



A narrative review of early surgery versus conventional treatment for infective endocarditis: do we have an answer?

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Abstract: The most appropriate strategy and timing for surgery in infective endocarditis (IE) remains an argument of debate. Despite some authors promote the adoption of an early surgical approach (within 48 hours) to limit mortality and complications, no robust randomized trials are available on this argument and the evidence on this subject remain at the “expert opinion” level. Additionally, the different messages promulgated by the American and European guidelines contributed to fuel confusion regarding the relative priority of the surgical over medical therapy in IE. The European Society of Cardiology (ESC) guidelines individuates three level of urgency: emergency surgery, to be performed within 24 hours; urgent surgery, recommended within a few days; elective surgery to be performed after 1–2 weeks of antibiotic therapy. Urgent surgery is recommended for most cases of IE. In the American Heart Association (AHA)’s guidelines define early surgery as “during the initial hospitalization and before completion of a full course of antibiotics.” Some of the available evidences showed that are no proven benefits in delaying surgery if a definite diagnosis of IE has been established. However, this argument is controversial across the literature and several factors including the center specific experience can play a role in decision-making. In this review the latest evidences on IE clinical and surgical characteristics along with the current studies on the adoption of an early surgical approach are analyzed to clarify whether enough evidence is available to inform an update of the guidelines.

Keywords: Infective endocarditis (IE); guidelines; treatment; management

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Introduction

Despite the progress achieved in recent years for the treatment of infectious endocarditis in both the medical and surgical fields, this clinical-pathological entity remains a serious disease carrying a significant risk of death and morbidity (1-4). The use of surgery has gained momentum in the treatment of infectious endocarditis and it is expanding. However, current guidelines are cautious in supporting broad application of

surgery in complicated left-sided infectious endocarditis (2,5,6). Although early surgery is highly recommended in patients with infective endocarditis (IE) who present with signs of congestive heart failure (3-6), the indications for surgery to prevent systemic embolism remain undefined (7-9). The main concern is for patients with large vegetation and a high risk of embolism (4,10). In these patients’ early surgery with complete excision of infected tissue and valve repair have

been achieved in high-volume centers with low mortality suggesting the benefit of early surgical management (1,4-6,11). However, concerns remain regarding the technical challenge of performing surgery in the presence of active infection and inflammatory response (1,12).

The 2014 American College of Cardiology-American Heart Association (ACC-AHA) guidelines (13) recommend the use of early surgery as class IIa indication only in patients who have recurrent emboli and persistent vegetation. Instead, the guidelines of the European Society of Cardiology (ESC) (6) recommend the use of early surgery as class IIIb indication in patients who have isolated and very large vegetations (>15 mm in diameter). The non-univocal recommendation from the two Society guidelines and the lack of randomized studies related to the presence of ethical, logistical, and financial constraints, impede to clarify the best indications for surgery and its timing (6).

The best timing for surgery is even more important in patients with prosthetic valve endocarditis (PVE), which present in 3% to 6% of the patients within 5 years of surgery and is associated with significant morbidity and mortality (14-17). Surgical debridement and valve replacement are recommended by consensus guidelines (6,14) in patients with IE who experience complications such as valve dysfunction, dehiscence, heart failure, cardiac abscess, or persistent bacteremia. However, these guidelines rely largely on expert opinion and limited observational data (18). There are several studies that have compared survival between patients undergoing surgery and medical therapy for PVE but they have reported conflicting results (15,18-25). Furthermore, their retrospective nature, low sample size and risk for treatment allocation bias profoundly limit the power of these studies.

The only randomized evidence comparing the use of early surgery to medical treatment enrolled only a small number of patients with native valve endocarditis due to the streptococcal pathogen (26). No randomized studies on PVE are currently available.

The objective of this review is to evaluate whether an answer can be given on the question regarding the best strategy to be adopted in the early treatment of IE.

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-3880>).

