Peer Review File
Article information: https://dx.doi.org/10.21037/cdt-22-230

Comment 1: Paragraph “Heart transplantation – Listing and outcome”

Reply 2: This paragraph was revised in the revision of the manuscript as detailed below in the answers to reviewer 2 and 3.

Comment 2: Please check the references 54, 55 56 and 57. They might not be appropriate.

Reply 2: The authors did remove the suggested citations as the main focus is treatment of endocarditis. Instead in the lines 258-265 the following two references were used (1, 2).

Comment 3: Cases and Figures.
In general, for the reader less familiar with ACHD it would be useful to include more explanations, symbols etc. on the figures to better identify the different structures. Specials comments, for Fig 1, please indicate TV mean anterograde gradient and TR systolic gradient. For Fig 3, please highlight much better the different structures you want to show, it is not clear for the reader.

Reply 3: We thank the reviewer for the comments and included the gradients across the tricuspid valve with a mean gradient of 10mmHg. Further, the authors did highlight the important structures in the figures.

Comment 4: In the Summary, the sentence “Furthermore the lack of randomized heart failure studies…” is redundant, please delete.

Reply 4: The authors thank the reviewer for the suggestion and did remove the sentence from the manuscript.

Comment 5: Authors could add a few lines on the impact of the new Heart allocation policy in 2018, Listing ACHD patients and outcomes. Considering the recent trend of increasing the use of temporary VAD instead of durable VAD in adults with non-CHD HF, what is the direction in ACHD patients?

Reply 5: We thank the reviewer for the comment and included into the manuscript on pages 10-11, lines 259-268: “As an option to reduce the waiting list time in ACHD patients the United Network of Organ Sharing (UNOS) did revise its organ allocation guidelines in October 2018 with the aim to reduce waiting list times and thus mortality in this patient population (3, 4). As a consequence of this revision, candidates supported with a temporary mechanical circulatory assist (MCS) device will receive a higher priority status than candidates with permanent or no MCS devices (3, 4). Recent data

could show that in the UNOS network the revision led to an increased use of temporary MCS devices. with the result of a relevant decline in waiting list times (5). Although waiting list time was reduced, some aspects could not be addressed in this study, such as information regarding the particular heart failure medication, the underlying INTERMACS level of the patients. and data on the underlying congenital heart defect. Thus, although the change of the allocation guidelines has resulted in a reduction in waiting times on the transplant list, additional data have to be collected in ACHD to demonstrate benefit in this patient cohort."

Comment 6: Use of VAD: only 10% of ACHD patients listed for HT are supported with VAD. However, there is no difference in 1-year post-HT outcomes between those supported with VAD or no VAD. Any speculation on how to increase VAD utilization in ACHD patients, considering the waitlist mortality of 25%.

Reply 6: The reviewer is correct with this statement. The two largest studies addressing this issue describe, on the one hand, a longer time on the waiting list resulting more often in successful transplantation and, on the other hand, a survival in ACHD with VAD comparable to non-ACHD patients with VAD (6, 7). Overall, the most likely problems in treating ACHD with VAD are center experience with VAD in ACHD, surgeons experience, complex pathologic anatomy, poor status at the time of evaluation for VAD therapy with additional comorbidities that preclude this therapy option in the patient.

The authors have therefore rephrased and added to this topic in the manuscript on page 13, lines 312-320:
"VAD treatment as bridge to transplant or destination therapy. In this context, it should be noted that recently a large study indicated that being an ACHD and being treated with a VAD prolongs the time on the waiting list for an organ transplantation, with a higher probability of successful transplantation (6). Further, a study may provide more evidence that survival rates are similar in ACHD and non-ACHD patients with a ventricular assist device (7). However, in this study ACHD more often required biventricular support or a total artificial heart, resulting in a higher mortality rate. Despite the still high mortality on the waiting list, ACHD are not often considered for VAD support because of the complexity of the anatomy, the paucity of VAD programs focused on ACHD, and the need for surgeons to be experienced to establish VAD therapy in ACHD (7, 8)."

