Infective Endocarditis

Epidemiologic transitions in the first decade of the 21st century

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ABBREVIATIONS

AKI - Acute kidney injury; Lesão renal aguda

ANA- Anti-nuclear antibodies

ANCA - Anti-neutrophil cytoplasmic antibody

CAIE - Community-acquired infective endocarditis; Endocardite infecciosa adquirida na comunidade

CKD - Chronic kidney disease; Insuficiência renal crónica

ICD - Implantable cardioverter defibrillator; Cardioversor desfibrilhador implantável

IE - Infective endocarditis; Endocardite infecciosa

IQR - Interquartile range; Amplitude interquartil

IVDA - Intra-venous drug abuse; Abuso de substâncias por via endovenosa

HAIE - Health-care associated infective endocarditis; Endocardite infecciosa associada aos cuidados de saúde

HF - Heart failure; Insuficiência cardíaca

MRSA - Methicillin-resistant *Staphylococcus aureus*

PVE - Prosthetic valve endocarditis; Endocardite de válvula prostética

TTE - Transthoracical echocardiography; Ecocardiograma transtorácico

TEE - Transoesophageal echocardiography; Ecocardiograma transesofágico

VRE - Vancomycin-resistant Enterococci *spp.*

ABSTRACT

Aims: The aim of this study is to provide an epidemiological profile of infective endocarditis (IE), to determine temporal trends through a direct comparison with a previous cohort and to assess factors that impact in-hospital mortality.

Methods and results: A total of 25 patients prospectively identified with clinical diagnosis of IE and definite or possible diagnosis according to modified Duke criteria were included in the study. Fifty-two percent of the episodes involved prosthetic valves and 17% were health-care associated (HAIE). Causative microorganisms were 32% Staphylococci *spp.*, 32% Streptococci *spp*. and 12 % Enterococci *spp*. *S.aureus* was the main isolated causative microorganism (24%). At least one complication occurred in 72% of the episodes and 84% had at least one surgical indication. Fifty-two percent of the patients were submitted to surgical treatment after a median 30 days after admission (IQR=11-40) in comparison to 29% after a median 38 days (IQR=29-59) in the previous cohort. In-hospital all-cause mortality was 28% comparing with 36% in the previous cohort. Six-month mortality was 30% (2 patients were lost to follow-up) comparing to 47% in the previous series. Seventy-five percent of the patients with surgical indication and not submitted to surgical treatment died in-hospital. In univariate analysis multidrug-resistant microorganisms (100% vs 28% p=0,042), health-care acquisition (75% vs 20% p=0,027), community acquisition (16% vs 80% p =0,005) and surgery (0% vs. 58% p=0,001) influenced in-hospital mortality.

Conclusion: We could observe a higher proportion of patients with prosthetic valves and other comorbidities. *S.aureus* was the main isolate cause of IE but Staphylococci *spp.* and Streptococci *spp*. cases were even. IE continues to present with high in-hospital and 6-month

mortality-rates though lower than in the last decade. The proportion of surgically treated patients has increased and surgery was associated with lower in-hospital mortality.

Keywords: Infective endocarditis; epidemiology; prognostic factors; in-hospital mortality; 6-month mortality.

RESUMO

Objectivos: O objectivo deste estudo é traçar um perfil epidemiológico de Endocardite Infecciosa (EI), analisar a sua evolução em comparação directa com uma coorte anterior e determinar factores com impacto na mortalidade intra-hospitalar.

Métodos e resultados: Foram incluídos neste estudo 25 doentes prospectivamente identificados com diagnóstico clínico de EI e diagnóstico definitivo ou possível de acordo com os critérios de Duke modificados. Cinquenta e dois porcento dos episódios foram em doentes com válvulas prostéticas e 17% tiveram aquisição associada aos cuidados de saúde (HAIE). Os microorganismos causadores incluiram 32% Staphylococci *spp.*, 32% Streptococci *spp.* e 12% Enterococci *spp.* O principal agente causador de IE isoladamente foi o *S.aureus* (24%). Pelo menos uma complicação clínica ocorreu em 72% dos episódios e 84% tinham pelo menos uma indicação cirúrgica. Foram submetidos a intervenção cirúrgica 52% dos doentes após uma mediana de 30 dias (IQR=11-40) depois da admissão em comparação com 29% após mediana de 38 dias (IQR=29-59) na coorte anterior. A mortalidade intra-hospitalar foi de 28% em comparação com 36% na coorte anterior. A mortalidade a 6 meses foi de 30% (perderam-se dois doentes no follow-up) em comparação com 47% na série anterior. Nos doentes com indicação cirúrgica que não foram submetidos a cirurgia a mortalidade intra-hospitalar foi de 75%. Na análise univariada microorganismos multi-resistentes (100% vs 28% p=0,042), a aquisição associada aos cuidados de saúde (75% vs 20% p=0,027), a aquisição comunitária (16% vs 80% p =0,005) e a cirurgia (0% vs. 58% p=0,001) tiveram impacto na mortalidade intra-hospitalar.

