Author's response to reviews

Title: Surgical treatment of infective endocarditis in active intravenous drug users: A justified procedure?

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Response to reviewers

We would like to thank Vipin Zamvar and David Taggart, Editors-in-Chief of Journal of Cardiothoracic Surgery, the Editorial Board and the two reviewers for the careful and constructive evaluation of our manuscript entitled "Surgical treatment of infective endocarditis in active intravenous drug users: A justified procedure?". We would like to thank the Editors-in-Chief for offering us the opportunity of a revised version of the manuscript according to the comments made by the reviewers, and the possibility of reconsidering it for publication. We understand that both the reviewers and the Editors-in-Chief found our work potentially interesting. We also understand that a number of issues were raised and therefore the manuscript was not found suitable for publication in its present form. We are confident that the raised issues can be resolved through a careful revision. Thus, we have prepared a revised version of the manuscript, which includes alterations, as suggested by the reviewers. Please find our point-by-point responses to the comments of the reviewers below. We have heeded all of the reviewer’s helpful propositions and prepared a revised version of the manuscript including alterations suggested by the reviewers. Below are our detailed point-by-point responses to the reviewer’s comments. We think our work has the potential to make a fine clinical contribution and hope to publish our paper in the highly respected Journal of Cardiothoracic Surgery. We would like to thank the honorable editorial board and the professionally founded reviewers for their consideration and look forward to their future support.

The final version of the revised manuscript can be found attached. All changes are marked in yellow.
Reviewers' Comments:

Philipp Kolat - Reviewer #1 comments to the author:

Dear Editorial Team,

The authors deal with a topic of great relevance and increasing frequency. Drug-associated endocarditic infections represent an enormous challenge, especially in patients with active drug abuse. The surgical procedure is demanding, the (long-term) outcome remains more than questionable. This is already revealed in the recent literature. The authors present their experience with this very special cohort of patients at the University Hospital in Heidelberg. 20 patients underwent surgery for infective endocarditis with a history of active intravenous drug abuse. The results presented here, illustrate that it is crucial to act in time and especially in a radical manner. Only the generous excision of infected tissue is able to control the infection and to preserve a chance of survival. This is supported by the fact that the survival rate remains the same between the 3rd and the 5th follow-up-year. This is surely remarkable. The structure of the manuscript is well balanced, statistical analysis is satisfactory, the writing is appropriate besides a few spelling mistakes. In summary, we can support the publication of this manuscript.

We would like to express our thanks to Reviewer #1 for the careful evaluation of the manuscript and the helpful and constructive suggestions. The reviewer found our study potentially interesting. However, the reviewer required addressing several aspects. We agree with the points raised by the reviewer, and we are confident that these issues can be resolved through a careful revision. Therefore, wherever possible we modified the manuscript as recommended.
Reviewer #1 questions:

1.) Why have the authors chosen a 90d cutoff?

Response: After in depth study of our entire patient cohort (n=20) during preparation of the manuscript we identified seventeen patients who survived until the end of follow-up, whereas 3 patients died at post-operative day 6, 8 and 591 days. The cause of death was severe sepsis in the first two cases and sudden cardiac death in the third. We are aware that our patient cohort is small. For that reason we chose the 90d cutoff to identify any prognostic markers during the first 90 days after surgery, which could have an impact on early postoperative mortality. The demographic and perioperative variables of the 90-day survivors and non-survivors were compared to identify the predictors of 90-day overall mortality. In our view, a later cutoff would not have been different because we had only one further death and in terms of the already small patient cohort even smaller subgroups would have been generated with significant weaker value.

2.) How huge was the extent of septic emboli, particularly the cerebral ones?

Response: Thank you for that interesting comment. We had one patient with partially nodular infiltrates with small cavernous fusions in both lungs in the CT examination, in the context of multiple septic emboli with clear dysatelectatic and atelectatic changes and pulmonary congestions symptoms. Additionally this patient demonstrated already preoperatively with hyperacute infarction of left insula cortex and posterior inferior cerebellar artery territory of right side cerebellum in terms of septic cerebral embolism. Moreover, in 12 patients splenectomy was performed simultaneously for severe abscess formation due to septic embolism, which was
diagnosed preoperatively (please see corresponding page 10, line 3-4 in the revised manuscript).

3.) How long had the patients been treated with antibiotics before operation?

Response: The preoperative duration of antibiotic treatment varied greatly according to the referring hospital and was 11.9 ± 17.8 days.

