A management framework for left sided endocarditis: a narrative review

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Abstract: Left sided endocarditis (LSE) can include the entirety or portion of mitral and/or aortic valve and the structures in their anatomical contiguity and represent a significant portion of emergency surgical activity. Literature and guidelines on the management of LSE relies mainly on observational studies given the difficulty in designing randomized trials in emergency settings. Heart teams (HT) are often called in to difficult decisions on the most appropriate strategy to adopted in case of LSE. Decision-making should take into account the localization and the extension of the infection, patient preoperative status and comorbidities, presence of a previous valve prosthesis and best timing for surgery. Despite evidence suggests that early surgery may improve survival in patients with complicated infective endocarditis (IE), an increased risk of recurrence and postoperative valvular dysfunctions has been reported. The most important factors associated with long-term outcomes are preoperative multiorgan failure, prosthetic mechanical valve IE, vegetation size ≥15 mm, and timing of surgical treatment. Importantly, up to one third of potential candidates do not undergo surgery and these patients experience extremely high mortality rates. Another important point regards the choice of the optimal valve substitute to be used according to the different clinical situation. The lack of RCT in this field and the difficulty to design this type of studies in the case of non-elective conditions further complicates the possibility to achieve a univocal consensus on the best strategy to be adopted in each form of LSE and further validation studies are needed. On the basis of the current evidences a decisional algorithm is proposed summarizing all the crucial aspects in the management of LSE.

Keywords: Left side infective endocarditis; mechanical valves; biological substitute; guidelines; treatment and management

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Introduction

Left sided endocarditis (LSE) is an infection of the entirety or portion of mitral and/or aortic valve and the structures in their anatomical contiguity. It may be determined by various pathogens, but bacterial origin is the most common. In developed countries, LSE are one of the most common causes of acute valves failure. In some reports, the estimated annual prevalence of infective endocarditis (IE) was 3 to 9 cases per 100,000 persons (1,2) and LSE affects native valves in 64% to 76.2% of the cases (3-5) and prosthetic valves in 89.9% (PVE) (6,7).

In patients with LSE, age, evolutive cardiogenic shock, PVE, left ventricular ejection fraction (LVEF) <40%, and recurrent infections are considered significant predictors of mortality (6-9). However, current evidence regarding the treatment and management strategy for LSE are not univocal and are often based on empirical practice.

This report aims at reviewing the current evidences on LSE and provides a basis for the management of this disease focusing on aspects of the heart team (HT) approach, on the selection of the most appropriate surgical strategy and on the importance of physician-patient discussion about the risks, benefits, and expectations after the surgery.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4439).

Methods

In December 2019, a search of the PubMed database using the terms "endocarditis", "left side endocarditis", "heart valve prosthesis", "allograft", "autograft", "cardiac valve surgery", "aortic valve replacement" was coordinated. Qualified abstracts were reviewed and the related articles were investigated. 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. It should be noted that weight of evidence regarding the different valve substitutes was not comparable among groups given the significantly larger number of observations for patients with xenograft (N=4,111), homografts (N=2,454) in comparison to mechanical prosthesis (N=655) Ross operation and valve repairs. Despite the majority of the observational studies are propensity matched, the lack of RCT and a number of other confounders limited the power of the analysis (*Tables 1,2*).

Management of LSE

The approach

In the 21st century the central role of the multidisciplinary team emerged in the treatment of endocarditis and this is crucial for LSE management. Early diagnosis of the either native valve endocarditis (NVE) and PVE can favor both the optimization surgical timing and avoidance of potential complications.

Lack of multidisciplinary integration could lead to delay in diagnosis, late referral for surgery of patients in more critical conditions after failure of medical treatment.

In an Italian study, a formalized multidisciplinary team approach including (I) initial evaluation within the first 12 hours, (II) indication for early surgery within 48 hours and (III) a re-evaluation of the patient's clinical condition every week, led to a reduction in hospital mortality from 28% to 13% (P=0.02) and in 3-year mortality from 34% *vs.* 16% (P=0.0007), regardless age and comorbidities (38). The importance of tertiary centers with advanced surgical and management competencies is even more evident in complex LSE, and referral to these units can be advantageous not only in terms of clinical outcomes but also in terms of cost-effectiveness for the national health systems. However, potential criticisms to this organizational model might regard the depletion of trained physicians in peripheral hospitals and the potential delays in transferring patients.

The treatment of IE in the current era requires a reconfiguration in the organizational standard towards a centralized system of care or, alternatively, the creation of a hub-and-speak model that is based on the activity of a multidisciplinary center reviewing clinical cases. This model would allow rapid and qualified initial management of IE and should be established on the basis of clinical evidence. There is no reason to doubt that the implementation of a centralized care can improve decision making, surgery timing, and short- and long-term results. Furthermore, the efficacy and validity of a centralized model could be readily tested in a study evaluating the difference between the before and after its creation (*Figure 1*).

Risk assessment

The risk assessment models for LSE aimed to assist the decision-making process of multidisciplinary team has a pivotal role during the discussion in HT (*Figure 1*, *Table 3*).

Gaca *et al.* (39) elaborated a surgical risk score for the IE based on the Society of Thoracic Surgeon's database. The authors identified 13 risk factors for mortality, including emergency status, cardiogenic shock, hemodialysis, and "active endocarditis".

Another single-center pilot study (40) included 440 patients who had the surgery for NVE and reported six predictors for early postoperative mortality. Variables were entered in a mathematical model with good predictivity [area under receiver operating characteristic curve (AUC-ROC) of 0.88]. The authors identified six predictors along with their assigned scores including age (5–13 points), renal failure (5), NYHA class IV (9), critical preoperative

Table 1 Observational studies and propensity matched comparing the allogenic and autologous substitute with conventional prosthesis

