



Sharing of decision-making for infective endocarditis surgery: a narrative review of clinical and ethical implications

Francesco Pollari¹, Cristiano Spadaccio^{2,3}, Michela Cuomo⁴, Massimo Chello⁵, Antonio Nenna⁵, Theodor Fischlein¹, Francesco Nappi⁶

¹Department of Cardiac Surgery, Klinikum Nürnberg-Paracelsus Medical University, Nuremberg, Germany; ²Department of Cardiac Surgery, Golden Jubilee National Hospital, Glasgow, UK; ³Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK; ⁴Division of Pediatric Cardiac Surgery, University of Erlangen, Erlangen, Germany; ⁵Department of Cardiovascular Surgery, University Campus Bio-Medico of Rome, Rome, Italy; ⁶Department of Cardiac Surgery, Centre Cardiologique du Nord de Saint-Denis, Paris, France

Contributions: (I) Conception and design: F Pollari, F Nappi; (II) Administrative support: T Fischlein, F Nappi; (III) Provision of study materials or patients: F Nappi; (IV) Collection and assembly of data: F Pollari, F Nappi; (V) Data analysis and interpretation: F Pollari, F Nappi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Francesco Pollari, MD, PhD. Department of Cardiac Surgery, Klinikum Nürnberg-Paracelsus Medical University, Breslauer Strasse 201, 90471 Nuremberg, Germany. Email: francesco.pollari@klinikum-nuernberg.de.

Abstract: Infective endocarditis (IE) is nowadays one of the most challenging disease in cardiac surgery because of its multifaceted clinical and anatomical presentation. Despite the many clinical and surgical advances achieved in the past 60 years, there is a lack of evidence regarding the ideal strategy. The present review aims to investigate and highlight two main novel concepts for the decision-making of the best substitute. Firstly, the concept of an “endocarditis team”: a coordinated multidisciplinary effort in the diagnostic work-up, especially in conditions of high risk of embolization or clinical deterioration. A good “endocarditis team” has the role to overcome such problem, in order to ensure a prompt and balanced strategy. Secondly, which ethical considerations are required to drive the choice of valvular substitute. The choice of best valve substitute is a relevant issue of debate, not only with operative but also prognostic and accordingly ethical aftermaths. Many different solutions have been developed to substitute the infected valve. Among these: mechanical prosthesis (MP), biological stented prosthesis (BP), sutureless bioprosthesis and cryopreserved homografts (CHs). Patients need to be informed in detail about the technical issues pertaining the use of these valve substitute. We will discuss the evidences regarding the risk of recurrent infections or future potentially severe calcification of aortic homograft valve and wall (in other words, the failure of the homograft) and the difficulties in managing the reoperation.

Keywords: Multidisciplinary decision-making; infective endocarditis (IE); aortic homograft; pulmonary autograft; structural valve deterioration (SVD)

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Introduction

Infective endocarditis (IE) is nowadays one of the most challenging disease in cardiac surgery because of its multifaceted clinical and anatomical presentation. Despite the many clinical and surgical advances achieved in the past 60 years, there is a lack of evidence regarding the ideal strategy. As the current evidence on the best treatment

strategy for endocarditis does not follow a single direction and the results are controversial, a systematic approach to endocarditis management should be based on sharing of decision-making concerning clinical and ethical implications (1-8).

The present review aims to investigate and highlight two main novel concepts for the decision-making of the best

substitute. Firstly, the concept of an “endocarditis team”: a coordinated multidisciplinary effort in the diagnostic work-up. This issue wants to deeply discuss the need for early surgical referral, especially in conditions of high risk of embolization and/or clinical deterioration (i.e., with signs of heart failure notwithstanding the establishment of the appropriate antibiotic therapy). Secondly, which ethical considerations are required to drive the choice of valvular substitute. This issue will analyze the risk of future potentially severe calcification of aortic homograft valve and wall (in other words, the failure of the homograft) and the difficulties in managing the reoperation of right and left outflow tract when homovital Bentall procedure is performed. Ethical consideration will include prognostic, familiar, and social features that influence the choice between potential valve substitutes (2).

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-4626>).

