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Beatriz Gil de Oliveira Braga

A Systematic Review of Infective Endocarditis Treatment: Surgical Intervention *versus* Medical Treatment

Uma Revisão Sistemática do Tratamento da Endocardite Infeciosa: Intervenção Cirúrgica *versus* Tratamento Médico

março, 2019

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A Systematic Review of Infective Endocarditis Treatment: Surgical Intervention *versus* Medical Treatment

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Faculdade de Medicina da Universidade do Porto, 18/3/19

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Às minhas Avós.

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Intervenção Cirúrgica *versus* Tratamento Médico

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RESUMO

Introdução: A endocardite infeciosa está associada a elevada morbilidade e mortalidade. A melhor estratégia terapêutica nestes doentes está ainda em discussão. Atualmente, não existe evidência científica suficiente que compare a eficácia do tratamento médico e cirúrgico. O objetivo deste trabalho foi comparar a mortalidade hospitalar e a longo prazo do tratamento médico isolado *versus* tratamento cirúrgico através de uma revisão sistemática.

Métodos: Realizámos uma revisão sistemática da literatura nas bases de dados MEDLINE e EMBASE e incluímos artigos que apresentaram resultados de mortalidade hospitalar ou a longo prazo associados aos tratamentos médicos e cirúrgico da endocardite infeciosa. Excluímos estudos dedicados exclusivamente a endocardite associada a dispositivos cardíacos, tais como implante percutâneo da válvula aórtica ou *pacemaker*.

Resultados: Identificámos 2952 publicações de entre as quais incluímos 79. Apenas 10 artigos foram desenhados com o objetivo de comparar os dois tipos de tratamento. Relativamente à mortalidade hospitalar, 3 artigos reportaram diferenças não significativas entre os grupos e 3 demonstraram benefício no grupo cirúrgico. Quanto à mortalidade a longo prazo, a intervenção cirúrgica associou-se a menor risco de mortalidade a longo prazo em 5 estudos, enquanto 2 estudos não demostraram diferenças significativas e 2 estudos sugeriram maior sobrevivência nos doentes tratados apenas com antibióticos.

Conclusões: Nesta revisão sistemática, observámos uma tendência para melhores resultados com o tratamento cirúrgico, particularmente nos resultados a longo prazo. No entanto, a heterogeneidade entre os artigos remete para a necessidade de estudos futuros neste âmbito.

Palavras chave: Endocardite infeciosa; cirurgia cardíaca; antibióticos; mortalidade

ABSTRACT

Background: Infective endocarditis is associated with high morbidity and mortality. The best therapeutic approach to these patients is still under discussion. Currently, compelling scientific evidence is lacking comparing the efficacy of medical and surgical treatment. Our goal was to compare in-hospital and long-term mortality of medical treatment only *versus* surgical treatment through a systematic review.

Methods: We conducted a literature review using MEDLINE and EMBASE databases and included articles that presented in-hospital or long-term mortality associated with medical and surgical treatments of infective endocarditis. We excluded studies exclusively concerning endocarditis in cardiac devices, such as transcatheter aortic valves or pacemaker.

Results: We identified a total of 2952 articles of which 79 were included. Only 10 articles were designed with the purpose to compare both treatment groups. Regarding in-hospital mortality, 3 articles reported non-significant differences between groups and 3 showed benefit in surgical group. Concerning late mortality, surgical intervention was associated with lower long-term mortality risk in 5 articles, while 2 papers failed to reach significant differences and 2 suggested higher survival in patients treated only with antibiotics.

Conclusion: In this systematic review, we observed a trend towards better results with surgical therapy, particularly for long-term results. However, heterogeneity between studies suggests the need for further investigation in this area.

Keywords: Infective endocarditis; cardiac surgery; antibiotics; mortality;

Quadro de abreviaturas

IE	**Endocardite infeciosa**
PVE	Endocardite em válvula protésica
NVE	Endocardite em válvula nativa
RCT	Ensaio clínico randomizado

Abbreviations

IE	**Infective Endocarditis**
PVE	Prosthetic valve endocarditis
NVE	Native valve endocarditis
RCT	Randomized Controlled Trial

1. INTRODUCTION

Infective endocarditis (IE) is an infection of the endocardial surface of the heart [(1)] and despite its low prevalence, it is estimated to have a crude incidence of 1.5-11.6 per 100 000 people [(2)]. Although the management of IE has been improving, it remains associated with high morbidity and mortality (in-hospital mortality rate ranging from 15 to 30%) [(3)].

According to the most recent recommendation by the European Society of Cardiology, once diagnosed, a multidisciplinary “Endocarditis Team” [(3)] should discuss the best treatment approach for each patient. Empirical antibiotic therapy is recommended to start promptly and once the microorganism is identified; antibiotic therapy must be guided by microorganism susceptibility. Surgery plays an important role, especially when medical treatment success seems unlikely due to heart failure, uncontrolled infection or high risk of embolism [(3, 4)].

Surgical treatment indication is well defined in specific clinical scenarios such as, prosthetic valve endocarditis, right-sided IE, *Staphylococcus aureus* IE and patients with cerebral complications. However, in other situations, identifying which patients should undergo surgical treatment or anti-microbial treatment only is still controversial. Medical therapy aims microorganism eradication and has the advantage of being noninvasive, whereas surgery directly removes infected tissues allowing recovery of patients in whom antibiotics alone were unsuccessful. The inability of pharmacologic treatment to totally eradicate microorganisms is an important disadvantage of this non-invasive approach leading to a high probability of early mortality due to uncontrollable infection or hemodynamic instability related to significant valve dysfunction. On the other side, a high surgical risk is commonly associated to this disease and specific IE operative risk scores are not stablished [(3)].

Studies comparing the efficacy of therapeutic approaches for IE is currently lacking. So far, one randomized controlled trial (RCT) tried to assess this question (5). In left-sided IE with severe valve disease and large vegetation, Kang et al. found a significant reduction in composite end point of death from any cause and embolic events in surgical patients compared with medical treatment patients. In contrast, some observational studies showed non-significant differences between treatment groups (6, 7), while Vikram et al. (7) and Aksoy et al. (8) found a significant benefit from surgery in left-sided valve IE over 6 months and 5 years of follow-up, respectively.

In this study, we aimed to systematically review studies reporting IE-associated in-hospital and post-discharge mortality with medical treatment and/or surgical treatment.

2. METHODS

2.1. Literature Search

This systematic review was performed according to Preferred Reporting Items for Systematic reviews and metanalysis (PRISMA) guidelines. A comprehensive MEDLINE and EMBASE search of the literature addressing IE treatment including publications between January 1990 and December 2017. The main key-words were: "infective endocarditis", "cardiac surgery", "medical treatment" and "mortality". Please check the detailed search query applied at **Appendix 1**.

2.2. Eligibility criteria

We included full-size articles published in one of the following four languages: Portuguese, English, Spanish or French. All observational or randomized studies performed in human were considered eligible if the following criteria were met:

1. Inclusion of adult (>16years) and non-pregnant individuals;
2. Clear descriptive analysis of the two comparative groups: surgery group and medical therapy only group;
3. Sample size ≥ 30 patients.

We excluded those IE studies focused exclusively on IE associated with cardiac devices, such as transcatheter aortic valves or pacemaker. If the research returned more than one article from the same cohort, we included those with the most detailed report or with longer time of follow-up.

2.3.Study selection

After online search, all abstracts retrieved (n=2952) were reviewed to assess fulfilling inclusion criteria. One hundred and thirteen articles were selected to full-text revision: 7 were not included due to absence of access to the full-text and 27 were excluded after full text analysis due to either missing data, poorly defined or setting differently variables or not fulfilling the inclusion criteria.

