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Time Interval between Infective Endocarditis First Symptoms and Diagnosis: Relationship to Infective Endocarditis characteristics, Microorganisms and Prognosis

Running title: **Time interval between Infective Endocarditis symptoms and diagnosis**

(3059 words)

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Abstract: (194 words)

Objective

To analyze the characteristics and outcome of infective endocarditis (IE) according to the time interval between IE first symptoms and diagnosis.

Methods

Among the IE cases of a French population-based epidemiological survey, patients having early-diagnosed IE (diagnosis of IE within 1 month of first symptoms) were compared to those having late-diagnosed IE (diagnosis of IE more than 1 month after first symptoms).

Results

Among the 486 definite-IE, 124 (25%) had late-diagnosed IE whereas others had early-diagnosed IE. Early-diagnosed IE were independently associated with female gender (OR = 1.8; 95% CI [1.0-3.0]), prosthetic valve (OR= 2.6; 95% CI [1.4-5.0]) and staphylococci as causative pathogen (OR=3.7; 95% CI [2.2-6.2]). Cardiac surgery theoretical indication rates were not different between early and late-diagnosed IE (56.3% vs 58.9%), whereas valve surgery performance was lower in early-diagnosed IE (41% vs 53%; p=0.03). In-hospital mortality rates were higher in early-diagnosed IE than in late-diagnosed IE (25.1% vs 16.1%; $p < 0.001$).

Conclusions

The time interval between IE first symptoms and diagnosis is closely related to the IE clinical presentation, patient characteristics and causative microorganism. Better prognosis reported in late-diagnosed IE may be related to a higher rate of valvular surgery.

Keywords: Infective endocarditis; acute; chronic; stroke; mortality; septic shock; cardiac surgery; prognosis.

Key messages :

- Infective endocarditis, which time interval between first symptoms and diagnosis was less than one month, were mainly due to *Staphylococcus aureus* in France.

- *Staphylococcus aureus* infective endocarditis were associated with septic shock, transient ischemic attack or stroke and higher mortality rates than infective endocarditis due to other bacteria or infective endocarditis, which time interval between first symptoms and diagnosis was more than one month.

- Infective endocarditis, which time interval between first symptoms and diagnosis was more than one month, were accounting for one quarter of all infective endocarditis in our study and were associated with vertebral osteomyelitis and an higher rate of cardiac surgery performed for hemodynamic indication than other infective endocarditis.

Introduction

Infective endocarditis (IE) is a rare but severe disease with an in-hospital mortality rate of around 20% (1) and a 5-year mortality rate of 40% (2). It also has a high morbidity and cost burden: its treatment requires prolonged hospitalization; one out of two patients undergoes valve surgery during the acute phase of the disease; and quality of life and return to work are compromised in some patients (3-4). These could be partly due to the delay induced by the difficulties in diagnosing this polymorphic disease.

For decades, IE had been classified according to its mode of presentation, which led to consider acute, subacute and chronic IE (5); without treatment, IE is a uniformly fatal disease and the old categories of acute, subacute and chronic disease only referred to the time it was anticipated to take before the patient would die. Following the dramatic changes in predisposing factors (decreased prevalence of rheumatic heart disease and increased prevalence of patients with prosthetic valve), in the source of microorganism acquisition (e.g. increased healthcare-associated acquisition) (6), and the improvement of outcome, classification of IE is now multifaceted, taking into account predisposing factors (native valve, prosthetic valve, intracavitary devices), the source of acquisition (community-acquired, healthcare-related), as well as the patient's background (intravenous drug user, elderly), with some overlap between the different classifications (1). These changes in IE categorization result in part from widespread access to new imaging techniques (7), including transthoracic and transesophageal echocardiography, which make it easier to diagnose IE earlier.