Clinical implications: the ideal endocarditis team

The literature is poorly on data to afford the systematic approach to patients affected by IE. Moreover, up to now we do not have randomized studies that help us to orientate times and choices (1,9-11). In addition to surgical advances, such as new prostheses, technologies and procedures available, it is necessary to consider the advances offered in other fields of medicine, such as the new anticoagulant treatment, the new antibiotics and the new possible means for diagnosing the pathogens involved, so all committed to facilitating the successful outcome of the patient after surgery. In this way the discussion in the decision-making team of specialists can be focused on the emergency surgical criterion and on the clinical guidelines to be adopted in relation to the presented complications. A decision and a mutual discussion within the “endocarditis team” can add to sharing the best current knowledge for surgical treatment of endocarditis (although surgery is only part of the whole treatment), the most effective choices for anticoagulant therapy, optimal antibiotic treatment and postoperative follow-up.

First of all, the etiology, clinical presentation and anatomic extent of infection at preoperative imaging are included as determinants for identifying different patient categories in order to stratify and guide decision-making towards the most appropriate medical or surgical

strategy. Patients, who are habitually hospitalized with heart failure, can easily control the symptoms with medical treatment. Sometimes they present evidence of severe acute regurgitation or obstruction, resistant pulmonary edema or cardiogenic shock. The diagnosis and decision making could be challenging. An algorithm is proposed (*Figure 1*) in which the professional roles are highlighted. Internal medicine, microbiologists, imaging experts (12) and emergency physician are fundamental to promptly diagnose the suspicion of IE using Duke Criteria and initiate the referral; however, expense of time can delay the surgical procedure. The concern regarding the prolonged time required by the internists to achieve a diagnosis, rigidly conditioned to the strict respect of Duke Criteria, is often due to the difficulty in identifying the pathogen responsible (13). Indeed, in the presence of very aggressive and no detectable microorganisms, 24–48 hours of non-targeted antibiotic therapy can lead to extension of lesions with multiple valves involvement and destruction of large portions of the heart with consequent adverse outcomes. Evidence for this clinical scenario is represented by IE sustained by intracellular microorganisms, such as *Coxiella burnetii*, *Bartonella* species, or *Tropheryma whippelii*, in which the exposure and the status of the immune response of the host become decisive (14). In this direction, an effective support can be provided by the evaluation of anatomopathological criteria based on the characteristics of the infectious field: location, size and extension. Far to be irrespective of internist knowledge or practice, in our experience we highlighted that in some instances there is not a comprehensive understanding of the surgical challenges and of the consequent complications as well as the clinical course of these cases after surgery. This tendency combined with the difficulty of identifying the pathogen can lead patients to be offered for surgery at a late stage in significantly more compromised clinical conditions and higher intraoperative risk (15). A good coordinated “endocarditis team” has the role to overcome such problem, in order to ensure a prompt and balanced strategy (16).

Neurological complications

The concern of neurological complication is an ever-present spectrum. Several studies have highlighted the serious neurological implications being IE advising diagnostic and therapeutic procedural solutions. In 60% of patients, ischemic and hemorrhagic stroke often precede the diagnosis of IE, inviting to reflect on the timeliness of decisions that could reduce the risk of neurological