2.4.Data collection

A structured protocol to collect data was used, including geographic region of the cohort, sample size, patient's age; gender; number of cases undergoing valve surgery and medical therapy; follow-up time; most common microorganisms, type of valve IE (native or prosthesis); mortality data and risk estimates measures. A sample of 55 full text articles were selected to independently collect data by two reviewers (BGB and FS) and any disagreement was reviewed and resolved by consensus.

2.5.IE, Treatment and Outcomes Definition

Infective endocarditis: No specific definition of IE was required and 7 different endocarditis definitions were considered according to each article: 1) Duke, 2) modified Duke, 3) Von Reyn, 4) a modification of Von Reyn criteria (9), 5) ICD-10 codes and two other definitions: 6) one specifically defined by the authors (10); and 7) similar but not equal to Duke Criteria (11).

Surgical group: patients whose *a priori* defined treatment was cardiac surgery, regardless the type of surgery, the time that it had been done ("early" or "late" surgery were considered since it was *a priori* the determined treatment) and the presence or not of clinical criteria to surgery according to guidelines.

Medical group: patients whose *a priori* defined treatment was only medical therapy, regardless the type or duration of treatment (a patient whose medical treatment failed and died or underwent surgery was considered as medical).

Early mortality: mortality within 60 days after the IE first admission or in-hospital mortality.

Post-discharge mortality: mortality > 60 days after the first admission and after discharge.

3. RESULTS

3.1. Study Characteristics

A total of 2952 articles were identified: MEDLINE (n=2032) and EMBASE (n=920) of which 79 were included in this analysis (**Figure 1**). **Table 1** presents the main characteristics of the included studies. All studies were observational cohorts but one randomized controlled trial; 40 studies were retrospective, 37 prospective and 1 bidirectional. Regarding study region, 47 studies included patients from Europe, 11 from Asia, 15 from America, 1 from Oceania, 1 from Africa and the remaining 4 had multicenter international recruitment. Sample sizes ranged from 32 to 7603 individuals from IE populations according to each article criteria and definition. Duke criteria, modified Duke and Von Reyn were the most applicable criteria for sample selection, being used in 29, 29 and 4 articles, respectively. One article used ICD-10 codes, 4 articles used their own definitions without stating any pre-specified criteria, 1 used "similar to Duke criteria" and 9 didn't define IE criteria.

The most frequently affected valve was the aortic valve in 38 articles (out of 65 studies), the mitral valve in 22 articles and both aortic and mitral valves in 4 studies; one article investigated exclusively tricuspid IE. *Staphylococcus* and *Streptococcus sp.* were the most frequently reported causative agents (in 53 and 15 studies, respectively).

From the 79 studies including a total of 29783, 11694 patients were treated surgically and 17981 were treated medically only, and 35 studies (44%) reported the comparison between medical *vs*. surgical outcomes in the same cohort. Follow-up ranged from 30 days to 9 years and we grouped studies into: in-hospital and long-term (including 1-year, 1-to-3-year, 3-year, 3-to-5-year and > 5-year follow-up) mortality.

The results were provided in the entire cohort in 10 studies and 25 reported outcomes by specific subgroups of EI patients, such as:

- Patients with cerebral complications (n=2[12, 13]);
- Octogenarian patients (n=1[14]);
- Prosthetic valve endocarditis (PVE) (n=10: 6 without specific microbiological selection [15-20], 3 only by *Staphylococcus aureus* PVE[21-23], and 1 only by *Candida* spp PVE [24]);
- Native valve endocarditis (NVE) (n=7: 5 only left-sided [5, 7, 25-27] 3 of them with high risk of embolism[5, 25, 27], and 1 by *Staphylococcus aureus* [28]);
- Critically ill patients with left side IE (n=1 [29]),
- IE complicated by heart failure (n=1 [30]);
- Intravenous drug users with isolated tricuspid valve (n=1 [31]);
- *S.* aureus endocarditis (n=1 [32])
- Left side IE (n=1 [33]).

In-hospital death

Overall

In respect to the 10 articles whose main aim was to compare both treatments, 6 referred early mortality (**Table 2**). Three of them reported non-significant differences between medical and surgical groups [8, 34, 35] and the other three showed benefit in surgical group [10, 36, 37]

Subgroups

In-hospital death results and characteristics from 19 articles with medical *versus* surgical treatment in specific subgroups are presented in **Table 3.**

Prosthetic valve endocarditis

Nine studies reported surgical *versus* medical in-hospital outcomes in prosthetic valve endocarditis (PVE): 2 of them presented better results for surgical group [15, 17] , whereas other 2 reported worse in-hospital results in this group [20, 24]. The 5 remaining papers did not exhibit significant differences, but a trend to better results for medical group was reported in 2 articles [16, 19] and an opposite tendency was reported in the other 3[18, 22, 23] , two of them reporting *S. aureus* PVE [22, 23].

Staphylococcus aureus endocarditis

One article included only *Staphylococcus* aureus IE and projected, without statistical evidence, better in-hospital results in surgical patients [32].

Embolic risk

In native valve endocarditis with high embolism risk, 2 articles showed no differences in early mortality according to treatment group [5, 25]. One study found better results in medical group [27], while 3 favored the surgical group [26, 28, 38], one of them specifically regarding *S.* aureus NVE [28].

Long-term mortality

Overall

Nine articles assessed post-discharge mortality **(Table 4)**. Surgical group revealed better results in the crude relative frequencies of late death (≥ 5 years) comparing with medical group in 5 studies[10, 39-42].

Surgery was defined as protective for long-term mortality in 5 articles [8, 34, 39, 40, 42], while 2 papers failed to reach this result with a statistical significance difference [37, 41]. On the other side, two papers [10, 35] suggested better long-term survival in medical treated patients.

Subgroups

Post-discharge results and characteristics from 21 articles with medical *versus* surgical treatment according to specific subgroups are presented in **Table 5.**

Prosthetic valve endocarditis

Six studies exhibited better long-term results for surgery [15, 17-19, 21, 23], one of them considering only *S. aureus* PVE [21]. Another study reported a single late death occurring in the surgical group [20] and one showed a trend towards better medical results, even though results were not statistically significant [16].

Staphylococcus aureus

Surgery was associated with better long-term survival in the only paper exclusively about this microorganism [32] without additional subgroups involved.

Native valve endocarditis

Three articles regarding native valve IE favored surgical treatment [7, 26, 38] while three articles did not find statistical significance according to group treatment in left side native valve endocarditis with vegetation [5, 25, 27]. Furthermore, one of these provided a trend to worse results with surgery without reaching statistical significance [27].

4. DISCUSSION

In this study we observed that: (1) hospital mortality tended to be lower with surgical intervention than with medical treatment alone, however, no clear evidence support it; (2) long-term mortality was lower with surgical treatment; (3) all subgroups, namely PVE and *S.aureus* associated IE benefited with surgical intervention.

There is no clear benefit of surgical treatment over medical treatment alone on intra hospital mortality.

On one hand, Aksoy et al. [8] performed a propensity score matched analysis and compared discharged status without statistical significant differences between medical and surgical groups (death 18% *versus* 11.5%, p=0.176) and Bishara et al. [34] included 331 patients from a revision of medical records regarding a 10-year period in an Israelite hospital and also obtained a non-significant difference regarding in-hospital death for medically vs. surgically treated patients (18 % *vs.* 11%), although with a trend for worse outcomes in the medical group. Verheul et al. [35] included 141 cases, 91 from the authors' hospital and 50 referred from other centers and similar percentages regarding 1 month mortality (medical: 27% vs surgical: 26%) were found. Actually, Aksoy et al. [8] did not find statistical significance between age groups, whereas Bishara et al. [34] reported significant differences (mean age: surgical group: 58.5 years and medical group: 65.5 years) and Verheul et al. describes similar mean age groups (surgery: 45 years and medical group: 44 years).

