'évaluation diagnostique et des interventions thérapeutiques. Ces lignes directrices spécifiques traitent de 10 questions cliniques prioritaires et proposent des recommandations sur les sujets suivants : 1) utilisation de l'imagerie par résonance magnétique cardiaque; 2) utilisation des peptides natriurétiques cérébraux à des fins pronostiques; 3) tests génétiques; 4) stratégies pour l'instauration du traitement diurétique; 5) traitement médical axé sur les lignes directrices; 6) choix des agents inotropes et vasoactifs pour le soutien d'urgence; 7) stratégies de surveillance, dont le rôle des cathéters artériels pulmonaires; 8) moment opportun pour la mise en place d'un dispositif d'assistance ventriculaire de longue durée; 9) utilisation d'un dispositif de soutien circulatoire mécanique temporaire; 10) indications et moment opportun de la décompression auriculaire gauche chez les enfants sous oxygénation par membrane extracorporelle. Ces recommandations s'appuient sur des examens systématiques de données probantes, un cadre d'aide à la décision basé sur les données probantes et un consensus d'experts, la méthodologie détaillée et les données sur lesquelles elles s'appuient étant fournies dans le [matériel supplémentaire S1 à S11](#).

pediatric-specific evidence compared with that in adults with HF and many of the recommendations relied upon the expert opinion of the primary panel.

This update specifically addresses:

- Diagnostic and monitoring modalities. The utility and application of advanced diagnostics, including cardiac magnetic resonance imaging (CMR), N-terminal pro hormone brain natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP) testing, genetic evaluation, and invasive hemodynamic monitoring tools such as pulmonary artery catheters (PACs).
- Therapeutic strategies. Comparative effectiveness and timing of key interventions such as inotropic support, left atrial (LA) decompression in patients receiving extracorporeal membrane oxygenation (ECMO), initiation and escalation of guideline-directed medical therapy (GDMT), timing of durable ventricular assist device (VAD) implantation, and the use of temporary MCS (tMCS).

The diagnosis and management of a child with AHF is highlighted in [Figures 1 and 2](#), which also depict aspects of the algorithm that are discussed in this guideline in the various PICO questions. These recommendations can be used to guide care of patients with HF regardless of the underlying cardiac anatomy, including in some cases those with congenital heart disease (CHD).

These recommendations are informed by a comprehensive systematic review of the available literature and refined

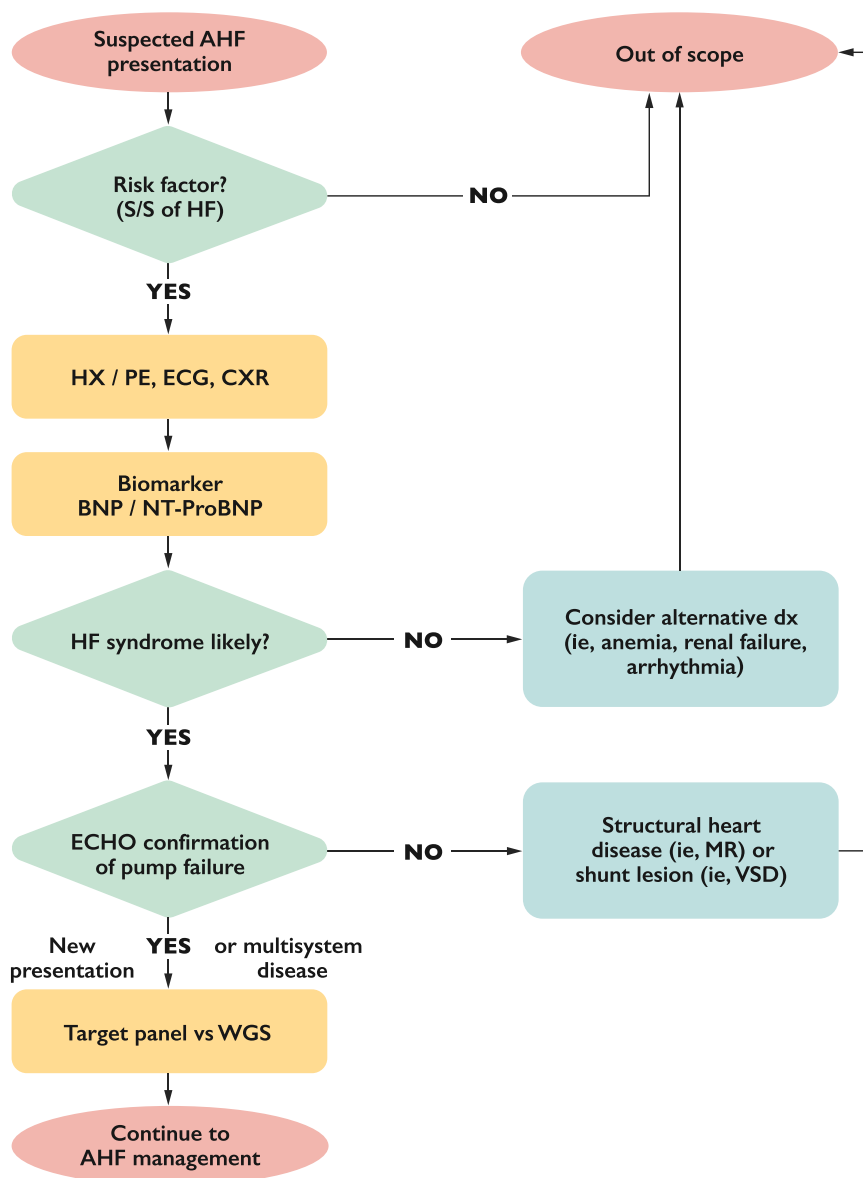


Figure 1. Diagnosis of acute heart failure (AHF) in children. Flow diagram depicts the diagnosis of a pediatric patient with new onset AHF. AHF, acute heart failure; BNP, B-type natriuretic peptide; CXR, chest radiograph; dx, diagnosis; ECG, electrocardiogram; ECHO, echocardiogram; HF, heart failure; HX, history; MR, mitral regurgitation; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; PE, physical examination; S/S, signs and symptoms; VSD, ventricular septal defect; WGS, whole genome sequencing.

through expert consensus. By addressing key clinical questions in pediatric AHF, this Canadian-led focused guideline aims to promote consistency in care, reduce practice variability, and ultimately improve outcomes for infants, children, and adolescents who experience HF.

Guideline Development Methodology

The guideline development process is described in detail in [Supplemental Appendix S1](#). The CCS Guidelines Committee approved the guideline's co-chairs plus the primary and review panel members. The co-chairs identified CCS members and additional experts from the broader community to be considered as primary and review panel members. Two methodologists from the CCS Guidelines Committee

Methodology Subcommittee joined the primary panel to conduct systematic reviews (with meta-analyses when appropriate) of the literature for each clinical question addressed and provided methodological support to the guideline development process.

The co-chairs selected and approved the topics from the primary panel and CCS Guidelines Committee. The list of outcomes was selected by the Committee and led according to their clinical relevance for all interest-holders, prioritizing patient-important outcomes. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the certainty of evidence for each PICO GRADE question and to systematically translate evidence into recommendations using the structured GRADE Evidence-to-Decision framework.¹⁰⁻¹³

