Cardiology in the Young (2015), **25(Suppl. 2)**, 154–159
doi:10.1017/S1047951115000955

Original Article

Review of the International Society for Heart and Lung Transplantation Practice guidelines for management of heart failure in children*

Steven D. Colan

Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, United States of America

Abstract In 2004, practice guidelines for the management of heart failure in children by Rosenthal and colleagues were published in conjunction with the International Society for Heart and Lung Transplantation. These guidelines have not been updated or reviewed since that time. In general, there has been considerable controversy as to the utility and purpose of clinical practice guidelines, but there is general recognition that the relentless progress of medicine leads to the progressive irrelevance of clinical practice guidelines that do not undergo periodic review and updating. Paediatrics and paediatric cardiology, in particular, have had comparatively minimal participation in the clinical practice guidelines realm. As a result, most clinical practice guidelines either specifically exclude paediatrics from consideration, as has been the case for the guidelines related to cardiac failure in adults, or else involve clinical practice guidelines committees that include one or two paediatric cardiologists and produce guidelines that cannot reasonably be considered a consensus paediatric opinion. These circumstances raise a legitimate question as to whether the International Society for Heart and Lung Transplantation paediatric heart failure guidelines should be re-reviewed.

The time, effort, and expense involved in producing clinical practice guidelines should be considered before recommending an update to the International Society for Heart and Lung Transplantation Paediatric Heart Failure guidelines. There are specific areas of rapid change in the evaluation and management of heart failure in children that are undoubtedly worthy of updating. These domains include areas such as use of serum and imaging biomarkers, wearable and implantable monitoring devices, and acute heart failure management and mechanical circulatory support. At the time the International Society for Heart and Lung Transplantation guidelines were published, echocardiographic tissue Doppler, 3 dimensional imaging, and strain and strain rate were either novel or non-existent and have now moved into the main stream. Cardiac magnetic resonance imaging (MRI) had very limited availability, and since that time imaging and assessment of myocardial iron content, delayed gadolinium enhancement, and extracellular volume have moved into the mainstream. The only devices discussed in the International Society for Heart and Lung Transplantation guidelines were extracorporeal membrane oxygenators, pacemakers, and defibrillators. Since that time, ventricular assist devices have become mainstream. Despite the relative lack of randomised controlled trials in paediatric heart failure, advances continue to occur. These advances warrant implementation of an update and review process, something that is best done under the auspices of the national and international cardiology societies. A joint activity that includes the International Society for Heart and Lung Transplantation, American College of Cardiology/American Heart Association, the Association for European Paediatric and Congenital Cardiology (AEPC), European Society of Cardiology, Canadian Cardiovascular Society, and others will have more credibility than independent efforts by any of these organisations.

Keywords: Heart failure; guidelines; pediatric

Received: 5 February 2015; Accepted: 1 May 2015

*Presented at Johns Hopkins All Children's Heart Institute, International Pediatric Heart Failure Summit, Saint Petersburg, Florida, United States of America, 4–5 February, 2015.

Correspondence to: S. D. Colan, MD, Department of Cardiology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, United States of America. Tel: +01 617 355 4886; Fax: +01 617 739 6282; E-mail: colan@alum.mit.edu

In 2004, practice guidelines for the management of heart failure in children by Rosenthal et al[1] were published in conjunction with the International Society for Heart and Lung Transplantation. These guidelines have not been updated or reviewed since that time. In general, there has been considerable controversy as to the utility and purpose of clinical practice guidelines, but there is general recognition that the relentless progress of medicine leads to the progressive irrelevance of clinical practice guidelines that do not undergo periodic review and updating. Paediatrics and paediatric cardiology, in particular, have had comparatively minimal participation in the clinical practice guidelines realm, and as a result most clinical practice guidelines either specifically exclude paediatrics from consideration, as has been the case for the adult heart failure guidelines, or else involve clinical practice guidelines committees that include one or two paediatric cardiologists and produce guidelines that cannot reasonably be considered a consensus paediatric opinion. These circumstances raise a legitimate question as to whether the International Society for Heart and Lung Transplantation paediatric heart failure guidelines should be re-reviewed.