Conclusão: Pudemos observar um aumento dos doentes com válvulas prostéticas e outras comorbilidades. Isoladamente o principal microorganismo causador foi o *S.aureus* mas a

frequência de Staphylococci *spp.* e Streptococci *spp*. foi igual. A EI continua a estar associada a elevadas taxas de mortalidade intra-hospitalar e a 6 meses apesar de ter havido uma diminuição das mesmas em relação à década passada. A proporção de doentes tratados cirurgicamente aumentou e a cirugia teve impacto positivo na mortalidade intra-hospitalar.

Palavras-chave: Endocardite infecciosa; epidemiologia; factores prognósticos; mortalidade intra-hospitalar; mortalidade a 6 meses.

INTRODUCTION

The epidemiological profile of infective endocarditis (IE) has changed substantially, particularly in developed nations, since its first modern clinical description by Osler in 1885 [a] (1).

Nowadays the classic manifestations and predisposing conditions are unusual; instead IE tends to present in an older population, with more comorbidities and with increasing presence of intracardiac devices or prosthetic valves (2–4). Also, the exposure to invasive healthcare procedures has been increasingly related with IE incidence (5,6). Regarding microbiology, it has been registered a trend that shows *Staphylocoocus aureus* as the predominant IE agent surpassing *Streptococcus viridans* (3,5–8). Despite being a rare disease, 3-10 episodes/100 000 person-years (2), and the fact that major advances have been made in both diagnostic and therapeutic procedures, it is still associated with poor prognosis, with in-hospital mortality ranging from 16,6% - 22,7% (5,8,9), 6-month mortality ranging from 18% to22% (3,10) and long-term mortality ranging from 56% to 69% (11,12).

In addition, IE is a very heterogeneous disease, presenting with several different manifestations, depending, among other factors, on the underlying health status, predisposing conditions of the patient and its causative microorganisms. Regarding treatment, it has been reported a protective effect of surgical treatment (5,11) in the course of IE but there is still no absolute consensus about indications, contra-indications and timing, particularly on critically ill patients (3,12–14). Moreover, geographical differences have been reported in IE (5) and for that reason a contemporary epidemiological study of this disease in Portugal seemed opportune. Additionally, it is important to assess the temporal trends regarding surgical approaches and intra-hospital mortality.

The aim of this study was 1) to assess factors that impact in-hospital mortality and 2) to provide an epidemiological profile of IE. We also aimed to determine temporal trends through a direct comparison with a previous cohort of IE patients.

METHODS

A total of 25 patients that were discharged from Hospital of University of Coimbra - Portugal between June 2013 and June 2014 were included in the study if prospectively identified with clinical and definite or possible diagnosis of IE according to modified Duke criteria (15).

Data collection

For each patient the following variables were collected:

- **Epidemiological**: age, sex, predisposing conditions for IE, cardiovascular risk factors, other comorbidities (pulmonary, hepatic, renal, immunosuppression), hemodialysis, presence of chronic intravenous catheter or arteriovenous fistula.
- **Microbiological:** blood cultures, serology and antimicrobial susceptibility testing.
- **Diagnostic tools**: transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), location and size of the vegetations, valvular regurgitation or stenosis, qualitative systolic function, paravalvular complications and time till TTE/TEE.
- **Clinical presentation**: constitutional symptoms, new regurgitation, heart murmur, vascular signs, neurological signs, confusion, anemia, chest pain, arthralgia respiratory symptoms, gastro-intestinal symptoms.

- **Complications**: Heart failure (HF), cerebral embolism, other embolic phenomena, acute pulmonary edema, acute kidney injury (AKI).
- **Surgical treatment**: type of surgery performed, type of implanted valve, time till surgery. Indications for surgery were 1) severe aortic or mitral regurgitation causing acute pulmonary edema or shock; 2) Severe aortic or mitral regurgitation and persisting heart failure; 3) Abscess, pseudoaneurysm or fistula; 4) Persisting fever and positive blood cultures for more than 10 days; 5) infection caused by multi-resistant microorganisms; 6) Vegetations with more than 10mm and predictors of complicated course (HF; uncontrolled infection); 7) Vegetations with more than 15mm.
- **Outcomes**: length of stay in hospital, in-hospital mortality rate, 6-month mortality rate, reinfection and need for another surgery.

Definitions

Acute kidney injury: Defined as an increase in serum creatinine > to 1.5 times baseline during in-hospital stay and considering the baseline as the value at admission (16).

Anemia: hemoglobin concentration < 12.0 g/dL for females and < 13.0g/dL for males.

Autoimmunity: ANA+ and/or ANCA+ and/or Anti ds-DNA+ and/or rheumatoid factor.

The following definitions were made according to the 2009 European Society of Cardiology Infective Endocarditis guidelines: community acquired IE, health-care associated IE (HAIE), early prosthetic valve endocarditis (PVE), late PVE, recurrence and relapse.