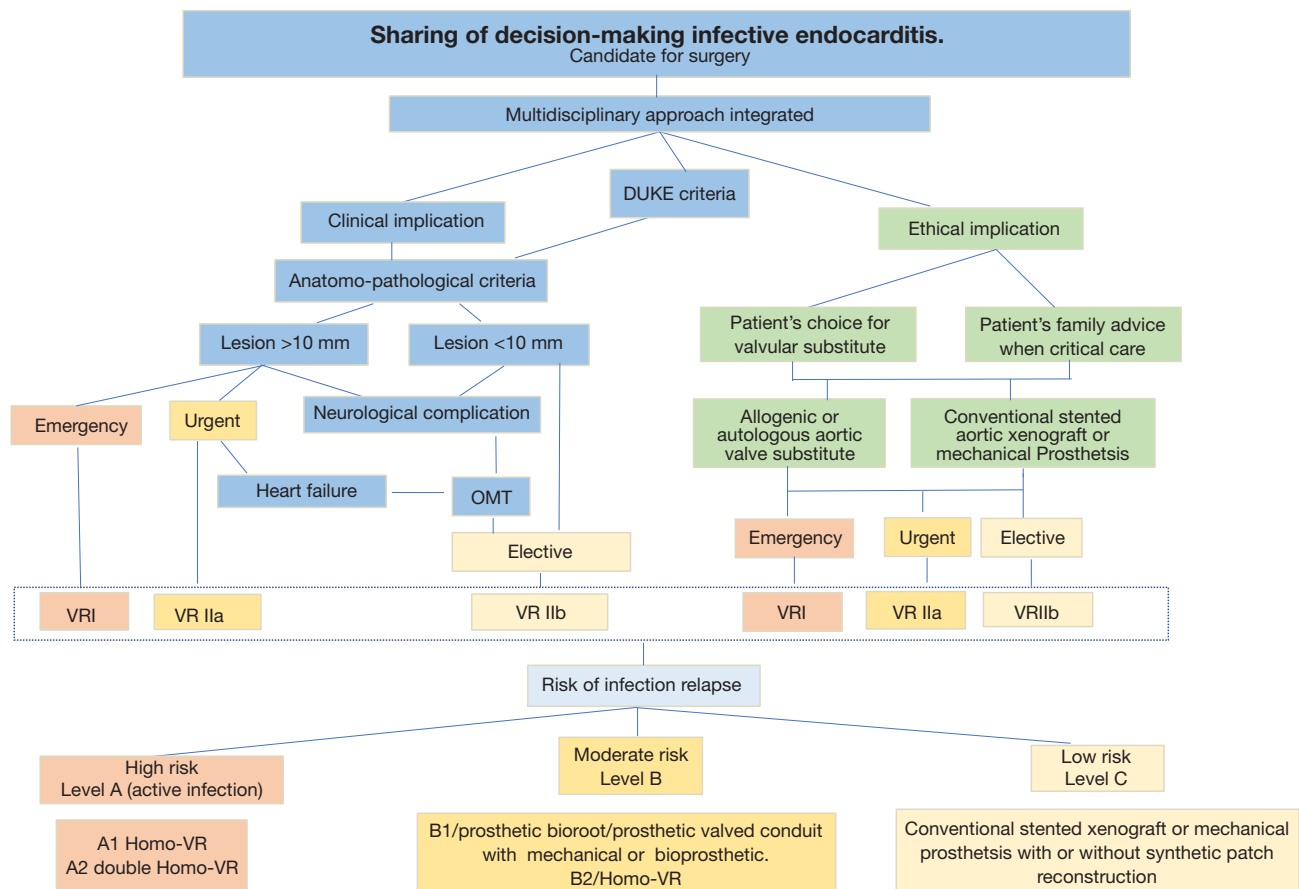


Figure 1 Clinical algorithm for the management of IE considering the clinical and ethical aspects. Class of recommendations and level of evidence are expressed according to international guidelines. IE, infective endocarditis; VR, valve replacement.

complications (17-19). Moreover, the presence of infectious foci such as, mycotic aneurysm and the cerebral abscess, could be cause of silent cerebral events, not clinically detectable and deserving of a particular investigation (20).

Lesions and vegetations

Another criterion for early intervention is represented by the presence of vegetations due to *Staphylococcus aureus* infection that are large, mobile that prominently involve patient with complex valve endocarditis with infected fields located in the mitral valve. Localization of abscess is crucial to guide surgery (21,22). The presence of vegetations from *Staphylococcus aureus* colonization >10 mm of the valves is indicative of a progressive risk of embolic events requiring urgent surgery (Figure 1). Conversely, in case of established cerebral localization of septic emboli with hemorrhagic evolution, surgery should be postponed and computed

tomographic (CT) scan or magnetic resonance imaging (MRI) perfusion scans should be performed to evaluate the progression of the lesion (15,20). Imaging specialists should therefore take over providing a clear picture of the valve status (vegetations, valve function) and of the risk of embolism (i.e., mobile vegetation, evidence of previous septic embolism) (20,22). At the same time the role of microbiologist is fundamental: for the correct diagnosis as well for orienting the appropriate antibiotic strategy (21,23,24). In this context, particular attention should be given to microorganisms difficult to identify and to culture, as this is one of the causes of delayed treatment and referral (19,24).

Once indication for surgery is established an accurate evaluation by the anesthetist should be performed targeting the comorbidities potentially harnessing the outcomes of the operation and the degree of hemodynamic stability of the patient. The final aim of this coordinated

multidisciplinary approach should be to guarantee an early referral to specialized centers and to avoid temporizing on the surgical decision, especially in complex and extensive endocarditis (15).