Evolution of the clinical practice guidelines

Jacobs et al[2] recently reviewed the 30-year history of the American College of Cardiology and American Heart Association Clinical Practice guidelines experience. The American College of Cardiology/American Heart Association effort was originally initiated in response to a United States governmental request, and since that time has developed into a sustained effort across multiple venues of cardiac care. The Jacobs review highlights the tension between evidence-based and consensus-based recommendations that characterises the clinical practice guidelines process, but rightly points out that it is often where evidence is lacking or incomplete that clinicians are most interested in guidance from clinical experts. This review also highlights the continuing evolution of the methodology used for producing guidelines[3] and notes that the clinical practice guidelines methodology itself is primarily a consensus rather than a data-driven product. The intrinsic uncertainty of the validity of both the process and, therefore, its outcome contributes to the scepticism that is frequently voiced concerning clinical practice guidelines, and the resistance that often accompanies efforts to enforce compliance with these recommendations. The American College of Cardiology/American Heart Association report also recognises the need to harmonise clinical practice guidelines between organisations and countries, because the differences between the guidelines from various sources is another factor that contributes to the uncertainty surrounding reliance on clinical practice guidelines.

Rationale for clinical practice guidelines

The American College of Cardiology/American Heart Association review[2] provided a definition of clinical practice guidelines taken from an Institute of Medicine report published in 2011: "statements that include recommendations intended to optimize patient care that are informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options". The Jacobs et al review[2] states that "when patients are treated according to American College of Cardiology/American Heart Association Class I recommendations, outcomes are improved", and cites as evidence data indicating that in-hospital mortality is significantly reduced when American College of Cardiology/American Heart Association Class I recommendations are followed.[4] Although use of guidelines may improve care in some instances, it is often not known whether this is the case because most clinical practice guidelines have not been systematically tested to document whether they improve outcomes and even the definition of "Class I recommendations" has changed over time; however, as noted by the Jacobs et al review, the even larger dilemma with clinical practice guidelines arises from the fact that very few recommendations qualify as Class I and there are very few data indicating that care is improved by Class II or III recommendations.

In addition to improved care, justifications for undertaking clinical practice guidelines that are frequently put forward include increased standardisation of care and documentation of specific areas of uncertainty where further investigation is required. It is also worth noting that once published, clinical practice guidelines are often used to justify re-imbursement and also as a basis of judging the quality of care, and, as such, these uses are often taken into consideration by the committees even if they do not constitute the primary motivation.

Clinical practice guidelines updates

The American College of Cardiology/American Heart Association review also touches briefly on the process for updating clinical practice guidelines. This includes a twice-annual review of late-breaking clinical trials published at major meetings and a scan

of the literature pertaining to each guideline topic.[2] The decision as to what "new evidence" gets included in these twice-annual reviews is based on a number of criteria intended to improve the level of confidence associated with the review, relying on criteria such as publication of a full report rather than an abstract, methodological adequacy, inclusion of data that affect safety and efficacy, consistency with other clinical practice guidelines, along with other considerations. The American College of Cardiology/American Heart Association methodology includes the option to publish focussed updates as standalone documents referencing but not duplicating the original clinical practice guidelines in the printed version, but, nonetheless, producing an electronically available document of the updated clinical practice guidelines. In addition to these interval updates, a full re-review is performed periodically, and the American College of Cardiology/American Heart Association Clinical Practice guidelines have on average a 4- to 5-year interval between revisions.

Among the criticisms that have been voiced concerning the clinical practice guidelines process, the exclusionary nature of the committees has been one of the factors that has limited their acceptance as "consensus" opinions. The committees are generally constituted by the same or nearly the same panel of experts for each update and re-review, with minimum changes in personnel that often span decades. This persistence of the same "experts" raises questions as to their willingness to recognise the deficiencies in their previous recommendations. Of note, although all clinical practice guidelines undergo peer review by a select group of content experts, there is no formal mechanism whereby interested individuals can provide commentary that might be of interest to the committee, and there is no mechanism for independent arbitration of conflicts.