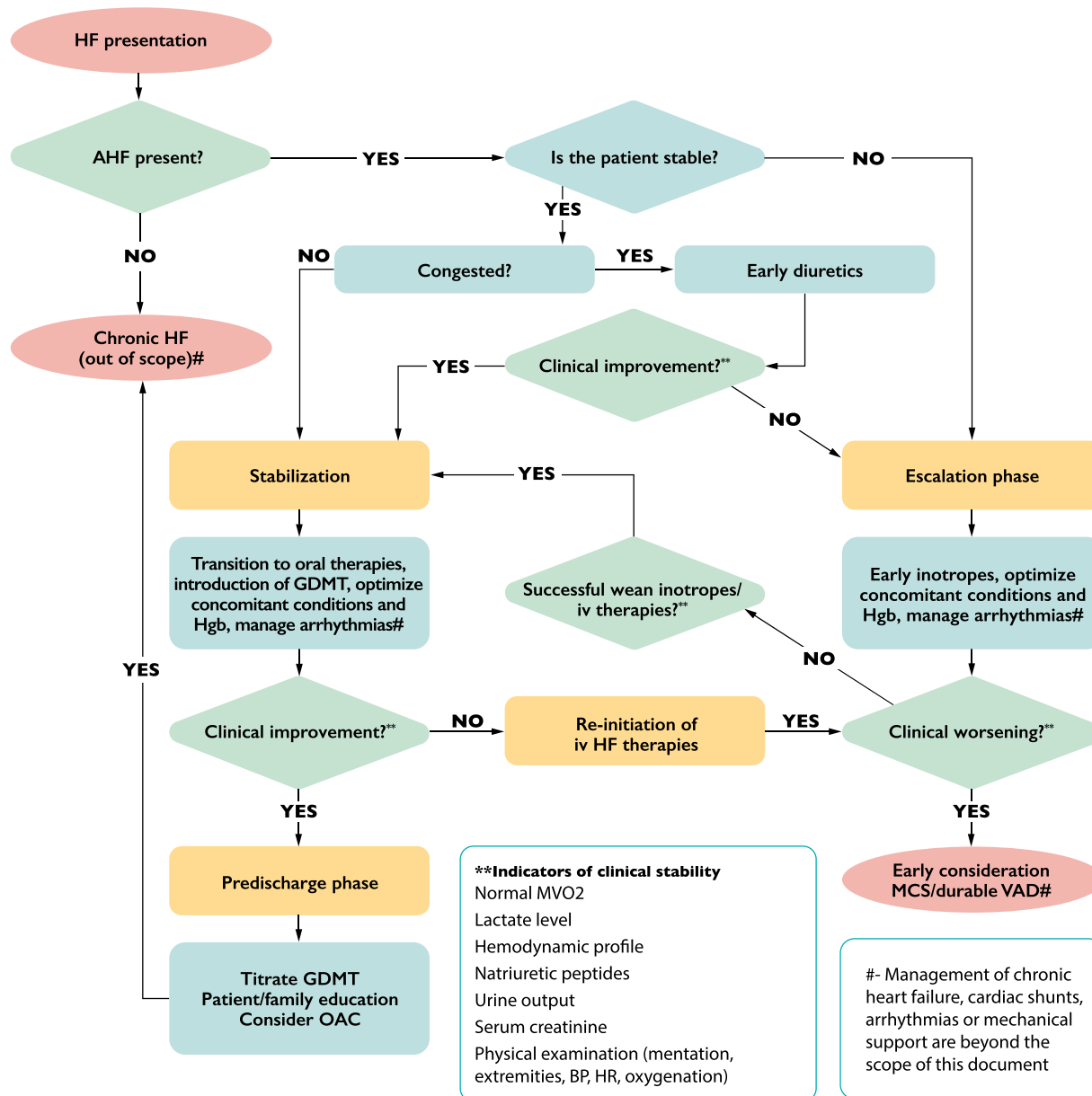


Figure 2. Management of acute heart failure (AHF) in children. Flow diagram depicts the investigations and management of a pediatric patient with AHF. The arrows in the blue indicator box depict alterations in clinical and biochemical parameters that guide decision-making for advanced or additional therapies. AHF, acute heart failure; BP, blood pressure; GDMT, guideline-directed medical therapy; HF, heart failure; Hgb, hemoglobin; HR, heart rate; iv, intravenous; MCS, mechanical circulatory support; MVO2, mixed venous oxygen saturation; OAC, oral anticoagulation; VAD, ventricular assist device.

Members of the primary panel who did not have direct conflicts of interest with the substance of a specific PICO question were allowed to vote on the specific PICO question. All recommendations in the guideline reached a majority (75%) agreement of eligible voters. A summary of the systematic reviews conducted plus GRADE Evidence-to-Decision frameworks for this guideline document is available online as [Supplemental Appendix S1](#). The guideline manuscript was peer-reviewed by the review panel. The CCS Guidelines Committee peer-reviewed the guideline manuscript before submission to the *Canadian Journal of Cardiology*. This report follows the recommendations from the Appraisal of Guidelines for Research and Evaluation

(AGREE) and Reporting Items for Practice Guidelines in Healthcare (RIGHT) checklists.¹⁴⁻¹⁶ [Table 1](#) includes a summary of the recommendations.

PICO Question 1: Should CMR be used as an evaluation tool in children with AHF suspected to be due to myocarditis?

Myocarditis presents a wide spectrum of acuity, ranging from mild cases with minimal symptoms to fulminant presentations with significant myocardial dysfunction, ventricular tachyarrhythmias, and cardiogenic shock.

There is no single test to prove or rule out myocarditis. Rather, the diagnosis is typically on the basis of a constellation of findings including symptoms, biomarkers, positive

Table 1. Summary of recommendations

Number	Recommendation	Strength; certainty*
1	We suggest a cardiac magnetic resonance study be performed in children with suspected myocarditis in whom it is feasible and can be performed with acceptable risk to confirm the diagnosis, define the degree of myocardial injury and edema, aid in risk stratification, and inform management.	Conditional recommendation; very low certainty evidence
2	We suggest the use of tissue-based natriuretic peptides (BNP or NT-proBNP) as a prognostic factor in the management of children with AHF.	Conditional recommendation; very low certainty evidence
3	We suggest performing WES rather than a targeted cardiomyopathy panel in children with AHF.	Conditional recommendation; very low certainty evidence
4	We suggest the use of early (ie, within 6 hours of presentation) rather than late diuretic therapy (> 6 hours) for children with new-onset symptomatic heart failure.	Conditional Recommendation; low certainty evidence
5	We suggest that alternating, rather than sequential, initiation of guideline-directed medical therapy can be used in children with new onset heart failure.	Conditional recommendation; low certainty evidence
6	We suggest milrinone as the preferred inotrope over dobutamine or levosimendan for children with AHF.	Conditional recommendation; very low certainty evidence
7	We suggest against the use of routine invasive monitoring with a pulmonary artery catheter in children with AHF.	Conditional recommendation against the intervention; Very low certainty evidence
8	We recommend VAD implantation before the development of cardiogenic shock or in children with medically unresponsive AHF (ie, INTERMACS/PEDIMACS profile ≥ 2) rather than or over waiting until cardiogenic shock is established (ie, INTERMACS/PEDIMACS profile 1).	Strong recommendation; very low certainty evidence
9	We suggest the use of temporary mechanical circulatory support (such as a centrifugal flow pump or percutaneous axial flow pumps) over VA-ECMO.	Conditional recommendation; very low certainty evidence
10	We suggest left heart decompression within the first 24 hours in children treated with VA-ECMO for AHF.	Conditional recommendation; low certainty evidence

AHF, acute heart failure; BNP, B-type natriuretic peptide; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; PEDIMACS, Pediatric Interagency Registry for Mechanically Assisted Circulatory Support; VAD, ventricular assist device; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; WES, whole exome sequencing.

* Strength of the recommendation and certainty of the evidence according to the GRADE methodology.

viral detection, imaging, and the absence of other features pointing toward an alternative diagnosis such as genetic variants of cardiomyopathy.¹⁷ Clear evidence of inflammation or detection of a causative agent (eg, viral particles) on endomyocardial biopsy has high specificity for myocarditis; however, the latter is reported to be falsely negative in approximately 50% of cases due to tissue sampling that is typically limited to the right ventricular aspect of the inter-ventricular septum.¹⁸ A positive serum nucleic acid test or immunoglobulin M serology of a myocarditis-associated virus supports the diagnosis. Elevated markers of myocardial injury (ie, troponin, creatine kinase), systemic inflammation (c-reactive protein and white blood cell count), electrocardiogram alterations, and echocardiographic signs of inflammation (effusion, myocardial swelling and/or hyperechogenicity) are not specific for myocarditis; however, their negative predictive value is high.¹⁷ The presence of other etiologies of ventricular dilation and dysfunction (ie, coronary artery anomalies, inheritable genetic cardiomyopathies, toxin-mediated, and metabolic conditions) decreases the likelihood of myocarditis. Some recent data have shown overlap and possible susceptibility to acute myocarditis for those that carry known cardiomyopathy variants.^{19,20}

CMR contributes to the diagnostic workup of suspected myocarditis. Adverse events related to CMR might occur,

especially related to sedation or general anaesthesia if needed, and typically in instances of severe cardiac dysfunction. Sedation is commonly required in younger children. General anaesthesia guarantees the best quality imaging but can potentially result in adverse events.²¹ In situations of cardiogenic shock, the practice of sedation and intubation with limited monitoring capabilities in the CMR scanner carries a significant risk of further decompensation. MCS devices generally present contraindications to CMR. Furthermore, CMR is not available in all clinical settings. The risk-benefit ratio of conducting CMR, including transferring a patient to a centre where CMR is available, needs to be considered in the decision for and timing of CMR in a fragile patient with presumed myocarditis.

CMR is the only noninvasive imaging modality that allows the characterization of myocardial tissue and is sometimes referred to as a “virtual” myocardial biopsy. Its ability to visualize and quantify myocardial edema, injury, scarring, and hyperemia is deemed to be valuable in patients with suspected myocarditis. Thus CMR is increasingly used in children and adolescents suspected to have myocarditis.²²

Myocardial edema appears bright on T2-weighted images. Similarly, the T2 time constant of the myocardium, assessed using parametric mapping, is prolonged in the presence of edema.

T1 is prolonged during inflammation but also due to chronic diffuse myocardial remodelling. Thus, the correlation with tissue changes is complex and depends on the acuity of the process. The fraction of myocardium that is comprised of tissue outside of the cardiomyocytes is the extracellular volume fraction (ECV) and can be approximated mathematically after measuring T1 before and after gadolinium administration. Like T1, ECV is elevated acutely as well as a result of chronic fibrotic remodelling. Late gadolinium enhancement (LGE) imaging is on the basis of tissue retention of gadolinium in injured myocardium. The typical distribution of LGE in myocarditis is patchy, subepicardial, and/or transmural. LGE might persist and eventually develop into chronic myocardial scar. Early gadolinium enhancement of the myocardium immediately after the administration of gadolinium is regarded as evidence of hyperemia (see Fig. 3 for the various CMR modalities used in patients with myocarditis).