The goal of the multidisciplinary team is to bring together several expertises in order to provide the best possible treatment for patients requiring difficult medical and surgical management. In our opinion no leadership is necessary, but agreement. Patient can be treated according to his/her status in medical or cardiology wards, however, in case of deterioration intensive care environments are recommended.

Ethical implication

The ethical implications find their role in the process of shared-decision not only for intervention but above all the type of valve substitute. Due to the complex and variable situations, ethical implications involve mainly three figures/groups: the patient, the patient's family, (especially when the patient is unable to express his will, as in critical situations) and finally the team of specialists involved in the care, whom prognostic evaluation is critical for the decision. The team of specialists should obviously not only inform but assist the patient and the family by orienting the best choice.

The choice of best valve substitute is a relevant issue of debate, not only with operative but also prognostic and accordingly ethical aftermaths. In the last 60 years many different solutions have been developed to substitute the infected valve. Among these: mechanical prosthesis (MP), biological stented prosthesis (BP) and cryopreserved homografts (CHs). Patients need to be informed in detail about the technical issues pertaining the use of these valve substitute.

As recommended by current guidelines, multidisciplinary decision-making regarding valve replacement (VR) strategies in IE should regard the longevity of the biological substitutes, the potential recurrence of infection and the risk of repeat surgery, which is often associated with extensive heart demolition. In this context, the balance between the risks and benefits should be taken into account when discussing with the patient or family the surgical options. The principal risk account of a prognostic structural valve deterioration (SVD) with potential valve dysfunction requiring further complex redo-surgery and tissue demolition; benefits are represented by a very low incidence of infection recurrence (25-30). However, thinking not

in a long-term perspective, but short, the main problem in patients treated for complex aortic or mitral-valve IE, frequently associated with extension in mitro-aortic continuity and evidence of fistula into a cardiac chamber or pericardium, is not SVD, but the relapse of infection (4,31-36). The extension to a single valve leaflet does not exclude the severe involvement of the annulus that requires a radical debridement with complete removal of necrotic tissue, vegetation and foreign material. Unfortunately, the general propensity seems to be oriented towards the use of the "simplest solution" but the easiest option is not always the one that leads to the best long-term results. Several reports showed that extensive and radical surgery was necessary in a large number of patients with IE receiving CH, but also MP or BP have been used in similar frequency in complex endocarditis (4,37,38). In the studies, abscess formation had an incidence from 40% and 67%, indicating the severity of the disease treated in this cohort.

The reoperation for a relapsing infection carries a higher mortality than the reoperation for SVD or dysfunction of an aortic homograft inserted in aortic root position. Some investigators reported, in largely number of patients with complex valve endocarditis, the preferentially use of MP as substitute for infected aortic valve compared to the stented BP (40.5% *vs.* 29.5%). This trend was also confirmed with the simultaneous involvement of the mitral valve (38% *vs.* 18.7%) (37). Although some reports praised the long-term outcomes of mechanical valves, it cannot be neglected that these prostheses are bond to a life-long anticoagulation which carries significant risks. Additionally, the population normally afflicted by endocarditis is relatively young and willing to conduct an active life and oral anticoagulation means a significant impairment in patient's quality of life. Also, in case of female patients, possibility of pregnancy is excluded. We believe that, in the context of endocarditis, treatment needs to be guided and inspired by principles regarding the avoidance of infection recurrence and valve functional outcomes, as re-do surgery in case or reinfection is particularly challenging and burdened by augmented risk. An important study from Germany evidenced that CHs processed with antibiotics possess antibacterial activity despite long-term storage over 5 years (39). Antibiotic combinations applied during CHs processing could have a significant influence on their infection resistance.

In particular, reinfection of synthetic prostheses or prosthetic materials, such as MP or BP, is even more daunting and technically demanding than in case of re-endocarditis on a previous CH. In this context, evidences

on safety and effectiveness of CHs over conventional prosthesis has been widely reported in several observational studies. A rate of 2% of patients with most relapse or recurrence of infection following aortic valve endocarditis surgery happening within the first year has been described at 10 years (31). A recent report showed a low recurrence of endocarditis in homograft even in complex cases with extensive injury of heart structure (32).

