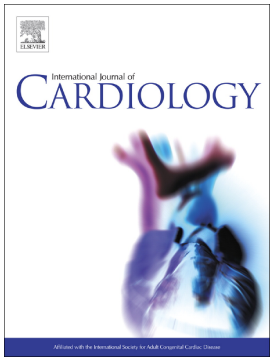

Long-term follow-up of patients with infective endocarditis in a tertiary referral center

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Long-term follow-up of patients with infective endocarditis in a tertiary referral center

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Key words: infective endocarditis, predictors, long-term outcome, reinfection, mortality

Abstract

Background: Infective endocarditis (IE) remains a severe disease with high mortality. Most studies report on short-term outcome while real world long-term outcome data are scarce. This study reports reinfection rates and mortality data during long-term follow-up.

Methods: A total of 270 patients meeting the modified Duke criteria for definite IE admitted to a tertiary care center between July 2000 and June 2007 were analyzed retrospectively. Early reinfection was defined as a new IE episode within 6 months; late reinfection as a new IE episode beyond 6 months follow-up.

Results: Median follow-up was 8.5 years. Early reinfection occurred in 10 patients (3.7%), late reinfection in 18 patients (6.7%). *Staphylococci* (39.7%) were the most frequent causative microorganisms, followed by *Streptococci* (30.0%) and *Enterococci* (17.8%). Independent predictors of any reinfection were heart failure (HR 3.02, 95% CI 1.42-6.41), peripheral embolization (HR 4.00, 95% CI 1.58-10.17) and implanted pacemakers (HR 3.43, 95% CI 1.25-9.36).

Survival rates were 71.1%, 55.2% and 43.3% at respectively 1-, 5- and 10-years follow-up. Independent predictors for mortality were age (HR 1.03, 95% CI 1.01-1.04), diabetes mellitus (HR 2.24, 95% CI 1.46-3.45), hemodialysis (HR 2.70, 95% CI 1.37-5.29), heart failure (HR 1.64, 95% CI 1.19-2.26), stroke (HR 1.73, 95% CI 1.18-2.52), antimicrobial treatment despite surgical indication (HR 5.53, 95% CI 3.59-8.49) and non-*Streptococci* causative microorganisms (HR 1.84, 95% CI 1.28-2.64).

Conclusions: Contemporary mortality rates of infective endocarditis remain high, irrespective of reinfection. Heart failure, peripheral embolization and presence of a pacemaker were predictors of reinfection.

1. Introduction

Infective endocarditis (IE) remains a severe disease in the current era with high mortality rates up to 30-40% due to complicated IE treatment and heart failure despite progress in diagnostic and therapeutic accuracy[1]. Previous studies mainly focused on short-term outcomes[2-4]. There is limited long-term data in the general IE without focusing on a subgroup of patients[5-8]. Most data originated from the 1980's and 1990's with up to 6.7% of patients lost to follow-up[5-7]. In the largest studies, respectively 303 and 392 patients were included over a long period of 24 and 16 years[5, 6]. These studies were therefore prone to temporal effects due to the evolution of diagnostics, treatment, and surgical techniques. More recent data were published by Fernández-Hidalgo with an inclusion period of 11 years, however the median follow-up was only 3.2 years for the survivors[8]. Our study provides a contemporary cohort with a comparable number of patients included over a 7-year period and with long-term follow-up. The aim of this study was to acquire a better understanding of the subsequent clinical trajectory and to identify the patients in which ongoing follow-up or treatment can be improved.

2. Methods

2.1 Study population

All patients with an episode of IE (the index episode) between 1 June 2000 and 30 June 2007 at the University Hospitals Leuven were included in a registry with last follow-up on June 30th, 2017. Consecutive patients 18 years of age or older meeting the modified Duke criteria for definite IE were eligible for inclusion[9]. For every patient in our hospital with suspicion of IE, the diagnostic work-up and the confirmation of the diagnosis of IE were made by a multidisciplinary endocarditis team including a cardiologist, an infectious disease specialist and a cardiac surgeon. As this multidisciplinary approach is widely implemented in the hospital, including the Geriatric Support Team and imaging departments, no case would have been missed. Patients with device related infections were only included if lead endocarditis was confirmed. All patients with non-infective endocarditis and intravenous drug-related right-sided IE were excluded. During follow-up 9 patients

were excluded, 3 because of missing data and 6 patients were lost to follow-up. The study complies with the Declaration of Helsinki and was approved by the ethical committee of the University Hospitals of Leuven. Regarding the design of the study the need for informed consents was waived.

2.2 Data collection and follow-up

All data were collected retrospectively in a registry following a predefined protocol designed jointly by a cardiologist, a specialist in infectious diseases and a cardiac surgeon. Data collection was based on a systematic review of the electronic medical records including all patient charts, echocardiography, and laboratory results. Every patient record is directly connected with the national death registry, therefore no out of hospital deaths could have been missed. Every patient record was opened at the ended follow-up period to ensure no information was lost. If further information about the medical condition of the patient was not available in our system, the referral hospital and/or the general practitioner was contacted. As tertiary center our hospital acts as a large regional center as well as important referral center. Microbiological investigations included blood cultures with antibiotic resistance and antimicrobial susceptibility testing, serology, valve or tissue cultures, polymerase chain reaction and microscopic examination. Before blood culture negative endocarditis (BCNE) was concluded, specific analyses including additional sets of blood cultures on enriched media and serological tests for *C. burnetii, Brucella spp., Mycoplasma pneumoniae, Chlamydia spp., Aspergillus spp., and Bartonella spp* were performed[4]. All patients were treated according to the American Heart Association and European Society of Cardiology guidelines[1, 10, 11] and predefined indications for surgical intervention[12]. At 1 and 2 months after completing the antibiotic therapy, 2 sets of surveillance blood cultures were systematically collected. Six months after the initial diagnosis, every patient underwent a transesophageal echocardiographic examination (TEE). Afterwards, routine follow-up consultations were provided at least yearly, often accompanied by transthoracic ultrasound examination. If a patient did more than one reinfection, only the first episode was included in the statistical analysis.