Methods

A search of the PubMed database using the terms

“endocarditis”, “left side endocarditis”, “right side endocarditis”, “aortic valve endocarditis”, “mitral valve endocarditis”, “tricuspid valve endocarditis”, “heart valve prosthesis”, “allograft”, “autograft”, “cardiac valve surgery”, “early surgery”, “delayed surgery”, was coordinated. Qualified abstracts were independently reviewed by two investigators and the related articles were evaluated. References for all selected studies were cross checked. Data from randomized controlled trials (RCT), unmatched observational series, observational series corresponding to propensity, meta-analysis, registries, and expert opinion were included.

Clinical evidence

Patient presentation

Patients with sepsis of unknown origin or fever in the presence of risk factors should always trigger the suspicion of IE. They should have a careful assessment of symptoms and should undergo a clinical and microbiological investigation followed by transthoracic echocardiography to assess the mechanism and severity of heart valve infection, as well as left ventricular size and function. The manifestations of sepsis can fluctuate from general malaise to shock because they are influenced both by the virulence of the pathogen and by the host's immune response (27,28). Usually Gram-positive Cocci of the staphylococcus, streptococcus and enterococcus species are responsible for 80–90% of infectious endocarditis. *S aureus* is the most frequently isolated pathogen in infectious endocarditis in high-income countries with a reported percentage of 30% of cases (29,30). In particular, a microbiological diagnosis of *S aureus* bacteraemia is associated with infectious endocarditis in 25–30% of cases and all patients must be received echocardiography (31,32).

Patients with IE who present in a critical phase should be judiciously evaluated for risk of embolism and hemodynamic deterioration towards heart failure. Risk factors as underlying hemodialysis or addiction to the intravenous drug should be considered (33). The infection can be localized on the native and prosthetic valves, and patients might be asymptomatic without clinical cardiovascular deterioration for few days after infection (*Figure 1*).