The 2018 Lake Louise Criteria synthesizes the mentioned tissue markers.²³ The combination of at least one T2-based marker (signal on T2-weighted imaging or prolonged T2 time) and one or more T1 markers (LGE, prolonged T1 time, or elevated ECV) is regarded as evidence for myocarditis. The 2021 American Heart Association (AHA) scientific statement on the diagnosis and management of

myocarditis in children elevated CMR to a “confirmatory test” for myocarditis.²⁴

We did not identify evidence on the effect of using CMR on clinical outcomes. Our systematic review identified 1 systematic review and meta-analysis in adults and 1 primary study in children focused on the diagnostic performance of the CMR markers (see Supplemental Table S1 for the summary of included studies). The meta-analysis in adults included patients with either biopsy-confirmed or a clinically suspected diagnosis of myocarditis. Elevated native T1 (positive likelihood ratio [LR+], 8.87; 95% confidence interval [CI], 3.69-21.34; negative likelihood ratio [LR-], 0.12; 95% CI, 0.06-0.26), LGE (LR+, 18.64; 95% CI, 4.93-60.43; LR-, 0.34; 95% CI, 0.24-0.47), increased T2 ratio signal (LR+, 7.33; 95% CI, 2.61-20.60; LR-, 0.36; 95% CI, 0.28-0.46), were all associated with a diagnosis of myocarditis.²⁵ One study in children²⁶ showed that T2 mapping contributed to the diagnosis of myocarditis (LR+, 6.26; 95% CI, 3.04-12.86; LR-, 0.25; 95% CI, 0.19-0.32). Similarly, in a more recent meta-analysis of 400 adult myocarditis patients and 266 controls, prolonged T2, T1, and increased ECV were all associated with a clinical diagnosis of myocarditis, although the specificity of T1 and T2 declined when only patients with a positive biopsy were included.²⁷

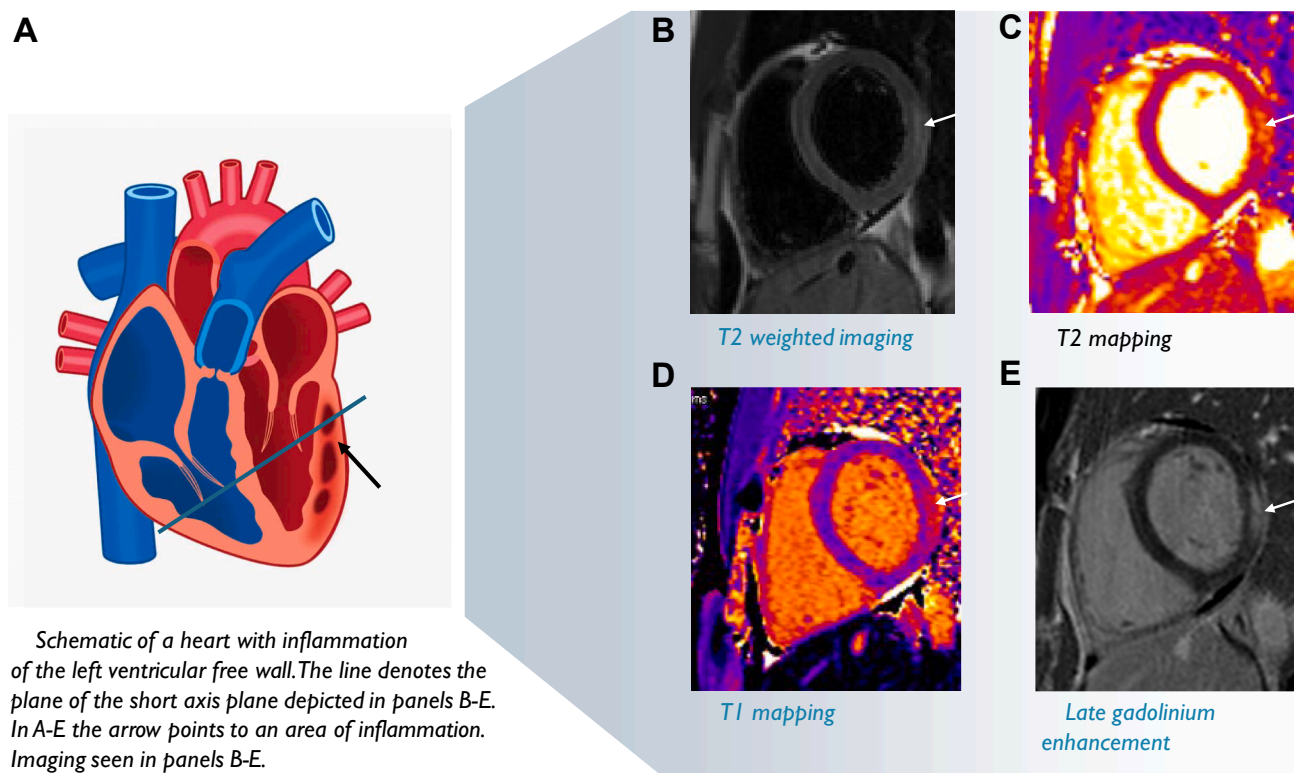


Figure 3. Tissue characteristics of myocarditis with cardiac magnetic resonance imaging. (A) The cross-sectional plane represented in panels B-E and the **arrow** denotes a region of myocardial inflammation that would be seen in myocarditis. T2 weighted imaging (B) shows an area of increased signal intensity within the left ventricular free wall (**arrows**), suggestive of myocardial edema. The same region shows augmented T2 times (C) and T1 times (D) using parametric mapping as well as positive late gadolinium enhancement (E). These tissue changes are a characteristic constellation in myocarditis. Note the regional distribution, confined to the lateral wall whereas the remainder of the left ventricle appears normal.

Confirmation of the diagnosis, especially in the presence of myocardial edema and/or myocardial injury might guide decision-making around treatment, however, the use of intravenous immunoglobulin and/or corticosteroids in patients with myocarditis is controversial. The occurrence and extent of LGE might also inform the duration of exercise restriction and follow-up. The certainty of the evidence was judged very low because of the indirectness (evidence mostly from adults), high risk of biases, and the lack of direct evidence on clinical outcomes.

The panel considered that CMR is beneficial because it allows risk stratification and might inform specific pharmacological management. CMR is a relatively safe diagnostic tool for pediatric myocarditis with a low risk of serious adverse events. Although CMR is expensive, evidence from the United States suggests that in children who are more severely ill, it might be cost-saving,¹⁸ although the overall hospital costs might increase. Furthermore, observational low-certainty evidence suggests the use of CMR might increase the likelihood of being discharged alive.²⁸ In summary, the beneficial effects seem to outweigh the harmful effects. A strong recommendation was not considered because of the low certainty of the evidence and the lack of evidence on the cost-effectiveness of the intervention in Canada.

Recommendation

1. We suggest a CMR study be performed in children with suspected myocarditis in whom it is feasible and it can be performed with acceptable risk to confirm the diagnosis, define the degree of myocardial injury and edema, aid in risk stratification, and inform management (Conditional Recommendation; Very Low Certainty Evidence).

Remarks

- Caution needs to be applied in children who are severely ill, in whom general anaesthesia or prolonged sedation is a risk for acute deterioration.
- Acceptable risk: the panel recommends carefully evaluating the risks of undergoing CMR during an episode of suspected myocarditis. A patient with a rapidly deteriorating clinical presentation and symptoms of imminent hemodynamic or respiratory instability should be stabilized before CMR.

Practical Tips

- The use of CMR helps to differentiate myocarditis from other conditions with overlapping clinical presentation and testing, most importantly, noninflammatory cardiomyopathies (eg, dilated cardiomyopathy).
- The presence and extent of myocardial injury and edema can be identified on CMR, which might affect the acute management of myocarditis. Acute tissue injury identified using CMR might transform into chronic myocardial scarring, which can be a harbinger of poor long-term outcomes, including ventricular dysfunction and arrhythmia. Post acute management

(type of testing, cadence, and duration of follow-up) might depend on CMR results.

Timing

- The panel recommends obtaining CMR as soon as possible after the presentation. In unstable patients, it is reasonable to postpone CMR. Studies performed more than 7–14 days after presentation might not be reflective of the acute episode of myocarditis.
- Post contrast imaging for LGE and T1 mapping should be an integral part of the CMR protocol. In a patient with a temporary contraindication to gadolinium contrast, CMR should be postponed until gadolinium can be safely administered.

CMR protocol

The following sequences are recommended in a CMR myocarditis protocol (Fig. 3).

- T2 weighted images to visualize and semiquantitatively assess edema, and/or
- T2 mapping to detect and quantify edema.
- T1 mapping before and after contrast administration.
- LGE.
- Cine imaging for ventricular function.
- Two-dimensional or 3D visualization of the coronary artery origins.
- Early gadolinium enhancement imaging to detect myocardial hyperemia (of less clinical utility compared with the other sequences previously mentioned).

Availability of CMR

If CMR is unavailable in the patient's clinical setting, it might be possible to diagnose myocarditis and rule out differential diagnoses on the basis of the clinical presentation and other testing. In cases when questions remain regarding the diagnosis or treatment decisions depending on myocardial tissue characteristics obtained using CMR, consideration should be given to transfer to a centre with CMR capability and expertise in managing pediatric myocarditis.

PICO Question 2: Should tissue-based natriuretic peptides (BNP or NT-proBNP) be used as a prognostic factor in children with AHF?

Myocardial biomarkers have an important role in early diagnosis of HF and have become increasingly popular for the purpose of determining HF prognosis in several settings. The pediatric literature suggests a possible role for natriuretic peptides (NP) in predicting future hospitalizations, requiring MCS, the ability to wean from inotropic therapy, and longer-term survival.^{29–33} Determining whether cardiac-specific biomarkers offer greater prognostic value than those that reflecting broader end-organ function is essential to assess whether a more comprehensive biomarker panel improves risk stratification in children with signs and symptoms of HF. Among multiple available biomarkers, few of which are validated in clinical trials, there is a bias toward using NP

secreted by cardiac tissue for prognosis. A secondary question arises as to whether there is sufficient evidence to use NP as a guide to initiating, modifying, or withdrawing medical or device therapies for HF.