2.3 Definitions

IE was defined based on the modified Duke criteria[9]. Early reinfection was defined as a new episode of IE within 6 months after the index episode caused by the same species (equals relapse) or another microorganism (reinfection). Late reinfection was defined as a new episode of IE 6 months or more after diagnosis of the index episode caused by the same species or another microorganism. Heart failure was defined as a presentation with at least 2 out of 3 of the following: NYHA class III-IV, acute decompensation on chest X-ray or echocardiogram, new peripheral edema. Stroke as both clinical or radiographical abnormalities consistent with acute stroke and included both the clinical presentation, during treatment and surgery-related stroke. Peripheral embolization as clinical and nuclear/radiographical imaging abnormalities consistent with embolization excluding stroke (including skin, eye fundus…). Time to late reinfection was counted from the moment of diagnosis of the index episode. Treatment strategies were divided into 3 groups: deliberate medical therapy (antimicrobial therapy in patients without an indication to surgery), perforce medical therapy (antimicrobial therapy despite an indication for surgery) and combined medical-surgical therapy. The primary endpoint was all-cause mortality, the secondary endpoint was any early or late reinfection. The timing of all endpoints was collected relative to the index episode.

2.4 Statistical analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. As all parameters showed a non normal distribution, data are presented as median with the 25th and 75th percentile. Categorical variables are presented as number and percentages. Continuous variables were compared using non-parametric Mann-Whitney-U and Kruskal-Wallis testing when appropriate. Categorical variables were compared using the Chi² test. Kaplan–Meier analysis with log-rank testing was used to compare endpoint rates. Cox proportional-hazards regression modeling was performed for the respective endpoints presenting Hazard ratios with the 95% confidence intervals. First, univariate analysis was performed for all variables. Subsequently, stepwise forward multivariate modelling was performed based on variables with a univariate p-value <0.100. A *p*-value <0.05 was

considered significant. In case of missing data the respective patients were not excluded from analysis. All statistical analyses were performed using SPSS (IBM statistics, version 25).

3. Results

3.1 Baseline characteristics

Overall, 270 patients were included in the analysis. The median follow-up time was 8.5 years (range of 2 days to 16 years and 11 months). For patients surviving beyond 6 months, the median time of follow-up was 11.0 years (range of 7 months to 16 years and 11 months). A detailed overview of the baseline characteristics at index episode is shown in table 1.1. The male to female ratio was 1.5:1. The median age was 63 years (range 18 years to 92 years). By far, most patients experienced a left-sided IE (n=254, 94.1%). In addition, 2 patients with pulmonary valve IE, 8 patients with isolated pacemaker lead endocarditis (PLE), 3 patients with isolated tricuspid valve IE and 3 patients with both, were included. In 86 patients (31.5%) there was prosthetic valve endocarditis (PVE). Within the group of prosthetic valves, 48 patients had mechanical valve prosthesis (55.8%), 31 patients bioprosthetic valve (36.0%), 3 patients a mitral annuloplasty ring (3.5%), 2 patients a homograft (2.3%) and 1 patient an autograft (1.2%). *Streptococci* were identified as the causative microorganism in 30% of the cases, *Staphylococcus aureus* was responsible for 27.1% of the cases, *Enterococci* for 17.8% and *CoNS* for 12.6%. Only 34 patients (12.6%) received perforce medically treatment at the index episode. A total of 29 patients (10.7%) had an implantable device at the index IE episode. Of these, the complete pacing hardware was removed in 14 patients (48.3%). In 5 patients with a pacemaker and medical-surgical treatment the pacing hardware was not removed at the index episode. A residual vegetation on control transesophageal echocardiography 6 months after diagnosis persisted in 8 patients (3.0%). The mean length of residual vegetation was 7.6 mm. During follow-up 28 patients (10.4%) had at least 1 reinfection, 10 (3.7%) early reinfections and 18 (6.7%) late reinfections were noted.

3.2 Reinfections

3.2.1 Early reinfections

The incidence of early reinfection was 3.7% (n=10), baseline characteristics and comorbidities are described in table 1.1. Significantly more patients with PVE at index did early reinfection compared to the patients with native valve endocarditis (NVE) at index (p=0.025). Of all the early reinfection episodes, 8 concerned PVE compared to 2 NVE (p<0.001) (table 1.2). One patient with *Streptococcus mutans* IE of the native aortic valve, did early reinfection with native tricuspid valve endocarditis, another patient with isolated prosthetic mitral valve endocarditis and a pacemaker did reinfection with PLE and native tricuspid valve endocarditis. Treatment strategy at the moment of early reinfection differed significantly from those at index or late reinfection (table 1.2, p=0.023). In all the patients who did early reinfection and were treated by surgery at index, the pre-operative blood cultures were already negated at the time of surgery.