Hemodynamic decompensation and heart failure

The most common indication to perform early operation

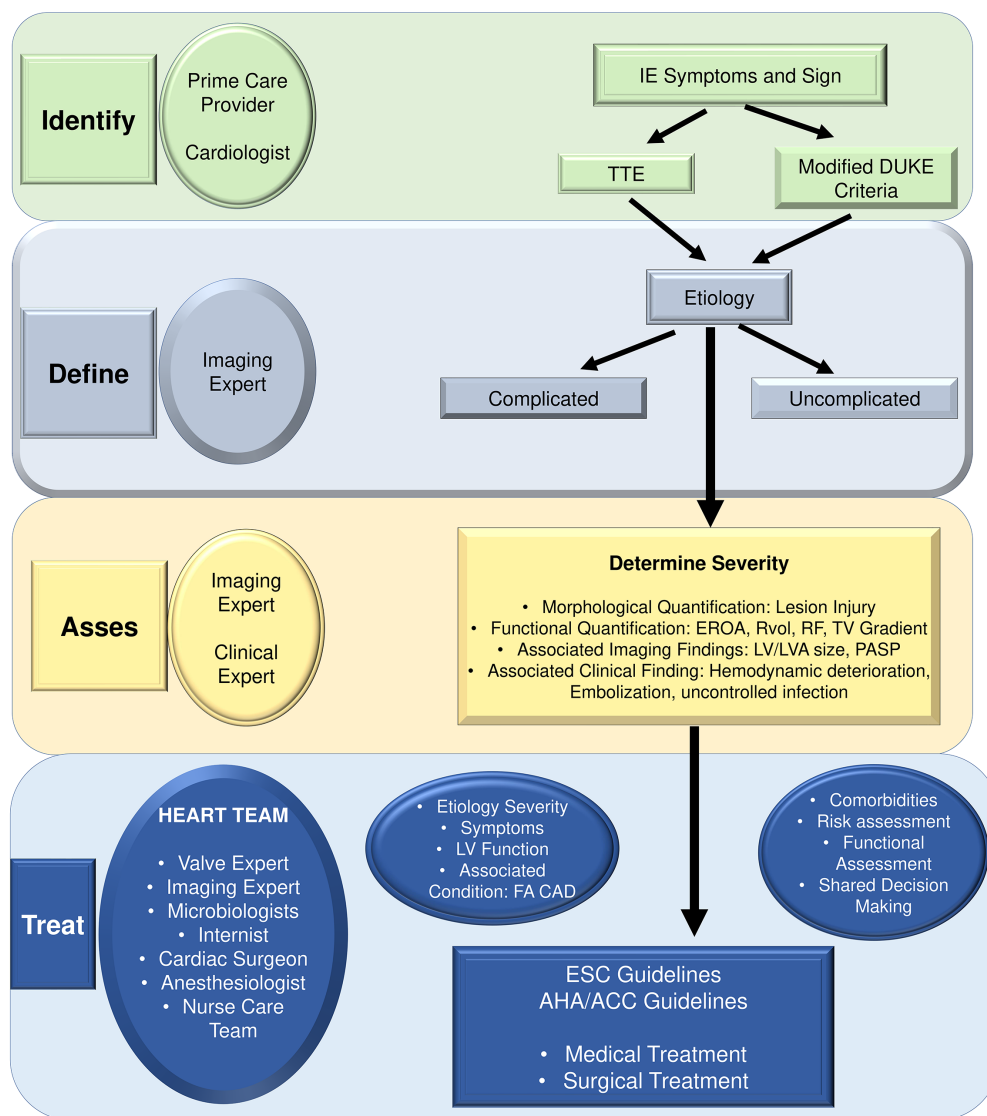


Figure 1 Pathway for Management of IE. ACC/AHA, American College of Cardiology/American Heart association; CAD, coronary artery disease; EROA, effective regurgitant orifice area; ESC, European Society of Cardiologists; FA, atrial fibrillation; IE, infective endocarditis; LV, left ventricle; LA, left atrium; PASP, pulmonary artery systolic pressure; TTE, transthoracic echocardiography; RF, regurgitant fraction; Rvol, regurgitant volume.

in patients with IE is the development of heart failure. Increasing severity of valve regurgitation, even among asymptomatic patients, imposes a volume load on the left ventricle, which, if sustained over time, results in ventricular dilatation, hypertrophy, neurohormonal activation, and heart failure. In addition, in presence of a mitral valve endocarditis elevation in the mean left atrial pressure leads to left atrial enlargement, atrial fibrillation, pulmonary congestion, and pulmonary hypertension. Valve obstruction

is another factor determining hemodynamic instability and heart failure. Evidence from numerous cohort studies revealed that the results were nefarious in patients who had not received emergency surgery because of the progression to pulmonary edema or cardiogenic shock (4,34-36). The presence of a large vegetation that compromises the functionality of the entire valve—rarely only a single leaflet is involved—can have a faster deterioration with progression of hemodynamic instability. These patients have valves