On the other hand, Martinez-Sellés et al.[36] and Olaison et al. [37] both reported that patients proposed to surgical intervention were younger than medical group patients: the latter found higher mortality in medical patients (12% *vs.* 8%), justified by their advanced age or contraindications to surgical procedures, while the former showed similar analysis attributing better in-hospital results to patients treated surgically (31% medical *vs*. 24% surgical, p=0.02), but described **urgent** surgery as an independent predictor of in-hospital mortality. If patients who have surgery are younger, it is reasonable to assume that these results are related do the fact that younger patients have better chances of survival to the operation. Also, Martinez-Sellés et al. separated urgent surgery from elective surgery: this might be important in obtaining significant results, since surgery performed in acute ill patients may lead to worse outcomes.

In fact, there's an overall trend to allocate more patients to the medical group. This is probably due to the fact that surgery is advised only when complications arise (and this does not occur in every case) and, if a patient has contraindications to the procedure, is treated only with antibiotics. Overall, they all present heterogeneity when it comes to IE definition, valve involved, country, microorganism involved and period of time, which may influence the results. Due to the small sample of articles comparing both treatment approaches without specific subgroups, it is hard to draw conclusions.

PVE had heterogeneous results in respect to in-hospital death, since most articles could not find significant results. *S.aureus* and embolic events subgroups both presented surgical benefits.

Alonso-Valle et al. [19], in their PVE study, found the medical group to be significantly younger and that more patients in the surgical group were in NYHA class IV. Nonetheless, they found a higher in-hospital mortality rate in the medical therapy alone group (42% *vs* 26% in the medical-surgical group, p>0.05), even though these results were not significant. Truninger et al. [16] showed also a non-significant trend towards worse results with surgery, whereas Akowuah et al [18] obtained higher crude mortality rates for patients treated medically; however, seven individuals included in the antibiotic group were considered too sick for curative surgical treatment and, when they were not included in the analysis, mortality in the remaining medically treated patients was not significantly different when compared with surgically treated patients ($p = 0.15$).

Yu et al. [15] obtained significant results favoring surgical treatment ($p<0.05$) and Gordon et al. [17], in their report about early onset PVE, revealed 30-days survival of 92% *vs*. 65% in surgical *vs*. medical groups.

Nevertheless, Rekik et al. [20] presented higher early mortality in the surgical group connecting this paradoxical result with a significant delay to diagnosis in surgical patients. With respect to fungal PVE, Rivoisy et al. [24] emphasized that their crude results do not support surgical treatment for all patients and call for schemes of antifungal therapy. However, this is the only article about fungal PVE, which should constitute a separate entity from PVE.

In patients with left-sided IE and large vegetations, the only RCT included in this review demonstrated similar results between groups regarding in-hospital mortality in patients with left-sided IE and large vegetations (1 hospital death in each group) [5, 43].

Long-term mortality was lower with surgical treatment than with isolated medical treatment.

In fact, Aksoy et al [8], Bishara et al.[34], Netzer et al. [39] and Bannay et al. [42] performed multivariate analysis to determine whether valve surgery had beneficial results. Bannay et al. detected changes in results according to time of follow-up and associated valve surgery with reduced long-term mortality only after 188 days of follow-up (HR: 0.55, 95% CI: 0.35 to 0.87). Aksoy and colleagues also reported a balance between perioperative risk and separate

Kaplan-Meier curves after 40 days, having found surgery as an independent predictor of survival in their multivariate analysis within the propensity score matched cohort (HR: 0.27, 95% CI: 0.13 to 0.55). Bishara et al. [34] stratified patients according to pathogens, infected valve and age: early surgery was considered to improve statistically significant survival rates only in *S.aureus* IE patients. Netzer et al. [39], in their 89 months of follow-up, found the absence of early surgical procedure to be predictive of overall long-term mortality (OR: 1.86, 95% CI: 1.25 to 2.75) even after excluding in-hospital death patients. The 10-year cohort of Krcmery et al. [40] with 339 patients from Slovak Republic, revealed antibiotic combined with surgery as significantly associated with better outcome in univariate analysis and the introduction of valve surgery in their second study period (1991-1997) was considered as the cause of reduced mortality in those years.

In their prospective analysis, Olaison et al. [37] reported a 3.45 relative risk for cardiac death at 5-years of follow-up in no surgery patients but without reaching statistical significant. Similar to this, overall 5-year mortality rates were 48% *vs.* 30% for medical *vs.* surgical in the 132 Denmark patients studied by Tran and colleagues [41], and they also did not find surgery to be independently associated to survival. In fact, the parallel progress of survival curves after 2.5 years and the multivariate Cox regression analysis adjusted to age, *Staphylococcus* aureus infection and PVE showed no statistical significance for type of treatment (HR for surgery: 0.755, p=0.319). However, a sub-analysis of the first 36 months of follow-up revealed benefit from surgery with reduced mortality comparing with medical group.

Nevertheless, Verheul et al. [35] suggested higher survival in medically treated individuals (10-year, medical 77± 6% *vs.* surgical 53±7%), but these patients had many adverse events and may have had valve replacement surgery during follow-up, contrary to what was stated for in-hospital mortality, although the difference was very small and we do not have information about statistics. For this reason, these results are biased: if patients received surgical therapy during follow-up and survival was better, probably surgery was necessary to improve outcome. Also, Yoshida et al. [10] showed amongst patients who were discharged alive, only patients in the surgical group died during the follow-up. However, in-hospital results point to better surgical outcomes, since patients in the medical group died from active IE complications but neither of these results were statistically analyzed.

As a matter of fact, Aksoy et al. [8] and Bishara et al. [34] were unable to present significant results regarding in-hospital mortality. However, when it comes to long-term mortality, they established important associations between surgery and improved outcome. On one hand, patients in the acute phase of the disease might be too ill to survive operation or are older with comorbidities and, therefore, are treated medically. On the other hand, patients that have indication to perform surgery have a complicated course of the disease, even though they are usually younger. However, concerning long-term mortality, surgical patients who survived totally eradicated the infection and are younger, therefore, survival will be higher in this group.

All subgroups favored surgery, except for left side NVE, namely with vegetations and with high risk for embolism, that also described non significant results.

With respect to PVE patients, the surgical reintervention showed better long-term results. Gordon et al.[17] revealed in an univariate analysis survival of 74% *vs.* 40% in the surgical *vs.* medical group, respectively at 1 year of follow-up. Alonso-Valle et al. [19] presented also improved outcomes in surgery, with survival rates of 71 % *vs.* 42%, at 1 year of follow-up. Yu et al. [15] corroborate these results through a multivariate analysis, considering medical therapy as an adverse predictor of 6-month mortality. Similar reports in *S. aureus* PVE were provided by John et al. [21] in their 3 months follow-up and by Akowuah et al [18] at 10-years of follow-up (survival 58% *vs*. 28% for surgical *vs*. medical patients, p=0.04). On the contrary, Chirouze et al. [23] didn't find statistically significant differences in their multivariate and propensity score adjusted models regarding early surgery in PVE. Nevertheless, a significant benefit in the surgical group comparing with non-surgery group was reported after 7 days of the surgical procedure.

However, Truninger et al.[16] presented non-significant results that suggested a trend towards worse surgical outcomes.

Staphylococcus aureus endocarditis patients seem to benefit from surgery according to higher survival rates referred by Remadi et al [32] (74±10.6% *vs.* 43±8.5% p<0.001).

In left sided native valve endocarditis (NVE), Funakoshi et al. [26] described lower estimated actuarial 7-year survival, free from IE-related death, for medical group (82%± 5%) comparing with early surgery group (94%±5%, p=0.011) and Vikram et al.[7] found similar results after adjustment for confounding factors and heterogeneity through propensity score models at 6 months of follow-up.