Comment 7: The authors pointed out that bi-VAD or total artificial heart is preferred in ACHD, but the INTERMACS study showed that mortality outcomes are worse with bi-VAD or TAH. Furthermore, this paper also reported that ACHD patients receiving VAD, ventricular morphology, and the presence of single ventricle physiology were not associated with increased mortality. This study from the INTERMACS database has to be interpreted with caution because of the low numbers- only 17 of 126 patients were diagnosed with single ventricle CHD. The ACTION multi-institutional registry study

has recently reported that VAD can effectively support patients with end-stage Fontan failure awaiting HT.

Reply 7: We thank the reviewer for the remark and revised this part of the manuscript. Thus, we included at page 13, lines 320-324:
“The previous published data, however, rise some points of discussion, as the number of patients with single ventricle anatomy, representing those with the most complex underlying congenital heart disease, was only 13% and the reader is not provided with information about the congenital heart disease in the other patients. Adding to this discussion is a study from a paediatric registry with end-stage HF and good outcomes in patients with VAD in end-stage Fontan hemodynamics (9).”

Comment 8: Line 48, I would suggest to replace with "different and more specific"

Reply 8: We thank the reviewer and changed the text

Comment 9: Line 61, suggest “IE” instead of “endocarditis” only

Reply 9: We did change the text as suggested

Comment 10: Why have the authors not performed a systematic review of literature according to the PRISMA as the current search might miss some relevant studies?

Reply 10: The authors did not choose to perform a systematic review to address a single question but submitted the written review as narrative review to the journal. A narrative review allows the question of heart failure and its related medical issues to be addressed in a broader scale than just answering one outlined specific question. as it is regularly the case in a systematic review.

Comment 11: Line 78, Can you please explain better the line with "in general in ACHD and combination of both"?

Reply 11: We thank the reviewer. We did remove “combination of both” from the text. Important in this context is that one aim is to review ventricular assist device therapy in ACHD and, on the other hand, device therapy with regard to cardiac resynchronization therapy or treatment with an ICD. Both aspects are mentioned in the manuscript and represent an important aspect in heart failure treatment.

Comment 12: Line 82, How did the authors assess the methodological quality of the studies?

Reply 12: We thank the reviewer for pointing out this aspect. To clarify this aspect and explain the method of evaluating a manuscript the authors added on page 3, lines 92-94: “…assessed independently the importance of the studies prior to their inclusion in

the review. A relevant manuscript was defined based on the impact factor of the journal, being a guideline manuscript, a society position paper, or a comprehensive review of the current literature."

Comment 13: Line 86, Please rather provide a range as you are referring later to unreliable literature on incidence and prevalence

Reply 13: In line with the comment of the reviewer we have modified this text and added the references (2, 10). Thus, a range of mortality is shown, including older patients with chronic heart failure of the Dutch CONCOR registry. Page 4, line 98: "Heart failure has a critical impact on ACHD morbidity and an approximate mortality rate of 25% up to 45% (1-5)."

Comment 14: Lines 100-101 needs some refinement as you are starting with the damage before the repair that occurred but referring also to age and cardioprotection

Reply 14: We thank the reviewer for pointing out that lines 100-101 do not contribute to the content of the text paragraph. Thus, both lines were removed from the text.

Comment 15: Line 103-104 and 109-113 needs some refinement. Also, the subtitle should be amended with "Current management" or similar rather than "care". Are data from RCTs lacking or RCTs are lacking? Suggest to rephrase with "CHD is frequently an exclusion criteria..."

Reply 15: The reviewer indicated two important points in this commentary, and we revised for lines 103-104 on page 4 lines 113-115: "Exercise capacity is often impaired in ACHD and is often unrecognized by affected individuals due to the fact that the process of deterioration often begins in early adolescence and often shows only slow progression (11)."

We further edited the lines 109-113 with the respective heading. This changed paragraph is shown on page 4, lines 120-125: "Current management of heart failure in ACHD patients. Current heart failure treatment is focusing on heart failure medication followed by additional treatment with evaluation for example for cardiac resynchronization therapy, data regarding treatment medications especially heart failure medication is currently lacking (12, 13). Sufficient data from randomized controlled trials in ACHD are currently lacking for many therapeutic interventions because of the heterogeneous patient population with underlying congenital heart defects, low number of patients in this study, and that being an ACHD is frequently an exclusion criterion in HF trials (13, 14)."