Adult HF studies suggest an increased likelihood of mortality associated with elevated single-point NT-proBNP levels (hazard ratio, 13.63; 95% CI, 12.15-15.10) > 12 hours after admission for acute symptomatic HF.³⁴ Increments in BNP are also predictive in adults, with an increase of 1 standard deviation of BNP level in a population of HF patients being associated with a 75% risk increase for a major adverse cardiac event.³⁵

The pediatric HF data are consistent with adult experience but more variable and scarcer. There are no randomized trials pertaining specifically to AHF, but 11 observational cohort studies were identified. The largest and most recent of these described a retrospective cohort of 800 children with AHF, in which BNP levels > 3304 pg/mL correlated with risk of poor outcomes, including mortality and multiorgan failure.³⁶ Although other authors identified a similar correlation, there is little agreement as to an absolute level of NP at which risk starts to increase. The threshold at which outcomes appear to worsen varies from BNP > 1738.5 ng/L in a cohort including myocarditis patients,³⁷ to that mentioned previously, whereas another study reported a lower threshold of 349 pg/mL in HF associated with CHD³⁸—all of these in hospitalized patients. Outpatient-based chronic HF studies reported that NP levels were associated with risk of poor outcomes but at much lower levels of NP elevation, even in the low hundreds.²⁹ Supporting this, NT-proBNP measurements have also shown predictive value within studies, but again at markedly different absolute values.^{32,39}

No prospective studies of BNP-guided therapy or intervention exist in the pediatric population, but 1 retrospective study showed an association with the ability to wean inotropic therapy in < 30 days.⁴⁰

There is a paucity of literature on alternative biomarkers and, in particular, those related to end-organ perfusion deficit compared with NP biomarkers in AHF in children. It is possible that the variability of thresholds of NP associated with poor outcomes might represent different scenarios of systemic “hypoperfusion” and that additional biomarkers might provide greater precision. At present, NP remain the best studied and validated circulating biomarkers that are directly associated with a number of outcomes in AHF. Of note, providers should be aware of the reference ranges for NP, which can vary depending on the age of the child in addition to clinical scenarios that can yield a false positive result, such as an elevated body mass index.

Recommendation

2. We suggest the use of tissue-based NP (BNP or NT-proBNP) as a prognostic factor in the management of children with AHF (Conditional Recommendation; Very Low-Certainty Evidence).

Remarks

- Early assessments (within 12-24 hours of the diagnosis) of either NT-proBNP or BNP, on the basis of institutional availability, have prognostic value and are useful for risk stratification of AHF in children.
- The interpretation of risk on the basis of single-point levels shows significant variance between studies and requires interpretation of modifying factors in HF pathogenesis in children.
- Natriuretic peptide-guided therapy is not yet well defined in children and requires further prospective controlled studies.
- The balance of effects favours the measuring of NP in pediatric AHF patients. These recommendations are conditional because of limited evidence. The evidence is, however, internally consistent and better established in adult populations than in children with HF.

Practical Tips

- Considering its wide availability, universal measurement is endorsed in the context of suspected AHF. Reasonable concordance has been established between BNP and NT-proBNP levels in pediatric patients, and so either measurement is valid, with the caveat that BNP levels might be elevated when patients are treated with neprilysin inhibitors and that concordance between values is less in neonates younger than 30 days old and in patients with diminished glomerular filtration rates.⁴¹
- NP measurement should ideally be performed within 12-24 hours after patient admission and establishment of a stable acute (peak) level.
- Frequency of serial levels of NP can be individualized, but in the inpatient setting these are typically required at least weekly to monitor treatment effect.
- Measurement of levels of NP is helpful at the time of initiation of inotropic support or MCS to provide a baseline measurement against which treatment effectiveness can be assessed.
- A predischARGE measurement of NP is helpful in establishing an ideal patient-specific baseline level of NP.
- Outpatient NT-proBNP or BNP levels are useful in the setting of HF with reduced ejection fraction and can be offered at periodic outpatient evaluations.

PICO Question 3: Should whole exome sequencing and/or whole genome sequencing be performed in new presentations (ie, at diagnosis) vs targeted cardiomyopathy panels for new onset symptomatic HF?

There are many etiologies leading to pediatric HF, thus, genetic testing is a recommended component in the assessment of new patients.^{40,42} Genetic testing has the potential to identify the underlying cause, provide information on prognosis and the potential for multi-systemic disease, as well as allow for accurate counselling regarding risk stratification and the chance of recurrence for other family members.⁴³ Historically, genetic testing via a targeted gene panel has been considered the standard of care for patients with cardiomyopathy.⁴⁴ Genetic

testing using targeted gene panels involves sequencing specific genes curated for their association with the phenotype. Whole exome sequencing (WES) involves sequencing all exons (protein-coding regions) of an individual's DNA, whereas whole genome sequencing (WGS) involves sequencing all introns and exons as well as providing information on copy number variants and the mitochondrial genome. Obtaining WES and WGS using trio (proband and parents) allows for variant filtering on the basis of inheritance, which aids in data interpretation.

As next-generation sequencing technology has become widely available and the cost and turnaround time of WES have decreased, it is important to consider whether WES should be used as a first-tier test for patients with AHF. In our systematic review we did not identify observational or randomized studies that compared the routine use of WES vs targeted clinical panel panels.

Moreover, evaluating the diagnostic accuracy of WES is inherently challenging because of the wide variability and heterogeneity of reference standards used to confirm specific diseases. Because of these challenges, the diagnostic yield measure has been used as indirect evidence to support decision-making in scenarios with no diagnostic or comparative clinical evidence of the tests. The diagnostic yield is defined as the percentage of cases and/or patients that successfully lead to a diagnosis, and it serves as a proxy for decision-making. Therefore, our systematic review included 5 studies that estimated the WES diagnostic yield, which ranged from 38.3% to 66.7%, with a mean of 50.7% (see [Supplemental Table S9](#) for the summary of included studies). This was higher than the yield obtained with targeted panels, which has been reported to range between 10% and 37% for pediatric dilated cardiomyopathy.⁴⁵⁻⁴⁹ Of note, there are a few important methodological differences between these studies (ie, trio vs singleton WES and the additional use of assessment of copy number variants and/or mitochondrial genome). In addition, none of these studies provide clarity on the optimal timing for testing, whether acute or late. In summary, WES appears to be superior in identifying potential causes compared with targeted panels, but the timing remains unclear, and outcomes related to genetic counselling have not been considered.

The writing panel considered that although the evidence is of very low certainty, the balance between the benefits and harms probably favours WES over targeted panels. It is important to note that with any genetic test, there is the possibility of obtaining unclear results in the form of variants of uncertain significance (VUS). Although the number of variants identified increases with broader testing, a trio approach helps filter and reduce the number of VUS reported on WES. However, VUS should be approached with caution because the probability of pathogenicity for a VUS can range anywhere between 10% and 90%. In most cases, a VUS should not be used for clinical decision-making or cascade testing of at-risk family members. Although we did not identify cost-effectiveness studies of WES, the costs of implementing WES were deemed to be moderate. Last, the panel considered that currently, WES should be feasible to implement, and its use is very likely acceptable among stakeholders. Although access to genetic services might differ

between centres, clinicians working in community settings are encouraged to liaise with local genetics centres and/or HF teams. Additional guidance for ordering clinicians can also be found in the CCS clinical practice update on cardiogenetic testing.⁵⁰ Although funding models for genetic testing varies between provinces, the implementation of guidelines might aid in the advocacy of more consistent funding across Canada. Thus, the panel considered that WES should be offered conditionally to children with a symptomatic onset of AHF.

Recommendation

3. We suggest performing WES rather than a targeted cardiomyopathy panel in children with acute HF (Conditional Recommendation; Very Low-Certainty Evidence).

Practical Tips

- In children with AHF, identifying a specific diagnosis might not immediately affect clinical management decisions. However, it can provide valuable insights for long-term care planning, including prognosis, cascade screening, family planning, and candidacy for heart transplantation—objectives that support the use of WES in patients with AHF.
- The panel considers that young patients (ie, younger than 2 years) or patients with a multisystem disease might benefit more from a WES as a first-tier test approach compared with in older patients. Rapid WES in critically ill infants has shown utility in informing immediate care and long-term management. In older pediatric patients who present with apparently isolated HF, the likelihood of an underlying multisystem disorder not represented on a cardiomyopathy gene panel is decreased. Therefore, a more targeted diagnostic approach might be considered depending on patient age and level of acuity.
- Testing for copy number variants and mitochondrial genome variants not covered by WES should also be considered.
- Although WES is currently the main clinically available technology in Canada for broad-based testing, WGS will likely replace WES in the coming years.

PICO Question 4: Should early vs late diuretic therapy be used for children with new onset symptomatic AHF?

Diuretics, in particular loop diuretics, are the cornerstone of management in reducing symptoms of congestion secondary to HF. The goal of using diuretics is to achieve balanced fluid volume status, with relief of symptoms and consequences of systemic and pulmonary fluid congestion, while maintaining optimal cardiac output.

Despite the widespread use of loop diuretics in pediatric HF patients, there remains a paucity of data on optimal

management approaches in this population, particularly concerning the timing of initial diuretic therapy. Our systematic review did not identify any randomized clinical trials in which early vs late diuretic therapy was compared in children with new onset AHF. Because of the paucity of data in pediatric populations, we sought evidence from studies in adults with HF, which suggests that prompt administration of diuretics yields better outcomes.⁵¹⁻⁵⁹ Analysis of the evidence from 4 observational studies^{53,54,57,58} suggests that early initiation of diuretic therapy (ie, as soon as possible and ideally within 6 hours of arrival to the emergency department) might potentially reduce 30-day mortality rates for adults who present in acute onset symptomatic HF (odds ratio, 0.75; 95% CI, 0.63-0.89). Data from a pooled meta-analysis showed there was little to no effect on other outcomes, such as in-hospital mortality or length of stay (LOS; see the forest plots for outcomes in [Supplemental Appendix S5](#)). On the basis of the available data, there is consensus from the CCS, AHA, American College of Cardiology (ACC), and the European Society of Cardiology supporting early initiation of diuretic therapy in adult patients with AHF.⁶⁰⁻⁶²

Recommendation

4. We suggest the use of early (ie, within 6 hours of presentation) rather than late diuretic therapy (> 6 hours) for children with new-onset symptomatic HF (Conditional Recommendation; Low-Certainty Evidence).