4.) Do the authors have a „plan B“ for potential reinfection?

Response: Generally, in case of potential reinfection we would not change our radical treatment policy for IE as described on page 6-7, line 13 (page 6) - line 13 (page 7) in the manuscript. Moreover from our point of view, an aggressive and specifically directed iv antibiotic therapy against the infecting microorganisms is absolutely mandatory and crucial in reinfection endocarditis. Our detailed antibiotic protocol has been described in the methods section of the manuscript (page 7-8, line 14 (page7) – line 2 (page 8)). Finally, in individual cases of severe reinfection we consider intravenous antibiotic therapy for more than 6 weeks postoperatively to ensure absolute pathogen eradication.
Michael S Firstenberg - Reviewer #2 comments to the author:

Weymann and colleagues present their experience with the surgical management of patients with infective endocarditis who are still considered active drug users at the time of presentation. Of the 451 patients who underwent surgical treatment for endocarditis, they present the 20 who had active IVDA (<5% of the total cohort). Their follow-up of 2504 +/- 1842 days was impressive as many studies on the topic only focus on short-term outcomes. In addition, their long-term survival at 1,5, and 10 years (90%, 85%, and 85%) is impressive and provides justification for intervention in a complex patient population. No patients required re-operation and several variables were identified for risk for long-term mortality. It must be remembered that this experience is in Germany. While this is an interesting paper and offers good insight into the justification for management of a challenging patient population, I have a few concerns that need to be addressed (both small and large issues) prior to feeling this manuscript being suitable for publication.

We would like to express our thanks to Reviewer #2 for the careful evaluation of the manuscript and the helpful and constructive suggestions. The reviewer found our study potentially interesting. However, the reviewer required addressing several minor and major aspects. We agree with the points raised by the reviewer, and we are confident that these issues can be resolved through a careful revision. Therefore, wherever possible we modified the manuscript as recommended.
Reviewer #2 questions:

1) The author’s comments that IE in IVDU is different than the general population– a population, which I assume, is a general population with endocarditis (???) –yet they do not prove this or elaborate further than a single reference. How is the IVDU sicker or different than some of the other patients that they operated on for IE? It is the experience of this reviewer that sometimes non-IVDU patients tend to be sicker because their IE is secondary to their co-morbidities, such as indwelling pacer/ICD leads, dialysis lines, chronic immunosuppression rather than a younger population sharing needles. (MAJOR)

Response: We agree with the reviewer, that this is an interesting and important point. In the introduction of the manuscript page 3, line 6-8 the authors state “IE in IVDUs differs substantially from that typically observed in the general population in terms of microbiology, the involvement of multiple heart valves and prognosis” and refer to [3] Sousa C, Botelho C, Rodrigues D, Azeredo J, Oliveira R. Infective endocarditis in intravenous drug abusers: an update. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology 2012; 31: 2905-2910. IVDU patients develop more than any other patient subgroup, due to high-risk IVDU behavior, severe sepsis, congestive heart failure, embolization, or other complications that lead to organ failure and to intensive care unit admission (ICU), as well as to surgery. Moreover, IVDUs have often polymicrobial endocarditis with multiple valve involvement compared to non-IVDUs, which is a strong risk factors for an increase in morbidity and mortality in IVDUs with IE. Polymicrobial endocarditis also sustains a very high mortality rate (greater than 30 %) and an uncommonly large number of patients (more than 50 %) need heart
surgery either to control the infection or to repair cardiac failings. For the above reasons IVDU patients are sicker and different compared to the non-IVDU endocarditis patients.

2) The authors describe a standard surgical technique to the management of IE – is their management any different in IVDU different than non-IVDU patients? (MINOR)

Response: Thank you for that important question. Generally, we apply our radical treatment policy for the management of infective endocarditis to IVDU and non-IVDU patients without any difference as described on page 6-7, line 13 (page 6) - line 13 (page 7) in the manuscript.

3) In their methods, they describe patients with active IVDU – this needs to be better clarified – do they mean using drugs up until the day of admission or a recent history. Furthermore, they comment on drug use history – but include some drugs that are typically not administered via an IV route – i.e. marijuana (smoking), cocaine (inhaling), amphetamines (oral), ecstasy and methadone (oral) – even though many of these can be administered in an IV form. Was this considered – for example endocarditis from smoking marijuana might be different than IE from sharing needles and heroin. (MINOR)

Response: The authors apologize for the confusion and low level of linguistic clarity in the manuscript. All patients were active intravenous drug abusers (heroin) until the day of admission (inclusion criterion). In fact, all patients were polytoxicomaniac and
had additionally taken marijuana, cocaine, amphetamines, ecstasy and methadone. In summary, all patients of our study were active intravenous drug abusers (heroin) until the day of admission and took additionally infrequent the above-mentioned drugs. These important issues have been inserted into the corresponding part of the methods section of the revised manuscript (page 5, line 10-11). Moreover, we refer to the corresponding discussion section of the manuscript, page 14, line 8-14.