Pivotal series from centers of proven experience showed very solid results in terms of mortality (intraoperative 5.5%) and durability (up to 23 years) when CHs were used as valvular substitute in endocarditis (29). More recently a study from the same group evidenced positive results at 27 years' follow-up after surgery with use of CH underlining the importance of allogenic tissue in infection of the heart (30). Historical series widely cited expressed favorably for the use of CH in the set of infected fields. One of these reported 13 years' experience with homografts in endocarditis showing excellent clinical performance and durability with a low rate of reinfection. Late mortality rate was 7.9%. Patient survival after discharge from hospital at 1 year was 97% and at 10 years was 91%, respectively (33). Similarly, for other investigators homograft aortic root replacement in active IE with peri annular abscess formation showed satisfactory early and long-term results with significantly better survival in native valve endocarditis than prosthetic valve endocarditis (35). Also, in prosthetic valve endocarditis, survival when using a homograft is higher than using prosthetic valves (5-year cumulative survival 88% *vs.* 66% in prostheses) as testified by Perrotta and colleagues (36). When comparing with MP an equal risk of reoperation between MP *vs.* BP was proved whichever the prosthesis type. More recently, the group from Cleveland clinic confirmed the safety of CHs clearly pointing at the advantage of homografts and valve preserving procedures (thus the preservation of a "native" aortic valve configuration) in terms of long-term durability and safety, with the additional benefit of the best postoperative hemodynamics and ventricular remodeling (34). Sometimes in presence of aggressive IE with extension to aorto-mitral junction and mitral valve, the use of a double homograft is possible (40). The technique of implant has given good results even in the presence of mitral tissue rendered more fragile by the presence of infection. Based on recent reports, the use of CHs for reconstruction after debridement of infective tissues has dramatically decreased, thus making the stented prostheses (MP and BP) the first choice as substitute in many centers worldwide (15,37,41). More

demanding surgical techniques, involving the surgery of CH, and the not readily availability in many centers could be responsible of this tendency. This causes an impairment in learning and subsequent skill in the technique of aortic homograft implantation (37,38,42). This surgical procedure is nowadays in many non-specialized centers only in the anecdotal experience of some cardiac surgeons at the end of his career. However, a clinical doubt raises the important question whether allogenic material should not be forgotten whereas an extensive surgery for endocarditis is planned (38,42,43).

Focusing on the long-term perspectives, the second question for the surgeon when choosing an allogenic tissue is the durability overtime and the risk of a redo operation for SVD because of calcification of the CH compared to conventional prostheses. In this situation a considerable skill is required to the surgeon for a technically demanding re-intervention that has a mortality of 4–10% and a morbidity of 34%, as reported in the literature (44). It should be considered that the extensive demolition of adhesences is necessary to access the heart where synthetic material was previously inserted and that the reoperation for re-endocarditis on prosthetic valve is more challenging and riskier than in case of previously implanted homograft. The foreign material constituting the stent of mechanical or biological prosthetic valve elicits a strong inflammatory reaction and might result in stronger adhesences complicating the operation. Definitive responses based on conclusive immunological evidence on the extent of the pro-inflammatory immune response in the allogenic grafts compared to the xenografts are not available. Concern related to the severity of the lesions is due by the host immune response and the key role played by cells and chemical mediators of inflammation in conditioning the immune response of the host. Certainly, the host immune response plays a pivotal role also in structural valve degeneration of homograft. Macrophages play a key role in the host immune responses. However, also the preservation modality is crucial in this context (45,46) and novel processes of decellularization of the homografts have been shown to provide more favorable tissue reaction with reduced risk of degeneration (47,48). Recent clinical experience with decellularized aortic homografts (DAHs) in children showed good mid-term results in term of SVD, but there is yet a lack of evidences in term of recurrence of IE (49). If on one hand xenografts (namely BP) are normally processed with chemical fixatives to avoid degeneration, on the other hand they present a significantly higher

amount of foreign materials (e.g., valve stents, suture skirt) which might elicit an even stronger inflammatory reaction generating annular pannus (especially if implanted with pledgeted sutures). In this context an aggressive tissue reaction might be even more daunting as requiring an extensive clearance of adherences with increased surgical risk. However, unlikely the prosthetic valves, CHs are very rarely affected by reinfection and dealing with SVD in homograft carries a significant minor burden in respect to redo surgery for infected prosthetic valve. The use homografts and the detrimental effect on immune response need to be contextualized in the clinical scenario of endocarditis. In this framework good hemodynamics with avoidance of long-term anticoagulation (often young patients) and, more importantly, avoidance of re-do surgery are the main tenets of treatment and can therefore weight towards the use of homografts especially in case of extensive endocarditis of aortic and mitral structures.