Comment 16: Lines 116-123 need some refinement, more precise discussion in a form typical to a review article.

Reply 16: We thank the reviewer for the remark and revised this part of the manuscript. Although still the main focus of heart failure patients, medication recommendations are not supported by large data studies. The part of the manuscript page 5, lines 130-139 thus was overworked:
“If systolic dysfunction of the morphologic left ventricle is present, usually medication with renin angiotensin aldosterone blockers should be established (ACE inhibitors, sartans), together with the class of mineralocorticoid receptor antagonists. Diuretics are most often used in acute decompensation or chronic volume overload (13). The cut-off regarding the decision to begin medical treatment is recommended with 40% ejection fraction (13). Regarding newer medication with sacubitril/valsartan and SGLT-2 inhibitors there are currently no data, however medication should be considered in ACHD with reduced ejection fraction of the left ventricle (12).

If the anatomic right ventricle has an impaired ejection fraction below 40% medical treatment is currently recommended if the patient is symptomatic and follows the same medication recommendations as for the left ventricle. Scarce information is present regarding medication of an univentricular heart and in these patients, medication should be according to the anatomic morphology of the ventricle present (13).”

Comment 17: Line 128-129, missing references, please explain why contradictory

Reply 17: We did remove the sentence as currently no real study data regarding medication in ACHD are published, thus study results cannot be contradictory either.

Comment 18: Line 137, Pls replace with "can progres" to avoid overstatement

Reply 18: The authors thank for the suggestions and did revise accordingly

Comment 19: Line 147, “they” is used for subjects and not conditions. Pls correct

Reply 19: The authors did change the sentence on page 6, lines 156-157: “These criteria are currently not obligatory to define advanced HF in patients, but can complicate treatment decisions.”

Comment 20: Lines 153-154 needs refinement, missing reference

Reply 20: We thank the reviewer for pointing out this issue and added into the text a citation referencing the criteria established for INTERMACS and some of the key points that the register promoted over the years with a decline of adverse events and a structured program for VAD treatment in UNOS. Please refer to page 6 lines 160-162:
“In this context, for most patients with advanced HF, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification is of potential to determine the treatment options (15).”

And pages 6 lines 165-167:
“Previous and current reports of INTERMACS show that by collecting data and including centers into the register outcomes of patients with advanced HF are improved and adverse events decreased, although only one publication thus far addresses VAD treatment in ACHD patients (7, 16, 17).”

Comment 21: Line 162, which kind of device treatment?!

Reply 21: We thank the reviewer for the comment. In the context the text in line 162 with:
“Thus, therapy of arrhythmias or device treatment could have a particular impact on the prevention or control of HF symptoms.” We did delete this text from the manuscript as the previous sentence referred to additional therapy options.

Comment 22: I suggest referring to “ACHD patients” or similar rather than just saying "in ACHD..."

Reply 22: We thank the reviewer for the suggestion. However, as all ACHD have some residual disease even after anatomical correction we would suggest to use ACHD in the manuscript as otherwise the word “patient” would mean the same as ACHD with both being diseased and suffering from an underlying disease. Thus, after discussing this issue, the authors did not change the wording in the manuscript.

Comment 23: Lines 170-172, missing references

Reply 23: As requested by the reviewer we include the references for the content in this line with (18, 19).

Comment 24: Paragraph "advanced HF treatment in ACHD" needs to be reorganized and structured in a better way as several thoughts are just put down in a disorganized way

Reply 24: Regarding the organization of the different aspects, the authors have chosen to present the current status of the definition of advanced heart failure in ACHD patients, followed by the most appropriate therapeutic treatment options of ventricular assist device therapy and heart transplantation, with emphasis on listing and outcomes of the patients.