4) In the introduction, the authors describe IVDU has having more complex disease – however in their experience (of 20 patients out of over 450) most patients only had single valve involvement with 40% being tricuspid. They mention 1 valve repair – but do not comment on whether more aggressive reconstruction was needed in any patients (as was outlined in their description of surgical approach). (MAJOR)

Response: The authors would like to sincerely express their apologies for this mistake. One patient with severe aortic valve/root destruction had several abscess cavities including periannular invasion that were filled with gentamycin-fibrin glue and subsequently closed with pericardial patches. After that an allograft was anchored in the reconstructed aortic root. The other patient with extensive, infiltrative aortic and tricuspid valve endocarditis needed closure of a ventricular septal defect with a Dacron patch caused by extension of abcess cavities. Large parts of the walls of the atria and the right ventricle were destroyed by the infection, so that additional reconstruction with Dacron patches had to be performed. Both patients survived the operation. According to the suggestion we have inserted this important information in the results section of the manuscript (page 9-10, line 25 (page 9) - line 3 (page 10)).
5) The authors describe 12 patients - >50% of their patients – as needed simultaneous splenectomy. This is an interesting and unusual approach to the problem of a splenic abscess. Was splenectomy performed at the same time as cardiac surgery or at a different time? What were the indications for intervention in this group. (MINOR)

Response: We agree with the reviewer, that this is an interesting and important point. Splenic emboli with subsequent infarction remain a common finding with life threatening complications such as delayed splenic rupture, persistent bacteraemia and re-endocarditis. These complications advocate for an immediate splenectomy upon diagnosis of ischemic or septic lesions. On the other hand, an extension of operation time due to the additional abdominal procedure and the enhanced cumulative operative trauma are regarded as a rational for a two-stage approach. Furthermore, splenectomy in high-risk patients may be associated with an increased risk for infective complications, such as development of an abscess or sepsis. According to our own policy, every patient who is admitted to our department for active valvular endocarditis undergoes a screening process involving abdominal ultrasound that is followed by a thoracic and abdominal CT scan. Upon diagnosis of fresh splenic lesions, a general surgical consultation and inter-disciplinary evaluation involving the departments of cardiac and general surgery and the diagnostic radiological department is pursued. In contrast to the regimen reported by others, splenectomy is performed immediately after the cardiac operation, resulting in a simultaneous procedure. In 12 cases, the diagnosis of splenic lesions highly suspicious of septic foci or infarction was established, and these patients underwent a one stage procedure consisting of a splenectomy through laparotomy immediately
following the cardiac surgical procedure. A one-stage approach consisting of cardiac surgery and immediately following splenectomy resembles a safe procedure with low perioperative mortality even in the high-risk cohort of endocarditis patients. In our study, we observed a trend, indicating that simultaneous splenectomy can have a protective effect due to removal of an additional source of infection and possible prevention of secondary spleen rupture. Evidently, the authors propose a surgical therapy as indicated whenever splenic infarction is diagnosed in order to remove all non-cardiac infectious tissue and thereby to reduce the incidence of prosthetic valve infection and unfavourable overall outcome. In the 2005 published statements of the American Heart Association on the diagnosis and treatment of infective endocarditis, surgical removal is recommended for splenic abscess, and this should be performed when possible before valve replacement surgery. Therefore, a one stage procedure consisting of valvular surgery for active endocarditis immediately followed by splenectomy may be a solution that considers the need for an early removal of the spleen on one hand, as well as the limitations on the time schedule imposed by the

6) Their results were very good – short and long-term. But, this is where I have my concerns. It is the experience of this reviewer – and in discussion with colleagues – that our collective experiences show a very high rate of recurrence in this population. Patient continue to use (abuse) drugs, re-infection rates are high, mortality from drug abuse is high and patient are lost to follow-up and disappear only to be presumed to be dead. Hence – how did the authors achieve success or how is their system able to “cure” the drug abuse? It is generally viewed the IE from IVDU is a catastrophic and often end-stage problem because of the poor survival rate of long-standing abusers of IV drugs. Please elaborate on this more and speculate why the outcomes are
better. How good is their national database as a source of death or are they just assuming that if they are not listed as being dead, they are still alive – I must question the accuracy of this method considering this patient population. How many patients had actual face-face follow-up contact during the study period? (MAJOR)

Response: Thank you very much for these very important questions. The authors do not think that they have “cured” the drug abuse. One point of our success could be our radical, surgical treatment policy together with close postoperative check-ups of the patients including the involvement of specialized social workers who are trained to work with IVDU patients.