Remarks

- This recommendation is conditional because of the absence of evidence in pediatric populations. The primary panel relied on observational evidence, from adult studies, with acknowledged uncertainty because of potential bias and indirectness. This evidence was important in helping the panel weigh the potential benefits of early diuretic therapy against the low likelihood of harm, provided that the response to treatment is adequately monitored.

Practical Tips

- Early diuretic therapy, preferably as an intravenous bolus, should be considered for children with AHF and signs of congestion, provided it is expected to be hemodynamically well tolerated and considering the low risk of associated harm.
- Adequate monitoring of patient response to diuretics, including evaluation of intravascular fluid status, electrolyte abnormalities, and renal function, is necessary to minimize the potential for harm.
- The etiology of HF in children can differ from that in the adult population, and in certain groups, such as those with restrictive filling physiologies (ie, restrictive and hypertrophic cardiomyopathy), presenting symptoms can include congestion and low cardiac output despite a normal ejection fraction. In these situations,

diuretics might not significantly improve symptoms and might result in further deterioration.

- Special caution and consideration should also be given to patients with baseline renal dysfunction, who often require an individualized approach, and to those that are diuretic-naïve and might benefit from lower initial doses, which can then be increased on the basis of response. Close monitoring of the urine output (mL/kg/h) and intake of fluids will also be required.
- Patients with AHF with evidence of poor cardiac output in addition to fluid overload might not tolerate early and aggressive diuretic therapy and require judicious, individualized approaches.

PICO Question 5: Should initiation and up-titration of GDMT be alternating vs sequential for children with new onset AHF?

GDMT is the mainstay for ongoing medical management of pediatric patients with new onset HF. After diuresis has been achieved, treatment with a renin angiotensin-aldosterone system (RAAS) inhibitor, specifically either an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin-receptor/neprilysin inhibitor (ARNI), and a β -blocker (BB) and mineralocorticoid receptor antagonists are usually initiated, unless there are contraindications for their use. RAAS inhibitors and BBs require titration, and previous adult and pediatric guidelines¹ have suggested sequential introduction of these medications. With this sequential strategy, the first medication is started at a lower dose and increased at intervals (ie, every 1-2 weeks or faster during hospitalization) until maximal recommended dose or maximal tolerable dose is reached, after which a second medication is started and titrated in a similar fashion ([Fig. 4](#)).

Revised adult guidelines⁶³ have suggested an option to “alternate” the initiation and titration of these medications in a more rapid fashion, aiming for therapeutic dosing in as little as 14 days. With this approach, medications are introduced relatively simultaneously (or as close as possible) then alternately titrated to a maximally recommended dose or maximally tolerable dose ([Fig. 4](#)). The rationale behind this approach is to target the various neurohormonal receptors involved in HF, ensure the prompt initiation of these medications without delay, and facilitate titration in the outpatient setting. Practitioners should be aware of the contraindications to GDMT agents, such as profound bradycardia and/or heart block, hypoglycemia, or reactive airway disease for BBs and severe preexisting renal dysfunction, electrolyte abnormalities, or hypotension for RAAS inhibitors.

No studies that included pediatric populations were identified in our systematic review of the literature for this question. One randomized trial⁶⁴ and 2 observational studies^{65,66} in > 3000 adult patients with AHF indirectly informed the panel about the effects of rapid up-titration of GDMT (alternating) over a step-wise (sequential) approach, suggesting that the intervention might reduce the risk of mortality and improve hospitalization outcomes, although the overall certainty was deemed very low. Although pediatric studies are lacking, there are previous data regarding the sequential approach to HF medication initiation, which has

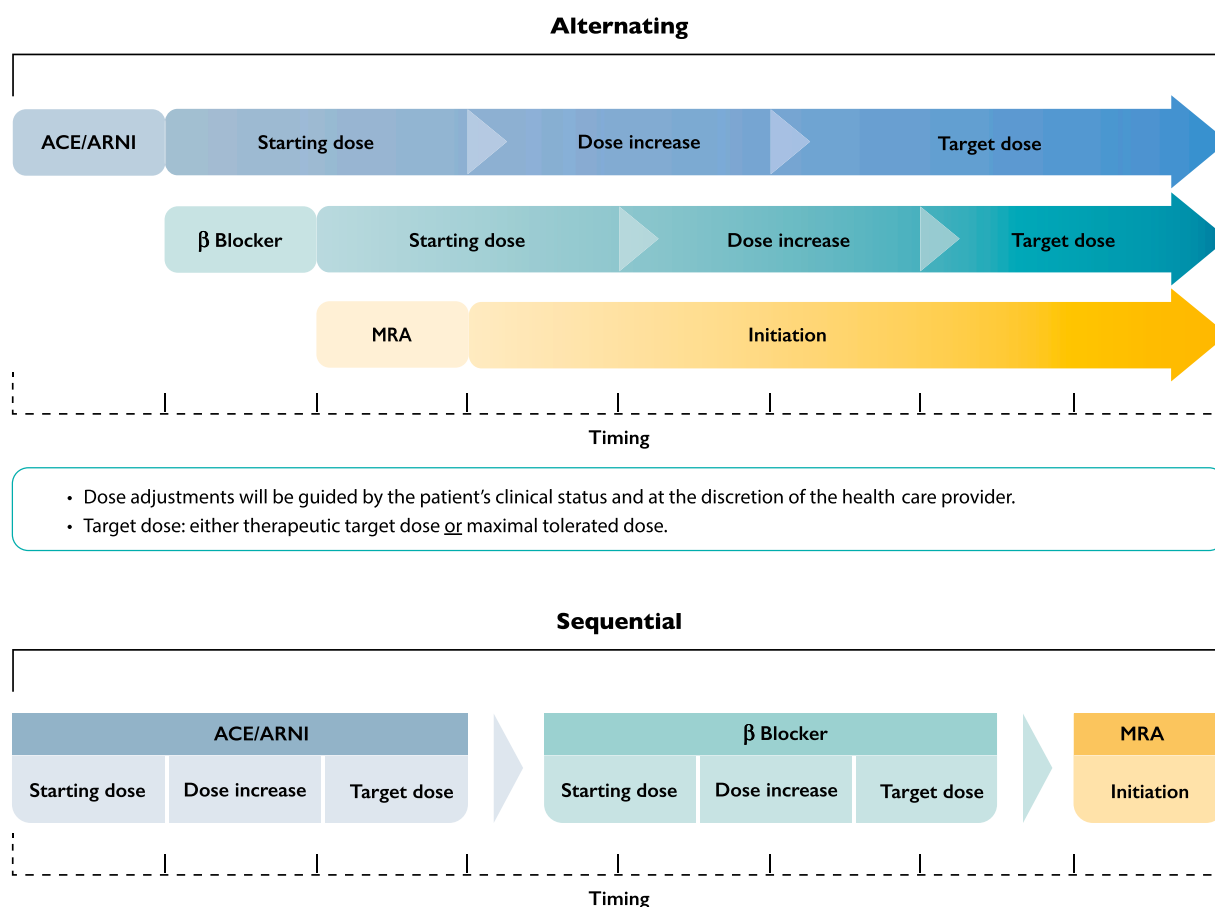


Figure 4. Initiation of guideline-directed medical therapy for children with acute heart failure (HF). The varying practice initiation of guideline-directed medical therapy in children who present with acute HF is illustrated. Traditionally, a sequential approach of initiation of HF medications one at a time was used. However, there is growing experience with a more rapid, multidrug, or alternating method for HF medication initiation. ACE, angiotensin converting enzyme; ARNI, angiotensin receptor/neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

been shown to be suboptimal in getting children on to all the classes of HF medications after discharge.^{67,68}

At this time, there is limited evidence to support the use of sodium-glucose cotransporter 2 inhibitors as routine GDMT for all pediatric patients with HF, and so no recommendation is made regarding how to introduce these agents.

Recommendation

- We suggest that alternating (ie, starting multiple HF medications relatively simultaneously at low doses), rather than sequential initiation (ie, starting one medication and completing the up-titration to target dosing before starting the next) of GDMT can be used in children with new onset HF (Conditional Recommendation; Low-Certainty Evidence).

Remarks

- It is important to note that in children, there is no evidence favouring one strategy over another, and that multiple factors might influence the physician's preference when starting and titrating HF medications.

- This recommendation is conditional because of the absence of evidence as outlined previously with a high risk of bias and uncertainty regarding the precise magnitude of the effect of the intervention. The guideline panel weighed the potential benefits of sequential initiation of GDMT with a low probability of harmful effects if adequate monitoring included blood pressure, heart rate, renal function, and electrolytes.

Practical Tips

- In a patient with clinically compensated new onset HF who has no contraindications for the initiation of either ACEi/ARNI or BB (ie, severe renal dysfunction, electrolyte abnormality, or heart block), an alternating GDMT strategy should be considered.
- Depending on the patient's clinical status or clinician preference, either a RAAS inhibitor or a BB may be initiated first.
- The starting dose and intervals for up-titration should be guided by the clinical response, but an alternate day dosage up-titration (ie, dose increases every 24-48 hours) are commonly used, especially for hospitalized patients.