The RCT long-term results regarding left sided native valve IE with high risk for embolism [5] revealed no differences between early surgery and conventional treatment in all-cause mortality at 4 years (8.1% and 7.7%, respectively; hazard ratio 1.04; 95% CI, 0.21 to 5.15; p=0.96) nor at 7-year survival rates of (87±6% in the surgical group vs 83±8% in the conventional group, Log-Rank p=0.768. Also, Kim et al. [25] could not find any significant differences at 5 year of follow-up. On the opposite side, Desch et al. [27] performed a multivariable analysis and the hazard associated with surgery was particularly high although non-significant (HR surgery: 3.9, 0.9-16.6; p=0.06).

Medical *versus* surgical groups

It is important to notice that only few articles included (n=10) specifically compared both approaches without focusing on specific subgroups. This probably reflects the complexity of the disease and the variety of contexts in which it can emerge. Also, it is hard to “isolate” subgroups, since articles usually analyze more than one variable and were very different concerning specific characteristics, such as region, affected valve, population, microorganism, etc., reason why it is hard to establish patterns.

On one hand, even though patients proposed to surgical treatment might be younger and have less comorbidities, they also may have worse in-hospital outcomes due to the invasive nature of this approach in the active phase of IE or a more serious disease. On the other hand, surgery allows direct removal of infected tissues and patients with surgical indications might have been allocated to the medical group due to comorbidities that do not allow the procedure. This said, we believe that cases must be assessed individually in respect to treatment decisions and a combined scheme of antibiotics and surgery might be beneficial in selected patients after weighting the risks and benefits of the possible approaches. However, given the high heterogeneity between studies, we could not perform a quantitative analysis and the interpretation should take into account the individual patient, its clinical characteristics, particular microorganisms evolved and also the expertise of each center do deal with this deadly disease.

Limitations

This systematic review has some limitations: 1) we only used two large databases (MEDLINE and EMBASE) to perform the literature search and although the references of the included studies were also investigated, it may be that some potentially eligible studies might have not been screened; 2) the screening of studies was performed only by one reviewer, although data from more than 50 were extracted by two reviewers; 3) the quality of studies was not systematically evaluated since we preferred to include most evidence regardless its quality due to the lack of unbiased studies in this area; 4) the quantitative synthesis of results was waived because of high heterogeneity between studies and lack of specific data in most of them; 5) the qualitative synthesis of results could also have some discrepancies due to different surgical and medical group definitions not only according to timing and duration of treatment in medical group but also according to type of procedures in surgery (replacement or repair).

5. CONCLUSION

We may conclude that 1) regarding in-hospital mortality, it is still controversial whether one treatment approach is superior to the other; 2) concerning long-term results, evidence seems to indicate that surgical treatment may have better results than medical treatment alone. Further investigation is required, ideally through randomized controlled trials.

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7. FIGURE CAPTION

Figure 1 – Flow chart search strategy;

n= number of articles

8. FIGURES AND TABLES

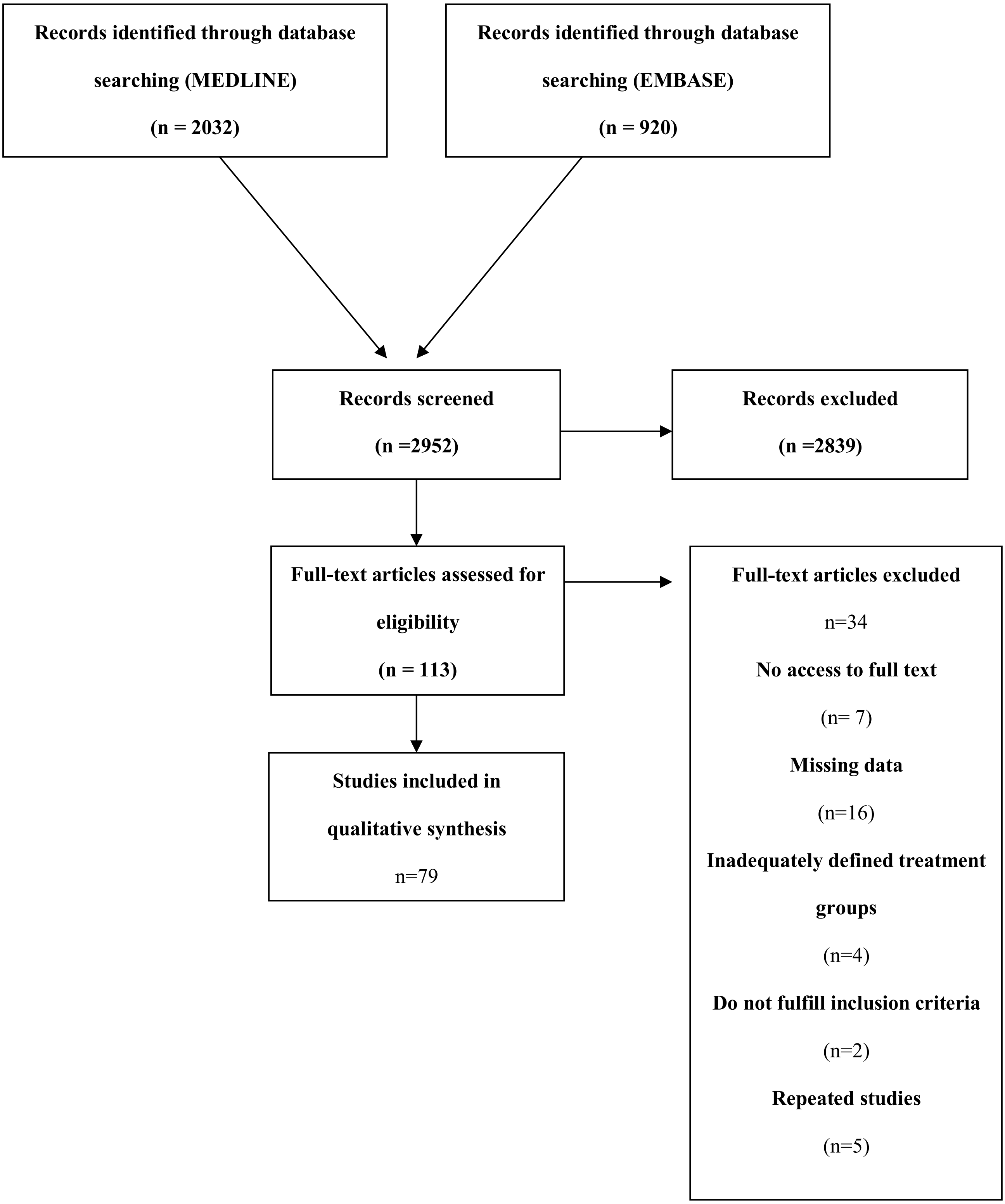

Figure 1 – Flow chart search strategy

Table 1 - Main characteristics of included studies

Author, Year	Region	IE definition	Surgical *vs.* Medical	Studied Outcomes	Follow-up	Study Type	N of patients or IE episodes
Yoshida, 1991[10]	Japan	Defined with non-specified criteria, non-specific IE	yes	In-hospital and post-discharge mortality	> 5 years	retrospective cohort	142
Tornos, 1992[44]	Spain	Defined with non-specified criteria, non-specific IE	no	In-hospital and post-discharge mortality	>5 years	prospective cohort	140
Witchitz, 1992[45]	France	Von Reyn criteria, non-specific IE	no	In-hospital mortality	1 - 3 years	retrospective cohort	471
Verheul, 1993[35]	Amsterdam	Von Reyn criteria, definite, possible or probable IE	yes	In-hospital and post-discharge mortality	≥ 5 years	retrospective cohort	141
Otaki, 1994 [46]	Japan	non-defined criteria, non-specific IE	no	Post-discharge mortality	> 5 years	retrospective cohort	32
Yu, 1994 [15]	USA	non-defined criteria, non-specific IE	yes, subgroups	in-hospital and post-discharge mortality	< 1 year	prospective cohort	74