However, taking into account the time interval between the first symptom and the date of diagnosis of IE may hold an interest in terms of diagnostic and prognostic assessment of individual patients. In the case of non-acute IE, in which the prolonged time interval before diagnosis reflects the difficulties in diagnosing IE, the diagnostic delay may be associated with higher rates of cardiac lesions (destructive valve lesions, peri-annular abscess) or extra-

cardiac complications (embolism, aneurysm) and consequently a worse outcome. Furthermore, revisiting the description of initial symptoms may help practitioners diagnose IE earlier in the era of these newer imaging techniques.

In this study, based on a large population-based survey on IE, we compared initial pre-hospital symptoms, microbiological profile, patients' clinical status at the time of diagnosis, the presence of an indication for surgical treatment and the overall IE prognosis in patients whose IE was diagnosed less than 1 month after first symptoms (early-diagnosed IE) and in patients whose IE was diagnosed more than one month after first symptoms (late-diagnosed IE).

Patients and Methods

Design and patients

For this study, we analyzed the database that had been created for the purpose of the French population-based epidemiological survey on definite IE in 2008, which methods and results have been published elsewhere (8). In brief, this survey had been conducted in seven regions of France (Paris, Lorraine, Rhône-Alpes, Franche-Comte, Marne, Ille-et-Vilaine, Languedoc-Roussillon), a population pool of 16 million inhabitants, during a 12-month-period. During this period, all IE cases that were diagnosed in adult patients, before or after their referral to hospital, were reported. A standardized case report form (CRF) was prospectively filled out during the study and each reported case was then validated by an adjudication committee. All IE that were not classified as definite according to modified-Duke criteria (9) were excluded from further analysis.

Collected data

The data related to patients' background, IE initial symptoms, IE in-hospital data (clinical, biological, microbiological and echocardiography) and outcome (in-hospital and 1 year mortality) were extracted from the survey database.

Classification of IE based on its acquisition source (community-acquired, nosocomial and healthcare-related but non-nosocomial) had been performed as previously reported (10). Pre-hospital symptoms or symptoms at the time of IE diagnosis, which were recorded as open responses in the original CRF, were secondarily summarized into categorical variables. The presence of a severe sepsis or septic shock, of transient ischemic attack or of stroke was also recorded in the original epidemiological survey. The binary "severe sepsis/septic shock" variable was set at 'yes' whenever severe sepsis or septic shock – based on usual definitions (11) – was observed during the course of the disease. All foci of infection other than

bloodstream, heart and presumed portal of entry were categorized as a "secondary site" of infection.

Time interval between initial symptoms and diagnosis

Patients were assigned to the early-diagnosed IE group when diagnosis of IE was established within 1 month of the first symptoms; patients were assigned to the late-diagnosed IE group when diagnosis was established later than 1 month after the first symptoms. In patients with community-acquired and non-nosocomial healthcare-related IE, such categorization was calculated using time interval between first symptoms and the date of hospitalization (a proxy for the date of diagnosis of IE); in patients with nosocomial healthcare-related IE, such categorization was calculated using time interval between the date of the first symptoms and the date of echocardiography. These time intervals were expressed in the original CRF as qualitative variables: less or equal to one month, between 1 and 3 months or more than 3 months. In 9 cases of nosocomial healthcare-related IE, the time interval was categorized as shorter than one month when the date of the first IE symptoms was doubtful. Moreover, to better appreciate the time interval between symptoms and diagnosis of all early-diagnosed IE (community-acquired, non-nosocomial health related and nosocomial IE), the time interval was also calculated as difference between the calendar date of first symptoms and that of hospitalization during which IE diagnosis was established, when these calendar dates of first symptoms and hospitalization were available and undoubtful in the original CRF.

Valve surgery

Theoretical indication for valve surgery during hospitalization had been determined by the treating physicians in each center and recorded prospectively in the original survey. For each

patient, in each investigating center, an investigator had classified each patient as having a theoretical indication for valve surgery according to current guidelines at the time of diagnosis (12). These indications were defined as either hemodynamic (aortic or mitral valve obstruction or aortic or mitral IE with fistula associated with heart failure or cardiogenic shock and aortic or mitral severe regurgitation associated or not with heart failure or cardiogenic shock), infectious (perivalvular abscess, persisting fever or positive blood cultures), embolic (very large vegetations or large vegetations associated with previous embolic event), or a combination of these, always in accordance with current guidelines at the time of diagnosis (12). The performance of cardiac surgery was also prospectively recorded.