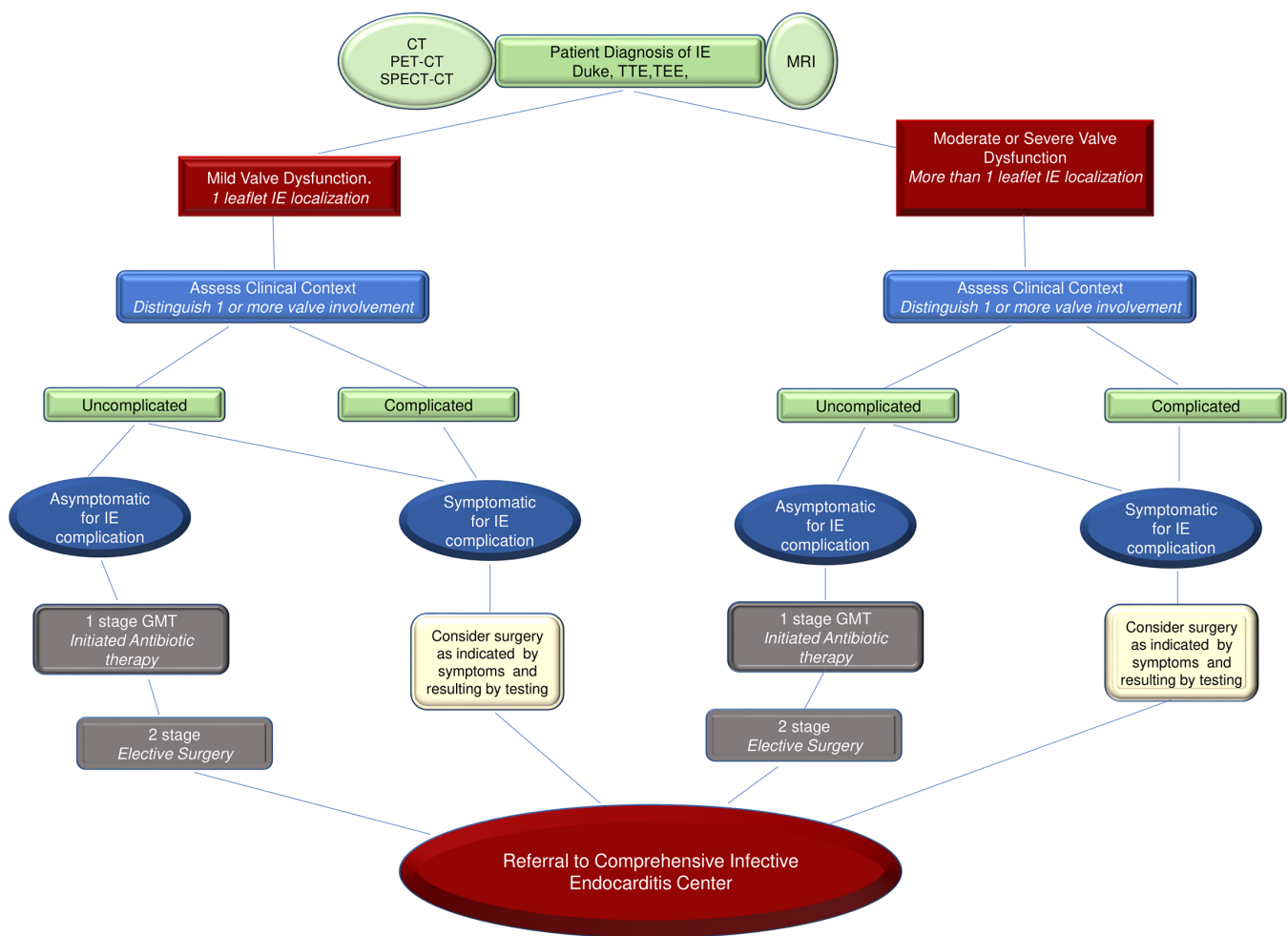


Figure 2 Clinical Algorithm for the Management of IE. CT, computed tomography; GDMT, guide direct medical therapy; MRI, magnetic; PET/CT, positron emission; TEE, transoesophageal echocardiography TTE, transthoracic echocardiography; SPECT, single-photon emission computed tomography.

seriously affected by infection with a cauliflower-like lesion (4,37). In patients with limited degree of valve regurgitation valve regurgitation surgery can be deferred surgery after a period of stabilization with antibiotic therapy, but there are no randomized controlled clinical trials that satisfactorily guide clinical practice in this area (37,38) (Figure 2).

Etiology of Infection

Coagulase negative staphylococci (e.g., staphylococcus epidermidis, Staphylococcus lugdunensis and Staphylococcus capitis) are omnipresent cutaneous commensals that are implicated in complicated infectious endocarditis. They can colonize native heart valves and

are the most common pathogens isolated in early PVE (19,21,39). It is not uncommon for coagulase negative staphylococci to cause hospital-acquired native valve endocarditis (40). In general, three blood culture series detect the presence of these pathogens in 96–98% of patients with bacteremia who have not yet started treatment with antibiotics (41,42). Blood culture does not need to be done at the febrile peak because the presence of the pathogen in the blood is not related to the extent of the fever. It is possible that patients in a compromised clinical condition have no pathogen growth from blood cultures delaying diagnosis (4). This situation is reported in up to 10% of cases and it is linked: (I) to the early administration of antibiotics before blood cultures; (II) to the sustained

infection by slow-growing pathogens or fungi and (III) to particular conditions in which an alternative diagnosis of non-bacterial thrombotic endocarditis is can be made as in patients with advanced cancer (43).