Status of the International Society for Heart and Lung Transplantation Paediatric Heart Failure guidelines

Although there are some differences in methodology and terminology between the process used in preparing the International Society for Heart and Lung Transplantation guidelines and the typical American College of Cardiology/American Heart Association process, the most notable difference is undoubtedly the lack of a systematic update process. Since the publication of these guidelines, there have been other clinical practice guidelines published that are of relevance to the paediatric community. The recent publication of an American College of Cardiology/American Heart Association guidelines for the management of heart failure[5] specifically excludes heart failure in children and heart failure secondary to congenital heart lesions in adults from its scope. Although the Yancy et al publication indicates that "the reader is referred to publically available resources to address questions in these areas", it does not actually cite any such resources. In point of fact, given the paucity of relevant data in children, these "adult" guidelines will certainly influence paediatric heart failure, and in most instances the data reviewed in these guidelines represent the only available information from which opinions concerning paediatric heart failure can be derived. Kantor et al[6] have recently published Canadian Cardiovascular Society guidelines for the presentation, diagnosis, and medical management of heart failure in children. The scope of the Canadian Cardiovascular Society's paediatric heart failure review was considerably broader than that of the International Society for Heart and Lung Transplantation, which primarily focussed on medical management. The methodology was also different, and defining equivalent categories between the International Society for Heart and Lung Transplantation and the Canadian Cardiovascular Society guidelines is, therefore, challenging; however, the Canadian Cardiovascular Society shared an important limitation with the International Society for Heart and Lung Transplantation guidelines in that it did not engage the several interested societies that may have been interested in co-sponsoring this effort. As noted in the American College of Cardiology/American Heart Association Clinical Practice guidelines review cited above,[2] independent guidelines from different organisations can result in conflicting advice that represents a source of concern to clinicians. If there are genuine differences between societies, it is problematic to label the outcome as consensus-based, let alone as evidence-based. A specific example of this is the independently published Hypertrophic Cardiomyopathy Clinical Practice guidelines published by the American College of Cardiology/American Heart Association[7] and the European Society of Cardiology.[8] The American College of Cardiology/American Heart Association guidelines rely on a genetically based definition of the disease limiting the term to sarcomeric gene defect-related disease and specifically excluding hypertrophic cardiomyopathy associated with systemic disorders such as Noonan Syndrome and Friedreich Ataxia, whereas the European Society of Cardiology guidelines rely on a phenotypically based definition of the disease, specifically including hypertrophic cardiomyopathy associated with systemic disorders such as malformation syndromes, infiltrative disease, metabolic and mitochondrial disorders, and endocrine disorders in their disease definition. A discrepancy as fundamental as how to

https://doi.org/10.1017/S1047951115000955 Published online by Cambridge University Press

define the disease raises considerable concern about the basis for the guidelines themselves, as, in theory, the evidence reviewed by the two committees would be fundamentally different in scope.

Problems with clinical practice guidelines

The limited clinician acceptance of and adherence to clinical practice guidelines have been well-documented and there are undoubtedly many factors that contribute to this resistance. Although there are undoubtedly a number of psychological factors that contribute, there are also a number of scientifically justified concerns about the outcome of clinical practice guidelines. As discussed above, systematic evaluation of whether clinical practice guidelines result in improved outcomes is rarely undertaken, leaving doubt about their scientific validity. There is also a well-documented progressive expiration of the validity of the findings in randomised controlled trials and clinical practice guidelines, with an average expiry of 5 years, as illustrated in Figure 1.[9]