- In the inpatient setting, after initiation or escalation of afterload and heart rate-reducing agents, it is recommended to monitor heart rate and blood pressure at baseline and every 30 minutes for up to 2 hours after dosing. In addition, there might be an expected increase in serum creatinine with RAAS inhibitors.
- If a patient develops symptomatic hypotension or bradycardia, dosing should be reduced to the previously tolerated dose. Caution should be taken in patients with severe HF and in infants.
- For effective RAAS inhibition, ACEi and ARNI have been studied in a recent clinical trial and are considered to have equivalent efficacy for clinical symptom improvement.⁶⁹
- It is essential if a patient is to change from an ACEi to an ARNI agent, that a 36-hour washout of the ACEi be observed to reduce the risk of angioedema and/or other adverse effects.

PICO Question 6: Should Milrinone vs other inotropes be used for children with AHF?

Milrinone is a potent phosphodiesterase III inhibitor that improves myocardial contractility with systemic and pulmonary vasodilator effects. It has been shown to improve low cardiac output syndrome (LCOS) after cardiopulmonary bypass in children.⁷⁰⁻⁷² It is a beneficial therapeutic option for the management of AHF and its unique pharmacological profile, combining inotropic and vasodilatory properties, makes it particularly applicable to the pediatric population.⁷³ It is preferred in children because of familiarity, and better tolerance and side effect profile.^{73,74} Longer-term use of milrinone in children with HF (whether in hospital or as part of home inotrope support) has been shown to be safe and efficacious as a bridge to oral GDMT or heart transplantation,⁷⁵⁻⁷⁷ in contrast to the potentially deleterious or minimal benefits observed in the adult population.⁷⁸ One prospective trial with > 900 adult patients with AHF was noted to have worse outcomes with ischemic etiologies but showed some benefit with respect to days in hospital, death, and readmission to hospital in those with nonischemic HF.⁷⁹ Caution is advised when using milrinone in pediatric patients with preexisting renal dysfunction and vasoplegia, because it has a longer half-life than some other inotropes, such as dobutamine, a β_1 sympathomimetic, commonly used in adult HF patients in the hospital setting.

In the absence of randomized clinical trials that have compared the use of milrinone with other inotropes for children with acute symptomatic HF, the recommendations that follow are on the basis of evidence from clinical trials in other pediatric populations, including post cardiac surgery and for LCOS.

Indirect evidence from 3 studies in children who underwent cardiac surgery and were receiving inotropic agents to prevent LCOS suggests that milrinone has similar efficacy and safety profiles compared with other inotropes.⁷⁰⁻⁷² However, this evidence remains highly uncertain, because there is heterogeneity in the populations compared, and only 1 study made a direct comparison with another inotrope (dobutamine).⁷²

The body of evidence in this population suggests no meaningful difference between milrinone and dobutamine in any of the efficacy outcomes.⁷² Milrinone is relatively safe for

use in pediatric AHF patients, with infrequent adverse events of hypotension and arrhythmias that rarely require treatment discontinuation.^{73,74}

Levosimendan is a calcium sensitizing agent that is used more commonly outside of North America as a HF therapy. There is currently no direct evidence to compare levosimendan and milrinone in children with AHF. Furthermore, there is a paucity of data on the use of levosimendan in pediatric populations with similar conditions (eg, LCOS) with limited evidence on its effects on several outcomes.⁸⁰ Levosimendan is not currently licensed for use in North America because of insufficient evidence to support its efficacy and safety in pediatric populations, although it is used in multiple countries for pediatric and adult HF patients.

Recommendation

6. We suggest milrinone as the preferred inotrope over dobutamine or levosimendan for children with AHF (Conditional Recommendation; Very Low-Certainty Evidence).

Remarks

- The evidence regarding the efficacy of 1 inotrope over another remains highly uncertain, preventing a strong recommendation. However, on the basis of expert opinion, widespread clinical practice, and accumulated experience, the recommendation for inotrope strategy in children with AHF was made, especially for those in LCOS.

Practical Tips

- Milrinone should be initiated in the setting of symptomatic HF and not purely on the basis of echocardiographic or other imaging findings alone.
- When milrinone is used, monitoring of blood pressure, heart rate, physical signs of perfusion, and markers of cardiac output (mixed venous saturation, lactate, etc) to detect changes and adjust dosing as necessary, and monitoring of renal and liver function is recommended. It is also important to monitor for side effects such as hypotension, arrhythmias, and thrombocytopenia.
- The duration of milrinone therapy should be as short as possible to achieve the desired clinical and hemodynamic response and with attempts to wean off with close monitoring and concurrent transition to enteral HF therapies.
- In instances of cardiogenic shock or hypotension, the choice of other inotropes (ie, epinephrine, norepinephrine, etc) might be preferred over milrinone and should be determined on a case-by-case basis.

PICO Question 7: Should PAC monitoring be used for children with AHF?

For the past few decades, PACs have been used as a diagnostic tool and a guide for treatment, because their use offers valuable insights into hemodynamics of the ventricle, thereby aiding therapeutic decision-making and trend

analysis.⁸¹ However, its use is not free of complications and adverse events. The **Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE)** trial showed that the additional use of PACs with standard management of adults with advanced HF did not improve patient outcomes and was associated with an unanticipated increase in adverse events.⁸² Consequently, the adult HF guidelines recommended limiting the use of PACs to patients with cardiogenic shock or mechanical ventilation (ACC-AHA class I, level of evidence C) and discourage PAC use in routine management of HF (ACC-AHA class III, level of evidence B).⁸³

In our review of the literature, we identified 5 observational studies, 4 of which were at high risk of bias,⁸⁴⁻⁸⁷ and 1 with moderate risk of bias.⁸⁸ Our meta-analysis, including all of the studies, initially suggested a positive effect of PAC use on mortality (relative risk, 0.75; 95% CI, 0.65-0.87). However, one study performed a confounding adjustment⁸⁸ in a multivariate analysis, suggestive that the effect on mortality was confounded by other coexisting factors. In addition, 2 studies reported complications associated with PAC use, with related mortality rates ranging from 5% to nearly 10%. The documented complications included atrioventricular node block, bloodstream infections, pneumothorax, and arrhythmias.^{86,87} All of the studies were in adult patients, with no evidence from children, and no randomized controlled trials were available.

In summary, nonrandomized very low certainty evidence from studies in adults suggests routine PAC use does not have an effect on mortality, and there is a risk of serious adverse events. The panel considered that the balance of benefits and harms of routine PAC use is not clear, and the feasibility and acceptability of using PACs vary across hospitals and cardiovascular units in Canada. Last, no adult or pediatric studies exist on the cost-effectiveness of PAC use. Furthermore, outcomes with PAC monitoring might be highly dependent on resources and/or personnel available at centres of PAC use in children with AHF. Considering all of this, the panel considered that there is not enough evidence to support the routine use of PACs in children with AHF.

Recommendation

7. We suggest against the use of routine invasive monitoring with a PAC in children with AHF (Conditional Recommendation Against the Intervention; Very Low-Certainty Evidence).

Remarks

- This recommendation is conditional, because all of the evidence is indirect from adult observational studies with a high risk of bias. There is no evidence available in children, and there are no randomized controlled trials to provide more robust evidence.
- Because of the limited, indirect, and very low-quality data on PAC monitoring for AHF in children, as well

as the potential for significant complications, the balance of effects would lean against the intervention.

- Considering the increased risk of significant complications and uncertainty of the effect of routine PAC placement on outcomes, routine use of PAC monitoring in children with AHF is discouraged. However, it is possible that there might be some benefit in selected high-acuity patients at centres where PACs are routinely placed in adults or real-world experience. Acceptance of this intervention might vary among centres according to their comfort level with its use.

Practical Tip

- The use of a PAC for monitoring in children with AHF might vary and evolve over time depending upon the availability of resources and expertise in children's hospitals and care centres. Use should be considered only in selected patients in whom the benefit of use outweighs risk of complications.

PICO Question 8: Should VAD implantation be considered before the development of cardiogenic shock (interagency registry for mechanically assisted circulatory support/pediatric interagency registry for mechanically assisted circulatory support profile 1 compared with profile ≥ 2) for children with AHF?

The ideal timing of durable VAD implantation in children with symptomatic HF can be challenging to determine. At one end of the spectrum are patients with advanced HF whose survival depends on MCS, whereas at the other end are those with relative milder disease, for whom the risk of adverse events with VAD support outweighs the benefits compared with ongoing medical management. This topic has been studied more extensively in adult HF patients, with multiple studies showing worse survival outcomes after VAD implantation among patients with critical cardiogenic shock (hereon referred to as profile 1) and progressive decline (profile 2) compared with those who were stable but inotrope-dependent (profile 3) or less sick (profile 4-7; Table 2).⁸⁹

There also appears to be a survival advantage of VAD implantation over medical therapy with improved functional status among some adult patients who are not inotrope-dependent.^{90,91} Other identified risk factors for mortality after VAD implantation include older age, renal dysfunction, hypoalbuminemia, and coagulopathy.⁹² The current International Society for Heart and Lung Transplantation guidelines for MCS has outlined the following recommendations for adults: "INTERMACS Profile 1 to 3 patients benefit in terms of survival from implantation of an LVAD (Class 1, Level of Evidence A)" and "INTERMACS Profile 4 may benefit in terms of survival from implantation of a VAD (Class IIb, Level of Evidence B)."⁹³

The data in pediatric patients are less robust, as evidenced by the lack of randomized clinical trials to compare implantation of VAD in either profile 1 or 1-2 vs profiles ≥ 2 or 3-7. Our systematic review identified 9 observational studies⁹⁴⁻¹⁰² that have compared VAD implantation at different profiles, of which 6^{94,98,99,101,102} provided sufficient data for analysis to inform outcomes (see Supplemental Table S26 and subsequent forest plots for the summary of included studies

Table 2. INTERMACS/PEDIMACS profiles with associated definitions and percent of pediatric implantations at each profile^{104,114}

INTERMACS profile	Description	Urgency and/or support recommendation	Percentage of pediatric implants (Edelson et al. ¹⁰³)
1	Critical cardiogenic shock (“crash and burn”)—life-threatening hypotension, organ hypoperfusion	Needs immediate mechanical circulatory support (ie, temporary MCS or durable VAD)	30.4%
2	Progressive decline despite inotropic support, worsening organ function	When stabilized with medical management and/or temporary MCS, consider durable VAD support	55.4
3	Stable with use of inotropes but dependent, with preserved organ function	Candidate for durable MCS with elective planning	11.1
4-7	Increasingly stable profiles with less urgent support needs	Medical management over durable MCS as considered less acute	2.4

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MCS, mechanical circulatory support; PEDIMACS, Pediatric Interagency Registry for Mechanically Assisted Circulatory Support; VAD, ventricular assistive device.