Imunosupression: Human immunodeficiency virus infection, malignancy, and/or long-term use of corticosteroids and/or other immunosuppressant (12).

Time till cardiac surgery: Time in days from TTE/TEE until the day of the surgery. If the patient has done both, counting from TEE day given its higher sensitivity and specificity to IE diagnose (17) and assuming that, TTE, if done first, was not conclusive.

Time till TTE/TEE: Time in days from admission to TTE/TEE whichever was done first. In case of transferred patients sometimes it presents has a negative value given that it was performed before admission in the hospital in study; these were not included for median calculation of time till TTE/TEE.

MRSA: methicillin-resistant *Staphylococcus aureus*

Multiresistant microorganism: Defined as Methicilin Resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci *spp.* (VRE) and penicilin-resistant Enterococci *spp.* and penicilin-resistant Streptococci *spp.*

New regurgitation: According to the following criteria 1) Patient with regurgitation and without previous heart valve disease 2) Patient with previous heart valve disease but presenting with severe regurgitation in a native heart valve 3) Patient with previous heart valve disease but presenting with mild regurgitation and vegetation in a native heart valve.

Periannular complications: Paravalvular leak, fistula, abscess, pseudoaneurysm.

Predisposing condition for IE: If a patient fills at least one of the following criteria 1) previous heart valve disease; 2) congenital heart disease; 3) previous infective endocarditis; 4) acute rheumatic fever; 5) prosthetic valve; 6) intracardiac device; 7) intravenous drug abuse (IVDA).

Statistical analysis

Continuous data were presented as medians and interquartile ranges (IQR), unless stated otherwise, and categorical data as the frequency. We used Kolmogorov-Smirnov for testing normality, Student's T-test for continuous variables and X^2-test for categorical variables. Values of $p < 0.05$ were considered to be significant. Due to low numbers and consequently, low power, we have refrained from hypothesis testing comparing the contemporary and the older IE cohorts. Results are presented numerically. Statistical analysis was performed using SPSS® 17.0 software package (IBM, New York, USA).

RESULTS

The median age of the cohort was 59 years (IQR = 50-75) and 72% were male. In the 24 cases in which was possible to determine acquisition, 79% (n=17) were community-acquired, 17% (n=4) were health-care associated, 1 was nosocomial and in 1 patient IE was associated with IVDA. Almost half of the patients were referred from another health-care facility (n = 12), as our hospital is a tertiary centre.

Clinical presentation

The distribution of underlying heart disease, cardiovascular risk factors and other comorbidities is shown in Table 1. In 76% of the patients was identified at least one predisposing condition for IE. The most common underlying heart conditions were

degenerative heart valve disease (52%) and a history of cardiothoracic surgery (52%), mainly aortic valve replacement (62%), resulting in a high proportion of patients with PVE (40%).

Among these patients in 90% of the cases it occurred more than 1 year after valve surgery and in equal proportion were related to mechanic or biological valves.

Clinical findings are summarized in Table 2. The most common manifestations of the disease were fever (80%), anemia (76%), mainly normochromic normocytic (89%), presence of a heart murmur (72%) and a new regurgitation (72%).

Table 1. IE type, risk factors, comorbidities and predisposing conditions

Variable	*n*	*Total n*	*%*
Demographic Data			
Age	(IQR = 50-75)	59	
Male gender	18	25	72%
IE type			
Native valve	15	25	60%
Prosthetic valve	10	25	40%
Early PVE	1	10	10%
Late PVE	9	10	90%
Mechanical Valve IE	5	10	50%
Biological Valve IE	5	10	50%
Cardiovascular risk factors			
Arterial hypertension	16	25	64%
Dyslipidemia	12	25	48%
Diabetes	8	25	32%
Comorbilities			
Degenerative heart valve disease	13	25	52%
Coronary disease	8	25	32%
Acute myocardial infarction	4	25	16%
Congestive heart failure	9	25	36%
Stroke	2	25	8%
Atrial Fibrillation	8	25	32%
Previous endocarditis	5	25	20%
Relapse	1	5	20%
Recurrence	4	5	80%
Congenital heart disease	5	25	20%
Bicuspid aortic valve	4	5	80%
Aortic coarctacion and interventricular communication	1	5	20%
Pacemaker or ICD	5	25	20%
Previous cardiothoracic surgery	13	25	52%
Mitral valve repair	1	13	8%
Aortic valve repair	1	13	8%
Aortic valve replacement	8	13	62%

Mitral valve repair and aortic valve replacement	1	13	8%
Mitral and aortic valves replacement	1	13	8%
Aortic coarctacion correction	1	13	8%
Rheumatical heart disease	2	25	8%
Lung disease †	5	25	20%
Cronic kidney failure	3	25	12%
Hemodialysis	0	25	0%
Chronic iv catheter	0	25	0%
Chronic liver disease	0	25	0%
Hepatitis	1	25	4%
Imunosupression	2	25	8%
IVDA	1	25	4%
Auto-immunity	7	25	28%
Rheumatoid factor	0	7	0%
Antinuclear antibodies (ANA)	5	7	71%
Anti-neutrophil cytoplasmic antibody (ANCA)	1	7	14%
Anti ds-DNA	1	7	14%
Minor Duke criteria - Predisposition	19	25	76%
Minor Duke criteria - Immunological phenomena	1	25	4%
† : including obstructive lung disease and pulmonary fibrosis			