First author (Ref.)	Total sample (N)	Number of patients/ endocarditis	Mean follow-up/ months	Number of aortic valve substitute implanted or repair	Main findings
Nappi 2018, *JTCVS* (10)	210	118	162	Ao-H [210]; χ Ao/Mitr-H [11]	Similar survival at 15 years Ao-H (61.3%) *vs.* stented xenograft (62.1%) and *vs.* mechanical prosthesis (60.6%); 15 years freedom from reoperation SVD 89.4%. Freedom from IE 98.1% at 20 years. MACCEs freedom from event at 15 years 50.6%
Schaefer 2018, *PLoS One* (11)	#154	35	48.7	SFS [77] (IE 19); XP [77] (IE 16)	30-day mortality (SFS 3/77; 3.9% *vs.* CP 4/77; 5.2%; P=0.699). All-cause mortality (SFS 20.8% *vs.* CP 14.3%; P=0.397); SVD (5.2% SFS *vs.* 0% CP; P=0.04); Reoperation due to SVD or prosthetic valve endocarditis (PVE) (9.1% SFS *vs.* 1.3% CP; P=0.04). Inferior survival after NVE in re-do surgery in SFS group (HR: 7.63; CI: 1.65±35.25, P=0.009)
Ratschiller 2017, *Semin Thorac Cardiovasc Surg* (12)	190	190	144	Ross Operation	30 days mortality for the total study population of 2.1%. Survival 93.8% [95% confidence interval (CI): 90.2–97.7) at 10 years and 86.1% (95% CI: 78.8–94.0) at 20 years. Freedom from reoperation on the auto- and homograft 94.1% (95% CI: 83.6–100.0) at 5 years, 87.4% (95% CI: 72.4–100.0) at 10 years, and 71.5% (51.1–100.0) at 15 years. Lower incidence of reoperation for autograft endocarditis 0.4%
Kim 2016, *JTCVS* (13)	304#	304	29.4	Ao-H [86]; MP [79]; XP [139]	Similar survival between valve substitute. Odds ratio 1.61; 95% confidence interval (CI), 0.73–3.40, P=0.23 (HR 1.10; 95% CI, 0.62–1.94, P=0.75). Reinfection 7.7%. No difference in freedom from reinfection rates (P=0.65). CAH did not significantly affect reinfection (HR 1.04; 95% CI, 0.49–2.18, P=0.93)
Kim 2016, *JTCVS* (14)	436#	IVDU 78; Non-IVDU 358	29.4	Ao-H [86]; MP [99]; XP [206]	Similar survival between group (IVDU *vs.* Non IDVU). (HR, 0.78; 95% CI, 0.44–1.37). No difference between valve substitute. Lower operative mortality in IVDUs (odds ratio, 0.25; 95% CI, 0.06–0.71). Better valve-related complications in IVDUs (HR, 3.82; 95% CI, 1.95–7.49; P<0.001) for higher rates of reinfection (HR, 6.20; 95% CI, 2.56–15.00; P<0.001)
Perrotta 2016, *Ann Thorac Surg* (15)	84	84	65	Ao-H [56]; MP [20]; XP [12]	10 years similar survival. CAH 58% *vs.* conventional prosthesis 75% (P=0.17). Higher incidence of reoperation for infection relapse in mechanical or xenograft valve prosthesis (12.9%) than CHA (0%) (P=0.006). Lower incidence of reoperation for SVD in CAH at 10 years (5.3%)
Arabkhani 2016, *JTCVS* (16)	353	115	137	Ao-H [115]	20 years survival 40.0% at (95% CI, 32–50%). 20 years predicted competing-risks analysis 31% death without reoperation, 39% reoperation, and 30% alive without reoperation. Low incidence of infection relapse (3.96%) and reoperation (2.26%)
Flameng 2015, *Ann Thorac Surg* (17)	69	69	96	Ao-H [69]	10 years survival 73%. 10 years freedom of reoperation 74%. Lower incidence of infection relapse and reoperation for IE (4.34%). Higher incidence of reoperation for SVD (18.84%)
Bourguignon 2015, *Ann Thorac Surg* (18)	2,559	111	79	XP [111] (CP bioprosthesis)	15- and 20-year survival 31.1% and 14.4% (95% CI). IE early

Table 1 (*continued*)

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First author (Ref.)	Total sample (N)	Number of patients/ endocarditis	Mean follow-up/ months	Number of aortic valve substitute implanted or repair	Main findings
Johnston 2015, *Ann Thorac Surg* (19)	12,569	450	68	XP [450] (CP bioprosthesis)	76% probability of death before explant for SVD and endocarditis at 20 years. Few probabilities of explantation for SVD (5.4%) and endocarditis (1.4%) at 20 years
Chiang 2014, *JAMA* (20)	#2,002	16	128	MP [9]; XP [7]	No difference in 30-day mortality XP (3%) *vs.* MP (3%) (P=0.49); No difference survival (P=0.74); 15-year survival XP (60.6%; 95% CI, 56.3–64.9%) *vs.* MP (62.1%; 95% CI, 58.2–66.0%). HR 0.97 (95% CI, 0.83–1.14). 15 years reoperation XP (12.1%) *vs.* MP (6.9%) (95% CI, 8.8–15.4% *vs.* 95% CI, 4.2–9.6%. HR: 0.52; 95% CI, 0.36–0.75)
Hussain 2014, *JTCVS* (21)	#775	537	84	Ao-H [357]; MP [25]; XP [139]	30 days mortality 7% for aortic valve and 14% for aortic and mitral valve IE. Survival at 5 years 75%. Rate of recurrence of infection 5.1%
Fukushima 2014, *JTCVS* (22)	840	101	420	Ao-H [101]	35 years survival 66%. 35 years reoperation rate for SVD 33.9%. 2 pts with CAH for more than 30 years. Lower incidence of infection relapse and reoperation for IE. Early reinfection 0.2%. Late relapse of IE 5.5%
Sénage 2014, *Circulation* (23)	617		44	XP [617] Mitroflow (models 12A/LX)	5 years survival 69.6% (95% CI, 65.7–73.9). Early SVD. 1-, 2-, and 5-year 0.2% (95% CI, 0.0–0.6), 0.8% (95% CI, 0.0–1.6), and 8.4% (95% CI, 5.3–11.3). 5-year SVD-free survival 91.6% (95% CI, 88.7–94.7). 13 patients accelerated SVD
Glaser 2014, Ann *Thorac Surg* (24)	1,219	8	50	XP (CP 864); XP (Mosaic 365)	No difference 8 years survival CP (63%) *vs.* Mosaic (57%) (P=0.971). (HR, 0.85; 95% CI, 0.65–1.11). No difference in reoperation (P=0.745). Lower incidence of IE recurrence
Grubitzsch 2014, *JTCVS* (6)	149	96	48	MP [11]; XP [80]; Ross Procedure [5]	Early death 31.5%. Late death 7.38%; overall and event-free survivals at 10 years were 75% +/- 3.8% and 64%, 4.0%; Freedom from recurrent infection and reoperation at 10 years were 81% +/- 3.6% and 91% +/- 2.6%
Kowert 2012, *Eur J Cardiothorac* Surg (25)	363	363	100	Ao-H [363]	Early death 8.9%. Survival 1 year (86%) and 5 years (77.4%). Mean time between homograft implantation and redo operation 8.4±3.6 years. Early and late recurrent endocarditis 9% (prior IE)
Manne 2012, *Ann Thorac Surg* (5)	428	282	12	Ao-H [173]; MP [24]; XP [84]; Ross operation [1]; Ao-R [12]	Higher 30-day mortality PVE *vs.* NVE (13% *vs.* 5.6%; P<0.01). No difference in survival NVE *vs.* PVE (35% *vs.* 29%; P=0.19). Higher 30 days mortality and 1 year mortality for Staphylococcus aureus infection (15% *vs.* 8.4%; P<0.05) and (28% *vs.* 18%; P=0.02). Few reoperation for persistent infection or relapse (2.4%)
Mayer 2012, *Eur J Cardiothorac Surg* (26)	100	100	31	MP [10]; XP [51]; Ross operation [6]; Ao-R [33]	Similar 30-day mortality Ao-R 9% *vs.* Ao-Rpl 18% (P=0.37). Better survival Ao-R (88%) *vs.* Ao-Rpl (65%) (P=0.047). Higher rate of reoperation Ao-R (35%) *vs.* Ao-Rpl (10%) (P=0.021)
Bekkers 2011, *Eur J Cardiothorac Surg* (27)	262	96	102	Ao-H [96]	30-day mortality 5.7%. Survival 77.0% (95% CI, 71–83%) at 10 years, and 65.1% (95% CI, 57–74%) at 14 years. Survival after re-operation 87.1% at 1 year and 79.3% at 9 years. Freedom from allograft re-operation 82.9% at 10 years and 55.7% (SE 5.7%) at 14 years. SVD 18.5% and infection relapse 0.7%

Table 1 (*continued*)