An overview of all causative microorganisms in early reinfection episodes is presented in Supplement 1. Of the 10 patients with early reinfection, 5 patients (50.0%) had a relapse (1 with *Methicillin-sensitive Staphylococcus aureus* (*MSSA*), 3 with *CoNS* and 1 with *Enterococcus faecalis*). All the relapses were non-*streptococci* infections. There was no difference in baseline characteristics or comorbidities between relapse and non relapse IE episodes. In 4 of the patients with relapse the index episode involved PVE, at the relapse episode all cases were PVE. *In 3 cases the index episode was treated with medical-surgical therapy, 1 with deliberate medical and 1 with perforce medical therapy. At relapse, 2 were treated medical-surgical and 3 perforce medical.*

3.2.2 Late reinfections

The incidence of late reinfection was 6.7% (18/270) in the total cohort, 9.1% (18/197) in the subgroup of patients who were still alive 6 months after the diagnosis of the index episode. The median time to late reinfection was 4 years and 5 months (range 1 year-12 years and 7 months). The baseline characteristics and comorbidities are described in table 1.1. None of the patients with a residual vegetation on control transesophageal echocardiography 6 months after the index episode, presented with a late reinfection. In the late reinfection cases, PVE was significantly more present (p<0.001) (table 1.2) as only 1 patient presented with a native valve reinfection. This patient had a

permanent pacemaker over 20 years and the last battery change dated from 3 years before the reinfection occurred.

An overview of all causative microorganisms in late reinfection episodes is presented in Supplement 1. There was no significant relation between the causative microorganisms at index and risk for late reinfection. *S. aureus* and *Enterococci faecalis* were responsible for halve of all late reinfections. Reinfection with a similar microorganism, relative to the index episode, was found in 4 cases: 3 cases with *MSSA* IE and 1 case with *Enterococci faecalis*.

Of 17 patients with late reinfection treated with a medical-surgical strategy at the index episode, 16 had already negative pre-operative blood cultures (94.1%). For all patients with late reinfections the control transesophageal echocardiographic examinations 6 months after the index IE was within the normal range.

A total of 6 patients had multiple reinfections: 2 patients had a late reinfection after an early reinfection, 1 patient had an early reinfection after a late reinfection, 2 patients had 2 late reinfections and 1 patient had 3 late reinfections. A detailed overview of these cases is presented in Supplement 2.

3.2.3 Prediction of reinfections

Uni- and multivariate Cox regression analysis for any reinfection, both early and late reinfection combined, is presented in Table 2.1. Heart failure at index episode, peripheral embolization and the presence of a pacemaker at the index episode were independent predictors of any reinfection. Separate Cox regression models for early and late reinfection are available as Supplement 3. Independent predictors of early reinfection were peripheral embolization at the index episode (HR 4.01, 95% CI 1.04-15.53) and PVE at index episode (HR 5.42, 95% CI 1.40-20.96). For late reinfections, heart failure at the index episode was the only univariate predictor (HR 6.49, 95% CI 2.43-17.35).

3.3 Predictors of mortality

3.3.1 6-months mortality

The overall 6-months mortality was 27.0% (73/270 patients) with an in-hospital mortality of 22.2% (60/270 patients). The 6-months mortality rates after early (30.0% or 3/10 patients) and late reinfection (22.2% or 4/18 patients) were comparable. All patients who died within 6 months of diagnosis of the early or late reinfection were non-*streptococci* IE and all were treated perforce medically.

3.3.2 Long-term outcome

The survival rates and Kaplan-Meier survival graphs are presented in Table 3 and Figure 1, respectively. Overall survival was 71.1%, 55.2% and 43.3% at 1, 5- and 10-years follow-up, respectively. At the end of follow-up there was no significant difference in survival between patients with and without early or late reinfection (Figure 1.A, p=0.94).

Survival differed significantly when comparing treatment strategies with worst survival in perforce medically treated patients (p<0.001, Figure 1.B). When comparing deliberate medical treatment with medical – surgical treatment, the latter had a significantly better survival rate (p=0.010). A comparison of baseline characteristics at the index episode according to treatment strategy is presented in Supplement 4. Patients treated with a medical – surgical approach were the youngest (p=0.016), were taken less immunosuppressants (p=0.029) and had less frequent PVE (p=0.001), the opposite was true for patients receiving perforce medical treatment. In case of abscess formation (n=52 or 19,3%) either medical - surgical or perforce medical treatment was initiated.

Uni- and multivariate Cox regression analysis for all-cause mortality is presented in Table 2.2. Age, diabetes mellitus, hemodialysis, heart failure and stroke at index episode were identified as independent risk factors for mortality together with perforce medical treatment. Mortality was also significantly higher in non-*Streptococci* infections. Baseline characteristics comparing *Streptococci* and non-*Streptococci* IE are presented in Supplement 5. Patients with *Streptococci* infections were younger (p=0.023), had less frequent PVE (p=0.018) and less frequent a pacemaker implanted at the index episode (p=0.044).

4. Discussion

In this retrospective large cohort of patients with IE and a medium follow-up of 8.5 years, we observed an early reinfection rate of 3.7% and late reinfection rate of 6.7%. Clinical presentation with heart failure, peripheral embolization and the presence of a pacemaker at the index episode were independent predictors of any reinfection. All-cause mortality remains high with survival rates of 71.1%, 55.2% and 43.3% at 1-, 5- and 10-years follow-up, respectively. Independent predictors of mortality included age, diabetes mellitus, hemodialysis, heart failure, stroke, treatment strategy and non-*Streptococci* infections.