Table 2. Clinical Presentation

Variable	*n*	*Total n*	*%*
Asthenia	11	25	44%
Anorexia	5	25	20%
Arthralgia	2	25	8%
Chest pain	6	25	24%
Nausea	3	25	12%
Vomit	1	25	4%
Cough	4	25	16%
Productive cough	2	25	8%
Dyspnoea	7	25	28%
Orthopnea	2	25	8%
Peripheral edema	9	25	36%
Acute pulmonary edema	3	25	12%
Fever	20	25	80%
Anemia	19	25	76%
Normocytic normochromic	17	19	89%
Microcytic	1	19	5%
Macrocytic	1	19	5%
Confusion	6	25	24%
Neurological Signs	6	25	24%
Vascular Signs	4	25	16%
Peripheral abscess	0	25	0%
Heart murmur	18	25	72%
New regurgitation	18	25	72%
Minor Duke criteria - fever	20	25	80%
Minor Duke criteria - vascular phenomena †	6	25	24%
† including not only vascular signs at admission but also complications			

Microbiology

Blood cultures were taken from all 25 patients to determine the causative microorganism. Of the 5 patients with negative blood cultures, the majority (3 patients) had received antibiotics before the blood samplings. The distribution of causative microorganisms and their resistances is displayed in Table 3. Streptococci *spp.* (32%) and Staphylococci *spp.* (32%) were equally common; Enterococci *spp.* were responsible for a minority of cases (12%). Inside the Staphylococci *spp.* the most frequent microorganism was *S. aureus* accounting for 24% of IE cases. Of these, 33% were due to MRSA. In 85% of all positive blood cultures antimicrobial susceptibility was tested and 20% of the microorganisms were considered multidrug-resistant.

Table 3. Microbiological analysis

Variable	*n*	*Total n*	*%*
Blood cultures	25	25	100%
IE with positive blood cultures	20	25	80%
Streptococcus viridans Group	5	25	20%
Streptococcus Pneumoniae	1	25	4%
Streptococcus Grupo D	1	25	4%
Staphylococcus aureus	6	25	24%
Staphylococcus epidermidis	1	25	4%
Staphylococcus Coagulase-negativa	1	25	4%
Enterococci (including *e.faecium* and *e.fecalis*)	3	25	12%
Salmonella enteritidis	1	25	4%
Staphylococci *spp.*	8	25	32%
Streptococci *spp.* *	8	25	32%
Enterococci *spp.*	3	25	12%
Others	1	25	4%
IE with negative blood cultures	5	25	20%
Previous treatment with antibiotics	3	5	60%
Serology	3	5	60%
Negative serology	3	3	100%
Serology	7	25	28%
Antimicrobial susceptibility testing	17	20	85%
MRSA †	2	25	8%
VRE ‡	2	25	8%
Penicilin resistant streptococci	0	25	0%

Multidrug-resistant microorganisms	4	25	16%
Major Duke criteria - blood cultures positive for IE	13	25	52%
Minor Duke criteria - microbiological evidence	7	25	28%

* in one transferred patient there was register of positive blood cultures for *streptococcus spp.* but no subgroup discrimination.
†in one of the *s.aureus* ntimicrobial susceptibility testing was not done
‡ Vancomycin-resistant enterococci

Echocardiography findings

In all 25 patients either a TTE (68%) or a TEE (88%) was performed within a median time of 5 days (IQR: 0 – 9 days). Table 4 summarizes echocardiographic findings. A major echocardiographic criterion according to the modified Duke criteria of IE (15) was found in 92% of the patients. These included vegetations in 72% of patients, abscess in 24%, severe prosthetic dehiscence in 30% of the patients with prosthetic valves and a new regurgitation in 72%. Severe regurgitation was commonly found (68%); still, the majority of the cohort had normal left-ventricular systolic function (76%).