Comment 25: None of the mentioned conditions (anatomy, catheters, ablation procedure...) are CHD-specific issues and do not differ from other cardiac patients, please re-phrase

Reply 25: We thank the reviewer for the remark. It is important that many current recommendations are not specific for ACHD but are an important part of advanced

heart failure treatment in ACHD. For example, the part addressing arrhythmias and the management and cardiac resynchronization therapy are not specific for ACHD but are put into the context by some of the expert consensus (20) or position papers (21). Thus, the authors did include these aspects into the manuscript to address this issue as well.

Comment 26: Line 189-190. 198-199, missing references

Reply 26: Regarding the section with device therapy in lines 189-190 and following, the authors cited the respective current guidelines describing indications for ICD or CRT treatment in ACHD. The citations were added at the end of the paragraph at line 203-207 on page 8 in the current revision of the manuscript with (20-22).

Regarding the treatment with a wearable defibrillator, results of the VEST study did not include ACHD, but only patients following myocardial infarction. The authors want to emphasize that in the context of complex pathologic anatomy and potential problems with implanted leads, treatment with a wearable defibrillator might be an option, but there is no specific evidence. We added the reference of the VEST study in line 213.

Comment 27: There is a bit of discussion about CRT in a few paragraphs, please re-organize

Reply 27: The reviewer is correct that device therapy and, especially, treatment with ICD or CRT are mentioned in the manuscript. However, the only part of the manuscript which discusses treatment of ACHD with CRT is in the section titled “Arrhythmia management and device therapy in ACHD patients with heart failure.” Further, data regarding potential indications and their class of recommendations are shown in this section on pages 9 lines 211-225.

Comment 28: I would suggest also discussing an option of OCS in view of longer waiting time for the organ due to surgical adhesions (refer to a reference – Verzelloni Sef A et al. Heart Transplantation in Adult Congenital Heart Disease with the Organ Care System Use: A 4-Year Single-Center Experience. ASAIO J. 2021 Aug 1;67(8):862-868.)

Reply 28: As suggested by the reviewer, we included the treatment option of the organ care system for increasing donor organ function during surgery. The text was added on page 12, lines 286-289: “Previous studies could as well show that more transplantations could be achieved with the use of special organ care systems which allow to deliver organs from donor to recipient in an adequate status and perform transplantation with a low rate of complications. A potential system currently used is the organ care system, which is achieving good results even in patients with advanced heart failure (23).”

Comment 29: Line 227, Please correct as ACHD and non-ACHD patients with LVADs had similar survival; survival was worse for patients on BIVAD/TAH support

Reply 29: We thank the reviewer for the comment. To clarify this text, we have rewritten the text passage as follows on pages 9-10 lines 234-238: “In the largest study to date, more ACHD were treated with a biventricular ventricular assist or a total artificial heart than non-ACHD patients (7). In this study ACHD had a higher mortality rate and more adverse events than non-ACHD patients, but the increased mortality rate was attributable solely to the higher use of biventricular ventricular assist devices and total artificial hearts (7).“

Comment 30: Line 236, pls refer to ventricular assist devices

Reply 30: We thank the reviewer for the suggestion and changed this in the text

Comment 31: Line 256, when mentioning listed/listing please refer to transplantation throughout the text. Suggest referring to Lo Rito et al. The Challenging Pathway Toward Heart Transplant Listing for Adult Congenital Heart Disease Patients. Artif Organs. 2018 Sep;42(9):911-917.

Reply 31: According to the suggestion, the authors changed in the manuscript the term “listing” to “transplantation listing” were feasible.

Regarding the suggested literature, the citation was added in the part Heart transplantation – Transplantation listing and outcome on page 10, lines 257-259: “Further, heart transplantation in ACHD is hard to obtain because of the high likelihood that patients will be rejected due to various comorbidities or multiple organ involvement. Studies could show that up to two-thirds of patients may be rejected for transplantation listing, which is associated with a high mortality rate.”

Comment 32: Line 272, which factors?! Please re-write “needs cardiac surgeons”

Reply 32: We thank the reviewer regarding the comment. The authors wanted to emphasize the importance of recipient specific factors that limit transplantation. Of course, it is not donor-specific issues prevent transplantation. In line 299 the term recipient-specific factors were included.