Infection related due to Viridans streptococci vehicle by oro-pharyngeal transmission remains more common in low-income countries (44). Serial blood cultures can lead to the discovery of *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus anginosus*, *Streptococcus mitis* and *Streptococcus sanguinis*. Of particular interest is the role played by group D streptococci (e.g., *Gallolyticus Streptococcus*, *Streptococcus bovis*) that are involved in the IE in patients with a coexisting colon tumor, which provides the portal circulation as a route of entry. The pathogens belonging to the group of Enterococci represent 10% of the overall cases (29,30).

Other forms of endocarditis are related to zoonotic infection as *Coxiella burnetii*, *Brucella* (cattle), *Bartonella henselae* (from cats) and *Chlamydia psittaci* (as parrots, pigeons).

Infections caused by Gram-negative bacteria (e.g., *Acinetobacter spp*, *Pseudomonas aeruginosa*) and *Legionella spp*, *Mycoplasma spp* and *Tropheryma whippelii* can be of particular concern (45). Furthermore, fungal endocarditis, usually caused by *Candida* or *Aspergillus*, are very aggressive and often fatal because it occurs in the immunosuppressed patient or after cardiac surgery, mainly in the prosthetic valve recipients (46).

A causative pathogen for IE can be identified in about two thirds of patients by additional microbiological tests (47). If the patient has negative cultures at 5 days, serological tests for *Coxiella* and *bartonella* are indicated and if these is also negative, the next step should involve testing for *brucella*, *Mycoplasma*, *Legionella*, and *chlamydia* (48). In the presence of an unrecognized infection, prolonged blood culture after 7 days does not provide further useful yields, even for the HACEK bacteria, which are typically slow-growing (48,49). After surgery the possibility of having samples the valve, can help in the microbiological diagnosis through the use of complementary molecular techniques as polymerase chain reaction for pathogen DNA (PCR) (50-52). These techniques are particularly useful in patients that received antibiotics, as bacterial DNA often persists even for non-cultivable pathogens such as *T whipplei* (51,53).

However, PCR carries the risk of a false positive result due to contamination of the sample. Clearly in this case PCR should not be used to guide the duration of therapy. New techniques combining PCR and mass spectrometry

promise direct characterization of bacteria in peripheral blood or valvular tissue (51).

During the IE a very important factor is the host immune response where the macrophages play a key role (54). In the most fragile patients and in the presence of very aggressive pathogens infection can be spread beyond the valve annulus. The use of echocardiography plays a key role in the diagnosis and identification of anatomopathological complications resulting from the progression and expansion of the infection. Extension of the lesion inducing the formation of abscess, pseudoaneurysm, fistula, or atrioventricular block define a complex IE. Although transthoracic echocardiography (TTE) is sensitive (75%) and specific (more than 90%) for detection of a vegetation, transoesophageal echocardiography (TOE) is required for detection of complicated extensive lesion because it offers a sensitivity of more than 90% (55). The TOE colour doppler analysis can reveal a pseudoaneurysm, i.e. a perivalvular cavity that communicates with the cardiovascular lumen. Conversely, an abscess is a thickened, pus-filled perivalvular cavity that has no such communication. A progressive perivalvular infection can evolve into the formation of fistula whose pathoanatomical feature is usually an aorto-cavitary aspect. The onset of this complication is burdened by a mortality rate greater than 40% even with surgery (56). For patients with persistent or relapsing infection or infection caused by aggressive or antibiotic-resistant microorganisms (e.g., *lugdunensis*, *pseudomonas*, fungi) there is an indication for emergency surgery (57) (Figure 2).

Risk of embolism

The risk of embolism with devastating complication occurs for a percentage of 25–50% of patients with IE (10). In the presence of left side endocarditis, the onset of a stroke is more common than infarction at level of the kidneys, spleen, limbs, mesenteric and coronary arteries. Furthermore, the localization of septic emboli in the context of the vascular structure can provoke a secondary infection related to the colonization of the “metastatic” vegetations. The inflammatory process that arises in the vascular wall is the cause of formation of a mycotic aneurysm. This lesion develops more frequently in the cerebral vessels and are visible on brain imaging in 3–5% of patients with IE, although in most cases they can remain clinically silent (10,58-60). The IE that are localized in right-sided of the heart are potentially at risk to determine lung embolism, or systemic embolism in patients