Perhaps the most worrisome fact is that the clinical practice guidelines advice can simply be wrong, as, for instance, in the case of the paediatric diagnostic criteria promulgated in the Hypertrophic Cardiomyopathy Clinical Practice guidelines put forward by the American College of Cardiology/American Heart Association in 2011[7] and by the European Society of Cardiology in 2014.[8] Both these organisations recommended a wall thickness z-score > 2 as the diagnostic criteria for hypertrophic cardiomyopathy in children. It is worth noting that this recommendation was not supported by any data or even a stated rationale. As, by definition, a z-score of 2 in normals represents the value 2 standard deviations above the mean value for the normal paediatric population, this criterion means (again, by definition) that 2.3% of the normal population will have values above this threshold. When compared with the estimated prevalence of hypertrophic cardiomyopathy in the adult population of 1/500 (0.2%),[10] this definition means that application of this diagnostic criterion in adults would result in >90% misdiagnosis. This, of course, is why the diagnostic threshold for the diagnosis of hypertrophic cardiomyopathy in adults is a wall thickness above 15 mm, which represents a value 7 standard deviations above normal (z-score = 7) in adult men as the normal range is 6–10 mm (mean = 8 mm and standard deviation = 1 mm);[11] however, the frequency of over-diagnosis in children is actually much higher than the predicted 11-to-1 value in adults, as disease onset is rarely seen before adolescence, resulting in an overall incidence of only 0.47 per 100,000 in children.[12] The fallacy of this

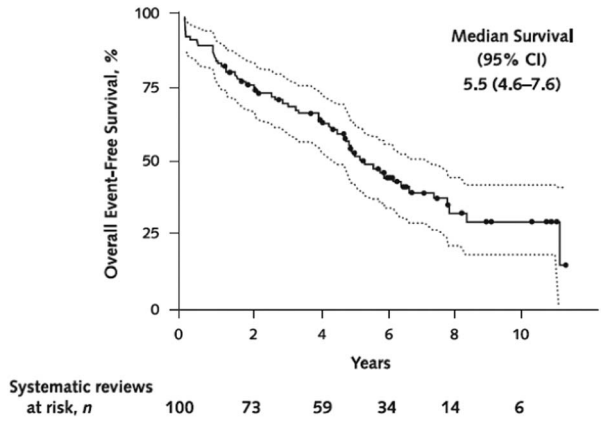

Figure 1.
Overall survival time (95% CI), free of signals for updating.

guideline can be further illustrated by the fact that a 17-year old of adult stature (body surface area = 1.8) with a wall thickness z-score of 3 would be, in accordance with the Hypertrophic Cardiomyopathy Clinical Practice guidelines published by the American College of Cardiology/American Heart Association and European Society of Cardiology, diagnosed with hypertrophic cardiomyopathy, only to learn upon achieving age 18 that he or she did not have even a suspicion of hypertrophic cardiomyopathy because the left ventricular wall thickness is only 11 mm. We can only hope that these guidelines are not followed, or else this 17-year old would be excluded from competitive sports with potential consequences that could include loss of college scholarship in addition to the depression, social isolation, and other adverse consequences commonly seen when this diagnosis is made during adolescence.

Issues specific to paediatric clinical practice guidelines

The rationale for the publication of paediatric-specific heart failure clinical practice guidelines was clearly delineated in the 2004 International Society for Heart and Lung Transplantation publication. First, this is an important issue for paediatric cardiology, as the burden of disease related to paediatric heart failure is high. Second, the aetiology of heart failure is usually quite different in children compared with the adult population. Although the primary cardiomyopathies are shared across all ages, CHD is more commonly the cause of heart failure in children, and both ischaemic heart disease and heart failure with preserved ejection fraction are rarely encountered in the young. Finally, the committee concluded that, although adult heart failure guidelines are available, "given the significant differences between adult and

https://doi.org/10.1017/S1047951115000955 Published online by Cambridge University Press

pediatric patients with heart failure, there is little reason to believe these guidelines are directly applicable to children".[1] Nevertheless, despite these notable reasons to not rely on data obtained from studies performed in adults with acquired heart disease, the clinical practice guidelines produced a total of 40 recommendations consisting of no Class I recommendations – that is, those based on multiple randomised controlled trials – 10% Class II – based on either a single randomised controlled trial or multiple non-randomised studies – and 90% Class III – based on expert consensus opinion.