Mathew, 1995 (9)	USA	Von Reyn modified criteria, definite, possible or probable IE	no	In-hospital mortality	in-hospital	bidirectional	125
Wolff, 1995 (47)	France	non-defined criteria, non-specific IE	no	Post-discharge mortality	1 - 3 years	retrospective cohort	122
Olaison, 1996 (37)	Sweden	Von Reyn criteria, non-specific IE	yes	In-hospital and post-discharge mortality	> 5 years	prospective cohort	126
Ostrowski, 1997 (48)	Poland	non-defined criteria, non-specific IE	no	In-hospital and post-discharge mortality	> 5 years	retrospective cohort	120
Roder, 1997 (49)	Copenhagen	Duke criteria, non-specific IE	no	In-hospital mortality	in-hospital	retrospective cohort	24
John, 1998 (21)	USA	Duke criteria, definite IE	yes, subgroups	Post-discharge mortality	1 - 3 years	retrospective cohort	33
Braun, 2000 (50)	Chile	Duke or Von Reyn criteria, non-specific IE	no	Post-discharge mortality	> 5 years	prospective cohort	258
Hricak, 1999 (28)	Slovak Republic	Duke criteria, definite IE	yes, subgroups	In-hospital mortality	in-hospital	prospective cohort	53

Truninger, 1999 [16]	Switzerland	Duke criteria, definite IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	prospective cohort	49
Gordon, 2000 [17]	USA	Duke criteria, definite IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	prospective cohort	77
Heiro M, 2000 [13]	Finland	Duke criteria, definite IE	yes, subgroups	Post-discharge mortality	< 1 year	retrospective cohort	218
Bishara, 2001 [34]	Israel	Modified Duke criteria, definite or possible IE	yes	In-hospital and post-discharge mortality	≥ 5 years	retrospective cohort	252
Chan, 2002 [11]	Canada	Similar to Duke criteria, non-specific IE	no	In-hospital and post-discharge mortality	1 - 3 years	prospective cohort	43
Karth, 2002 [51]	Austria	Duke criteria, definite IE	no	In-hospital mortality	in-hospital	retrospective cohort	33
Netzer, 2002 [39]	Switzerland	non-defined criteria, non-specific IE	yes	Post-discharge mortality	≥ 5 years	retrospective cohort	212
Wallace, 2002 [52]	London	Duke criteria, non-specific IE	no	In-hospital and post-discharge mortality	< 1 year	retrospective cohort	205

Akowuah, 2003 (18)	UK	Modified Duke criteria, definite IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	retrospective cohort	66
Di Salvo, 2003 (53)	France	Duke criteria, definite IE	no	In-hospital mortality	in-hospital	retrospective cohort	315
Krcmery, 2003 (40)	Slovak Republic	Duke criteria, non-specific IE	yes	Post-discharge mortality	>5 years	prospective cohort	339
Loupa, 2003 (54)	Greece	Duke criteria, non-specific IE	no	Post-discharge mortality	< 1 year	prospective cohort	101
Oyonarte, 2003 (55)	Chile	non-defined criteria, non-specific IE	no	In-hospital mortality	>5 years	prospective cohort	321
Vikram, 2003 (7)	USA	Duke criteria, non-specific IE	yes, subgroups	post-discharge mortality	< 1 year	retrospective cohort	513
Langiulli, 2004 (56)	New York	non-defined criteria, non-specific IE	no	In-hospital and post-discharge mortality	3 - 5 years	retrospective cohort	82
Mourvillier, 2004 (57)	France	Modified Duke criteria, definite IE	no	In-hospital mortality	in-hospital	retrospective cohort	228

Spies, 2004 [58]	Hawaii	Modified Duke criteria, definite IE	no	In-hospital mortality	in-hospital	retrospective cohort	40
Pachirat, 2005 [59]	Khon Kaen	Duke criteria, non-specific IE	no	Post-discharge mortality	1 - 3 years	retrospective cohort	200
Tornos, 2005 [60]	Europe	Duke criteria, definite or possible IE	no	In-hospital mortality	in-hospital	prospective cohort	159
Abramczuk, 2006 [61]	Poland	Duke criteria, definite IE	no	In-hospital mortality	< 1 year	retrospective cohort	152
Sohail, 2006 [22]	USA	Duke criteria, definite IE	yes, subgroups	In-hospital mortality	in-hospital	retrospective cohort	55
Tran CT, 2006 [41]	Denmark	Duke criteria, non-specific IE	yes	Post-discharge mortality	≥ 5 years	retrospective cohort	132
Aksoy, 2007 [8]	Durham	Modified Duke criteria, non-specific IE	yes	In-hospital and post-discharge mortality	> 5 years	prospective cohort	333
Hill, 2007 [62]	Belgium	Modified Duke criteria, non-specific IE	no	Post-discharge mortality	1 - 3 years	prospective cohort	193

Lopez, 2007 [63]	Spain	Duke criteria, non-specific IE	no	Post-discharge mortality	in-hospital	prospective cohort	66
Remadi, 2007 [32]	France	Duke criteria, definite IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	prospective cohort	116
Slater, 2007 [64]	**USA**	non-defined criteria, non-specific IE	no	Post-discharge mortality	1 - 3 years	retrospective cohort	364
Thuny, 2007 [65]	France	Duke criteria, definite IE	no	Post-discharge mortality	3 - 5 years	prospective cohort	109
Martínez-Sellés, 2008 [66]	Spain	non-defined criteria, non-specific IE	no	Post-discharge mortality	≥ 5 years	prospective cohort	222
Alonso-Valle, 2009 [19]	Spain	Duke criteria, definite IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	retrospective cohort	133
Rekik, 2009 [20]	Tunisia	Modified Duke criteria, definite or possible IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	retrospective cohort	48
Kim, 2010 [25]	Korea	Duke criteria, definite IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	prospective cohort	132

Bannay, 2011 (42)	France	Duke criteria, definite IE	yes	Post-discharge mortality	≥ 5 years	prospective cohort	449
Funakoshi, 2011 (26)	Japan	Modified Duke criteria, definite or possible IE	yes, subgroups	In-hospital and post-discharge mortality	≥ 5 years	retrospective cohort	212
Kiefer, 2011 (30)	international	Modified Duke criteria, definite or possible IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	prospective cohort	1359
López-Wolf, 2011 (67)	Spain	Duke or Modified Duke criteria, definite or possible IE	no	In-hospital mortality	in-hospital	prospective cohort	618
Ramirez-Duque, 2011 (68)	Spain	Modified Duke criteria, definite or possible IE	no	In-hospital and post-discharge mortality	< 1 year	prospective cohort	961
Rasmussen, 2011 (38)	Denmark	Duke criteria, definite or possible IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	prospective cohort	323
Fernandez-Hidalgo, 2012 (69)	Spain	Modified Duke criteria, definite or possible IE	no	In-hospital mortality	3 - 5 years	prospective cohort	438
Kazelian, 2012 (70)	Argentina	Duke criteria, non-specific IE	no	In-hospital mortality	in-hospital	prospective cohort	152