The incidence of early reinfection in this study was comparable with previous reports. Mansur *et al.* reported an incidence of 3.3%[6]. Thuny *et al.* reported an early reinfection rate and prosthetic valve dysfunction at 6 months of 7.6%[13], which is consistent with our observation of more frequent early reinfections in patients with PVE as index episode. In contrast, reinfection beyond 6-month follow-up was not related to the presence or absence of PVE at the time of first diagnosis and not related to the presence or absence of residual vegetation on control transesophageal echocardiographic examinations 6 months after diagnosis. Similar results were recently described by Østergaard *et al*., in a large Danish Endocarditis Registry including 305 patients with a median follow-op of 3.6 years[14]. Note that none of the patients with early reinfection in our study were deliberately treated medically because they all had an indication for surgical treatment. Finally, only 6 out of 10 patients underwent surgery, others were treated perforce medically.

The incidence of late reinfection in our cohort and the male predominance were similar to other reported series[6]. *Staphylococcus aureus* was after *Streptococci* the most frequent causative microorganisms at the index episodes and in the reinfections even the most common. This probably reflects the general trend of increasing incidence of *S. aureus* IE[2, 4, 15]. *S. aureus* is an aggressive pathogen with a high rate of complications and mortality[15, 16], in part attributable to the exclusive capacity of *S. aureus* to adhere to cardiac valves[17]. In contrast to the findings of Heiro *et al.,* in our cohort diabetes mellitus and hemodialysis were not significant risk factors for early or late

reinfection[5]. However, presentation with heart failure and the presence of a pacemaker were independent predictors, results comparable with a recent report by Thornhill *et al.*[18]. Within the subgroup of patients with early or late reinfection, there is a significantly greater contribution of PVE in comparison with NVE, again consistent with previous studies[6, 19]. PVE and PLE were significantly associated with non-*streptococci* IE. In contrast to early reinfection, late reinfection was more likely to occur in patients who had undergone cardiac surgery for the index IE episode. Half of the patients with late reinfection were treated with surgery, similar to rates reported by Baddour *et al.*[20]. The absence of late reinfection in the perforce medical subgroup can be explained by competing risk due to the high mortality rates in this subgroup.

In our cohort we report an in-hospital mortality of 22.2% and a 6-months mortality of 27.0%, comparable to mortality rates published by Castillo *et al.* (21.0%)[7]. Hill *et al.* investigated already the short term follow-up in a part of these patients and announced a six months mortality of 22%[4]. However, the 10-year survival rate in this study (43.3%) was lower when compared to those reported by Heiro *et al.* (49.0%)[5] and Netzer *et al.* (50.0%)[21]. It should be emphasized that our patients were approximately 10 years older and more often surgically treated. Earlier studies reported that surgery was performed in approximately 50.0% of cases[7, 22]. Also, the amount of PVE at index in this study was much higher in comparison with previous reports[5, 21, 23]. These differences could potentially be related to the complexity of the pathology in our tertiary referral center. We observed a trend towards higher overall mortality for PVE compared to NVE and for IE complicated with perivalvular abscess formation. In the presence of a perivalvular abscess and if the patient was considered operable**,** surgical treatment was preferred[24, 25].

Multivariate Cox regression analysis identified age, diabetes mellitus, hemodialysis, heart failure, stroke, non-*Streptococci* IE and perforce medical treatment as independent predisposing risk factors for long-term mortality. Age, causative microorganisms and treatment group were already identified by Hill *et al.* as independent risk factors of 6-months mortality[4]. Delahaye *et al.* and Netzer *et al.*

founded similar risk factors of fatal long-term outcome (age, renal insufficiency, not-*Streptococci* IE and absence of surgery). Heart failure and stroke were previously identified as independent predictors of mortality in IE[21, 26]. Site of infection was, similar to earlier trials, not associated with worse long-term outcomes[21, 27]. Remarkably, neither early nor late reinfection was associated with increased mortality when analyzed both separately and combined as any reinfection. This may be explained by the competing risk between mortality and reinfection, particularly since one third of the mortality occurred in-hospital. Hence, before a patient could have developed reinfection. Similar to patients without late reinfection, those with non-*streptococci* IE or those treated perforce medically appeared to have a poor prognosis.

5. Limitations

The main limitation of this study is its single-center retrospective design. A selection bias could be present as the study was conducted at a tertiary care referral center, resulting in more complex cases and lower survival. Further, the interpretation of our manuscript should reflect the era of the inclusion period. Second, all-cause mortality was reported without distinction between cardiac and non-cardiac mortality as the cause of death was unknown in 36.4% of the patients. Lastly, although the overall sample size was large and the follow-up was solid with minimal dropouts, the proportion of patients presenting with early or late reinfection was limited.

6. Conclusion

Contemporary mortality rates of IE remain high despite progress in diagnostic and therapeutic accuracy, independently of any reinfection. Age, causative microorganisms, diabetes mellitus, hemodialysis, heart failure, stroke and treatment strategies were consistent predictors of poor outcome. Future research should avoid retrospective analyses by starting multicenter collaborations with prospective registries, such as the European Infective Endocarditis registry by the EURO-ENDO investigators[15].

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Figure legends

Figure 1. Kaplan-Meier survival graphs

A. Survival by clinical evolution

B. Survival by treatment strategy at the index episode

C. Survival by causative microorganisms at the index episode

Table 1.1 Baseline characteristics at index episode.