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First author (Ref.)	Total sample (N)	Number of patients/ endocarditis	Mean follow-up/ months	Number of aortic valve substitute implanted or repair	Main findings
Musci 2010, *JTCVS* (28)	1,136	1,136	62	Ao-H [221]	10 years survival 47.3%±5.6%. Lower incidence (5.4%) of infection relapse and reoperation for IE. Lower incidence of reoperation for SVD 8.6%
El-Hamamsy 2010, *JACC* (29)	166	4	90	Ao-H [76]; Freestyle bioprosthesis [90]	Freestyle less progressive aortic valve dysfunction and a lower need for reoperation (100%±0% *vs.* 90%±5%; P=0.02). 30-day mortality 4.8%. No difference in survival freestyle *vs.* homograft (80 +/-5% *vs.* 77 +/- 6%; P=0.9)
Nguyen 2010, *Eur J Cardiothorac Surg* (30)	167	167	60	Ao-H [77]; MP [109]; XP [31]	30-day mortality XP (19.4%), Ao-H (7.4%), MP (10.1%) (P=0.27). XP lower overall 5-year survival </=65 years [adjusted HR 4.14 (1.27–13.45), P=0.018] but not >65 years [adjusted HR: 1.45 (0.35–5.97), P=0.60]. No difference between Ao-H and MP [HR 0.46; 95% CI, (0.15–1.42), P=0.18]
Klieverik 2009, *Ann Thorac Surg* (31)	138	138	96	Ao-H [106]; MP [32]	Higher 30-day mortality for CAH (P=0.25). No difference in survival at 15 years (CAH 59%±6% and MP 66%±9% (P=0.68) and freedom from recurrent infection (P=0.29). Higher rates of reoperation for CAH (P=0.02)
David 2007, *JTCVS* (3)	383	383	73	Ao-H [18]; MP [214]; XP [133]	15 years survival 44%. Relapse of IE independent predictors of death (HR 2.2, 95% CI, 1.2–3.9). 15 years freedom from recurrent IE 86% for all patients without difference between type of valve implanted. 15 years freedom from reoperation 70%
Yankah 2002, *EJCTS* (14)	816	816	60	Ao-H [182]	10 years survival 91%. Lower incidence of early (2.7%) and late (3.6%) infection relapse and reoperation for IE (P=0.0001). 10–13 years freedom from reoperation for SVD 85%
Sabik 2002, *Ann Thorac Surg* (32)	103	103	51	Ao-H [103]	30-day mortality 3.9%. Survival at 10 years 56%. Few recurrent PVE at >/=2 years (peaked at 9 months)
Moon 2001, *Ann Thorac Surg* (31)	306[#]	306	183	Ao-H [20]; MP [65]; XP [221]	20 years survival 46% mechanical, 41%, stented xenograft, 58% CAH; P>0.27. Lower risk of infection relapse without group difference. 5 years 2.1% mechanical prosthesis, 2.3% stented xenograft, and 3.6% CAH; P>0.88. After 5 years 0.5% mechanical prosthesis, 1.1% stented xenograft and 3.1% CAH; P>0.25. 10- and 15-year freedom from reoperation for mechanical prosthesis 74.6%; 10- and 15-year freedom from reoperation for xenograft prosthesis 56.6%, 22.6% P>0.64

Of total N=436 Valve repair was performed in N=45. #, propensity score; χ Ao/Mitr-H, cryopreserved mitro-aortic homograft replacement; IVDU, intravenous drug user.

status (39), failure to achieve preoperative blood culture negativity (5) and perivalvular involvement (5). They have outlined four risk classes ranging from "very low risk" (≤5 points, expected average mortality of 1%), and "very high risk" (≥20 points, mortality of 43%).

Martínez-Sellés *et al.* (41) included 26 observational reports with over 1,000 patients treated for LSE (NVE =315 and PVE =122). They reported a significant reduction in in-hospital mortality in patients who underwent early surgery compared to those were managed with medical therapy (24.3% *vs.* 34%; P=0.02). A risk score called PALSUS was developed which aimed to evaluate hospital mortality using seven prognostic variables with a similar predictive value. Variables included were: prosthetic valve, age ≥70, significant intracardiac destruction, Staphylococcus spp, urgent surgery, sex [female], EuroSCORE ≥10 (42).

Table 2 Meta-analysis and registries reporting the use of aortic homograft and conventional

First author (Ref.)	Total sample (N)	Number of patients/ endocarditis	Mean follow-up/ months	Number of aortic valve substitute implanted	Main findings
Wang 2017, *Ann Thorac Surg* (33)	42,305	–	Mean times to valve failure (MTTF)	Medtronic Porcine [9,619]; Edwards Porcine [3,886]; Sorin Pericardial [6,632]; Edwards Pericardial [22,177]	Sorin pericardial showed higher SVD risk; P<0.001 for all other three valve type (lower risk-adjusted MTTF). No significant differences in SVD risk among the other three valve types (P=0.716)
Foroutan 2016, *BMJ* (34)	53,884	–	Cumulative incidence of Death and SVD at 10, 15 and 20 years	Xenograft [53,884]	Survival 89.7%,78.4%, 57.0%, 39.7% and 24.7% at 2, 5, 10, 15 and 20. 10, 15, and 20 years freedom from SVD 94.0%, 81.7%, 52% at (evaluated for 7,603 pts). SVD increases rapidly after 10 years, and particularly after 15 years
Savage 2014, *Ann Thorac Surg STS database* (35)	11,560; 8,491 prior, 3,139 reoperative	11,560	2005 to 2011	Ao-H [588]; XP [5,396]; MP [2,144]; Other [293]	AVR prior 88.5% *vs.* reoperative 58.7%; RR prior 7.2% *vs.* reoperative 29.9%; Prior operation XP increased (57% to 67%). MP decreased (30% *vs.* 24%) Ao-H decreased (9% *vs.* 6%) P<0.001. Reoperation XP increased (38% to 52%) MP decreased (20% *vs.* 17%) Ao-H decreased (38% *vs.* 28%) P<0.001. Ao-H most used in reoperation
†Reece 2014, *Ann Thorac Surg STS database* (36)	2,188	307#	1994 to 2010	Ross [1,094]; Non-Ross [1,094]	Ross higher perioperative complications and operative mortality (2.7% *vs.* 0.9%; P<0.001). Ross *vs.* No Ross OR 3.00 (95% CI, 1.47 to 6.11; P=0.002)
†Brennan 2013, Circulation (37)	39,190	452	150	XP [644]; MP [376]	No difference in survival (HR, 1.04; 95% CI, 1.01–1.07). XP higher reoperation (HR, 2.55; 95% CI, 2.14–3.03) and endocarditis (HR, 1.60; 95% CI, 1.31–1.94), and lower risks for stroke (HR, 0.87; 95% CI, 0.82–0.93) and bleeding (HR, 0.66; 95% CI, 0.62–0.70)

†, PM; #, all Ross operation.