Mortality and outcome

The in-hospital mortality rate was defined as the number of patients with IE who died during the initial hospital stay, whatever the cause of death, divided by the study population. The all-cause one-year mortality was also determined; the patient living status was obtained from patient's physician or, when not available, from the register of births and deaths.

Statistical analysis

Quantitative variables were expressed as mean ± SD and qualitative variables were expressed as frequency and percent.

For intergroup comparison, we used ad hoc methods (1-way analysis of variance or Kruskal Wallis test for quantitative variables and Pearson chi-square test or Fisher exact test for qualitative variables), and 0.05 was the level of statistical significance.

All clinical characteristics of interest (among patients' background characteristics, presumed source of infection, IE valvular localization, microorganisms, vegetation size and

intra-cardiac abscess existence) with a p value <0.20 were entered in a multivariate logistic regression model to investigate factors independently associated with early-diagnosed IE. A stepwise variable selection method was used with an enter p value of 0.2 and a remove p value of 0.05.All statistical analyses were performed using SAS (version 9.2) software (SAS Institute Inc., Cary, NC, USA).

Results

The data of 486 patients with definite IE were analyzed; of these, 356 patients had community-acquired, 105 had nosocomial, and 14 non-nosocomial healthcare-related IE; the presumed mode of acquisition was unknown in 11 patients.

Time interval between initial symptoms and diagnosis

Most patients (362 representing 74.5% of the entire cohort) had an early-diagnosed IE while 124 (25.5%) had a late-diagnosed IE. Among the 235 early-diagnosed IE patients with available calendar date of the first symptom onset, the time interval between diagnosis of IE and first symptoms was less than 7 days in 70.2% of the patients, between 7 and 14 days in 17.5% and above 14 days in 12.3%. Of note, in 42 of the 124 late-diagnosed IE patient group (33.9%), first IE symptoms occurred more than 3 months before diagnosis.

Clinical characteristics and causative microorganisms according to the time interval

The clinical characteristics of IE according to the time to diagnosis are described in Table I. There was a lower proportion of males (72.4% vs 83.1%, p=0.01) and a higher proportion of intravenous drug users (7.2% vs 2.4%, p=0.05) in early-diagnosed IE than in late-diagnosed IE. Valve prosthesis IE (24% vs 11.3%, p=0.009) and nosocomial IE (24.8% vs 12.1%, p=0.007) were more frequently observed in early-diagnosed IE than in late-diagnosed IE.

Causative microorganisms in early-diagnosed IE and late-diagnosed IE patients are reported in Table I and supplementary Table I. Among the 130 *Staphylococcus aureus* IE, 119 (91.5%) occurred in early-diagnosed IE patients group. Among the 46 coagulase negative staphylococcus IE, 34 (73.9%) occurred in early-diagnosed IE patients group (Figure 1) (supplementary Table I). *Enterococci and* group D streptococci were less frequently observed in early-diagnosed IE patients group, whereas pyogenic streptococci, *S. pneumoniae*, and *S.*

agalactiae were almost exclusively observed in early-diagnosed IE. Other *Streptococcus* species were equally distributed between early-diagnosed IE and late-diagnosed IE patients groups (supplementary Table I).

Factors independently associated with early-diagnosed IE were female sex (OR = 1.8; 95% CI [1.0-3.0]), the presence of a prosthetic valve (OR= 2.6; 95% CI [1.4-5.0]) and staphylococci as the causative pathogen (OR=3.7; 95% CI [2.2-6.2]).

IE symptoms and biological values at presentation

Symptoms occurring before or at the time of IE diagnosis are reported in Table II. Fever, severe sepsis/ septic shock, and nausea were more frequently observed in early-diagnosed IE than in late-diagnosed IE. Mean C Reactive Protein was higher in early-diagnosed IE than in late-diagnosed IE. Weight loss and fatigue were less frequently observed in early-diagnosed IE than in late-diagnosed IE.