Further, the indicated part of the text was rewritten and two additional citations included stressing the importance of treating ACHD in a specialized center. Page 12, lines 301-302: “should only be done in centers with a high level of experience in treating ACHD (2, 8) “.

Comment 33: Line 285, pls avoid repetition related to the anatomical limitations

Reply 33: We thank the reviewer for pointing out this repetition. In line with the comments of reviewer 2 this part of the manuscript was overworked.

Comment 34: Lines 287-290 need some refinement and need to be re-written

Reply 34: We thank the reviewer for the comments. As mentioned in our previous reply we did change this part of the manuscript. Page 13 lines 313-325:
“VAD treatment as bridge to transplant or destination therapy

In this context, it should be noted that recently a large study indicated that being an ACHD and being treated with a VAD prolongs the time on the waiting list for an organ transplantation, with a higher probability of successful transplantation (6). Further, a study may provide more evidence that survival rates are similar in ACHD and non-ACHD patients with a ventricular assist device (7). However, in this study ACHD more often required biventricular support or a total artificial heart, resulting in a higher mortality rate. Despite the still high mortality on the waiting list, ACHD are not often considered for VAD support because of the complexity of the anatomy, the paucity of VAD programs focused on ACHD, and the need for surgeons to be experienced to establish VAD therapy in ACHD (7, 8). The previous published data, however, rise some points of discussion, as the number of patients with single ventricle anatomy, representing those with the most complex underlying congenital heart disease, was only 13% and the reader is not provided with information about the congenital heart disease in the other patients. Adding to this discussion is a study from a paediatric registry with end-stage HF and good outcomes in patients with VAD in end-stage Fontan hemodynamics (9).”

Comment 35: Although 3 interesting case presentations are provided, I am not sure which additional value to the review article they provided. In particular, the clinical cases need to be rewritten.

Reply 35: We thank the reviewer for the comment. In conjunction with the previous parts of the manuscript, the cases were selected to underline aspects of the content of this manuscript. The selection of cases is particularly noteworthy because the first represents a successful transplantation of a young female patient with advanced heart failure, the second sheds lighter on the often-present comorbidities that preclude patients from transplantation listing, and the third case highlights the option of successful therapy with a ventricular assist device in a patient with complex anatomy and multiple prior surgeries who was not a candidate for transplant. Thus, the cases are included to emphasize the content by showing clinical examples.

Comment 36: The 1st patient was not newly diagnosed if she had 3 previous surgeries, please re-phrase. Some language mistakes, please correct to “followed by a closure”, pulmonary, “aortic valve” and not “AV valve”. Several language mistakes in the whole paragraph, gender of patient changed to male at the end. Please correct.

Reply 36: We thank the reviewer for the comments. We have revisited the case and included a figure with the content highlighted.

Comment 37: Figure 1A - first image not representing anything specific, please replace. Figure legends need to be more descriptive.

Reply 37: In context with the reviewers comments we included the description into the figure and added text to the legend to describe the content of the figure.

Comment 38: I suggest shortening the case presentation 2 as it is not representing a successful transplant or to justify why did the authors decide to present it. Text needs to be re-written, abbreviation CoA not explained, pls remove “6th World conference”.

Reply 38: Case 2 is described in detail because of the comorbidities present in the patient and the subsequent decision not to list the patient for transplantation due to the high surgical risk and the needed heart and lung transplantation. The suggestions regarding the content were included.

Comment 39: Line 364, Why the patient 3 was evaluated for LVAD? Case presentation 3 needs to be re-written – it is finishing with “patient currently slowly recovering…

Reply 39: For the remark regarding case 3 by the reviewer, we included this case to demonstrate the feasibility of VAD treatment in advanced heart failure, although the patient was in a too poor condition for listing for heart transplantation. VAD as a bridge to transplant is an option as ccTGA patients in this case have a suitable anatomy for VAD treatment. The authors have revised the wording of the case and added important details in the figure to describe the important structures.