Mokhles, 2012[71]	Netherlands	Modified Duke criteria, definite IE	no	In-hospital mortality	≥ 5 years	retrospective cohort	191
Chambers, 2013 [72]	international	Modified Duke criteria, definite or possible IE	no	In-hospital mortality	≤ 1 year	prospective cohort	77
Chirillo, 2013 [73]	Italy	Duke criteria, non-specific IE	no	Post-discharge mortality	1 - 3 years	prospective cohort	99
Jones, 2013 [74]	London	Duke criteria, definite IE	no	In-hospital mortality	1 - 3 years	retrospective cohort	42
Ternhag, 2013 [75]	Sweden	ICD-10 codes criteria, non-specific IE	no	In-hospital mortality	1 - 3 years	retrospective cohort	7603
Desch, 2014 [27]	Germany	Modified Duke criteria, non-specific IE	yes, subgroups	In-hospital and post-discharge mortality	≥ 5 years	retrospective cohort	71
Gálvez-Acebal, 2014 [33]	Spain	Modified Duke criteria, non-specific IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	prospective cohort	316
Hsieh, 2014[76]	Eastern Taiwan	Modified Duke criteria, definite IE	no	In-hospital mortality	in-hospital	retrospective cohort	55

Martínez-Sellés, 2014 [36]	Spain	Modified Duke criteria, non-specific IE	yes	In-hospital mortality	in-hospital	prospective cohort	1000
Mirabel, 2014 [29]	France	Modified Duke criteria, non-specific IE	yes, subgroups	Post-discharge mortality	≥ 5 years	prospective cohort	198
Wang, 2014 [77]	New Zealand	Modified Duke criteria, non-specific IE	no	In-hospital and post-discharge mortality	3 - 5 years	retrospective cohort	35
Agca, 2015 [78]	Turkey	Modified Duke criteria, definite IE	no	In-hospital mortality	in-hospital	retrospective cohort	85
Arshad, 2015 [79]	Pakistan	Modified Duke criteria, non-specific IE	no	In-hospital mortality	in-hospital	retrospective cohort	84
Chirouze, 2015 [23]	international	Modified Duke criteria, non-specific IE	yes, subgroups	In-hospital and post-discharge mortality	1 - 3 years	prospective registry	167
Chu, 2015 [80]	international	Modified Duke criteria, non-specific IE	no	In-hospital and post-discharge mortality	1 - 3 years	prospective cohort	1296
Samol, 2015 [81]	Germany	Modified Duke criteria, definite IE	no	In-hospital and post-discharge mortality	≥ 5 years	retrospective cohort	216

Shetty, 2015 [31]	London	Defined with non-specified criteria, non-specific IE	yes, subgroups	Post-discharge mortality	1 - 3 years	retrospective cohort	38
Kang, 2016 [5]	Korea	Duke criteria, definite IE	yes, subgroups	In-hospital and post-discharge mortality	≥ 5 years	Randomized clinical trial	76
Park, Cohort X, 2016 – ICE-PCS [82]	USA	Modified Duke criteria, definite IE	no	In-hospital and post-discharge mortality	< 1 year	prospective cohort	4049
Park, Cohort Y, 2016 – ICE-PLUS[82]	USA	Modified Duke criteria, definite IE	no	In-hospital and post-discharge mortality	< 1 year	prospective cohort	1197
Pilmis, 2016 [83]	Paris	Modified Duke criteria, non-specific IE	no	In-hospital mortality	in-hospital	retrospective cohort	121
van den Brink, 2016 [84]	Netherlands	Defined with non-specified criteria, definite or possible IE	no	Post-discharge mortality	1 - 3 years	retrospective cohort	216
Murai, 2017 [12]	Japan	Modified Duke criteria, definite or possible IE	yes, subgroups	In-hospital mortality	1 - 3 years	retrospective cohort	170

Oliver, 2017[14]	France	Duke criteria, non-specific IE	yes, subgroups	Post-discharge mortality	1 - 3 years	prospective cohort	454

Abbreviations: **IE:** Infective Endocarditis; **ICE-PCS:** International Collaboration on Endocarditis–Prospective Cohort Study; **ICE-PLUS:** International Collaboration on Endocarditis - PLUS; **N:** Number; **UK:** United Kingdom; **USA**: United States of America

Table 2 - In-hospital death results and characteristics from 6 articles with medical *versus* surgical main aim.

Author, Year	Region	Total (n)	Surgery Group (n)	Medical Group (n)	Central measure Age (S / M)	Male Gender (n)	Most prevalent microorganism	In-Hospital Death		Measure of Association (95% CI)	Most prevalent affected valve
								Surgery Group	Medical Group		
Yoshida, 1991	Japan	142	116	26	-	-	-	6 (5%)	7 (27%)		Mitral
Verheul, 1993	Amsterdam	141	43	98	45	104	*Streptococcus*	11 (26%)	26 (27%)		Aortic
Olaison, 1996	Sweden	126	26	100	60	63	*Staphylococcus*	2 (8%)	12 (12%)		Aortic
Bishara, 2001	Israel	252	44	208	64	136	*Streptococcus*	5 (11%)	37 (18%)		Aortic
Aksoy, 2007	Durham	333	78	255	57	186	*Staphylococcus*	9 (12%)	46 (18%)		Mitral
Martínez-Sellés, 2014	Spain	1000	437	563	61 / 66	301	*Staphylococcus*	106 (24%)	173 (31%)		Mitral

Abbreviations: **CI:** Confidence Interval; **IE:** Infective Endocarditis; **N:** Number; **S:** Surgery; **M:** Medical;

Table 3 - In-hospital death results and characteristics from 19 articles with medical *versus* surgical treatment in specific subgroups

Author, Year	Region	Subgroup	Total (n)	Surgery Group (n)	Medical Group (n)	Central measure Age (S / M)	Male Gender (n)	Most prevalent microorganism	In-Hospital Death		Measure of Association (95% CI)	Most prevalent affected valve
									Surgery Group	Medical Group		
Yu, 1994	USA	PVE	74	22	52	63	-	*Staphylococcus*	3 (14%)	20 (38%)		Mitral
Truninger, 1999	Switzerland	PVE	49	39	10	50/ 59	41	*Staphylococcus*	(15%)	(0%)		Mitral
Gordon, 2000	USA	PVE	77	54	23	65	56	*Staphylococcus*	4 (7%)	8 (35%)	RR surgery: 0.21 (0.07-0.64)	Mitral
Akowuah, 2003	UK	PVE	66	38	21	51 / 64	42	*Staphylococcus*	9 (24%)	6 (29%)		Aortic

Alonso-Valle, 2009	Spain	PVE	133	107	26	59	87	*Staphylococcus*	28 (26%)	11 (42%)		Aortic
Rekik, 2009	Tunisia	PVE	48	20	28	38	31	*Staphylococcus*	7 (35%)	4 (14%)		Aortic
Sohail, 2006	USA	PVE&*S.aureus*	55	32	23	64	33	NA	9 (28%)	11 (48%)		Aortic & Mitral
Chirouze, 2015	international	PVE&*S.aureus*	167	74	93	59.2 /64	98	NA	18 (24%)	45 (48%)		Aortic
Rivoisy, 2017	France&Spain	PVE&*Candida*	46	19	27	66	36	NA	4 (21%)	10 (37%)		Aortic
Rasmussen, 2011	Denmark	NVE	323	193	127	59 / DCT= 66 & ICT= 65	228	*Staphylococcus*	21 (11%)	27 (21%)	HR surgery: 0.40 (0.22–0.73)	Aortic
Funakoshi, 2011	Japan	NVE left sided	212	73	139	55/53	129	*Streptococcus*	1 (1%)	10 (7%)		Aortic