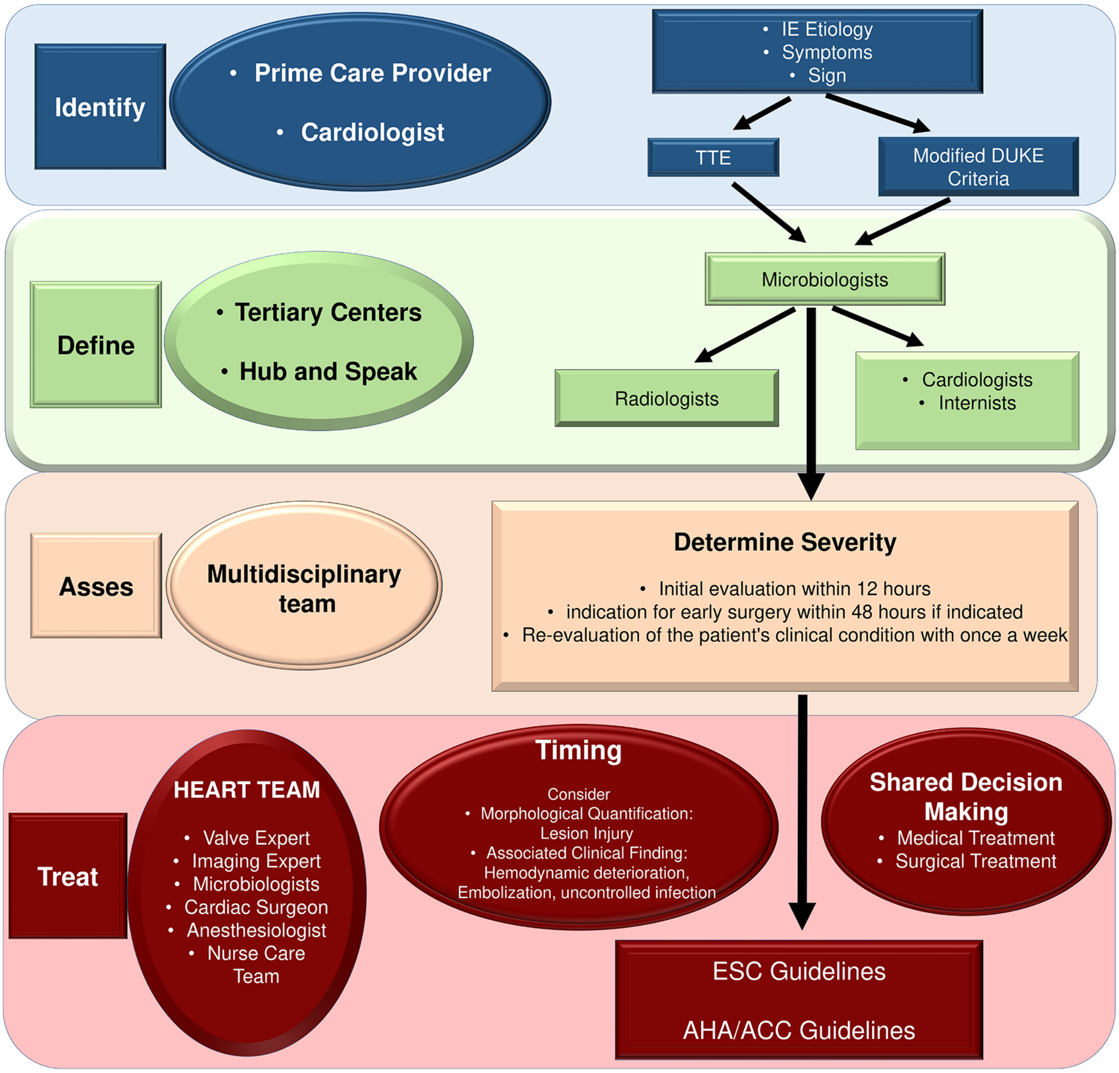

Figure 1 Clinical evaluation and diagnosis flowchart for LSE. For detailed explanation and references see text. ACC/AHA, American College of Cardiology/American Heart association; ESC, European Society of Cardiologists; IE, infective endocarditis; LSE, left side endocarditis; TTE, transthoracic echocardiography.

Hospital mortality ranged from 0% in patients with a PALSUSE score from 0 to 45.4% in patients with a PALSUSE score >3. Since the prognosis for IE surgery is highly variable, the PALSUSE score could help identify patients with higher hospital mortality.

Timing of surgery

The timing of surgery, especially in emergency status, is a lively topic of discussion in the HT and is often opposed to the use of medical treatment. The Heart Team works on the path laid out by the European Society of Cardiology (43) and AHA (44) who have classified the appropriate timing for surgery based on class and level of evidence (*Figure 2*, *Table 3*). The guidelines often do not correlate with real world scenarios faced by the multidisciplinary team. Chu *et al.* (45) highlighted that the main predictive factors for non-surgical referral were liver diseases [odds ratio (OR) for surgery: 0.16; 95% CI: 0.04 to 0.64], S aureus infection (OR: 0.50; 95% CI: 0.30 to 0.85) and stroke prior to surgical decision (OR: 0.54; 95% CI: 0.32 to 0.90). In contrast, patients with severe aortic regurgitation, abscess

Table 3 Timing for surgery based on guidelines based evidence and clinical situation

Clinical situation	Surgical timing	Level of evidence
Large vegetation (>15 mm), heart failure, periannular abscess	Immediate intervention required	Class Ia, level B
Minor cerebral event (transient ischemic attach of silent cerebral embolism)	Immediate intervention required	Class I, level B
Stroke without evidence of cerebral hemorrhage or coma	Immediate intervention possible	Class IIa, level B
Stroke with suspicion of intracranial hemorrhage or cerebral septic emboli with potential hemorrhagic evolution	Defer surgery for 1 month; Obtain CT scan	Class I, level C

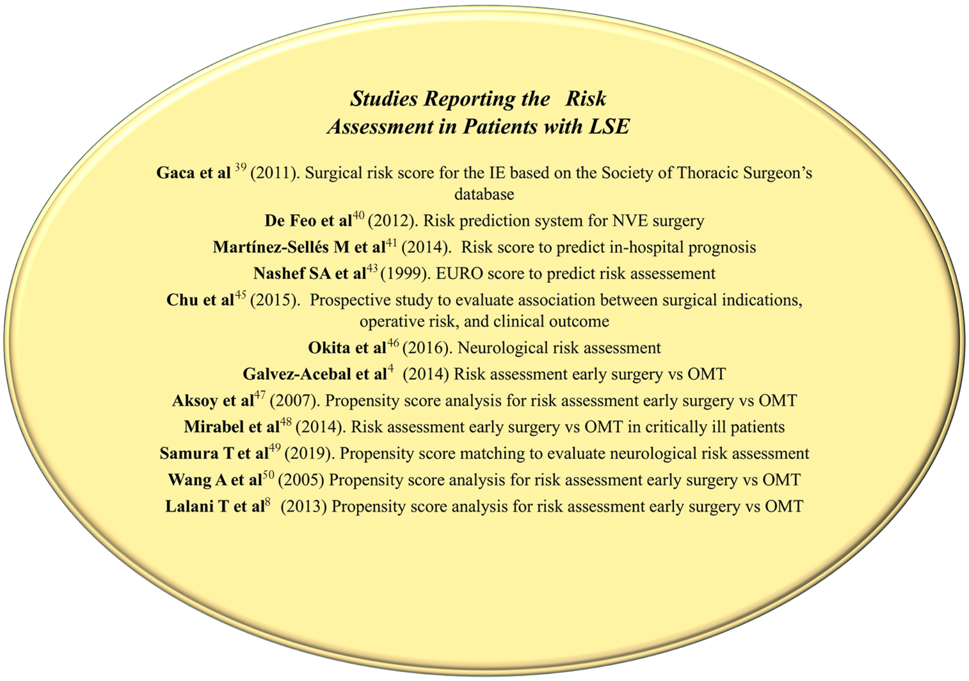

Figure 2 Studies reporting the risk assessment in patients with LSE (4,8,39-42,45-50). NVE, native valve endocarditis; OMT, optimal medical therapy; ACC/AHA, American College of Cardiology/American Heart association; ESC, European Society of Cardiologists; IE, infective endocarditis; LSE, left side endocarditis; TTE, transthoracic echocardiography.

and embolization were likely to undergo surgery. The authors concluded that surgical decision making in LSE is largely consistent with established guidelines, however nearly a quarter of patients with surgical indications did not receive surgery. Furthermore, evidence shows that the presence of the pathogen S. aureus in LSE was significantly associated with non-surgical management (45). The STS-IE score provides prognostic information for survival after the operative period, but a significant proportion of operations are actually never performed.