Table 4.Echocardiography Findings

Variable	*n*	*Total n*	*%*
TTE	17	25	68%
TEE	22	25	88%
Time till TTE/TEE (days) *	5	IQR = 0-9	
TTE or TEE	25	25	100%
Vegetations	18	25	72%
Mitral vegetation	4	18	22%
Aortic vegetation	7	18	39%
Mitral and aortic vegetation	4	18	22%
Tricuspide vegetation	2	18	11%
Pacemaker lead vegetation	1	18	6%
Left-sided IE	15	18	83%
Right-sided IE	2	18	11%
Register of vegetation size	13	25	52%
Vegetation > 10 mm	9	25	36%
Vegetation >15 mm	5	25	20%
Mitral regurgitation	19	25	76%
Mild mitral regurgitation	7	19	37%
Moderate mitral regurgitation	4	19	21%
Severe mitral regurgitation	8	19	42%
Mitral stenosis	1	25	4%
Aortic regurgitation	14	25	56%

Mild aortic regurgitation	1	14	7%
Moderate aortic regurgitation	2	14	14%
Severe aortic regurgitation	11	14	79%
Aortic stenosis	1	25	4%
Tricuspid regurgitation	12	25	48%
Mild tricuspid regurgitation	5	12	42%
Moderate tricuspid regurgitation	5	12	42%
Severe tricuspidregurgitation	2	12	17%
Tricuspid stenosis	0	25	0%
Regurgitation in more than 1 valve	15	25	60%
Mitral and tricuspid regurgitation	5	25	20%
Mitral and aortic regurgitation	4	25	16%
Mitral, aortic and tricuspid regurgitation	6	25	24%
Severe regurgitation	17	25	68%
Severe regurgitation in more than 1 valve	4	17	24%
New regurgitation	18	25	72%
Paravalvular complications	7	25	28%
Abscess	6	25	24%
Fistula	4	25	16%
Pseudoaneurysm	2	25	8%
Paravalvular leak	2	25	8%
Severe prosthetic valve dehiscence	3	10	30%
Mild to moderate prosthetic valve dehiscence	2	10	20%
Qualitative left ventricular systolic function			
Normal	19	25	76%
Mild to moderate impairment	4	25	16%
Severe impairment	2	25	8%
Major Duke Criteria - Echocardiography	23	25	92%

* Negative values for time because TTE/TEE has been performed in the previous hospital (transferred patients) have been registered as "0".

Complications

The main complication was congestive heart failure (60%), either if new or an acute decompensation of a previous stable condition; approximately half of the patients (56%) had AKI. Cerebral embolism was identified in 4 patients (16%) and embolism in other locations in 3 patients (12%); 2 of them had an embolic episode in both locations (8%). A total of 7 patients (28%) developed shock (either septic, cardiogenic or mixed) and 3 patients suffered acute pulmonary edema. A total of 18 patients (72%) had at least one clinical complication during the stay in hospital.

Surgical indications and treatment

The majority of patients (84%) had at least one indication for urgent or emergent surgery as presented in Table 5. Approximately half of the patients were submitted to valve replacement or repair (48%) after a median 30 days after admission (IQR = 11-40). Table 6 presents all surgeries performed. The most common interventions were either aortic replacement (46%) or aortic replacement and mitral repair (31%). Out of the 8 patients who had surgical indication and did not underwent surgery, 6 died during the index hospitalization (75%).

Table 5. Indications for surgery and outcomes

Variable	*n*	*Total n*	*%*
Heart Failure	9	25	36%
Severe aortic or mitral regurgitation causing APO † or shock	8	25	32%
Severe aortic or mitral regurgitation and persisting heart failure	6	25	24%
Uncontrolled infection	8	25	32%
Abscess/False aneurysm/fistula	6	25	24%
Persisting fever and positive blood cultures for > 10 days	1	25	4%
Infection caused by multiresistant microorganisms	4	25	16%
Prevention of embolism	9	25	36%
Vegetations >10mm and predictores of complicated course ϫ	6	25	24%
Vegetations >15mm	5	25	20%
Urgent and Emergent Surgical indications	21	25	84%
More than one surgical indication	8	21	38%
Surgical indication not submitted to surgery	8	21	38%
Surgical indication not submitted to surgery who died in-hospital	6	8	75%
Surgical indication submitted to surgery	13	13	100%
Surgical indication submitted to surgery who died in-hospital	0	13	0%
† APO: acute pulmonary oedema			
ϫ Predictors of complicated course: Heart faillure and uncontrolled infection			

Table 6. Surgical Treatment			
Variable	*n*	*Total n*	*%*
Surgery	13	25	52,00%
Time till Cardiac Surgery (days)	IQR(11-40)	30	
Surgery designation			
Mitral valve repair and aortic replacement	4	12	33%
Aortic replacement	6	12	50%
Mitral valve repair	1	12	8%
Mitral valve replacement	1	12	8%
Pacemaker leads removal	1	25	4%
Valve replacement or repair	12	25	48%
Mechanical prothesis	6	11	55%
Biological prothesis	5	11	45%

Outcomes

Mean length of stay in hospital was 42 days (IQR = 27-50). In-hospital all-cause mortality rate was 28%. The 6-month mortality rate was 30%; two patients were lost to follow-up, no deaths were registered after hospital discharge up to 6 months later. During this period 1 patient had to be submitted to a new surgery due to immediate surgical complications (1 day after the initial surgery) and 1 patient had a re-infection (15 days after initial infection).