There are many reasons for the shortage of randomised trials in paediatrics in general, and in paediatric cardiology in particular. When new therapies are introduced, it is generally agreed that the most ethical choice is to first test these therapies in adults who can provide their own consent for research participation rather than in children, for whom consent is always by proxy. The primary exception to this is for diseases that occur primarily or only in children. Heart failure clearly sits on the edge of this stipulation because, although heart failure is more commonly seen in adults, many of the underlying causes in children are primarily paediatric diseases, raising the possibility that the same symptom complex may have a fundamentally different therapeutic response in children. The question as to whether the unique aetiologies in paediatric heart failure are associated with any potential differences in the neurohormonal response that is the dominant target of heart failure therapies remains unanswered. Consequently, in the absence of data suggesting that the response to therapy in adults cannot be extrapolated to children, once even questionable evidence of efficacy in adults is obtained, in practice there is usually a very short window of opportunity between evaluation of safety in children and loss of equipoise.[13] This dilemma can at times be avoided, as has been the case for losartan as therapy for Marfan syndrome,[14] where multiple trials were launched simultaneously in adults and children shortly after the promising work in animals was published. The fact that testing in children and adults was synchronous is in large part attributable to alleviation of the usual ethical concerns, because this was a new indication for an approved drug with no significant safety issues.

A second huge obstacle to randomised clinical trials in children is rarity of disease and difficulty in recruitment. The angiotensin-converting enzyme inhibitor after anthracycline trial[15] included 4308 participants, 401 of whom were eligible for participation, with a total of 146 participants finally enrolled. This sample size was adequate to document a small but predictable fall in blood pressure associated with therapy and an associated reduction in wall stress, but no significant improvement in exercise tolerance or ventricular function. The sample size required to detect efficacy in diseases such as heart failure is quite large – for example, one of the seminal studies documenting the efficacy of angiotensin-converting enzyme inhibitor therapy for heart failure, the SOLVD study,[16] enrolled 4228 heart failure patients with an average ejection fraction of 28%, randomised them to placebo versus enalapril, and followed-up the participants for 3 years. They found a lower rate of heart failure-related hospitalisations in the treatment group, but even a study of this size failed to document a mortality benefit. The need to achieve enrolment of this magnitude represents a nearly insurmountable obstacle for paediatric heart disease.

To date, these obstacles have led to an extreme paucity of randomised controlled trials in heart failure in children. The likelihood that this will change measurably in the foreseeable future, particularly for issues that can be addressed in adults, is quite small. In fact, in the absence of data suggesting that there is a difference in the physiological milieu of heart failure in children it is difficult to justify withholding therapy of proven efficacy in adults. There are indeed different diseases and different causes of disease in children that require independent study in children, and these should be the target of proposed randomised controlled trials. The paediatric clinical practice guidelines process should focus on review of not merely the results of randomised controlled trials in children, but also on the data concerning the underlying physiology to determine those conditions characterised by physiological cardiovascular effects that are similar versus distinct from the heart diseases characteristic of adults. Moreover, one of the charges for the clinical practice guidelines committee should be to identify areas where the level of knowledge concerning the age-specific physiology of therapeutic targets is inadequate, rather than limiting the review to the proven benefits of therapies.