In LSE the timing of surgical treatment is closely related to the appearance of the neurological complication. In patients with stroke, surgery should not be postponed in the absence of coma and cerebral hemorrhage (class IIa, level B). The diagnosis of minor neurological events, such as the appearance of a transient ischemic attack or silent cerebral embolism, are criteria to recommend surgery without delay (class 1, level B) (43).

In contrast, the manifestation of devastating neurological events, such as intracranial hemorrhage and brain localization of septic emboli with an CT features indicating hemorrhagic evolution, should delay surgery by at least 1 month. According to the guidelines, repeated CT scans or MRI perfusion scans allow to evaluate the progression of the lesion (class IIa, level B) (43).

Okita *et al.* (46) retrospectively reported a multicenter cohort of 568 patients undergoing surgery for active LSE. Of those 118 patients had non-haemorrhagic cerebral infarction, 54 had intracranial hemorrhage and 396 had no brain events. Patients with non-haemorrhagic injury in which surgery was postponed for 2 weeks after the neurologic event had a higher incidence of hospital death. In particular, patients who were operated between 15 and 28 days or after 29 days from the onset of non-haemorrhagic cerebral infarction had higher incidences of hospital death compared with those who had surgery within 7 days. [Odds ratio 5.90 (P=0.107) and 4.92 (P=0.137)]. Conversely, in presence of intracranial hemorrhage, patients who received surgery between 8 and 21 days or after 22 days had lower incidences of hospital mortality compared to early surgery (within 7 days) [odds ratio 0.79 (P=0.843) and 0.12 (P=0.200)].

Another decisive point of discussion is related to the priority between early surgery and antibiotics in the treatment of LSD complicated by heart failure, risk of embolization or in case of extensive infection. In the past 9 years, several large studies have supported the survival benefit associated with the use of early surgery in patients with LSE in larger studies with long-term follow-up.

Gálvez-Acebal *et al.* (4) in a propensity matched study on 417 patients with LSE with a mean follow-up was 1.3±21 years showed that early surgery within 48 hours of diagnosis had a significantly better in-hospital mortality and late mortality rate than those managed conservatively with antibiotics [26.8% *vs.* 41.8%; absolute risk reduction (ARR), −15.2%; P=0.004 and 29.7% *vs.* 46.2%; ARR, −16.5%; P=0.002, respectively]. This study clearly supported the benefit of surgical treatment of left-sided IE especially in patients in which moderate or severe heart failure and paravalvular extension of infection occurred (4).

In another propensity match study from Duke university (47), on 426 patients with LSE the mortality rate associated with early surgical management was decreased (HR, 0.27; 95% CI, 0.13–0.55). Patients who had an early surgical treatment were more likely to have Staphylococcus aureus infections, congestive heart failure, larger vegetations, intracardiac abscess, and undergoing hemodialysis without a chronic intravascular access. Diabetes mellitus (HR, 4.81; 95% CI, 2.41–9.62), the presence of chronic intravenous catheters (HR, 2.65; 95% CI, 1.31–5.33), and paravalvular complications (HR, 2.16; 95% CI, 1.06–4.44) were risk factors for mortality

Mirabel *et al.* (48) included 198 patients who were prospectively evaluated for IE across 33 adult intensive care units (ICU) in France, and reported a 69% long-term mortality at median follow-up time of 59.5 months in critical LSE. Sepsis-related Organ-Failure Assessment score (SOFA) calculated the day of surgery was the only factor independently associated with long-term mortality (HR =1.59; 95% CI, 0.77–3.28 for SOFA 5–9; 3.56, 1.71–7.38 for SOFA 10–14 and 11.58, 4.02–33.35 for SOFA 15–20; reference category SOFA 0–4; P<0.003).

Samura *et al.* (49) evaluated the impact of emergency surgery in 152 patients (45 propensity score-matched pairs) with left-sided native valve IE complicated with acute cerebral infarction. The authors reported a significant higher hospital mortality in patients who underwent delayed surgery compared to those who received early valve operation (16% *vs.* 2%; P=0.058). The survival rates at 5 years in patients who were managed with early valve operation was higher than in delayed surgery [97% *vs.* 80%, (P=0.029)].

Wang *et al.* (50) compared the effect of early surgery in patients with prosthetic valve IE in relation to age, causative microorganism, intracardiac abscess, and congestive heart failure. Surgery group (n=145) was associated with higher survival rates than the antimicrobial therapy group (n=207) (OR for death, 0.56; 95% CI, 0.23–1.36). Predictive factors of in-hospital mortality were brain embolization (OR 11.12; 95% CI, 4.16–29.73) and Staphylococcus aureus infection (OR 3.67; 95% CI, 1.29–9.74).

In a study from Cleveland Clinic (5), surgery for PVE (n=180) was compared to NVE (n=248) in 428 consecutive patients who were followed for a maximum of 5 years. In-hospital mortality was higher in PVE *vs.* NVE group (13% *vs.* 5.6%) and, after multivariate analysis, Staphylococcus aureus infection was the only independent predictors of in-hospital death (15% *vs.* 8.4%; P<0.05), 6-month (23% *vs.* 15%; P=0.05) and 1-year mortality (28% *vs.* 18%; P=0.02). There was a non-significant survival benefit in the PVE group in respect to NVE (35% *vs.* 29%; P=0.19).

In large propensity matched study from the International Collaboration on Endocarditis–Prospective Cohort Study Investigators (8), including 1,025 PVE patients (aortic valve, 71%; mitral valve, 45.1%), there was no significant difference in 30-day and 1 year survival in the early valve replacement group compared with medical therapy (HR for death, 0.44; 95% CI, 0.38–0.52, P<0.001 and 0.57; 95% CI, 0.49–0.67, P<0.001).

Surgery for LSE

Current trends in the surgical practice

The surgery of endocarditis has been regarded as the most effective strategy for several categories of patients affected by the LSE. Long-term substitute durability is the key factor for the success of the surgery in patients with LSE (10,21,22,28,35,51-53). To date, no definitive guidelines support the selection of one substitute over the other, and the choice of the best valve remained more a matter of art than of science. In the last 4 decades several substitutes have been proposed, 5 have passed the test of time with different success: homograft, autograft, stented or non-stented xenograft prosthesis and mechanical prosthesis.

Currently, the clinical benefits of using conventional biological prosthesis to replace an infected heart valve are well established, and this surgical option represents the tenet of modern valve surgery. Despite robust evidence suggests that the use of a biological valve, rather than mechanical prosthesis, is associated with further advantage in long-term outcomes, the effectiveness and safety of each substitute is related to the age and location of the implant (18,19,24,33,34). For mitral valve mechanical valve represent still an adequate choice in patients up to 70 years old (54), while the benefit of aortic mechanical prosthesis disappears after 55 years of age (38,39). The benefit in terms of lower risk of reoperation with mechanical valves is counterbalanced by the higher risk of bleeding and stroke in some age groups (20,54).

Evidence suggests that the choice of a homograft or an autograft is useful in younger high-risk patients, such as those with complex valve endocarditis or in patients with PVE. The benefit of their use becomes more evident within the first post-operative decade because of the reduced risk of recurrent infection (10,15-17,22,32,52,53). However, the risk of structural valve deterioration increases with time (10,16,22,25,27). The use of cryopreserved homograft does not change the extent of the survival advantage (13). Nevertheless, the surgical community seemed reluctant to a wider adoption to these substitutes for a number of reasons.