	All patients	No reinfection	Early reinfection	Late reinfection	p-value
n	270 (100%)	242 (89.6%)	10 (3.7%)	18 (6.7%)	
Male	164 (60.7%)	147 (60.7%)	5 (50.0%)	12 (66.7%)	0.688
Age (y)	63 (53-71)	69 (57-75)	63 (57-68)	63 (48-71)	0.191
Diabetes mellitus	30 (11.1%)	27 (11.2%)	1 (10.0%)	2 (11.1%)	0.994
Immunosuppressants	25 (9.3%)	21 (8.7%)	2 (20.0%)	2 (11.1%)	0.462
Hemodialysis	11 (4.1%)	11 (4.5%)	0 (0.0%)	0 (0.0%)	0.515
Causative microorganism					
Streptococci	81 (30.0%)	73 (30.2%)	2 (20.0%)	6 (33.3%)	0.473
MSSA	55 (20.4%)	48 (19.8%)	3 (30.0%)	4 (22.2%)	
MRSA[a]	18 (6.7%)	18 (7.4%)	0 (0.0%)	0 (0.0%)	
Enterococci[b]	48 (17.8%)	42 (17.4%)	2 (20.0%)	4 (22.2%)	
BCNE	24 (8.9%)	20 (8.3%)	0 (0.0%)	4 (22.2%)	
CoNS	34 (12.6%)	31 (12.8%)	3 (30.0%)	0 (0.0%)	
Other[c]	7 (2.6%)	7 (2.9%)	0 (0.0%)	0 (0.0%)	
Candida-Aspergillus	3 (1.1%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	
Prosthetic valve endocarditis	85 (31.5%)	74 (31.6%)	7 (70.0%)	4 (22.2%)	0.025
Involved valves					
Mitral	122 (45.2%)	111 (45.9%)	5 (50.0%)	6 (33.3%)	0.886
Aortic	104 (38.5%)	93 (38.4%)	3 (30.0%)	8 (44.4%)	
Mitral and aortic	28 (10.4%)	22 (9.1%)	2 (20.0%)	4 (22.2%)	
Tricuspid	3 (1.1%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	
Pacemaker	8 (3.0%)	8 (3.3%)	0 (0.0%)	0 (0.0%)	
Tricuspid & pacemaker	3 (1.1%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	
Pulmonary	2 (0.7%)	2 (0.8%)	0 (0.0%)	0 (0.0%)	
Abscess	52 (19.3%)	51 (21.1%)	1 (10.0%)	0 (0.0%)	0.069
Pacemaker	29 (10.7%)	24 (9.9%)	3 (30.0%)	2 (11.1%)	0.132
Recent procedure[d]	7 (24.1%)	7 (29.2%)	0 (0.0%)	0 (0.0%)	0.382
Pacemaker removed	14 (48.3%)	14 (58.3%)	0 (0.0%)	0 (0.0%)	0.060
Heart failure	85 (31.5%)	71 (29.3%)	2 (20.0%)	12 (66.7%)	0.003
Stroke	54 (20.0%)	47 (19.4%)	3 (30.0%)	4 (22.2%)	0.694

Peripheral embolization	31 (11.5%)	25 (10.3%)	3 (30.0%)	3 (16.7%)	0.125
Treatment strategy					
Medical-surgical	182 (67.4%)	159 (65.7%)	6 (60.0%)	17 (94.4%)	0.131
Deliberate medical	54 (20.0%)	50 (20.7%)	3 (30.0%)	1 (5.6%)	
Perforce medical	34 (12.6%)	33 (13.6%)	1 (10.0%)	0 (0.0%)	
Follow-up (y)	8.5 (3.9-13.9)	6.6 (0.3-12.4)	6.7 (0.5-11.3)	10 (5.0-14.2)	0.078
Time to reinfection (y)	2.8 (0.3-5.1)		0.3 (0.1-0.3)	4.4 (2.9-7.1)	<0.001

[a] *2 patients with methicillin-resistant Staphylococcus lugdunensis are counted for MRSA*

[b] *44 patients with Enterococcus faecalis, 3 patients with Enterococcus faecium and 1 patient with Enterococcus durans IE*

[c] *1 patient with Pseudomonas Aeruginosa, 1 with E. coli, 1 with Cardiobacterium hominis, 1 with Corneybacteria, 1 with Actinobacillus actinomycetencomitans, 1 with Rothia dentocariosa and 1 with Erysipelothrix rhusiopathiae IE*

[d] *Implanted or battery changed 6 months or less before index episode*

Table 1.2 Comparison between index episodes, early and late reinfection.