Kim, 2010	Korea	NVE left + veg	132	64	68	46 /51	39/47	*Staphylococcus*	2 (3%)	2 (3%)	Aortic
Desch, 2014	Germany	NVE left + veg	71	59	12	66	45	*Staphylococcus*	25 (42%)	1 (8%)	Mitral
Kang, 2016	Korea	NVE left + veg	76	37	39	47	51	*Streptococcus*	1 (3%)	1 (3%)	Mitral
Hricak, 1999	Slovak Republic	NVE&*S.aureus*	53	11	42	-	-	NA	1 (9%)	22 (52%)	Aortic
Remadi, 2007	France	*S.aureus*	116	55	61	54 / 58	76	*Staphylococcus*	9 (16%)	21 (34%)	Aortic & Mitral
Kiefer, 2011	international	IE & HF	1359	839	514	59	914	*Staphylococcus*	321 (38%)	463 (90%)	Mitral
Gálvez-Acebal, 2014	Spain	left-sided IE	316	158	158	61	220	*Staphylococcus*	42 (27%)	66 (42%)	Aortic
Murai, 2017	Japan	cerebral comp.	170	76	94	60	93	*Streptococcus*	6 (8%)	32 (34%)	Aortic

Abbreviations: CI: Confidence Interval; **Comp.:** Complications; **DCT:** Deliberate conservative treatment; **ICT:** Imposed conservative treatment ;**IE**: Infective Endocarditis; **HR**: Hazard Ratio; **HF**: Heart Failure; **M:** Medical ; **N:** Number; **NVE:** Native Valve Endocarditis; **PVE:** Prosthetic Valve Endocarditis; **RR**: Risk Ratio; **S**: Surgery; ***S.aureus***: *Staphylococcus aureus;* **UK:** United Kingdom*;* **USA:** United States of America*;* **Veg:** vegetations;

Table 4 – Post-discharge results and characteristics from 9 articles with medical *versus* surgical treatment

Author, Year	Region	Total (n)	Surgery Group (n)	Medical Group (n)	Central measure Age	Male Gender (n)	Most prevalent microorganism	Post-discharge mortality / survival		Follow-up (years)	Measure of Association (95% CI)	Most prevalent affected valve
								Surgery Group	**Medical Group**			
Yoshida, 1991	Japan	142	116	26	-	-	-	7 (6%)	6 (23%)	≥ 5		Mitral
Verheul, 1993	Amsterdam	141	43	98	45	104	*Streptococcus*	- / 77%	- / 53%	≥ 5		Aortic
Olaison, 1996	Sweden	126	26	100	60	63	*Staphylococcus*	-	-	≥ 5	RR medical: 3.45(0.72-16.66)	Aortic
Bishara, 2001	Israel	252	44	208	64	136	*Streptococcus*	-	-	≥ 5		Aortic

Netzer, 2002	Switzerland	212	81	131	53	160	*Staphylococcus*	36 (44%)	83 (63%)	≥ 5	OR medical: 1.86 (1.25-2.75)	Aortic
Krcmery, 2003	Slovak Republic	339	144	195	-	245	*Staphylococcus*	9 (6%)	51 (26%)	≥ 5		Aortic
Tran CT, 2006	Denmark	132	70	66	54	80	*Streptococcus*	25 (36%) ; (48%)	33 (50%) ; (30%)	≥ 5	HR surgery: 0.76 (p=0.319)	Aortic
Aksoy, 2007	Durham	333	78	255	57	186	*Staphylococcus*	-	-	≥ 5	HR surgery: 0.27 (0.13-0.55)	Mitral
Bannay, 2011	France	449	240	209	61	334	*Streptococcus*	61 (25%)	99 (47%)	≥ 5	HR surgery: 0.55 (0.35-0.87)	Aortic

Abbreviations: CI: Confidence Interval; **HR**: Hazard Ratio; **IE**: Infective Endocarditis; **M:** Medical ; **N:** Number; **OR:** Odds Ratio; **RR**: Risk Ratio; **S:** Surgery;

Table 5 – Post-discharge results and characteristics from 21 articles with medical *versus* surgical treatment according to specific subgroups

Author, Year	Region	Subgroup	Total (n)	Surgery Group (n)	Medical Group (n)	Central measure Age (S / M)	Male Gender (n)	Most prevalent microorganism	Post-discharge mortality / survival		Follow-up (years)	Measure of Association (95% CI)	Most prevalent affected valve
									Surgery Group	Medical Group			
Yu, 1994	USA	PVE	74	22	52	63 years		*Staphylococcus*	5 (23%)	29 (56%)	< 1	OR medical: 1.4 (1.1-1.7)	Mitral
Truninger, 1999	Switzerland	PVE	49	39	10	-	41	*Staphylococcus*	(18%)	(14%)	1 – 3		Mitral
Gordon, 2000	USA	PVE	77	54	23	65		*Staphylococcus*	- / 74%	- / 40%	1 – 3	RR surgery: 0.44 (0.25-0.78)	Mitral

Akowuah, 2003	UK	PVE	66	38	28	51 / 64	42	*Staphylococcus*	- / 58%	- / 28%	1 – 3		Aortic
Alonso-Valle, 2009	Spain	PVE	133	107	26	59	87	*Staphylococcus*	- / 71%	- / 42%	1 – 3	RR surgery: 0.43 (0.24-0.75)	Aortic
Rekik, 2009	Tunisia	PVE	48	20	28	38	31	*Staphylococcus*	1 (5%)	0	1 – 3		Aortic
Rasmussen, 2011	Denmark	NVE	323	193	127	59 / DCT= 66 & ICT= 65	228	*Staphylococcus*	-	-	1 – 3	HR surgery: 0.41 (0.25-0.68)	Aortic
Kim, 2010	Korea	NVE left + veg	132	64	68	46 / 51		*Staphylococcus*	1 (2%)	2 (3%)	1 – 3		Aortic
Desch, 2014	Germany	NVE left + veg	71	59	12	66	45	*Staphylococcus*	35 (59%)	2 (17%)	≥ 5	HR surgery: 3.9 (0.9-16.6)	Mitral
Kang, 2016	Korea	NVE left + veg	76	37	39	47	51	*Streptococcus*	3 (8%)	4 (10%)	≥ 5	HR surgery:	Mitral

												1.04 (0.21-5.15)	
Funakoshi, 2011	Japan	NVE left side	212	73	139	55/ 53	129	*Streptococcus*	-	-	≥ 5	HR surgery: 0.40 (0.18-0.91)	Aortic
Mirabel, 2014	France	ICU, left sided	198	103	95		138	*Staphylococcus*	57 (55%)	80 (84%)	≥ 5		Mitral
Remadi, 2007	France	*S.aureus*	116	55	61	54 / 58	76	*NA*	- / 74%	- / 43%	1 – 3		Aortic & Mitral
John, 1998	USA	*S.aureus* PVE	33	14	19	-	20	NA	2 (14%)	12 (63%)	1 – 3	RR surgery: 0.18 (0.04-0.89)	Aortic
Chirouze, 2015	international	*S.aureus* PVE	167	74	93	59.2 /64	98	NA	25 (34%)	55 (59%)	1 – 3	RR surgery: 0.53 (0.30–.97)	Aortic
Gálvez-Acebal, 2014	Spain	left-sided ie	316	158	158	61	220	*Staphylococcus*	47 (30%)	73 (46%)	1 – 3		Aortic

Heiro M, 2000	Finland	Neurol. Complicat.	218	53	165	54	141	*Staphylococcus*	5 (9%)	25 (15%)	< 1	Aortic
Vikram, 2003	USA	Complic. NVE left	513	230	283	53 /57	331	*Streptococcus*	37 (16%)	94 (33%)	< 1	Mitral
Kiefer, 2011	international	IE complicated by HF	1359	839	514	59	914	*Staphylococcus*	244 (29%)	300 (58%)	1 – 3	Mitral
Shetty, 2015	London	TV IVDU	38	7	31	35	17	*Staphylococcus*	3 (43%)	8 (26%)	1 – 3	Tricuspid
Oliver, 2017	France	octogenarian	454	259	195	-	331	*Enterococcus*	25 (10%)	58 (30%)	1 – 3	Aortic