A recent analysis of the Society of Thoracic Surgeons (STS) database revealed that, in the United States, the use of stented xenograft prosthetic valves is increased and a total of 8,421 patients (73%) with IE cases received a conventional biological valves, both for primary operations and reoperations, compared to 3,139 patients (27%) who were managed with mechanical valves (35). The use of homograft is rare during the primary operation but is more common in patients requiring reoperation (32.2% *vs.* 7.0%, P<0.0001) and when extensive intervention on the aortic root is required (53.2%) (35). An analysis of the trend of the last 2 decades, based on a significant amount of observational data, has showed that the use of homograft has decreased over time in cases of first-time replacement of the aortic valve (from 9.4% to 5.6%) and for reoperations (from 37.5% to 28.5%) (35).

The reasons for the low use of mechanical valves and homografts are complex and multifactorial. More than two decades ago data reported by Washington University of St Louis showed that 50% of patients with IE underwent surgery with mechanical prosthesis while since 2009 only 14% of the patients were treated with this type of valve. The evident change in the surgeons' attitude has been probably determined on the one hand by the reported trends towards better survival and complication rate with biological valves, and on the other, by the increase in re-hospitalization for clinical events related to anticoagulation-related problems in recipients of mechanical valves (20,54). In this scenario, managing both the short term and the long-term adverse event, including the prevention of thrombotic complication, can be the drivers of the surgical decision-making process because of the potential economical implications for the institutions. In fact, the costs of managing valve thrombosis was estimated to exceed $30,000 for a single event. The costs of acute management of embolism and anticoagulant-related hemorrhage were between $8,000 and $11,500 (55).

The use of homograft and allograft for LSE—when and how

The reluctance shown by surgeons for the widespread adoption of cryopreserved homograft in IE finds its roots in lack of RCT investigating the effective benefit of the use of these substitutes (10,13,16,22,31,32,51,56,57). Evidence from several reports have reported no significant differences in overall mortality and infection recurrence when comparing mechanical versus biological substitutes (13,31,51,56,57). Klieverik *et al.* (56) revealed a similar rate of recurrent endocarditis in patients who underwent homografts or mechanical prosthesis implantation, but a lower freedom from reoperation (76% *vs.* 93% respectively). Sabik *et al.* (32) showed that patients with prosthetic IE, including 78% with periannular and radical abscesses, had a freedom from recurrent infection of more than 2 years of 95% and an operating mortality of 3.9% when treated with a homograft. Although the risk of homograft root re-operation for structural valve deterioration is higher, reduced rate of reinfection was noted in the long-term follow-up (between 14 and 27 years) (10,16,17,22,25,27,53), probably due to their favorable responses to antibiotics (16,22).

Despite the survival benefits associated with the use of pulmonary autograft (PA) are well established (29,57-62), its use to replace the aortic valve is recommended only in the US guidelines (Class II b, Evidence Level C) (63) and not mentioned in the European guidelines (43). The use of autograft in the setting of the LSE has been considerably reduced because of the indisputable technical complexity in the execution of the Ross operation. The data from STS database have showed 3-fold increase in operative mortality with Ross operation compared with conventional AVR, probably as an effect of lack of experience of low volume of cases (36,64). Despite these evident criticalities, the use of PA in patients with LSE is indicated at a young age or with contraindication for long-term anticoagulant treatment, in women of childbearing age, in PVE and in patients who choose this substitute for the type of style of life they lead (12,65-68). However, it should be taken into consideration that potential complications of this operation involve both the aortic and pulmonary valve and carry an additional clinical burden (69).

Surgery in complex LSE

Kim *et al.* (13) reported outcomes of 131 patients treated with extensive and radical surgery for LSE. Homografts but also mechanical valves or xenografts have been used in these cases. The authors found that abscess formation had an incidence of 43.09%, which is higher than the mean frequency (36–38%) for LSE of native valve (10,21) and PV (58%) reported by several international studies (3). Abscess formation was treated in 40.5% with a mechanical valve and in 29.5% with xenograft.

The selection of the type of graft to be used should be guided by several parameters including age, extension of the infection (especially to the mitral valve), involvement of other heart structures and resistance to infections. The latter is particularly important since redo surgery in case of reinfection is particularly demanding and burdened by increased perioperative risk and poor early and mid-term outcomes. It is noteworthy that reinfection of synthetic prostheses or prosthetic materials after complex endocarditis were reported as more daunting and technically demanding than reinfection occurring on a previous homograft (10,52,53,62,66-69) (*Figure 3*).

In this context, evidences on safety and durability of homograft has been widely reported. A pivotal study of Stanford University (31) revealed a reinfection rate of 2% at 10 years with the majority of the cases occurring following aortic valve endocarditis surgery within the first year. More recently, the group from Cleveland clinic confirmed the long-term durability and safety of homografts for LSE with the additional benefit of improved postoperative hemodynamics and ventricular remodeling. The fact that no difference in outcomes was demonstrated between mechanical and biological prostheses suggests that in complex endocarditis and in patients with extensive PVE, the choice of the use of an allogeneic tissue is a priority (5,21).

There is currently a sizable body of evidence to support the use of homografts in the setting of complex LSE. A report (17) showed a low recurrence of endocarditis in homograft even in complex cases. The larger series by Erasmus group (16) showed very solid results in terms of mortality and durability. The authors published their follow-up at 27 years underlying the importance of homografts in complex endocarditis. Musci *et al.* (28) used a homograft aortic roots in active IE with periannular abscess formation in a large series of patients with LSE showing satisfactory early and long-term results. Finally, as reported by Perrotta (15) survival benefit with the use of a homograft is higher than in prosthetic valves (5-year cumulative survival 88% versus 66% in prostheses).

Although structural valve deterioration is considered the Achilles' heel responsible for the limited use of allogenic tissue (10,25,27,68,69), relapse of infection represents a daunting problem in patients treated for complex active LSE and should be given consideration. Notably, the reoperation for a relapsing infection carries a higher mortality than the reoperation for structural valve deterioration or dysfunction of an aortic homograft inserted in aortic root position (4–10%) (10,69,70).

Another important point is the reinfection in presence of the synthetic material. The strong inflammatory reaction elicited by the foreign material constituting the stent of mechanical or biological prosthetic valves demands for extensive demolition and debridement increasing the complexity of the procedure. However, reoperation after previous homograft is considered less demanding