Modified from Stevenson et al.¹⁰⁴ courtesy of Edelson et al.

and meta-analysis). For mortality, 5 studies were included^{94,98,99,101,102} that compared VAD implantation at profile 1 or 1-2 with profiles ≥ 2 or 3-7 and showed that pediatric patients who received a VAD implanted while they were in cardiogenic shock had worse survival compared with less sick patients (ie, profiles 2-7). Our own meta-analyses showed that VAD placement at profile 1 in comparison with profiles > 2 had little to no effect on outcomes such as stroke, transplant, major bleeding, device malfunction, or serious adverse events, but the evidence remains uncertain.

The certainty of the evidence for this recommendation is therefore low, on the basis of the observational nature of the data available and the potential for bias in such studies. Although there are consistent findings to support implanting a VAD before the development of cardiogenic shock when feasible, there are few data to guide decisions around the timing of VAD for less sick pediatric patients with HF. Important data are lacking in pediatric patients treated with medical therapy in profiles 2-7 compared with VAD to justify a recommendation regarding medical therapy vs VAD implantation at specific **Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)/Pediatric Interagency Registry for Mechanically Assisted Circulatory Support (PEDIMACS)** profiles. The recent **Advanced Cardiac Therapies Improving Outcomes Network (ACTION)** VAD registry report showed that very few pediatric patients undergo VAD implantation at profiles ≥ 3 , with approximately 85% of implantations done at profiles 1 and 2, thus describing a real-world practice of VAD implantations in more acutely ill children.^{103,104}

It is difficult to answer the question of best timing for VAD implantation in children with AHF, because a clinical trial of VAD implantation that requires randomization to medical management vs immediate implantation at the various profiles would be logistically and ethically challenging in this population. Furthermore, using the INTERMACS/PEDIMACS profile at implantation as a surrogate for timing ignores the variability in profile at the time of initial VAD consideration, as well as variability in whether a child will worsen or improve in the time between presentation and VAD implantation. It is perhaps not surprising that observational studies that compared outcomes in patients who received a VAD implanted at profile 1 vs profile ≥ 2 show

worse outcomes in the sicker cohort. Whether these results correctly imply that an individual’s outcome will be better if VAD implantation occurs at profile ≥ 2 vs waiting until they progress to cardiogenic shock is not clear. In addition, data on cost-effectiveness, quality of life, and value to patients and/or families relating to VAD implantation at profile ≥ 2 are lacking. Where the true “sweet spot” for ideal VAD implantation lies for children with AHF is still an area deserving of further research.

The panel considered that the desirable effects of VAD implantation at profiles ≥ 2 probably outweigh the undesirable effects. Therefore, although the certainty is very low and the costs might be significant, the balance of effects favours the intervention. Thus, the panel considered that the recommendation should be strong, in favour of VAD implantation (strong recommendation; low certainty of evidence) before cardiogenic shock is established

Recommendation

8. We recommend VAD implantation before the development of cardiogenic shock or in children with medically unresponsive acute HF (ie, INTERMACS/PEDIMACS profile ≥ 2) rather than/over waiting until cardiogenic shock is established (ie, INTERMACS/PEDIMACS profile 1) (Strong Recommendation; Very Low-Certainty Evidence).

Practical Tips

- The mode of MCS might be in the form of tMCS devices or durable VADs, which might vary between centres because of infrastructure and expertise.
- The ideal timing or INTERMACS/PEDIMACS profile for VAD implantation in children with symptomatic HF is not yet known, and decisions should be individualized with guidance from an HF team with experience in MCS.
- Some children present to care at INTERMACS/PEDIMACS 1, and there is no opportunity to wait for a better risk profile; in such cases, there still might be reasonable hope for meaningful survival, and they

should not be precluded on the basis of their INTERMACS profile.

- In low-volume MCS or resource-limited centres, it would be recommended to initiate early discussion in patients with AHF with an MCS-experienced program to potentially avoid implantation when cardiogenic shock is established.

PICO Question 9: Should temporary MCS (ie, centrifugal pumps with or without an oxygenator) be used rather than venoarterial ECMO in children with AHF?

Acute decompensated HF in pediatric patients is a critical condition, necessitating timely and effective MCS to prevent organ failure and death. Venoarterial (VA)-ECMO is widely used in these scenarios and has traditionally served as the standard of care for the short-term delivery of MCS in pediatric patients. This strategy permits the delivery of adequate blood circulation and oxygenation in acute end stage HF when the heart is unable to do so. However, VA-ECMO is associated with a significant mortality and morbidity risk, including the occurrence of bleeding, thrombosis, and neurologic injury, which in turn can result in long-term complications.¹⁰⁵

The specific forms of MCS are dependent in part on the needs of the patient. For example, for patients who require cardiopulmonary support, ECMO has traditionally been used. When cardiac support alone is required, tMCS strategies, largely through VAD, have been increasingly used, with evolving technologies and availabilities. This strategy offers numerous potential benefits when used in experienced centres with dedicated pediatric VAD programs, including fewer complications and improved survival, particularly in settings where only cardiac support is needed.^{106,107} Developing evidence-based pediatric recommendations to guide the use of these devices is critical, because current practice is inconsistent, leading to variations in outcomes across institutions. Guidelines to address the effects of VAD vs VA-ECMO strategies can help clinicians make more informed decisions, including appropriate patient selection, to ultimately improve the survival and quality of life of pediatric patients.

In the systematic review and meta-analysis accompanying this guideline, 13 observational studies were included,¹⁰⁸⁻¹²⁰ and 11 evaluated in-hospital mortality among pediatric patients supported with VAD vs VA-ECMO. The use of a VAD was associated with a reduction in the odds of mortality (odds ratio, 0.51; 95% CI, 0.29-0.90), corresponding to an estimated 138 fewer deaths per 1000 patients treated (95% CI, 24-222) compared with ECMO. Similar benefits were observed for long-term mortality and reductions in the rates of clinically significant complications such as stroke, thrombosis, infection, and bleeding. Despite these findings, the serious risk of bias in the body of evidence limits the certainty about the effect estimates. Because a randomized controlled trial is unlikely to be feasible or ethical the writing group concluded that the cumulative evidence and clinical experience support the preferential use of tMCS via VAD over ECMO in children with AHF, particularly in centres with established VAD programs.

Further high-quality research is critical to address the current gaps in evidence, especially considering the very

low certainty of the existing data. Priorities for future research include randomized controlled trials that compare tMCS with VA-ECMO in pediatric populations, with a focus on long-term survival, quality of life, and neurodevelopmental outcomes. Research should be conducted to investigate specific subgroups, such as neonates and patients with CHD, to determine whether certain groups benefit more from one intervention over the other. Moreover, equity effects and cost-effectiveness analyses that consider evolving health care costs and resource utilization are needed to guide future decision-making.

Recommendation

9. We suggest the use of temporary MCS (such as a centrifugal flow pump or percutaneous axial flow pumps) over VA-ECMO (Conditional Recommendation; Very Low-Certainty Evidence).

Remarks

- Because of the very low certainty of the evidence but the potential for meaningful improvement in outcomes, this recommendation is made as a conditional one, allowing flexibility on the basis of individual patient circumstances, centre expertise, and resource availability.
- When possible, in centres with established VAD programs, preferential utilization of temporary VAD therapy to support cardiac output should be sought in children with AHF.

Practical Tips

- The recommendation should be carefully applied across different subgroups of pediatric patients with AHF. Specifically, younger children, such as neonates and infants, might experience different risks and benefits from tMCS compared with older children or adolescents. Neonates might be more prone to complications such as thrombosis or infection because of their smaller size and immature immune systems.
- Additionally, patients with different underlying etiologies of HF, such as CHD vs acquired heart conditions, might respond differently to tMCS or VA-ECMO. Clinicians should consider these factors when selecting the most appropriate MCS device, and tailor their decisions on the basis of patient-specific characteristics and institutional experience.
- In patients with or at risk of significant pulmonary congestion or underlying primary lung pathology, initial VA-ECMO support might be needed to facilitate acute stabilization before transitioning to VAD strategies.
- Implementing tMCS as a preferred intervention over VA-ECMO will require adjustments in clinical practice, particularly in institutions that might lack experience with advanced ventricular devices. High-volume centres with established protocols for using a variety of devices are better positioned to adopt this approach, whereas low-volume programs might face challenges because of the technical complexity and resource requirements of

tMCS. Efforts should be made to provide training and support for clinical teams, ensuring that medical and surgical staff are prepared to manage these devices effectively. Additionally, institutions must ensure the necessary infrastructure, including specialized equipment and postoperative care support, to manage these patients.