presenting a patent foramen ovale. In a large percentage of patients emboli give a clinical manifestation in the first 2 weeks after the diagnosis and the risk decreases rapidly after the initiation of therapy with antibiotics (61,62). Vilacosta *et al.* (61) evaluated the risk of systemic embolization in 217 patients with left-sided IE who had initiated an adequate antibiotic treatment. In patients undergoing antibiotic therapy reduced rate embolic events was observed [12.9% vs. 87.1%; relative risk of new embolization (RR) 1.73; 95% CI, 1.2 to 2.93; P=0.05]. The majority of emboli (52%) affected the central nervous system, and 65% of the embolic events occurred during the first two weeks after initiation of antibiotic treatment. The authors showed that there was an increased risk of embolization parallel to vegetation size (RR 3.77, 95% CI from 0.97 to 12.57; P=0.07). In addition, both the presence of large (>10 mm) vegetation caused by staphylococcal *Aureus* pathogens (P=0.04) and the location on the mitral valve (P=0.03) had a higher incidence of embolism (61). In another report, 1,437 patients with IE were studied to determine the relationship between the initiation of antimicrobial therapy and the temporal incidence of stroke. During the study, the approximate incidence of stroke in patients receiving appropriate antimicrobial therapy was 4.82/1,000 patient days in the first week of therapy with a reduction to 1.71/1,000 patient days in the second week. Note that after one week of antimicrobial therapy, only 3.1% of the cohort had a stroke and reduced stroke rates was evident regardless of the type of valve or pathogen involved (62).

In patients who have experienced a stroke, surgery should not be postponed in cases with no coma and cerebral hemorrhage (class IIa, level B). In patients with neurological diagnosis of minor brain events, such as transient ischemic attack or silent cerebral embolism, the criterion is to recommend surgery without delay (class 1, level B) (5). Conversely, in patients who have experienced devastating neurological events such as intracranial hemorrhage and brain localization of septic emboli with hemorrhagic evolution intervention should be delayed for at least 1 month. In this category of patients it is recommended to perform CT scans or MRI perfusion scan to evaluate the progression of the lesion according to the guidelines (class IIa, level B) (5). Okita *et al.* specific investigations revealed that early surgery (<7 days) demonstrated safety and efficacy in patients included in class I and IIa level B without preoperative haemorrhagic stroke (63). CT scans repeated immediately before surgery can rule out hemorrhagic

evolution of cerebral infarction or the development of mycotic aneurysm (64) (Figure 2).

Clinical considerations

Over the past 20 years 7 RCT were published on antibiotic treatment (65-70), but only one RCT (26) investigated the comparison between medical therapy and early surgery within 48 hours. Thus, conclusive evidence to indicate which of these interventions is superior is missing.

In patients with IE the use of early surgery performed within 48 after diagnosis revealed a decrease in the rate of death from any causes as well as a reduction of the risk of systemic embolism (4,5,26,71,72). The concern related to the use of early surgery may be related to an increase in operative mortality and an increased risk of recurrence of IE. However, in patients who underwent emergency surgery we observed improvements in clinical outcomes were achieved without an increase in operative mortality or recurrence of infectious endocarditis (4,5,71-73). These results were comparable to those by Kang *et al.* (26). The mortality rate is related to the extension of infectious lesion and the etiology and the localization vegetation on the mitral valve leaflet (4,59). Particular attention should be given to the risk of embolization which has been reported to be particularly high in the first week before diagnosis (7) and affecting the central nervous system in up to 65% (1,2,74).

Nonetheless, several propensity matched analyses showed contradictive results in terms of surgery morbidity and mortality (26,75,76). This might be related to the weight of embolic stroke and heart failure as determinants of long-term mortality. However, treatment allocation bias, underpowering and survivor bias affecting retrospective studies surely have played a role (26,75,77).

In the sole RCT (26) the rate of embolism in patients who received early surgery was markedly reduced as compared to those who had conventional treatment. The rate of embolism in the medical treatment arm was similar to that reported in other prospective multicenter study (10) or RCT (68).