Valve surgery

Rates and types of theoretical indications for surgery were different according to groups. A theoretical indication for valve surgery was less frequent in early-diagnosed IE patients. Valve surgery was also less frequently performed (whether for heart failure or embolism prevention) in early-diagnosed IE than in late-diagnosed IE (Table III).

Mortality and outcome

Table III presents IE complications and mortality rates in the early-diagnosed IE and late-diagnosed IE patients groups and also according to the microorganism in the early-diagnosed IE group. Early-diagnosed IE patients had more frequently septic shock, transient ischemic attack or stroke; both in-hospital and one-year mortalities were higher in early-diagnosed IE

than in late-diagnosed IE groups. Vertebral osteomyelitis was less frequently observed in early-diagnosed IE than in late-diagnosed IE in-hospital.

In hospital mortality was higher in early-diagnosed IE patients than in late-diagnosed IE patients (25.1 vs 16.1%) such was one-year mortality (51.9% vs 17.7%) (Table III). Among early-diagnosed IE group, *Staphylococcus aureus* species mainly accounted for in-hospital or one-year mortalities, as well as for the presence of septic shock or transient ischemic attack or stroke (Table III). Results were the same when the 11 late-diagnosed IE due to *Staphylococcus aureus* (supplementary Table I) were removed from analysis (data not shown).

Discussion

In this large population-based study on definite IE focusing on the initial presentation of IE, we reported a marked difference in clinical presentation as well as in-hospital outcome which are related more to the nature of the microorganisms than intrinsically to the rapidity of diagnosis. Diagnosis of IE was established over one month after the beginning of symptoms in 25% of patients, and as long as 3 months in 8 %.

The design of this multiregional prospective population-based study allowed us to exclude referral bias and to properly assess the epidemiological and clinical presentation of IE. We could assume that clinical data presented here were robust enough to describe the diagnostic timeline and the polymorphic clinical presentation of IE. Despite the fact that the time interval between the first IE symptom and the diagnosis of IE depends in part on the healthcare system, which could vary according to country, we think that the clinical presentation of IE reported in the present study may be close to those of patients suffering from IE in other countries.

Early-diagnosed IE represents a heterogeneous population of IE patients, who can, based on our results, also be subdivided into two subgroups: early-diagnosed IE due to virulent bacterial species (such as *Staphylococcus aureus* and pyogenic streptoccocci) and early-diagnosed IE due to other bacteria. The first subgroup is composed of patients for whom the infectious and/or inflammatory manifestations of IE are prominent. These IE are mainly due to virulent microorganisms such as *Staphylococcus aureus* and pyogenic streptococci. Infectious manifestations (fever, septic shock...) lead to a sound presentation, and early diagnosis and care. As reported by others, this acute presentation is associated with a poor prognosis, with mortality rates over twice as high as in late-diagnosed IE (14). The overrepresentation of *Staphylococcus aureus* in this sub-group explains the high proportion of nosocomial infections, and of prosthetic valve IE. This high proportion of patients with

prosthetic valve in the early-diagnosed IE (which is an independent associated factor for early-diagnosed IE) is also probably due to an earlier evocation of the possibility of IE in case of symptom occurrence in these patients clearly recognized at high incidence of IE. The high rate of early mortality and septic shock probably explains than almost one-third of patients theoretically having cardiac surgery indications finally did not undergo surgery. IE prognosis in this subgroup of patients seems to be more related to control of the bacterial infection than to valve dysfunction. These data support the interest of an empiric antibiotic strategy active against *Staphylococcus aureus* and "virulent streptococci" in patients with acute IE, pending for blood culture results. The second sub-group of patients included in the early-diagnosed EI group has a clinical and microbiological profile which is quite similar to that of late-diagnosed IE patients. It probably represents IE which has been diagnosed rapidly after the onset of first symptoms despite a less symptomatic presentation, due to more specific initial symptoms and/or greater practitioner attentiveness.