Today considerable advantages for the VR in case of SVD can be provided by use of transcatheter aortic valve implantation (TAVI) and sutureless aortic valve replacement (Su-AVR), that can meet the surgeon when complex injuries are evident (50,51). These procedures might be applied with relatively lower risk (in comparison to standard AVR) in case of massive calcification of homograft. Transcatheter aortic valve in valve procedure has given a considerable support in case of SVD that occurs in biological substitutes implanted in the aortic position. This consolidated technique was firstly anticipated by Kowert *et al.* that reported a survival rates after 1 and 5 years of 86.0% and 77.4%, respectively after homograft redo operation and identified in trans-apical TAVI a safe and feasible procedure if the valve is not infected (52). After the experience of Dainese that described the use of sutureless in the younger population requiring reoperation for AVR and the TAVI in older ones with promising results to reduce mortality and morbidity other centers have taken this course (53). However, in this case the incidence and burden of a patient-prosthesis mismatch or of a subclinical thrombosis (also known as hypoattenuated leaflet thickening, “HALT”, and abnormal motion) are unknown due to the low number of disposable evidences and lacks of large series comparing hemodynamics outcome with the surgery (54).

Some special consideration should be reserved to the new generation of BP for aortic valve disease, the so-called “sutureless” (i.e., Perceval, Livanova) and “rapid-deployment” (Intuity, Edwards) prostheses. Such prostheses are the result of an evolution of conventional BP that allows a rapid implantation. Thanks to a special stent, similar to

the TAVI’s prostheses, they do not need any (sutureless) or only three (rapid deployment) sutures to be implanted. Their use assumes the integrity of the aortic annulus to ensure the stability, and for this reason they were indicated primary for the treatment of aortic valve stenosis and the presence of endocarditis was an exclusion criterion for their use (55). However, their ability to shorten significantly the surgical times represented a theoretical advantage for high risk patients affected by severe disease and compromised hemodynamic. The off-label use of the sutureless prosthesis as valve substitute for patients affected by endocarditis has been reported in little samples with good results (56). A single report from Germany showed its use also in mitral position in a case of endocarditis, where an adequate valvular substitute was not disposable (57). At the best of our knowledge, up to now any use of Intuity valve in case of endocarditis has been yet reported.

Last but not least, patient opinion may determine the choice of treatment conditioning the surgeon’s orientation that is faced with ethical issues. As noted by Stulak (58) regarding the use of pulmonary autograft in Ross operations, the use of biological derivative poses some ethical issues when the chances for failure of the procedure or reoperations are not infrequent. Would some patients prefer taking the risk of potential recurrence of infection, whether a possibility of a vast and extensively radical debridement could be avoided? Does the surgeon need to inform the patient of the technical issues involved using a homograft that may pose difficulties during surgery, questions that may need to be addressed in an otherwise healthy or young patient? Simply the age of the patient may also direct the choice for the prosthesis to be used even in the presence of complex valve endocarditis with largely infected field? What would the risk for a redo operation be using a homograft *vs.* a prosthesis? Clearly, the heart team discussion cannot neglect patient’s preference and willing. A very extensive operation might be considered daunting by patients and clinicians are required to explain in details the steps of the procedure, the potential complications and the postoperative course in order to provide the majority of the information for the patient to take a conscious decision. Patient needs to be made aware of the complexity of the disease and on the potential need of extensive debridement to achieve good and stable results. Performing a quicker operation with a prosthetic valve within a context of a significant infective involvement of aortic tissues provides a very unstable situation with high potential for infection recurrence. We believe that the option to undergo a

minimized operation with known potential for re-infection should be discouraged (59-63).

Conclusions

To conclude, decision on surgery is always deriving from a balance between the risk of the procedure and the benefit achievable; considering the significant risk during endocarditis surgery and the even higher risk represented by a redo-operation for re-infection in this context. The best outcome is probably achievable through a harmonic patient-clinicians alliance, respecting the needs and willing of the first, and the competences of the seconds.

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