We have reported that with a careful selection of patients could result in low in-hospital mortality and 6-months mortality (4,5,71,72). Poor prognostic factors, such as moderate to severe congestive heart failure, altered mental status and staphylococcal infection lead to increased mortality, substantially comparable to that of other studies (26,78-83). In our experience, patients with vegetations >15 mm at high risk of mobility and located on the mitral

valve, derive a considerable benefit from emergency surgical treatment, as confirmed elsewhere (4,5,37,38,71,72).

Emergency surgical treatment within 48 hours can be offered to patients who experienced an infection with severe anatomic-pathological injuries with development of abscess, extracardiac fistula or aortic root involvement. In this case the risk of mortality is higher considering the technical demand and the preoperative patient's conditions.

In these patients an extensive and radical surgery is necessary and homografts, conventional mechanical valves or xenografts are used in similar complex endocarditis. In a study reported by Harvard group (79) the abscess formation had an incidence of 43.09% (n=131), which is higher than the mean frequency (25–30%) reported by other international studies, indicating the severity of the disease treated in this cohort. In any case out of 131 patients with abscess formation 40.5% received a mechanical valve and while 29.5% were treated using xenograft. Selection of the type of graft to be used should be driven by the resistance to infection, as re-do surgery in case of reinfection is particularly challenging and burdened by augmented risk. In particular, reinfection of synthetic prostheses or prosthetic materials is even more daunting and technically demanding than in case of re-endocarditis on a previous homograft. In this context, evidences on safety and durability of homograft surgery has been widely reported. Already in 2001, Moon *et al.* (84) revealed a reinfection rate of 2% at 10 years with the majority of infection relapse following aortic valve endocarditis surgery and occurring within the first year. More recently Flameng *et al.* (85) showed a low recurrence of endocarditis in patients who received a homograft to treat complex IE. Excellent results are reported in the large series of Arabkhani *et al.* (86) with a rate of intraoperative mortality of 5.5% and durability up to 27 years.

Although some reports, as the current from Harvard (79), praised the long-term outcomes of mechanical valves, it cannot be neglected that these prostheses are bound 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. Moreover, if we take into consideration the final objective of endocarditis treatment, there is a significant lower infection recurrence using homografts (87,88) even in the context of previous prosthetic valve (89).

We reported the use of cryopreserved homograft for

AVR in 210 patients (72) and one half of the patients had endocarditis, 21% of these had an abscess formation. In our series the use of a cryopreserved aortic homograft was associated with no early reinfection and only 4 late relapses of endocarditis. In presence of extensive infection, in young patients with complex aorto-mitral endocarditis or aortic root involvement we used a living pulmonary autograft (90-95) or a double homograft valve replacement (4,5,71). In our experimental studies from a mechanical point of view, the use of a PA has shown efficacy compared to the use of dacron (96,97).

We believe that in case of extensive infection performing a quicker operation using a prosthetic valve with or without a dacron graft provides a very unstable situation with high potential for infection recurrence (72). Decision on surgery is always deriving from a balance between the risk of the procedure and the benefit achievable. Therefore, considering the significant risk during endocarditis surgery and the even higher risk represented by a redo-operation for re-infection, we believe that the option to undergo a minimal operation with known potential for re-infection should be discouraged (*Figure 3*).

Conclusions

The indication for early surgery in IE has not yet been appropriately defined and it differs significantly between the European (5) and US guidelines (13) fueling the confusion regarding the relative priority of surgical or medical management. The ESC guidelines (5) individuates three moments for the surgical indication. Emergency surgery which is performed within 24 hours, urgent surgery which is recommended within a few days and elective surgery which is performed after 1–2 weeks of antibiotic therapy. Urgent surgery is recommended for most cases of IE. Instead, the AHA's guidelines (13) define early surgery as “during the initial hospitalization and before completion of a full course of antibiotics.” We believe that in the presence of a clear diagnosis of IE and when an indication for surgery has been established, there are no proven benefits in delaying surgery (4,26). The choice to perform an intervention for IE in the early hours or with a delay of 48 hours depends on the way the heart team works in the shared decision-making process (4). There is evidence that has shown very low mortality in centers of excellence with high level experience in the management of complex patients and a RCT (26) has supported the role of early surgery. However, further evidences are needed to inform guidelines on the surgical