The late-diagnosed IE group accounted for one-quarter of all definite IE, and were frequently associated with weight loss, and asthenia; late-diagnosed IE were mainly due to non-virulent microorganisms such as oral or digestive streptococci on native valve diseases. These data first suggested that intravenous ampicillin could be the drug of choice for empirical treatment of late-diagnosed IE in the context of this study. Moreover, these data also suggested that health education of patients with native valve disease could reduce the time interval between symptoms like asthenia and diagnosis or between dental procedure and diagnosis. Interestingly, fever was absent in more than 25% of cases (Table II); clinicians should keep in mind the diagnosis of subacute IE and look for heart murmur abnormalities when faced with asthenia or weight loss in patients with or without previous IE predisposing cardiac conditions even without fever (15). In fact, the diagnosis of subacute IE still remains difficult due to this non-specific and polymorphic clinical presentation. This is illustrated by

the long time interval before diagnosis (more than 3 months after the beginning of symptoms) in some patients. No clinical sign reported here was specific enough to help the clinician easily make the diagnosis of IE. This long time interval before diagnosis of IE is associated with a high rate of valve destruction, which had time to occur, and with a high rate of indications for hemodynamic surgery, which was finally performed in most of the patients. This assertion is confirmed by the data of DeSimone and colleagues, which provides evidence of a higher diagnosis delay and a higher surgery rate in euthermic endocarditis than in febrile endocarditis (15).

As demonstrated in our study, *Staphylococcus aureus* (which are responsible for early-diagnosed IE) carried a poor prognosis as compared to all other patients, whether or not they belonged to the early-diagnosed IE or to the late-diagnosed IE patients. Considering the subgroup of oral streptococci IE, the chronicity of the infection is associated with high rates of valvular damage, valvular surgery which was both indicated and performed most often in this situation. The early-diagnosed versus late-diagnosed IE classification which was already debated fifty years ago (5), could remain of interest from a diagnostic point of view, because it still underlines the persistent need for a high degree of suspicion of sub-acute endocarditis in case of weight loss or asthenia in a community setting in patients without previously known IE predisposing cardiac conditions. Moreover, the frequent occurrence of cardiac surgery in late-diagnosed IE patients group without any significant increase of mortality suggested that this time interval may also hold an interest in the evaluation of IE outcome in further studies evaluating the impact of surgery on outcome of IE.

We acknowledge several limitations to our study. First, the determination of initial symptoms has been obviously made *a posteriori* by patients and practitioners (but prospectively in the study) and could be affected by recall bias. Furthermore, as most of these symptoms are non-specific, it is difficult to ascertain that they were really related to IE.

Second, we did not take into account any microorganism virulence factors, which could differ within microorganism species according to strain and could be responsible for the diversity of IE presentations.

In the present report, the time interval to diagnosis of IE is closely related to the types of IE clinical presentation, themselves closely related to patient characteristics, microorganism virulence and capacity to induce severe inflammatory response syndrome, and practitioner propensity for considering the possibility of IE diagnosis. Taken together, this leads to distinct clinical IE presentations, with different treatment priorities, in which cardiac surgery plays a major role. In non-*Staphylococcus aureus* IE, the late diagnosis resulting in more extensive valve lesions (suggested by the higher rate of cardiac surgery performed for hemodynamic indication) does not appear to impact prognosis, maybe because of frequent use of valve surgery. Given the poor prognosis of IE, practitioners must be educated to evoke this disease systematically, most obviously in case of septic presentation, but also in case of atypical presentations whether or not fever is present.

Annex 1:

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Statistical analysis: F. Alla, ML Erpelding

Competing interests

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Figure captions

Figure 1: Repartition of microorganisms according to the time interval between first symptoms and diagnosis.

White bars: Late-diagnosed infective endocarditis (first IE symptoms occurring >1 months before diagnosis of infective endocarditis; n=124)

Black bars: Early-diagnosed infective endocarditis (first IE symptoms occurring ≤ 1 month before diagnosis of infective endocarditis; n=362)

Table I: Clinical characteristics of the 486 patients according to time interval between first symptoms and diagnosis of definite infective endocarditis (IE).