	Index episode	Early reinfection	Late reinfection	p-value
n	270	10	18	
Causative microorganism				
Streptococci	81 (30.0%)	0 (0.0%)	3 (16.7%)	<0.001
MSSA	55 (20.4%)	1 (10.0%)	4 (22.2%)	
MRSA	18 (6.7%)	1 (10.0%)	2 (11.1%)	
Enterococci	48 (17.8%)	2 (20.0%)	3 (16.7%)	
BCNE	24 (8.9%)	2 (20.0%)	4 (22.2%)	
CoNS	34 (12.6%)	3 (30.0%)	0 (0.0%)	
Other[a]	7 (2.6%)	0 (0.0%)	2 (11.1%)	
Candida-Aspergillus	3 (1.1%)	1 (10.0%)	0 (0.0%)	
Prosthetic valve at index IE	85 (31.5%)	7 (70.0%)	4 (22.2%)	0.024
Prosthetic valve at reinfection IE	85 (31.5%)	8 (80.0%)	17 (94.4%)	<0.001
Involved valves				
Mitral	122 (45.2%)	6 (60.0%)	6 (33.3%)	0.119
Aortic	104 (38.5%)	2 (20.0%)	10 (55.5%)	
Mitral and aortic	28 (10.4%)	0 (0.0%)	1 (5.6%)	
Tricuspid	3 (1.1%)	1 (10.0%)	1 (5.6%)	
Pacemaker	8 (3.0%)	0 (0.0%)	0 (0.0%)	
Tricuspid & pacemaker	3 (1.1%)	1 (10.0%)	0 (0.0%)	
Pulmonary	2 (0.7%)	0 (0.0%)	0 (0.0%)	
Abscess[b]	52 (19.3%)	4 (40.0%)	5 (27.8%)	0.204
Treatment strategy[b]				
Medical-surgical	182 (67.4%)	6 (60.0%)	8 (44.4%)	0.023
Deliberate medical	54 (20.0%)	0 (0.0%)	5 (27.8%)	
Perforce medical	34 (12.6%)	4 (40.0%)	5 (27.8%)	

[a] *2 late reinfections with Lactococus gerviae and Acinetobacter*

[b] *Presentation / treatment strategy at the index or reinfection episodes respectively*

Table 2. Uni- and multivariate Cox regression analysis for endpoints.

2.1 First reinfection (early and late reinfections combined)

	Univariate		Multivariate	
	HR(95% CI)	**p-value**	**HR(95% CI)**	**p-value**
Age(/y)	1.00 (0.98-1.03)	0.971		
Male sex	0.87 (0.41-1.85)	0.708		
Diabetes mellitus	1.48 (0.44-4.95)	0.524		
Immunosuppressants	2.01 (0.70-5.84)	0.197		
Hemodialysis	0.05 (0.00-48225.38)	0.667		
Heart failure	2.84 (1.35-5.97)	0.006	3.02 (1.42-6.41)	0.004
Stroke	1.73 (0.73-4.06)	0.212		
Peripheral embolization	3.45 (1.39-8.53)	0.008	4.00 (1.58-10.17)	0.004
Non-*Streptococci*	1.47 (0.65-3.34)	0.358		
PVE at index episode	1.70 (0.79-3.63)	0.172		
Abscess at index episode	0.19 (0.03-1.39)	0.102		
Pacemaker present at index episode	2.51 (0.95-6.63)	0.063	3.43 (1.25-9.36)	0.016
Perforce medically treatment	1.22 (0.16-9.10)	0.848		

2.2 All-cause mortality.

	Univariate		Multivariate	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Age(/y)	1.04 (0.02-1.05)	<0.001	1.03 (1.01-1.04)	<0.001
Male sex	0.88 (0.65-1.20)	0.420		
Diabetes mellitus	2.16 (1.44-3.25)	<0.001	1.89 (1.22-2.93)	0.004
Immunosuppressants	1.54 (0.97-2.46)	0.070		
Hemodialysis	3.86 (2.06-7.21)	<0.001	2.70 (1.36-5.34)	0.005
Heart failure	1.68 (1.23-2.28)	0.001	1.64 (1.19-2.26)	0.002
Stroke	1.45 (1.02-2.06)	0.041	1.73 (1.18-2.52)	0.004
Peripheral embolization	1.76 (1.15-2.69)	0.009		
Non-*Streptococci*	1.85 (1.30-2.63)	0.001	1.78 (1.25-2.55)	0.002
PVE at index episode	1.36 (0.94-1.86)	0.055		
Abscess at index episode	1.40 (0.98-2.02)	0.068		
Pacemaker present at index episode	1.27 (0.80-2.03)	0.315		
Perforce medically treatment	6.18 (4.14-9.23)	<0.001	5.48 (3.52-8.53)	<0.001
Any reinfection	0.99 (0.63-1.56)	0.963		

Table 3. Survival rates according to clinical evolution and treatment strategy.

	1 year	3 years	5 years	10 years	15 years
Overall	71.1%	61.1%	55.2%	43.3%	33.1%
By clinical evolution					
None	67.4%	59.1%	51.7%	43.0%	35.3%
Early reinfection	70.0%	60.0%	60.0%	40.0%	20.0%
Late reinfection	100.0%	88.9%	72.2%	50.0%	25.0%
By treatment strategy					
Medical-surgical	79.1%	71.4%	67.1%	53.3%	42.4%
Deliberate medical	77.8%	59.3%	42.6%	35.2%	22.9%
Perforce medical	14.7%	8.8%	8.8%	2.9%	0.0%