Moreover, the patients are medicated with methadone in a highly regulated methadone clinic, generally associated with an outpatient department of a hospital, or as an independent medical office. Oral doses of methadone stabilise patients by mitigating opioid withdrawal syndrome or making it more tolerable. As a result, properly dosed methadone patients can reduce or stop altogether their use of drugs. In addition, enrollment in methadone substitution programs has the potential to reduce the transmission of infectious diseases associated with injection, such as hepatitis and HIV. New patients are required to visit the clinic daily so that they may be observed taking their dose by the dispensing nurse, but may be allowed to leave the clinic with increasing supplies of "take home doses" or "carries" after several months to years of adherence to the clinic's regulations, including consistent negative drug-screening results. Many patients report that methadone is the only long-term treatment option that has ever proven to be truly effective at the cessation of illicit drug use. This is primarily due to the fact that methadone is a chemical replacement for the previously abused illicit opiate, such as heroin. Moreover, these patients receive psycho-social support on-site. Patients are often required to attend several
hours or more of therapy per week, having their daily dose withheld (or immediately reduced on a schedule) for failure to comply.

Furthermore, the provision of clean injection materials (sterile syringes and needles) by urban medical centers in our country for patients who are incompliant and carry on with iv drug abuse may reduce mortality and explain partly the good results of our study.

Mortality was determined using the German bureau of vital statistics database. We worked very close together with the bureau of vital statistics, with the GP or urban medical center of the patients and could achieve a very good follow-up. Patients must be registered to receive methadone so it was possible to monitor patients and track statistical information. Every patient had face-to-face contact with at least a study doctor/nurse in our clinic or if not possible with the GP or dispensing nurse of their urban medical center during methadone substitution program. In such a case, the GP or dispensing nurse was interviewed by telephone utilizing an interview question spreadsheet to obtain relevant information for our study.

7) An additional concern is the conclusions – the multivariate analysis that is performed on the outcomes of 20 patients. It is unclear as to whether this is a large enough patient population to support definitively the conclusions –particularly considering the number of patients at risk at >10 years (MAJOR)

Response: We completely agree that our patient population is not large, however it is a unique cohort of patients who underwent surgery for infective endocarditis and at the same time were active intravenous drug abusers and despite extensive literature research we could not find similar studies. We appreciate your opinion regarding the
conclusion of the present study and double-checked the statistical power of our results with our statistician. In order to be statistically correct and taking into consideration that the multivariate analysis did not reveal any statistically significant independent predictors, we changed our results section in the abstract and replaced “factors predictive of” and “predictors” to factors associated with 90-day mortality which is statistically correct (page 2, line 16-19). Also, our limitations emphasize a limited statistical power of our analysis. Nevertheless larger studies need to confirm our preliminary results however it is extremely difficult to conduct a study with larger number of intravenous drug abusers undergoing surgical treatment for endocarditis. Accordingly, please find changes on page 2, line 25.

8) The graphs at the end while somewhat interesting, are in general probably not necessary and contribute to making the manuscript longer than necessary. (MINOR)

Response: From our point of view, we consider the information in the graphs as important and necessary for the reader and would be very happy to leave them in the manuscript. Particularly, it is important to show number of patients at risk in the Kaplan-Meier Survival Estimation and significantly higher body temperature of non-survivors.

9) Of the variable that did predict 90d death – operative duration (but not cross-clamp or bypass time, interestingly) was predictive – why was this so? (MINOR)
Response: We think the small sample size of the 90d non-survivor group is causally responsible for the non-significant result in terms of cross-clamp time and bypass time. On the other hand, the two patients who died early postoperatively after 6 and 8 days had very friable tissue conditions of the whole heart together with disturbances of the clotting system and a long period of extracorporeal circulation that were causative for massive bleeding mainly from the suture lines. This fact cumulated in a very long operative duration; nearly twice as long as the 90d survivor group with massive transfusion requirements of 2900±141ml RBC in the non-survivor group vs. 1267±833ml RBC in the survivor group. For that reason operative duration due to massive bleeding and significantly increased transfusion requirements, which is a known factor for inferior short and long-term outcomes, cumulated in prediction of 90d survival.