	All IE n=486	Early-diagnosed IE n=362 (74.5)	Late-diagnosed IE n=124 (25.5)	p
Background characteristics				
Age (years) (mean±SD)	62.4 ±15.9	62.1±16.6	63.3±13.7	0.660
Male sex	365 (75.1)	262 (72.4)	103 (83.1)	0.010
Charlson score° (mean±SD)	1.9±2.2	2.0±2.3	1.7±2.1	0.090
Malignancies	87 (17.9)	63 (17.4)	24 (19.4)	0.070
Intravenous drug use	29 (6.0)	26 (7.2)	3 (2.4)	0.050
IE characteristics				
Presumed mode of acquisition of IE *				
Community-acquired IE	356 (74.9)	251 (71.3)	105 (85.4)	0.007
Non nosocomial health related	14 (2.9)	11 (3.0)	3 (2.4)	
Nosocomial IE	105 (22.1)	90 (24.8)[£]	15 (12.1)	
Previously known native valve disease	130 (26.1)	91 (25.1)	39 (31.5)	0.009
Prosthetic valve IE	101 (20.8)	87 (24.0)	14 (11.3)	0.009
Left-sided IE	390 (80.2)	288 (79.6)	102 (82.3)	0.510
Intracardiac device associated IE	25 (5.1)	21 (5.8)	4 (3.2)	0.260
Microorganisms				
Streptococci	177 (36.4)	118 (32.6)	59 (47.6)	0.0028
Oral *streptococci*	91 (18.7)	58 (16.0)	33 (26.6)	0.0091
Group D *streptococci*	62 (12.8)	37 (10.2)	25 (20.2)	0.0042
Pyogenic *streptococci*	24 (4.9)	23 (6.4)	1 (0.8)	0.0139
Enterococci	52 (10.7)	31 (8.6)	21 (16.9)	0.0092
Other *Streptococcaceae*	8 (1.6)	5 (1.4)	3 (2.4)	0.4266
Staphylococcus aureus	130 (26.7)	119 (32.9)	11 (8.9)	<0.0001
Coagulase-negative *staphylococci*	46 (9.4)	34 (9.3)	12 (9.7)	0.9254
Other microorganisms	40 (8.2)	29 (8.0)	11 (8.9)	0.7636
≥2 Microorganisms	9 (1.9)	6 (1.7)	3 (2.4)	0.6995
No microorganism identified	24 (4.9)	20 (5.5)	4 (3.2)	0.3078
Vegetation size §				
≤15 mm	218 (44.9)	162 (44.7)	56 (45.1)	0.600
>15mm	124 (25.5)	89 (24.6)	35 (28.2)	
Valvular or paravalular abscess	100 (20.6)	79 (21.8)	21 (16.9)	0.430

Note: Number (%) or specified

Late-diagnosed infective endocarditis (first IE symptoms occurring >1 months before diagnosis)

Early-diagnosed infective endocarditis (first IE symptoms occurring ≤ 1 month before diagnosis)

° Charlson score [13]

* In 11 patients, the mode of acquisition of IE was unknown.

[£] In 9 out of the 105 nosocomial IE, the time interval between first symptoms and IE diagnosis was doubtful and classified as shorter than 1 month.

§ Missing data = 144 (29.6)

Table II: Clinical Symptoms and biological data (before hospitalization and at the time of diagnosis) of the 486 patients according to the time delay between first symptoms and diagnosis of definite Infective Endocarditis (IE).