Author statement

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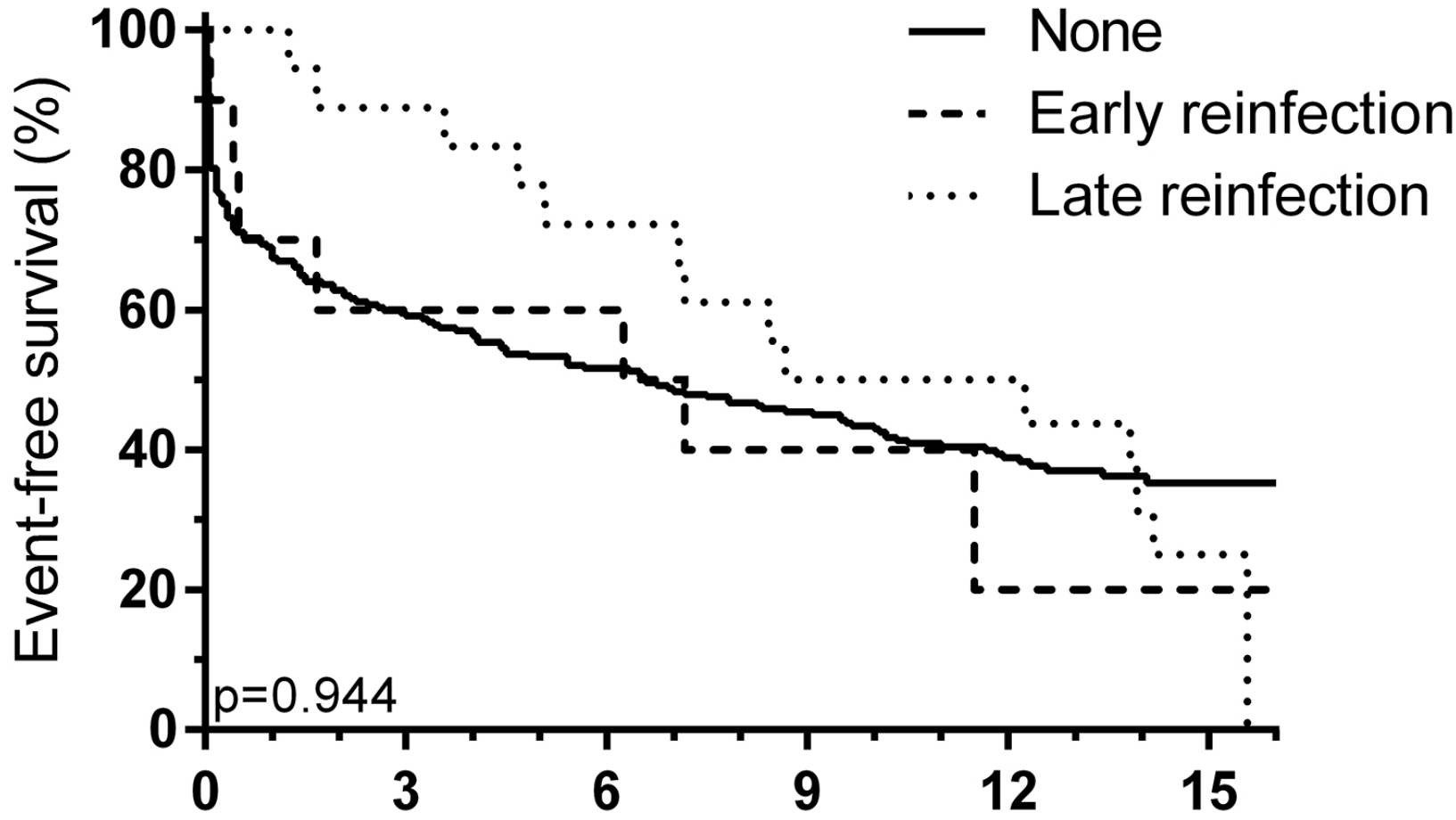
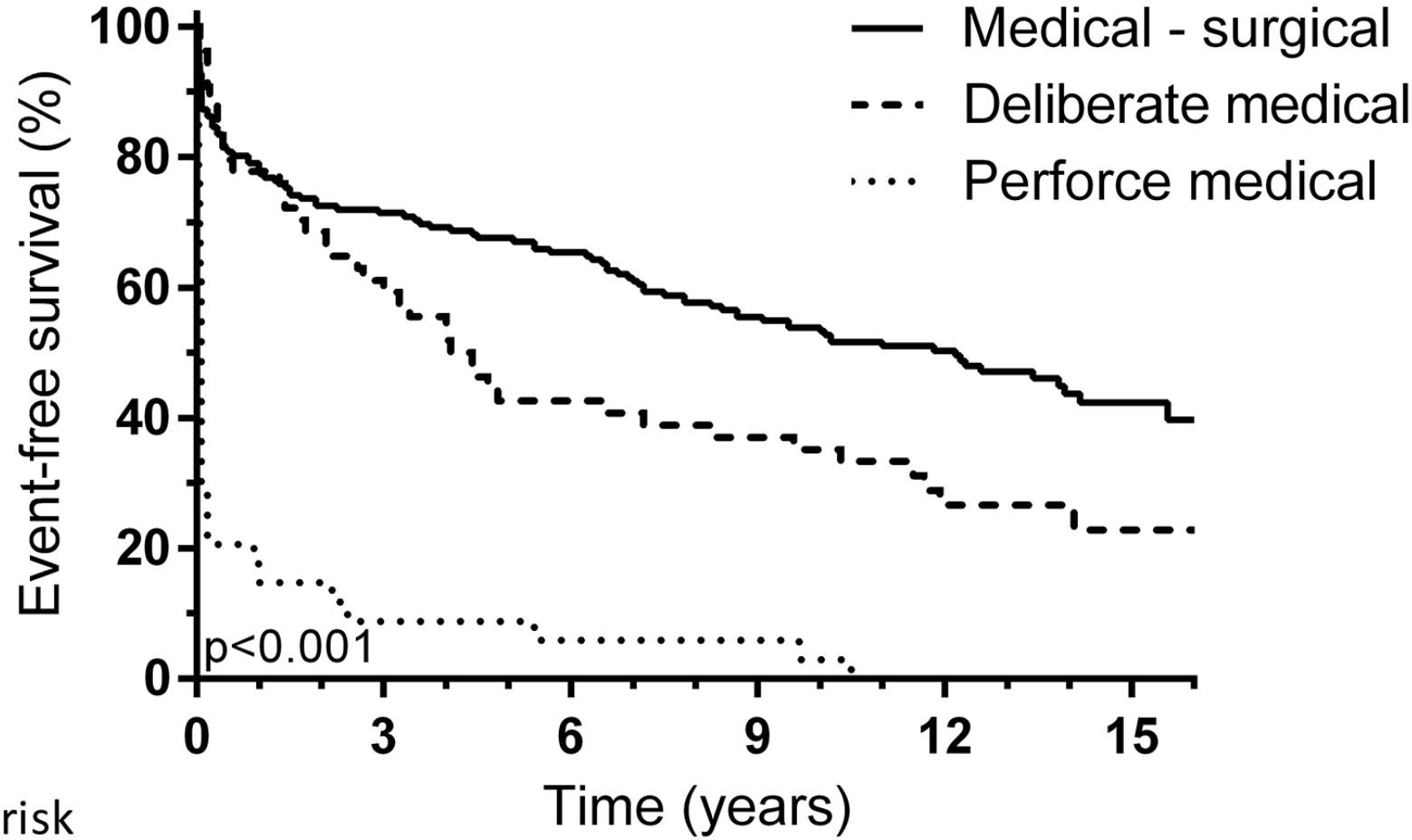
Highlights