Summary

The time, effort, and expense involved in producing clinical practice guidelines should be considered before recommending an update to the International Society for Heart and Lung Transplantation Paediatric Heart Failure guidelines. There are specific areas of rapid change in the evaluation and management of heart failure in the paediatric population that are undoubtedly worthy of updating. These include areas such as use of serum and imaging biomarkers,[17] wearable and implantable monitoring devices,[18,19] and acute heart failure management and mechanical support.[20–22] At the time the International Society for Heart and Lung Transplantation guidelines were published, echocardiographic tissue Doppler, 3D imaging, and strain and strain rate were either novel

https://doi.org/10.1017/S1047951115000955 Published online by Cambridge University Press

or non-existent and have now moved into the mainstream. Cardiac MRI had very limited availability, and since that time imaging and assessment of myocardial iron content, delayed gadolinium enhancement, and extracellular volume have moved into the mainstream. The only devices discussed in the International Society for Heart and Lung Transplantation guidelines were extracorporeal membrane oxygenators, pacemakers, and defibrillators. Despite the relative lack of randomised controlled trials in paediatric heart failure, advances continue to occur. These advances warrant implementation of an update and review process, something that is best done under the auspices of the national and international cardiology societies. Cardiology (AEPC), European Society of Cardiology, Canadian Cardiovascular Society, and others will have more credibility than independent efforts by any of these organisations.

Acknowledgements

None.

Financial Support

This review received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflicts of Interest

None.

References

1. Rosenthal D, Chrisant MR, Edens E, et al. International Society for Heart and Lung Transplantation: practice guidelines for management of heart failure in children. J Heart Lung Transplant 2004; 23: 1313–1333.
2. Jacobs AK, Anderson JL, Halperin JL. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 64: 1373–1384.
3. Jacobs AK, Kushner FG, Ettinger SM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 61: 213–265.
4. Peterson ED, Roe MT, Mulgund J, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. J Am Med Assoc 2006; 295: 1912–1920.
5. Yancy CW, Jessup M, Bozkurt B, et al. ACCF/AHA 2013 guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013; 128: e240–e327.
6. Kantor PF, Lougheed J, Dancea A, et al. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. Can J Cardiol 2013; 29: 1535–1552.
7. Gersh BJ, Maron BJ, Bonow RO, et al. ACCF/AHA 2011 guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011; 124: 2761–2796.
8. Elliott PM, Anastasakis A, Borger MA, et al. ESC 2014 guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014; 35: 2733–2779.
9. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007; 147: 224–233.
10. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. J Am Med Assoc 2002; 287: 1308–1320.
11. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440–1463.
12. Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003; 348: 1647–1655.
13. Li JS, Colan SD, Sleeper LA, et al. Lessons learned from a pediatric clinical trial: the Pediatric Heart Network angiotensin-converting enzyme inhibition in mitral regurgitation study. Am Heart J 2011; 161: 233–240.
14. Lacro RV, Dietz HC, Sleeper LA, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. N Engl J Med 2014; 371: 2061–2071.
15. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. J Clin Oncol 2004; 22: 820–828.
16. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors. N Engl J Med 1992; 327: 685–691.
17. Kantor PF, Rusconi P, Lipshultz S, Mital S, Wilkinson JD, Burch M. Current applications and future needs for biomarkers in pediatric cardiomyopathy and heart failure: summary from the second international conference on pediatric cardiomyopathy. Prog Pediatr Cardiol 2011; 32: 11–14.
18. Hutchinson LJ, Stuart G, Walsh MA. Implantation of the new Medtronic LINQ loop recorder in an infant with ventricular tachycardia. Cardiol Young 2014: 1–3.
19. Bui AL, Fonarow GC. Home monitoring for heart failure management. J Am Coll Cardiol 2012; 59: 97–104.
20. Vanderpluym CJ, Fynn-Thompson F, Blume ED. Ventricular assist devices in children: progress with an orphan device application. Circulation 2014; 129: 1530–1537.
21. VanderPluym C, Urschel S, Buchholz H. Advanced therapies for congenital heart disease: ventricular assist devices and heart transplantation. Can J Cardiol 2013; 29: 796–802.
22. Vanderpluym CJ, Rebeyka IM, Ross DB, Buchholz H. The use of ventricular assist devices in pediatric patients with univentricular hearts. J Thorac Cardiovasc Surg 2011; 141: 588–590.