Clinical symptoms	All IE n=486	Early-diagnosed IE n=362	Late-diagnosed IE n=124	p
Patients' reported symptoms				
Fever	395 (81.4)	303 (83.9)	92 (74.2)	0.016
Fatigue	158 (32.5)	95 (26.2)	63 (50.8)	<0.0001
Weight loss	134 (27.6)	75 (20.7)	59 (47.6)	<0.0001
Pain				
Headache	15 (3.1)	13 (3.6)	2 (1.6)	0.374
Thoracic pain	19 (3.9)	18 (5.0)	1 (0.8)	0.055
Abdominal pain	18 (3.7)	11 (3.0)	7 (5.6)	0.180
Rachialgia	49 (9.9)	32 (8.8)	16 (12.9)	0.190
Nausea/Vomiting	25 (5.1)	23 (6.4)	2 (1.6)	0.039
Cough	21 (4.3)	15 (4.1)	6 (4.8)	0.742
Dyspnea	103 (21.2)	78 (21.5)	25 (20.2)	0.744
IE manifestations				
Congestive heart failure	173 (35.6)	132 (36.5)	41 (33.1)	0.495
Extra cerebral embolism	21 (4.3)	16 (4.4)	5 (4.0)	0.854
Transient ischemic attack or stroke	21 (4.3)	17 (4.7)	4 (3.2)	0.480
Severe sepsis/septic shock	54 (11.1)	48 (13.3)	6 (4.8)	0.010
Secondary site of infection	83 (17.1)	56 (15.5)	27 (21.8)	0.107
Splenomegaly	41 (8.4)	28 (7.7)	13 (10.5)	0.341
Laboratory parameters at the time of IE diagnosis				
White blood cell count (G/l)	13.8±11.6	13.8±11.7	13.8± 11.4	0.893
C reactive protein (mg/l)	138.8±111.5	153.8±115.9	96.1±84.5	<0.0001
Creatininemia (µmol/l)	124.4±101.6	129.4± 107.4	110.2±81.6	0.116

Note: Late-diagnosed infective endocarditis (first IE symptoms occurring >1 months before diagnosis)
Early-diagnosed infective endocarditis (first IE symptoms occurring ≤ 1 month before diagnosis)

Table III: Valve surgery, mortality and complications according to *Staphylococcus aureus* species and to time interval between first symptoms and diagnosis of definite Infective Endocarditis (IE).

	Early-diagnosed IE n=362	**Early-diagnosed IE *(S. aureus)* n=119 (32.9)**	**Early-diagnosed IE (other microorganisms) n=243 (67.1)**	**Late-diagnosed IE n=124**	**P§**	**P***
Age	62.1±16.5	59.8±18.4	63.2±15.4	63.3±13.7	0.22	0.95
Charlson score (mean±SD)	2.03±2.29	1.98±2.22	2.05±2.32	1.7±2.1	0.21	0.10
Septic shock **	72 (19.9)	40 (33.6)	32 (13.2)	8 (6.5)	<0.0001	0.05
Transient ischemic attack or stroke**	92 (25.4)	35 (29.4)	57 (23.5)	20 (16.1)	0.01	0.10
Vertebral osteomyelitis	21 (5.8)	8 (6.7)	13 (5.3)	18 (14.5)	0.05	0.0078
Cardiac surgery theoretical indication	204 (56.3)	63 (52.9)	141 (58.0)	73 (58.9)	0.35	0.87
Type of cardiac surgery theoretical indication						
- hemodynamic	119 (32.8)	27 (22.7)	92 (37.9)	58 (46.8)	<0.0001	0.10
- infectious	91 (25.1)	32 (26.9)	59 (24.3)	26 (21.0)	0.28	0.47
- embolism prevention	77 (21.2)	33 (27.7)	44 (18.1)	36 (29.0)	0.82	0.01
Valvular surgery performed	151 (41.7/74.0°)	44 (37.0/69.8°)	107 (44.0/75.8°)	66 (53.2/90.4°)	0.01	0.09
In-hospital mortality	91 (25.1)	48 (40.3)	43 (17.7)	20 (16.1)	<0.0001	0.70
One year mortality	118 (51.9)	56 (47.1)	62 (25.5)	22 (17.7)	<0.0001	0.09

Note:
Number and (%) or specified;
Late-diagnosed infective endocarditis (first IE symptoms occurring >1 months before diagnosis)
Early-diagnosed infective endocarditis (first IE symptoms occurring ≤ 1 month before diagnosis)
S. aureus: Staphylococcus aureus

§ p value when Early-diagnosed IE due to *S. aureus* were compared to Late-diagnosed IE
* p value when Early-diagnosed IE due to all microorganisms except *S. aureus* were compared to Late-diagnosed IE
** including initial presentation and following events
° rate as compared to the number of patients with theoretical indications.