Predictors of in-hospital mortality

In univariate analysis, previous heart valve disease (8,33% vs. 46% p = 0,03), previous congestive heart failure (13% vs. 56% p = 0,02) immunosuppression (22% vs. 100% p = 0,018), minor Duke criteria for microbiological evidence (11% vs. 71% p = 0,003), multidrug-resistant microorganisms (14% vs. 100% $p < 0.001$) and shock (11% vs. 71% p = 0,003) were associated with a poorer in-hospital prognosis. Both MRSA and VRE patients suffered a very high mortality rate compared with other blood culture-positive patients (100% vs 28% p=0,042). HAIE was associated with a higher in-hospital mortality rate compared with non-HAIE (75% vs 20% p=0,027) and community-acquired IE (CAIE) was associated with a better prognosis

than non-CAIE (16% vs 80% *p* =0,005). Surgery was associated with decreased in-hospital mortality (0% vs. 58% p=0,001).

As for continuous variables, baseline serum creatinine level (1,16 ± 0,66 vs. 1,82 ± 1,20 mg/dL p = 0,045), time from hospital admission till cardiology service admission (3 +/- 4 vs . 13 ± 14 days p = 0.004) and the time till TTE/TEE (3 ± 4 vs. 16 ± 8 days p < 0.001) influenced in-hospital mortality. Older age was numerically associated with in-hospital mortality (57 ± 16 vs. 68 ± 5 years p = 0,06), but did not achieve statistical significance.

Comparison with the 2005-2010 cohort

As part of the analysis conducted in this study, we assessed the temporal trends of IE patients admitted in our cardiology department. A cohort of 75 patients admitted from January, 1st 2005 to December, 31st 2010 was compared with our contemporary cohort of 25 patients. The comparison of IE characteristics in the two study periods are shown in Table 7.

Of note, the incidence of IE on prosthetic valves has slightly increased (31% to 40%); patient risk profile was higher regarding cardiac comorbidities, except for prior cardiothoracic surgery, that has remained almost unaltered. The presence of an intracardiac device has slightly decreased (27% to 20%). Regarding diagnosis, there was an increase of patients submitted either to TTE or TEE (95% to 100%) and more patients were submitted to TEE (69% to 88%).

A causative microorganism was found more frequently in the contemporary cohort (66% to 80%). The incidence of IE due to *Streptococci viridans* has doubled (10% to 20%), while it has remained stable for Staphylococci *spp.* and Enterococci *spp.* More patients were submitted to surgical treatment (29% to 52%) and this difference is even more accentuated if

only valve replacement or repair is considered (9% to 48%). Both in-hospital (36% to 28%) and 6-month (47% to 30%) mortality rates have numerically decreased.

Table 7. Comparison of 2005-2010 and 2013-2014 cohorts

	2005-2010			2013-2014		
Variable	n	Total n	%	n	Total n	%
Demographic Data						
Age		IQR= 51,5-70,5	62		IQR = 50-75	59
Male gender	57	75	76%	19	25	76%
Classification						
Native valve	52	75	69%	0	0	60%
Prosthetic valve	23	75	31%	10	25	40%
Cardiovascular risk factors						
Arterial hypertension	35	75	47%	16	25	64%
Dyslipidemia	22	75	29%	12	25	48%
Diabetes	14	75	19%	8	25	32%
Comorbidities						
Previous degenerative heart valve disease	35	75	47%	13	25	52%
Coronary disease	5	75	7%	8	25	32%
Acute myocardial infarction	3	75	4%	4	25	16%
Previous congestive heart failure	21	74	28%	9	25	36%
Previous endocarditis	4	74	5%	2	25	20%
Pacemaker/ICD	20	75	27%	5	25	20%
Previous cardiothoracic Surgery	35	74	47%	13	25	52%
Cronic Kidney Failure	9	74	12%	3	25	12%
Imunosupression	6	74	8%	2	25	8%
IVDA	4	75	5%	1	25	4%
Transthoracic and transesophageal echocardiography						
TTE	59	74	80%	17	25	68%
TEE	51	74	69%	22	25	88%
TTE or TEE	70	74	95%	25	25	100%
Vegetations	55	70	79%	18	25	72%
Mitral vegetation	19	55	35%	4	18	22%
Aortic vegetation	29	55	53%	7	18	39%
Mitral and aortic vegetation	2	55	4%	4	18	22%
Tricuspide vegetation	5	55	9%	2	18	11%
Left-sided IE	50	55	91%	15	18	83%
Right-sided IE	5	55	9%	2	18	11%
Modified Duke Criteria						
Major DUKE criteria						
Blood cultures	27	75	36%	13	25	52%
Echocardiography	63	75	84%	23	25	92%
Minor DUKE criteria						
Predisposing condition	51	74	69%	19	25	76%
Fever	56	75	75%	20	25	80 %
Vascular phenomena	13	75	17%	6	25	24%
Immunological phenomena	4	75	5%	0	25	0%
Microbiological evidence	12	75	16%	7	25	28%
Microbiology						
Blood cultures	71	75	95%	25	25	100%
IE with positive blood cultures	47	71	66%	20	25	80%