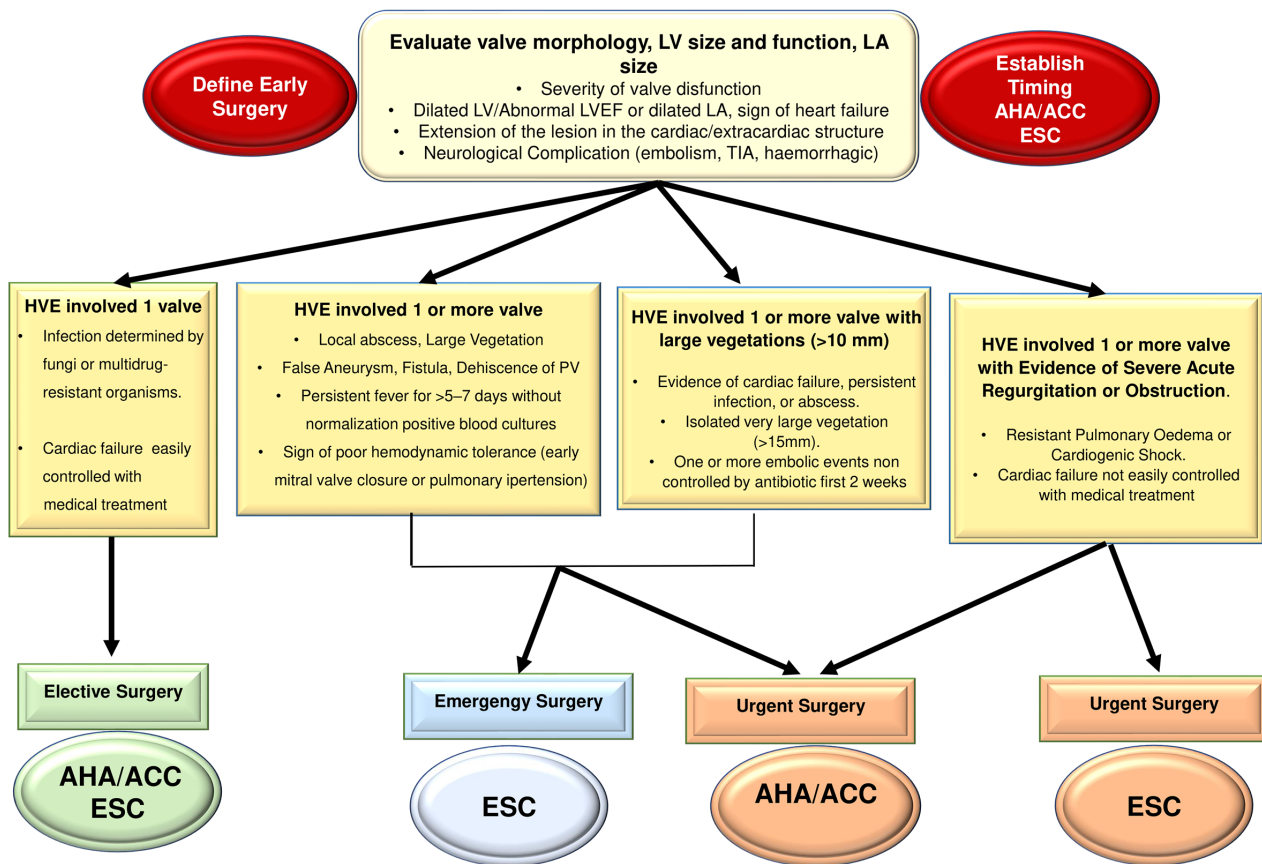


Figure 3 Decision Tree for Distinguishing Early Surgery in HVE. LV, left ventricle; LA, left atrium; ACC/AHA, American College of Cardiology/American Heart association; ESC, European Society of Cardiologists; HVE, heart valve endocarditis; LVEF, left ventricular ejection fraction; TIA, transient Ischemic attack.

management of IE (Figure 3).

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Footnote

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