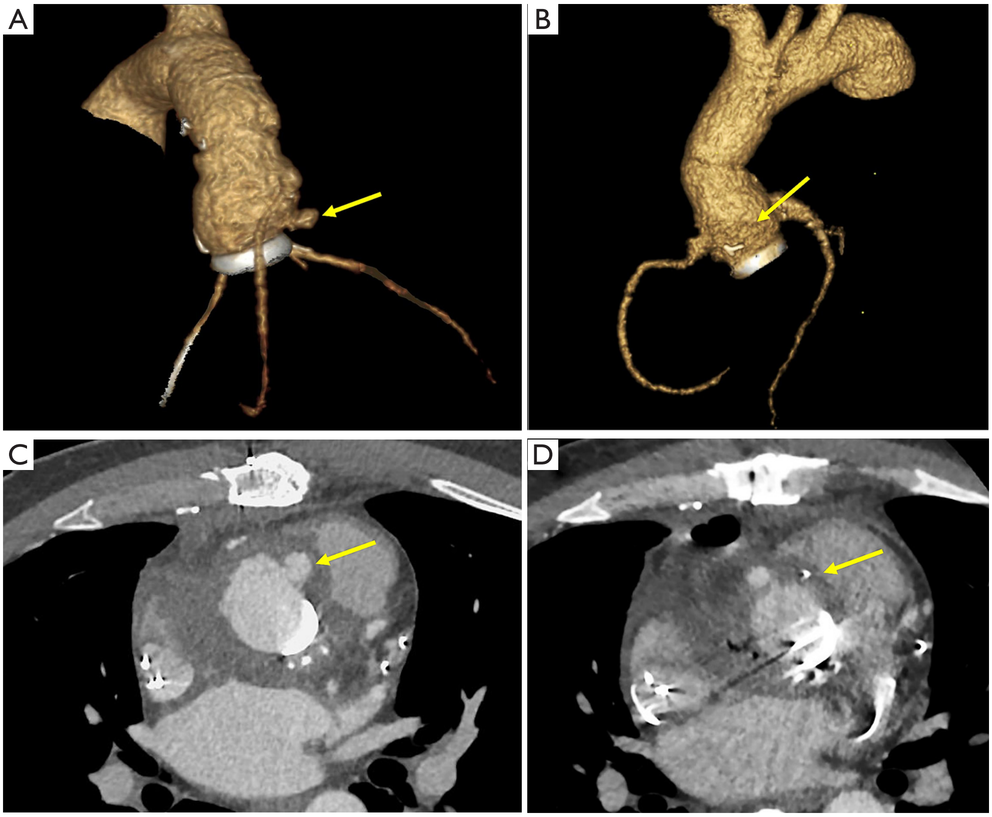

Figure 3 Aortic abscess (A,C) treated using a prosthetic valved conduit with mechanical valve (B,D).

even in the presence of massive calcification of the aortic root (71-73).

In LSE abscess formation is common. Avoiding the use of a homograft in favor of a prosthetic valve in aortic IE implies to treat the abscess with a circumferential patch to repair the ventricular-aortic discontinuity. Similarly, in the case of localized lesions involving only a part of the aortic annulus, the aorto-mitral continuity or aortic root, the cardiac structure still needs to be reconstituted with use of a partial Dacron or equine pericardial patch (3,5,21,26,30,32). Recurrence of LSE involving the myocardium underlying the left coronary cusp is at even higher-risk and may require a Bentall or Cabrol operation.

Infection of more than one valve has been reported in 24.2% to 46.8% of the cases (3,10,13,52) with mitral or tricuspid valve being more commonly involved in intravenous drugs user (11).

Clearly, complex LSE treated with prosthetic valves could lead to a further increase in the risk of mortality in the event of extensive reinfection of two prostheses (3,26). In a very recent Harvard series, associated mitral valve involvement reached up 25% of the cases (13). We have proposed the use of a double homograft in complex LSE with extension to aorto-mitral junction and mitral including both total and partial mitral insertion techniques with satisfactory results at 18 years (10,52,53,69).

Surgery and ethical implication

As recommended by current guidelines, selection of the most appropriate valve replacement strategy in LSE should consider the longevity of the biological substitutes, the potential recurrence of infection and the risk of redo surgery. The best choices are made through a shared decision-making process that includes the patient, the patient's family, an interventional cardiologist, a cardiac surgeon and, preferably, the patient's general cardiologist or general practitioner (43,63).

Patient's preferences and will also take a considerable part in the decision-making. Patients may be discouraged from large and demanding operation. Therefore, the role of the heart team is fundamental in providing detailed explanations of the indications, the steps of the procedure, the potential complications and the postoperative course to allow an informed decision-making. In educating the patient, the experts should explain the potential need for extensive debridement to obtain good and stable results. For example, proposing a faster operation by recommending a prosthetic valve instead of the use of autologous or allogenic tissue in the context of significant involvement of the aortic or mitral valves, can provide misleading information about a situation with a high potential for recurrence of infection. The decision on the surgical option and the choice of the ideal substitute always derives from a balance between the risk of the operation that the surgeon should perform and the obtainable benefit. In the case of complex LSE, both the risk of the procedure and the potentially even higher risk of a redo operation for infection relapse or valve degeneration should be taken into account. Obviously, these considerations are also ultimately subjected to the surgeon and unit's experience in complex procedures and the option of referral to tertiary centers should be explored according to the clinical conditions.

Interestingly, Stulak *et al.* (64) addressed the ethical problem after the use of autograft in Ross's operation. The use of biological derivatives in fact poses some ethical problems when the chances of procedure failure or reintervention are not negligible. The problem of durability of allogeneic and autologous tissues should be addressed with the patient during the counselling process. On the other hand, the benefit of low risk of infection relapse and the impact on quality of life related to the avoidance of life-long anticoagulant therapy should be discussed.

Take-home messages and an algorithm based on evidence

The evidence discussed above indicates that modern LSE surgery should involve the use of a different strategies according to the location and extent of the infection. Conventional stented xenograft and mechanical prosthetic should be considered similar alternatives for localized LSE or combined with patch reconstruction in case of more abscess formation; mechanical valves should be preferred in cases of mitral valve endocarditis and biological valves should be used in patients older than 55 years of age in aortic position.

Due to its higher risk of structural valve deterioration, lack of availability and difficult learning curve, the use of homografts is limited to PVE or when complex reconstruction of the mitro-aortic curtain or aortic root is needed. The miniroot implant is probably the most adaptable technique for complicated LSE and most appropriate in case of demolitive surgery. Cryopreserved mitro-aortic tissue allows the complete or partial replacement of the mitral valve in case of aggressive lesions involving the trigones, the aortic root or cardiac and extracardiac fistulas. However, this type of surgical approach requires adequate surgeon's and center's experience.

The use of the autograft can be considered in young patients or in particular conditions such as women in childbearing age or in case of contraindications to long-term anticoagulation. The use of PA should be limited to centers that have proven experience with solid results and only to cases where a conventional biological or mechanical prosthesis is not indicated for clinical or technical reasons.

On the basis of the evidence examined in this study, we propose an algorithm assisting the choice of the valve substitute in different clinical conditions (*Figures 4,5*). In this algorithm, technical, anatomical and imaging determinants are considered, as well as the clinical characteristics of the patient, the orientation of the guidelines and institutions with the greatest experience in the treatment of LSE.

Due to the strong impact on post-operative mortality, special relevance should be given to timing, which influences the risk of neurological complications, and the extension of the infection. Despite evidence suggests that early surgery may improve survival in patients with complicated IE, an increased risk of recurrence and postoperative valvular dysfunctions has been reported (6,11,14,23,26,30).

The most important factors associated with long-term outcomes are preoperative multiorgan failure, prosthetic mechanical valve IE, vegetation size ≥15 mm, and timing of surgical treatment. Importantly, up to one third of potential candidates do not undergo surgery and these patients experience extremely high mortality rates (37,74,75).