- Ongoing monitoring is essential to ensure the safe and effective use of tMCS. This includes regular evaluation of device performance, complication rates (eg, bleeding, thrombosis, infection), and patient outcomes, such as survival rates and quality of life. Clinical registries that track patient outcomes for pediatric AHF treated with tMCS vs VA-ECMO should keep providing valuable real-world data to refine future recommendations. In addition, standardized protocols for anticoagulation and infection prevention in tMCS patients should be implemented to minimize adverse events.

PICO Question 10: Should early left heart decompression vs late decompression be used for children who receive ECMO for AHF?

VA-ECMO is used in the setting of AHF with cardiogenic shock. Although VA-ECMO can rescue AHF and provide end-organ perfusion, there are known complications. One such complication is left ventricular (LV) distension secondary to the increased afterload, which can impair ventricular recovery and lead to pulmonary edema and myocardial ischemia. There is a longstanding thought that left heart decompression, which can occur by a variety of methods, might improve clinical outcomes, but the timing of this intervention remains controversial. There are some suggestions that pediatric hearts might be more compliant than adult counterparts and thus have a greater risk for LV distention and concomitant LA hypertension and thus could potentially benefit from early left heart decompression. Current strategies for providing left heart decompression include balloon atrial septostomy, surgical placement of a vent in the left atrium or ventricle, or the use of a percutaneous micro-axial pump such as the Impella (Abiomed, Danvers, MA; Fig. 5).

Left heart decompression strategies may be used preemptively upon the institution of ECMO or later on with the development of LA hypertension. We evaluated the evidence of randomized trials that compared early vs late decompression from adults and from observational studies in children (see [Supplemental Table S37](#) for the summary of included studies and description of the interventions).¹²¹⁻¹²⁹ In our meta-analyses, neither the pooled effect size of randomized trials in adults (RR, 1.03; 95% CI, 0.73-1.45),^{123,126} nor the pooled effect size of observational studies in children (RR, 1.07; 95% CI, 0.69-1.67), showed benefit of early compared with delayed approaches.^{121,122,124,125,127-129}

Beyond mortality, early left heart decompression was also not associated with differences in ECMO duration (mean difference [MD], -2.54 days; 95% CI, -12.51 to 7.43) or hospital LOS in adults (MD, -2.54 days; 95% CI, -12.51 to 7.43). However in children, it was associated with decreased time of ECMO (MD, -3.0; 95% CI, -4.66 to -1.34) and LOS (MD, -16.6; 95% CI, -27.88; see forest plots in [Supplemental Appendix S11](#)).^{122,129} Regarding other ECMO related outcomes, such as cerebrovascular accidents, transplantation, transition to durable VAD, and mechanical ventilation, no other clinically significant findings were noted in the literature for either adults or children.

The panel considered that early decompression seems to affect only LOS and ECMO duration in children, although the certainty of the evidence is low. However, the intervention is feasible to implement, does not seem to be more expensive, and the panel considers the balance of benefits vs harms more likely to favour the early intervention. The primary panel considered that a conditional recommendation in favour of early decompression should be a better course of action, in part because of the potential susceptibility of LA hypertension in children receiving ECMO and the potential for associated complications to arise.

Recommendation

10. We suggest left heart decompression within the first 24 hours in children treated with VA-ECMO for acute HF (Conditional Recommendation; Low-Certainty Evidence).

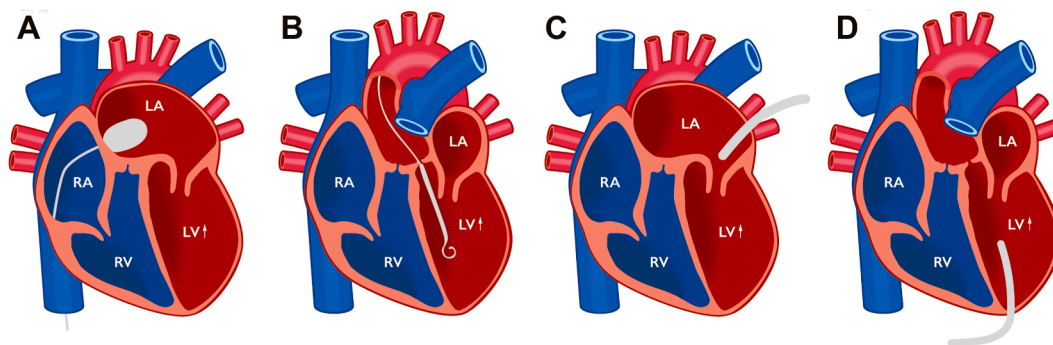


Figure 5. Current strategies for left heart decompression. Four different methods of left heart decompression strategies for a pediatric patient receiving extracorporeal membrane oxygenation are illustrated: (A) balloon atrial septostomy; (B) percutaneous microaxial pump; (C) surgically placed left atrial vent; and (D) surgically placed left ventricular vent. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Remarks

- Although the available data on early left heart decompression strategies are limited and of low certainty, the potential risks of delaying intervention suggest that the overall balance of effects favours proceeding with the intervention in light of the significant morbidity associated with LA hypertension.
- This recommendation is conditional because of limited evidence, primarily from studies in adults. These recommendations have erred on the side of early decompression to try to avoid the consequences of developing LA hypertension and clinical sequelae. Further research in pediatric patients is needed to better understand the timing of this intervention.
- No adult or pediatric study was able to show cost-effectiveness or challenges with feasibility for intervention of early left heart decompression. It should be noted that outcomes might be highly dependent on resources and/or personnel available at centres that provide ECMO care.

Practical Tips

- Depending on the resources and expertise available at pediatric cardiac care sites, left heart decompression strategies vary but may include balloon atrial septostomy, a surgically or catheter-placed LA or LV vent, or percutaneous micro-axial pumps. The choice of strategy will also be dependent on the underlying cardiac anatomy, comorbidities (ie, intracardiac thrombus), and the size of the patient.
- Sites that deliver ECMO care should be vigilant for the early changes that occur with LA hypertension (ie, loss of pulsatility on the arterial line, increasing pulmonary congestion) such that left heart decompression should occur before florid LA hypertension occurs.

Conclusion

The landscape for the diagnosis and management of pediatric HF has evolved considerably since the initial CCS guideline. This document represents a focused update on AHF in children, and highlights the unique challenges due to the distinct physiological and developmental characteristics of pediatric patients. The writing committee reviewed the current diagnostic approaches that emphasized the importance of early recognition through clinical assessment, imaging, and biomarkers to promptly identify and stratify the severity of HF. In addition, management strategies focus on stabilizing the patient with diuretics, inotropes, and vasodilators, tailored to the individual needs of the child. This document also provides guidance on the role of MCS in relation to appropriate timing and management strategies to rescue the failing myocardium. Although these recommendations are to be designed to help provide guidance, we cannot overlook the importance of prompt recognition of the signs and symptoms of AHF in pediatric patients, access to health care to enable early diagnostics and therapies, and liaising with pediatric cardiologists with a subspecialty in HF.

However, the limited pediatric data for many of the recommendations in this guideline serve as a sobering and

important reminder that much work needs to be done in pediatric HF. Many of the recommendations in this update leveraged the broader adult HF literature nuanced with the consensus from the primary panel drawing on the cumulative North American expertise in pediatric AHF. Future directions in the management of pediatric AHF include building on the current knowledge gaps with studies using multicentre data sets, the development of novel pharmacological agents, personalized medicine approaches, and improved protocols for early intervention and long-term care. In recent years there has been substantial progress in pediatric HF research, specifically in genetic and molecular mechanisms that underlie HF in children. Results from such research might hold promises for more targeted and effective treatments, analysis of large data sets to investigate important clinical outcomes, and ongoing device development, potentially transforming not only survival but also the quality of life for this vulnerable population.

Acknowledgements

The authors thank:

- Ms Christiana Fashola, Ms Carolyn Gall Casey, and Ms Stephanie Hong for their contributions and support to the co-chairs, primary panel, and document preparation process;
- Dr Dennis Ko, CCS Guidelines Committee member, who provided support, guidance, and advice through the duration of development of this guideline as Guidelines Committee Liaison;
- Dr Yetiani Roldan for contributions to the whole systematic review process; and
- Dr Andres Estupinan-Bohorquez and Dr Sydney Goldfeder for contributions to some systematic reviews.

The authors acknowledge and recognize the ongoing volunteer contributions of all writing panel members, the CCS Guidelines Committee, CCS members, and CCS staff involved in the development, publication, and dissemination of CCS guidelines.

Ethics Statement

All research reported in the current article adheres to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article because this is a guideline document; no patients were involved in the development of the guideline.

Funding Sources

The CCS verifies that funding for systematic review services was provided from its general Guidelines Administration budget. The CCS gratefully acknowledges the annual contribution of \$10,000 from the Canadian Cardiovascular Society Academy (CCSA) to support, in part, the development of high-certainty Guidelines and Clinical Practice Updates. Please read about the important work of the CCSA here: <https://ccs.ca/canadian-cardiovascular-society-academy/>.

The CCS provided a grant-in-aid to support Dr Ivan D. Florez and Dr Carlos Cuello-Garcia for the project entitled: “Systematic review for the Canadian Cardiovascular Society Guideline on the Presentation, Diagnosis, and Medical Update of the Management of Heart Failure in Children (CCS HF in Children Guideline).”

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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 and at <https://doi.org/10.1016/j.cjca.2025.12.035>.