Abbreviations: CI: Confidence Interval**; Complicat.:** Complicated; **DCT:** Deliberate Conservative Treatment; **HF:** Heart Failure; **HR:** Hazard Ratio; **ICT:** Imposed Conservative Treatment ;**ICU:** Intensive Care Unit; **IE**: Infective Endocarditis; **IVDU**: Intravenous Drug Users; **M:** Medical; **NVE:** Native Valve Endocarditis;

9. APPENDIX

Search query “((((((((((((((((((((((mortality [Subheading]) OR Mortality [Mesh]) OR Mortality, Premature [Mesh]) OR Hospital Mortality [Mesh]) OR Survival [Mesh]) OR Disease-Free Survival [Mesh]) OR Survival Analysis [Mesh]) OR Survival Rate [Mesh]) OR Death [Mesh]) OR Recurrence [Mesh]) OR Reoperation [Mesh]) OR Recidive) OR Reintervention) OR Reoperation) OR Recurrence) OR Mortality) OR All-causes mortality) OR Survival) OR Freedom of death) OR Recurring) OR Recurrence)) AND ((((((((Pharmaceutical Preparations[MeSH Terms]) OR Therapeutics[MeSH Terms]) OR drug therapy [Subheading]) OR Anti-Bacterial Agents[Mesh]) OR Conservative Treatment[Mesh]) OR ((medical (therapy OR management OR treatment)))) OR ((conventional (therapy OR management OR treatment)))) OR ((conservative (therapy OR management OR treatment))))) AND ((((((Cardiac Surgical Procedures[MeSH Terms]) OR Thoracic Surgery) OR Cardiac surgery) OR Valv* surgery) OR Surgical debridement) OR Surgical management)) AND (((((endocarditis) OR endocarditis[MeSH Terms]) OR infective endocarditis) OR Endocarditis, Subacute Bacterial[MeSH Terms]) OR Endocarditis, Bacterial[MeSH Terms])”.

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Aos meus irmãos, como exemplos académicos que sempre tive presente.

ANEXO

Normas de Publicação da Revista Portuguesa de Cardiologia

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- O manuscrito deve seguir sempre a mesma ordem: a) resumo estruturado em português e palavras-chave; b) resumo estruturado em inglês e palavras-chave; c) quadro de abreviaturas em português e em inglês; d) texto; e) bibliografia; f) legendas das figuras; g) tabelas (opcional) e h) figuras (opcional)-

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Texto

Deverá conter as seguintes partes devidamente assinaladas: *a)* Introdução; *b)* Métodos; *c)* Resultados; *d)* Discussão e *e)* Conclusões. Poderá utilizar subdivisões adequadamente para organizar cada uma das secções.

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Capítulo em livro: Autores, título do capítulo, editores, título do livro, cidade, editora e páginas. Exemplo:

23. Nabel EG, Nabel GJ. Gene therapy for cardiovascular disease. En: Haber E, editor. Molecular cardiovascular medicine. New York: Scientific American 1995. P79-96.

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30. Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Mansel Dekker; 1993. P. 33.

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Cada tabela será escrita a espaço duplo numa folha aparte.

- Incluem um título na parte superior e na parte inferior são referidas as abreviaturas por ordem alfabética.
- O seu conteúdo é auto-explicativo e os dados que incluem não figuram no texto nem nas figuras.

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Nº máximo de palavras do Resumo - 250

Nº máximo de Figuras - 10

Nº máximo de quadros - 10

Nº máximo de ref. bibliográficas - 100

3. Cartas ao Editor

Devem ser enviadas sob esta rubrica e referem-se a artigos publicados na Revista. Serão somente consideradas as cartas recebidas no prazo de oito semanas após a publicação do artigo em questão.

- Com espaço duplo, com margens de 2,5 cm.
- O título (em português e em inglês), os autores (máximo quatro), proveniência, endereço e figuras devem ser especificados de acordo com as normas anteriormente referidas para os artigos originais.
- Não podem exceder as 800 palavras.
- Podem incluir um número máximo de duas figuras. As tabelas estão excluídas.

4. Casos Clínicos

Devem ser enviados sob esta rubrica.

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder 10 palavras

Os autores (máximo oito) proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.

O texto explicativo não pode exceder 3.000 palavras e contem informação de maior relevância. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.

Contêm um número máximo de 4 figuras e pode ser enviado material suplementar, como por exemplo vídeoclips.

5. Imagens em Cardiologia

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder oito palavras
- Os autores (máximo seis), proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.
- O texto explicativo não pode exceder as 250 palavras e contem informação de maior relevância, sem referências bibliográficas. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.
- Contêm um número máximo de quatro figuras.

6. Material adicional na WEB

A Revista Portuguesa de Cardiologia aceita o envio de material electrónico adicional para apoiar e melhorar a apresentação da sua investigação científica. Contudo, unicamente se considerará para publicação o material electrónico adicional directamente relacionado com o conteúdo do artigo e a sua aceitação final dependerá do critério do Editor. O material adicional aceite não será traduzido e publicar-se-á electronicamente no formato da sua recepção.

Para assegurar que o material tenha o formato apropriado recomendamos o seguinte:

	Formato	Extensão	Detalhes
Texto	Word	.doc ou docx	Tamanho máximo 300 Kb
Imagem	TIFF	.tif	Tamanho máximo 10MB
Audio	MP3	.mp3	Tamanho máximo 10MB
Vídeo	WMV	.wmv	Tamanho máximo 30MB

Os autores deverão submeter o material no formato electrónico através do EES como arquivo multimédia juntamente com o artigo e conceber um título conciso e descritivo para cada arquivo.

Do mesmo modo, este tipo de material deverá cumprir também todos os requisitos e responsabilidades éticas gerais descritas nessas normas.

O Corpo Redactorial reserva-se o direito de recusar o material electrónico que não julgue apropriado.

ANEXO I

DECLARAÇÃO

Declaro que autorizo a publicação do manuscrito:

Ref.ª ....

Título ....

....

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do qual sou autor ou c/autor.

Declaro ainda que presente manuscrito é original, não foi objecto de qualquer outro tipo de publicação e cedo a inteira propriedade à Revista Portuguesa de Cardiologia, ficando a sua reprodução, no todo ou em parte, dependente de prévia autorização dos editores.

Nome dos autores:

....

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Assinaturas:

ANEXO II

Símbolos, abreviaturas de medidas ou estatística

Designação	Português	Inglês
Ampere	A	A
Ano	ano	yr
Centímetro quadrado	cm_2	cm_2
Contagens por minuto	cpm	cpm
Contagens por segundo	cps	cps
Curie	Ci	Ci
Electrocardiograma	ECG	ECG
Equivalente	Eq	Eq
Grau Celsius	°C	°C
Grama	g	g
Hemoglobina	Hb	Hb
Hertz	Hz	Hz
Hora	h	h
Joule	J	J
Litro	L ou L	l ou L
Metro	m	m
Minuto	min	min
Molar	M	M
Mole	mol	mol
Normal (concentração)	N	N
Ohm	Ω	Ω
Osmol	osmol	osmol
Peso	peso	WT
Pressão parcial de CO_2	pCO_2	pCO_2
Pressão parcial de O_2	pO_2	pO_2
Quilograma	kg	kg
Segundo	s	sec
Semana	Sem	Wk
Sistema nervoso central	SNC	CNS
Unidade Internacional	UI	IU
Volt	V	V
Milivolt	mV	mV
Volume	Vol	Vol
Watts	W	W

Estatística:

Designação	Português	Inglês
Coeficiente de correlação	r	r
Desvio padrão (standard)	DP	SD
Erro padrão (standard) da média	EPM	SEM
Graus de liberdade	gl	df
Média	χ	χ
Não significativa	NS	NS
Número de observações	n	n
Probabilidade	p	p
Teste «t» de Student	teste t	t test