The lack of RCT in this field and the difficulty to design this type of studies in the case of non-elective conditions further complicates the possibility to achieve a univocal consensus on the best strategy to be adopted in each form

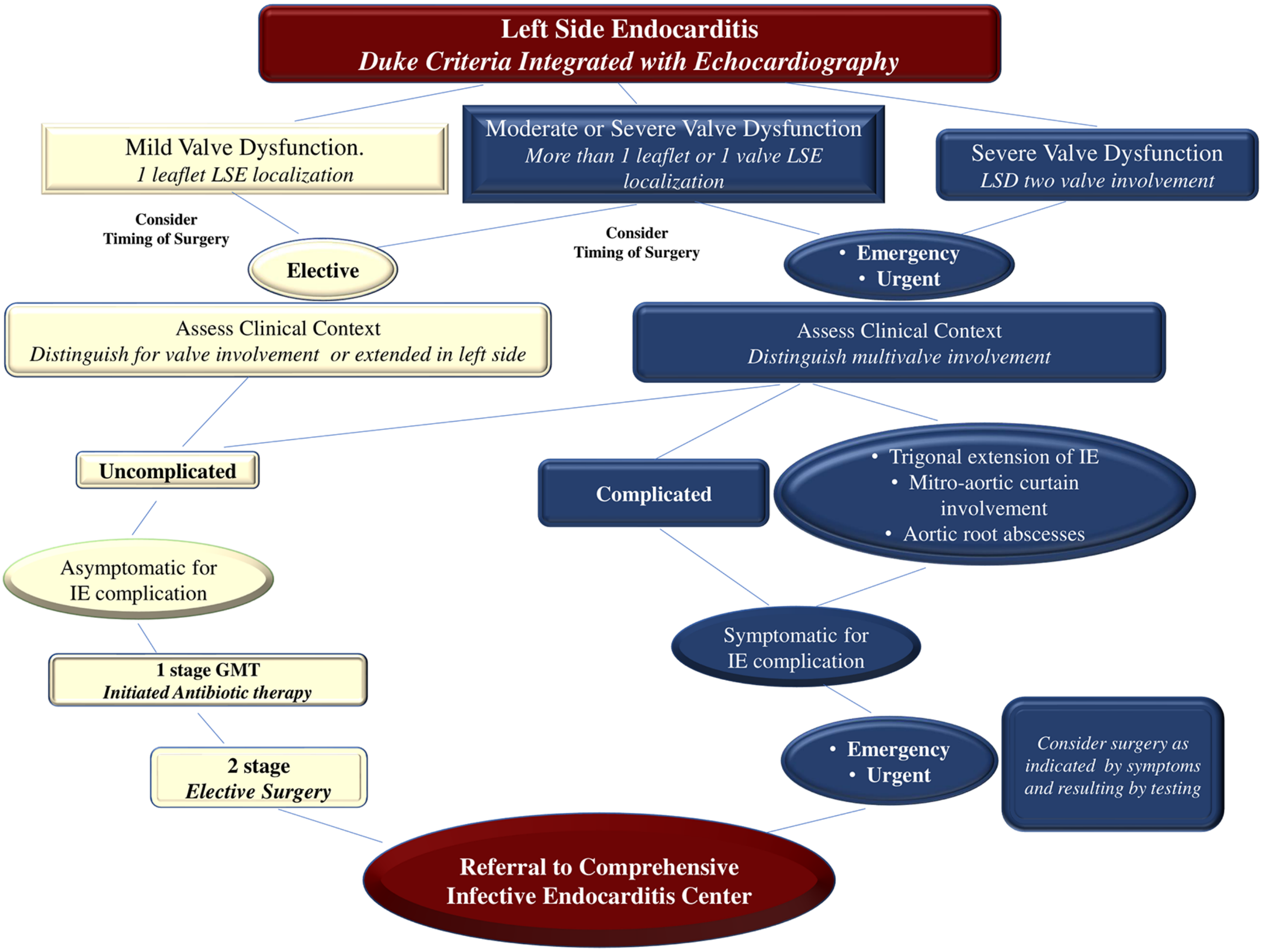

Figure 4 Take-Home Messages and Clinical Algorithm for the Management of Left Side Endocarditis. GMT, guide medical therapy; ACC/AHA, American College of Cardiology/American Heart association; ESC, European Society of Cardiologists; IE, infective endocarditis; LSE, left side endocarditis; TTE, transthoracic echocardiography.

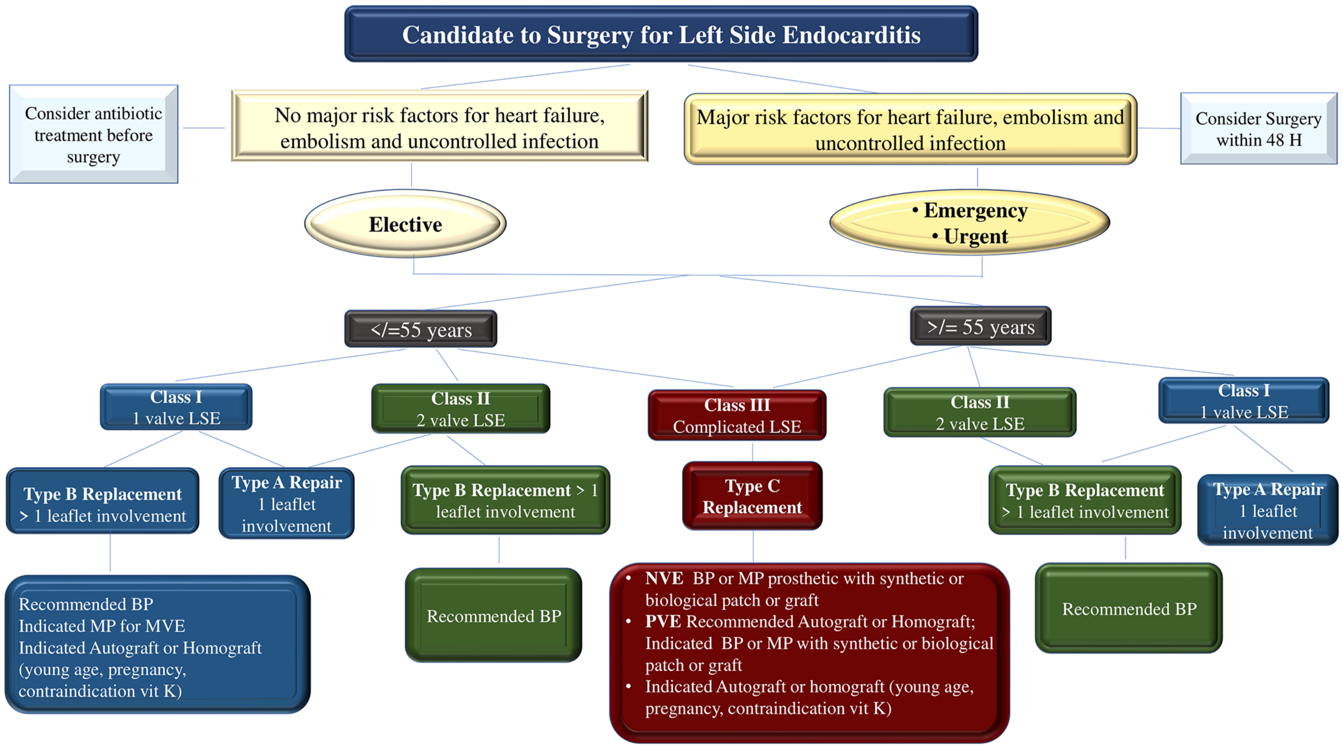

Figure 5 Take-home messages and clinical algorithm for the choice of optimal valve substitute for LSE. BP, bioprosthetic; MP, mechanical prosthetic; PVE, prosthetic valve endocarditis; ACC/AHA, American College of Cardiology/American Heart association; ESC, European Society of Cardiologists; IE, infective endocarditis; LSE, left side endocarditis; TTE, transthoracic echocardiography.

of LSE and further validation studies are needed.

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Footnote

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