Supplementary Table I: Streptococci and Staphylococci species involved in microbiologically documented Infective Endocarditis (IE) (n=413) according to time interval between first symptoms and diagnosis of IE.

Streptococcaceae	**Early-diagnosed IE n=154 (65.0%)**	**Late-diagnosed IE n=83 (35.0%)**
Pyogenic streptococci	**31 (20.1%)**	**1 (1.2%)**
Streptococcus pyogenes	2 (1.3%)	0 (0%)
Streptococcus agalactiae	13 (8.4%)	1 (1.2%)
Streptococcus dysgalactiae subsp. equisimilis	8 (5.2%)	0 (0%)
Streptococcus pneumoniae	8 (5.2%)	0 (0%)
Digestive streptococci	**63 (40.9%)**	**41 (49.4%)**
Streptococcus gallolyticus	25 (16.2%)	19 (22.9%)
Streptococcus infantarius	2 (1.3%)	0 (0%)
Streptococcus lutetiensis	1 (0.6%)	1 (1.2%)
Streptococcus pasteurianus	4 (2.6%)	0 (0%)
Enterococcus faecalis	29 (18.8%)	19 (22.9%)
Enterococcus faecium	2 (1.3%)	2 (2.4%)
Other streptococci	**60 (39.0%)**	**41 (49.4%)**
Abiotrophia defectiva	1 (0.6%)	0 (0%)
Aerococcus viridans	0 (0%)	1 (1.2%)
Gemella sanguinis	1 (0.6%)	0 (0%)
Gemella sp.	1 (0.6%)	1 (1.2%)
Granulicatella adiacens	2 (1.3%)	1 (1.2%)
Streptococcus anginosus	3 (1.9%)	4 (4.8%)
Streptococcus australis	0 (0%)	1 (1.2%)
Streptococcus constellatus	1 (0.6%)	0 (0%)
Streptococcus cristatus	1 (0.6%)	0 (0%)
Streptococcus gordonii	4 (2.6%)	5 (6.0%)
Streptococcus gr unspecified specie	5 (3.2%)	5 (6.0%)
Streptococcus mitis	8 (8.2%)	3 (3.6%)
Streptococcus mitis/oralis	1 (0.6%)	1 (1.2%)
Streptococcus mutans	3 (1.9%)	1 (1.2%)
Streptococcus oligofermentans	1 (0.6%)	0 (0%)
Streptococcus oralis	18 (11.7%)	8 (9.6%)
Streptococcus parasanguis	1 (0.6%)	1 (1.2%)
Streptococcus salivarius	4 (2.6%)	3 (3.6%)
Streptococcus sanguinis	5 (3.2%)	4 (4.8%)
Streptococcus sp.	0 (0%)	2 (2.4%)

Staphylococcaceae	**Early-diagnosed IE n=153 (86.9%)**	**Late-diagnosed IE n=23 (13.1%)**
Staphylococcus aureus	**119 (77.8%)**	**11 (47.8%)**
Coagulase negative staphylococci	***34 (22.2%)***	***12 (52.2%)***
Staphylococcus capitis	2 (1.3%)	1 (4.3%)
Staphylococcus epidermidis	24 (15.7%)	9 (39.1%)
Staphylococcus haemolyticus	1 (0.7%)	1 (4.3%)
Staphylococcus lugdunensis	3 (2.0%)	1 (4.3%)
Staphylococcus sp.	4 (2.6%)	0 (0.0%)

Note: Late-diagnosed infective endocarditis (first IE symptoms occurring >1 months before diagnosis)
Early-diagnosed infective endocarditis (first IE symptoms occurring ≤ 1 month before diagnosis)