Positive blood cultures with possible contaminations	7	71	10%	0	25	0%
Streptococcus viridans Group	7	71	10%	7	25	28%
Streptococcus Pneumoniae	0	71	0%	1	25	4%
Streptococcus Grupo D	0	71	0%	1	25	4%
Streptococcus agalactiae	1	71	1%	0	25	0%
Staphylococcus aureus	11	71	15%	6	25	24%
Staphylococcus Coagulase-negativa	2	71	3%	1	25	4%
Staphylococcus epidermidis e staphylococcus hominis	10	71	14%	1	25	4%
Enterococcus	5	71	7%	3	25	12%
Salmonella enteritidis	0	71	0%	1	25	4%
*abiotrophia defectiva (*nutrionally variant streptococci)	1	71	1%	0	25	0%
klebsiella pneumoniae	1	71	1%	0	25	0%
candida albicans	1	71	1%	0	25	0%
*Serratia marcescens(*enterobactereacea)	1	71	1%	0	25	0%
Streptococci *spp.*	9	71	13%	9	25	36%
Enterococci *spp.*	5	71	7%	3	25	12%
Staphylococci *spp.*	23	71	32%	8	25	32%
Others	3	71	4%	0	25	0%
IE with negative blood cultures	24	71	34%	5	25	20%
Antimicrobial susceptibility testing	40	47	85%	17	20	85%
MRSA	5	75	7%	2	25	8%
Vancomycin and penicilin resistant enterococci	0	75	0%	2	25	8%
Penicilin resistant streptococci	2	75	3%	0	25	0%
Multidrug-resistant microorganisms	7	75	9%	4	25	16%
Surgical Treatment						
Surgery	22	75	29%	13	25	52%
Implantation/substitution/removal of pacemaker/ICD leads	15	75	20%	1	25	4%
Valve replacement or repair	7	75	9%	12	25	48%
Time till Cardiac Surgery (days)		IQR(29- 59)	38		IQR(11-40)	30
Lenght of stay in hospital (days)		IQR=(17 - 51)	36		IQR=(27-50)	42
In-hospital mortality rate	27	75	36%	7	25	28%
6-month mortality rate	35	75	47%	7	23	30%

x Negative values for time because TTE/TEE has been performed in the previous hospital (transferred patients) have been registered as "0".

DISCUSSION

In this prospective observational study on a contemporary IE cohort we registered a decrease in both in-hospital (36% to 28%) and 6-month (47% to 30%) mortality rates, in comparison with a previous cohort collected during the last decade. Nonetheless, both values are still higher than those presented in other contemporary reports (3,5,8,9).

Of note, the proportion of patients with prosthetic valves (40%) was especially elevated (5,8) and that might help explain the high mortality rate, giving that PVE is associated with poor prognosis (2). A considerable proportion of cases in this study were identified as having recent health care exposure (17%), though inferior to contemporary reports (25% - 30%) (5,8,10). The percentage of surgically treated patients, which has substantially increased in comparison with the previous series (from 29% to 52%) was consistent with other recent studies (3,5,8). With concern to causative agents *S. aureus* IE, which has numerically increased compared with the previous cohort (15% to 24%), was slightly less frequent than the percentages found in other studies (27% - 32%) (3,5,6,8,10). Anyhow MRSA prevalence (33%) was approximately the same found in other series (3,6).

Our hospital is a tertiary referral center with a cardiac surgery unit and therefore there was a high proportion of transferred patients (48%). Nonetheless only two in-hospital deaths were registered in this group, allowing us to conclude that referral patients may not contribute to a higher intra-hospital mortality, as previously noticed by other studies(5). Anyway, it should be mentioned that 85% of all surgeries were performed in referred patients, introducing a possible selection bias.

Regarding the clinical presentation and baseline characteristics of the population, it was also registered a significant proportion of patients with cardiovascular risk factors, particularly diabetes in 32% of the patients, a value superior to that registered in several other reports (5,8) and quite concerning because of its association with poor outcomes of IE (2,18). The presence of an intracardiac device (pacemaker or implantable cardioverter-defibrillator) (20%) in this cohort was also superior to that registered in the literature (5,8). However, only one patient had a pacemaker lead vegetation. An increasing number of predisposing conditions for IE as well as other comorbidities was registered, being particularly common the presence of degenerative valve disease (52%) following the trend registered in the last decades.

Previous heart valve disease (8,33% vs. 46% p = 0,03), previous congestive heart failure (13% vs. 56% p = 0,02) and immunosuppression (22% vs. 100% p = 0,018) were associated with increased in-hospital mortality concurring with the existing idea that patients with baseline comorbidities tend to have worse prognosis (2).

Despite not being statistically relevant (p = 0,06) patients who died in-hospital had a approximately 10 years more (57 ± 16 vs. 68 ± 5) and this reproduces the literature, that associates increasing age with poorer prognosis (5,10).