- Real world long-term outcome data in infective endocarditis is scarce.
- Early reinfection rate was 3.7%, whereas late reinfection rate was 6.7%.
- Survival rates were 71.1% at 1 year and 43.3% at 10-years follow-up.



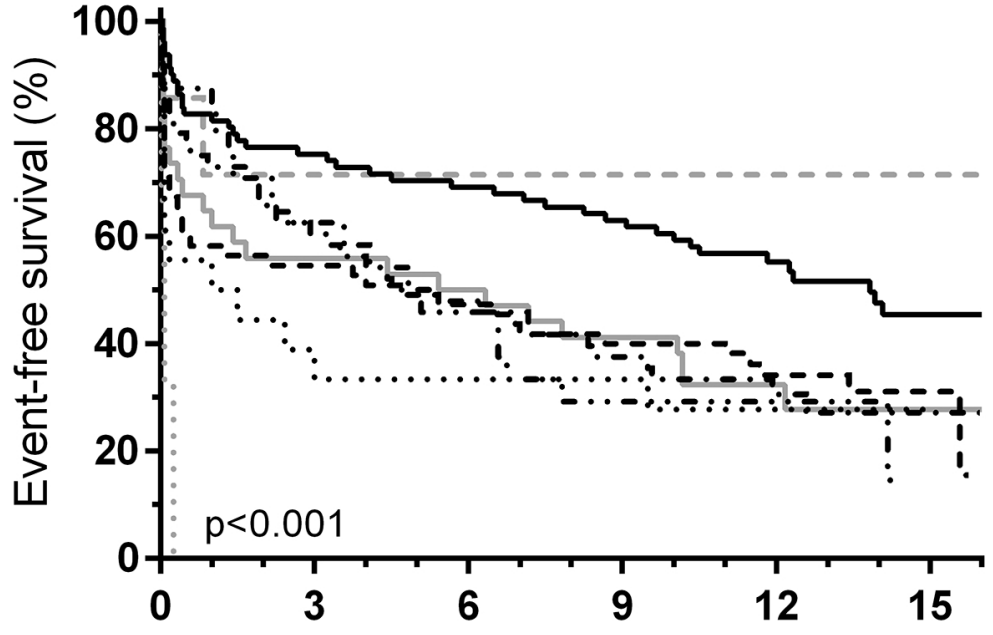
Numbers at risk						
None	242	144	125	110	72	36
Early reinfection	10	6	6	4	1	1
Late reinfection	18	16	13	9	8	4

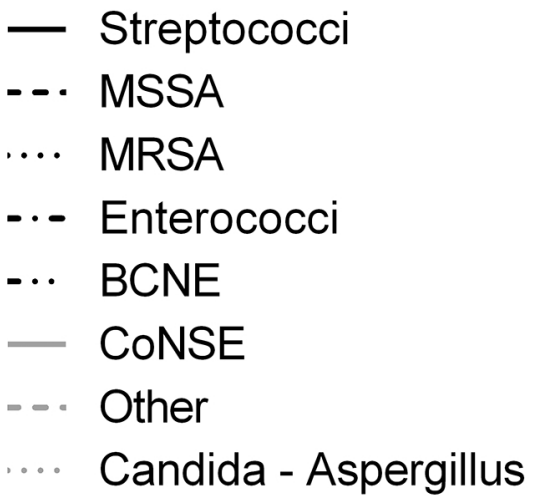
Figure 1A



Numbers at risk						
Medical - Surgical	182	130	119	102	69	31
Deliberate medical	54	33	23	20	12	6
Perforce medical	34	3	2	2	0	0

Figure 1B





Numbers at risk						
Streptococci	81	61	56	51	35	22
MSSA	55	30	26	22	17	10
MRSA	18	7	6	6	5	5
Enterococci	48	29	23	18	11	8
BCNE	24	15	11	7	7	0
CoNSE	34	19	17	14	12	6
Other	7	5	5	5	5	5
Candida - Aspergillus	3	0	0	0	0	0

Figure 1C