10) HIV status was predictive – but what was the extensive of this disease burden? How many had end-stage HIV, active treatment, low CD+ counts, high viral loads, etc. Any insight into this would be useful – although there was only 1 patient in each group and hence definitive conclusions are difficult to make. (MINOR)

Response: Both HIV patients took antiretroviral therapy. The 90d-survivor took lopinavir/ritonavir 800 mg/200 mg daily. His HIV Western blot test revealed 7088 copies/ml, absolute CD4 count of 268 cells/mcL (HIV stage I II). The 90d non-survivor took a triple antiretroviral therapy consisting of emtricitabine-tenofovir, raltegravir, and etravirine. The laboratory results demonstrated absolute CD4 count of 447 cells/mcL (HIV stage II), and a viral load of 14100 copies/ml. Both patients were not in end-stage HIV disease (AHD/AIDS) according to international guidelines. As the reviewer already suggested definite conclusions are difficult to make from theses informations.
11) In general, the authors describe that this is their experience with a high-risk group, but they offer no comparison. How did the 20 with a history of active IVDU compared with the >400 other patients they took care of who didn’t have active IVDU? Similarly, was there any data on risk stratification of these patients – such as Euroscore – to help put some of their comorbidities into context? A review of an experience of 20 patients probably should include much more comprehensive assessment of risk factors and some of the other problems these patients encountered to get the excellent outcomes. How many were discharged home? How many had recurrent admissions for endocarditis but were not operated on (many surgeons will not perform re-ops on patients still actively using)? What was the post-op drug treatments did these patient participate in? This reviewer is also surprised that over a 20 year period that only 20 patients with active IVDU were operated on. This reviewer and his colleagues are seeing an epidemic of this disease in our practices (and far greater than 5% of all endocarditis patients are active IVDU). Where there many cases of IE with IVDU admitted to this hospital that did not undergo surgery? If so, why not and how did these patients do? Given the small patient population studied, there probably should have been a comparison group to better understand how these patients should be managed especially since it is unclear if this truly represents a comprehensive cohort. (MAJOR)

Overall, this is a very interesting topic on a challenging patient population but the number of patients studied over a 20-year period make definitive conclusions difficult to relate to current practice experiences – especially if the question is whether these patients should be managed differently or if their outcomes are different.
Response: Thank you for these important considerations. We will try to answer as closely and accurately as possible. The non-IVDU patient cohort with endocarditis is now under preparation for publication. As regards the results obtained to date from this large patient cohort, I think it can be said, that the overall results were good and not significantly better than the IVDU patients. The non-IVDU endocarditis patients were more often involved in prosthetic valve endocarditis, only a small number had polymicrobial endocarditis or fungal endocarditis and there was a trend to better long-term reinfection prognosis compared to active IVDU endocarditis patients. However it must be stated that results of more than 400 patients can hardly be compared to the results of 20 patients.

In fact, after calculating EUROSCORE II for each patient included and comparison of survivors and non-survivors, we found out that there was a statistically significant difference between survivor and non-survivors (6.89±2.83 vs. 11.04±3.35, p=0.036). We added this important issue to our results on page 2, line 16-19, page 11, line 9 and Table 1 on page 20.

18 patients were discharged to cardiology department after postoperative recovery (2 early postoperative deaths) and from there home or to their assisted living departments. Eleven patients experienced recurrent IE during follow-up and were managed with i.v. antibiotics without the need for surgery. We added this important information as well to the results section page 10, line 17-19. All patients received postoperatively methadone (please see answer 6). We are also aware that the reviewer is surprised that only 20 patients with active IVDU were operated over a 20 year period. Our department is situated in Heidelberg a small town in the south of Germany with only 150.000 inhabitants. IVDU patients are a rarity in our region and not comparable with the immense experience of the reviewer who works in the Cleveland area in the United States where more than 5% of all endocarditis patients
are active IVDU. We greatly respect the opinion of the reviewer and have to apologize the small patient numbers. Moreover, all endocarditis patients are admitted from our cardiology department. Patients are only admitted to us when they are not manageable with antibiotics. For that reason we have no information and cannot make any statement if IVDU patients were admitted and treated without surgery. We apologize this issue as well.