Time from hospital admission till cardiology service admission (2,55 ± 4 vs. 13,28 ± 14 days p = 0.004) and time till TTE/TEE (3,33 ± 4 vs. 15.85 ± 8 days p<0,001) influenced in-hospital mortality rate. We might speculate from this data that patients in which the suspicion for IE was raised sooner had a better prognosis, highlighting the importance of IE awareness in patients with predisposing conditions. Therefore, patients with fever of unknown origin must be closely followed and IE should be one of the working differential diagnosis.

As mentioned before a relevant proportion of HAIE was registered. This type of IE, which appears to be a different entity from non-HAIE (13) has been considered an independent predictor of increased mortality (14) and further study of this entity should be encouraged. Univariate analysis also supported this difference: HAIE was associated with a higher in-hospital mortality rate compared with non-HAIE (75% vs 20% p=0,027) and CAIE was associated with a better prognosis than non-CAIE (16% vs 80% p =0,005).

With concern to microbiology, it is also worth mentioning that the frequency of *S. viridans* was similar to other cohorts (5,8), though the proportion of Streptococci *spp.* was higher than in most reports (23% - 29%) (3,5,10). The reason for this is not very clear but it might be due to the dimension of the cohort, as it has been referred elsewhere (2) that the shift from predominantly streptococcal IE to predominantly staphylococcal IE is not evident in

population-based studies. Also, it might be due to the fact that oral health services are not contemplated in the national health service plans in Portugal for the general population; poor oral hygiene is an established risk factor for IE (19). Moreover, it seems relevant to state that there was a considerable increase on *S.viridans* IE (10% to 20%) comparing with the previous cohort. Though, we suppose that it might be related with the much higher proportion of negative blood cultures IE in the older cohort, assuming that in case of previous antibiotic therapeutic this agent is among the ones most often untraceable (2).

In this series Enterococci *spp.* presented as the third most frequent causative microorganism (12%), a value consistent with other reports (5,8). Of note, two out of the three were VRE, two of the patients died in-hospital and the third patient was dead at last contact/ follow-up (201 days after discharge). There is a paucity of data on Enterococci *spp.* IE, so further understanding of this trend should be promoted. Regarding the two patients with VRE, it should be referred that these tend to be very challenging patients with significant underlying disease and to whom is very difficult to provide efficient bactericidal antimicrobial therapy (20). In univariate analysis multidrug-resistant microorganisms (including MRSA e VRE) were associated with poorer prognosis ($p = <0.001$).

The only clinical complication associated with increased mortality in univariate analysis was shock (11% vs. 71% $p = 0,003$). Despite the high incidence of AKI (52%) comparing with previous studies (8), only baseline serum creatinine ($1,16 \pm 0,66$ vs. $1,82 \pm 1,20$ mg/dL, $p = 0,045$) was associated with a poorer prognosis. The proportion of patients with at least one clinical complication (72%) was similar to literature (3), as were the episodes of congestive HF (60%), cerebral embolism (16%) and non-cerebral embolism (12%) (3,5,8).

With concern to echocardiography findings, the proportion of patients with abscess (24%) and severe regurgitation (68%) was higher than in other series. Both these findings are predictors

of poor outcome in patients with IE (2) and might have contributed to the high in-hospital mortality rates registered.

Although the proportion of patients that were surgically treated (52%) was comparable with contemporary reports (3,5,8), the median time from diagnosis till surgery was 30 days IQR (11-40) days, a value higher than reported in other cohorts (6-10 days) (3,8). Taking in account that 84% of the patients had at least one indication for urgent or emergent surgery (2), the delay until surgery might have influenced the in-hospital mortality rate, though literature is controversial about the impact of surgical timing on outcomes (9,12–14).

Also, it would be important to better recognize the contra-indications for surgery, considering that the group of patients with a guideline-supported indication for surgery who had access only to medical treatment was the subgroup with worst prognosis. The in-hospital mortality of this group of patients was 75%, upholding to the conclusions of recent reports (3,12). However, it would be expected to reach this conclusion giving that normally patients who are not submitted to surgery despite indication are also usually those in worst condition.

Finally, it would be important to mention that considering the comparison between the two cohorts, the decrease on mortality rates is probably best explained by an increase in surgically treated patients (from 29% to 52%), given that surgery in both cohorts (21), as in other reports, is a critical factor associated with reduced mortality (5,9).

CONCLUSION

In summary, we conclude that IE continues to impose significant in-hospital mortality, although a trend to a lower number of deaths was registered during this 10-year period. Gram-positive agents continue to be the most common pathogens and the initial antibiotic scheme must reflect this reality. Surgery is clearly associated with better results and a surgical

approach has almost numerically doubled. This may explain the better survival results. IE is one of the deadlier cardiovascular diseases and must be approached by a multidisciplinary team in a high-dependency environment.

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"Sei que o tempo caminha veloz,
Que tudo na vida tem fim,
oh Mondego que segues, correndo para a foz,
Não afastes Coimbra de mim "

(Canção ao Mondego, TMUC)

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