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Annals of Medicine

Original article

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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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45 **Abstract: (194 words)**

46 **Objective**

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

49 **Methods**

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

53 **Results**

54 Among the 486 definite-IE, 124 (25%) had late-diagnosed IE whereas others had early-
55 diagnosed IE. Early-diagnosed IE were independently associated with female gender (OR =
56 1.8; 95% CI [1.0-3.0]), prosthetic valve (OR= 2.6; 95% CI [1.4-5.0]) and staphylococci as
57 causative pathogen (OR=3.7; 95% CI [2.2-6.2]). Cardiac surgery theoretical indication rates
58 were not different between early and late-diagnosed IE (56.3% vs 58.9%), whereas valve
59 surgery performance was lower in early-diagnosed IE (41% vs 53%; p=0.03). In-hospital
60 mortality rates were higher in early-diagnosed IE than in late-diagnosed IE (25.1% vs 16.1%;
61 p < 0.001).

62 **Conclusions**

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

66

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

69

70 Key messages :

71

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

74

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

79

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

85

86 **Introduction**

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

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

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

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

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

120

121 **Patients and Methods**

122 *Design and patients*

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

133

134 *Collected data*

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

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

146 bloodstream, heart and presumed portal of entry were categorized as a “secondary site” of
147 infection.

148

149 *Time interval between initial symptoms and diagnosis*

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

166

167 *Valve surgery*

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

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

179

180

181 *Mortality and outcome*

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

186

187 *Statistical analysis*

188 Quantitative variables were expressed as mean \pm SD and qualitative variables were expressed
189 as frequency and percent.

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

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

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

200

201 **Results**

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

205

206 *Time interval between initial symptoms and diagnosis*

207 Most patients (362 representing 74.5% of the entire cohort) had an early-diagnosed IE while
208 124 (25.5%) had a late-diagnosed IE. Among the 235 early-diagnosed IE patients with
209 available calendar date of the first symptom onset, the time interval between diagnosis of IE
210 and first symptoms was less than 7 days in 70.2% of the patients, between 7 and 14 days in
211 17.5% and above 14 days in 12.3%. Of note, in 42 of the 124 late-diagnosed IE patient group
212 (33.9%), first IE symptoms occurred more than 3 months before diagnosis.

213

214 *Clinical characteristics and causative microorganisms according to the time interval*

215 The clinical characteristics of IE according to the time to diagnosis are described in Table I.
216 There was a lower proportion of males (72.4% vs 83.1%, $p=0.01$) and a higher proportion of
217 intravenous drug users (7.2% vs 2.4%, $p=0.05$) in early-diagnosed IE than in late-diagnosed
218 IE. Valve prosthesis IE (24% vs 11.3%, $p=0.009$) and nosocomial IE (24.8% vs 12.1%,
219 $p=0.007$) were more frequently observed in early-diagnosed IE than in late-diagnosed IE.

220 Causative microorganisms in early-diagnosed IE and late-diagnosed IE patients are
221 reported in Table I and supplementary Table I. Among the 130 *Staphylococcus aureus* IE, 119
222 (91.5%) occurred in early-diagnosed IE patients group. Among the 46 coagulase negative
223 staphylococcus IE, 34 (73.9%) occurred in early-diagnosed IE patients group (Figure 1)
224 (supplementary Table I). *Enterococci* and group D streptococci were less frequently observed
225 in early-diagnosed IE patients group, whereas pyogenic streptococci, *S. pneumoniae*, and *S.*

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

229 Factors independently associated with early-diagnosed IE were female sex (OR = 1.8;
230 95% CI [1.0-3.0]), the presence of a prosthetic valve (OR= 2.6; 95% CI [1.4-5.0]) and
231 staphylococci as the causative pathogen (OR=3.7; 95% CI [2.2-6.2]).

232

233 *IE symptoms and biological values at presentation*

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

239

240 *Valve surgery*

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

245

246 *Mortality and outcome*

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

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

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

260

261 Discussion

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

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

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

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

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

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

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

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

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

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

Annex 1:

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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 ^o (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				
<i>Streptococci</i>	177 (36.4)	118 (32.6)	59 (47.6)	0.0028
Oral <i>streptococci</i>	91 (18.7)	58 (16.0)	33 (26.6)	0.0091
Group D <i>streptococci</i>	62 (12.8)	37 (10.2)	25 (20.2)	0.0042
Pyogenic <i>streptococci</i>	24 (4.9)	23 (6.4)	1 (0.8)	0.0139
<i>Enterococci</i>	52 (10.7)	31 (8.6)	21 (16.9)	0.0092
Other <i>Streptococcaceae</i>	8 (1.6)	5 (1.4)	3 (2.4)	0.4266
<i>Staphylococcus aureus</i>	130 (26.7)	119 (32.9)	11 (8.9)	<0.0001
Coagulase-negative <i>staphylococci</i>	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 paravalvular 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)

^o 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 (<i>S. aureus</i>) 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%)
<i>Pyogenic streptococci</i>	31 (20.1%)	1 (1.2%)
<i>Streptococcus pyogenes</i>	2 (1.3%)	0 (0%)
<i>Streptococcus agalactiae</i>	13 (8.4%)	1 (1.2%)
<i>Streptococcus dysgalactiae subsp. equisimilis</i>	8 (5.2%)	0 (0%)
<i>Streptococcus pneumoniae</i>	8 (5.2%)	0 (0%)
<i>Digestive streptococci</i>	63 (40.9%)	41 (49.4%)
<i>Streptococcus gallolyticus</i>	25 (16.2%)	19 (22.9%)
<i>Streptococcus infantarius</i>	2 (1.3%)	0 (0%)
<i>Streptococcus lutetiensis</i>	1 (0.6%)	1 (1.2%)
<i>Streptococcus pasteurianus</i>	4 (2.6%)	0 (0%)
<i>Enterococcus faecalis</i>	29 (18.8%)	19 (22.9%)
<i>Enterococcus faecium</i>	2 (1.3%)	2 (2.4%)
<i>Other streptococci</i>	60 (39.0%)	41 (49.4%)
<i>Abiotrophia defectiva</i>	1 (0.6%)	0 (0%)
<i>Aerococcus viridans</i>	0 (0%)	1 (1.2%)
<i>Gemella sanguinis</i>	1 (0.6%)	0 (0%)
<i>Gemella sp.</i>	1 (0.6%)	1 (1.2%)
<i>Granulicatella adiacens</i>	2 (1.3%)	1 (1.2%)
<i>Streptococcus anginosus</i>	3 (1.9%)	4 (4.8%)
<i>Streptococcus australis</i>	0 (0%)	1 (1.2%)
<i>Streptococcus constellatus</i>	1 (0.6%)	0 (0%)
<i>Streptococcus cristatus</i>	1 (0.6%)	0 (0%)
<i>Streptococcus gordonii</i>	4 (2.6%)	5 (6.0%)
<i>Streptococcus gr unspecified specie</i>	5 (3.2%)	5 (6.0%)
<i>Streptococcus mitis</i>	8 (8.2%)	3 (3.6%)
<i>Streptococcus mitis/oralis</i>	1 (0.6%)	1 (1.2%)
<i>Streptococcus mutans</i>	3 (1.9%)	1 (1.2%)
<i>Streptococcus oligofermentans</i>	1 (0.6%)	0 (0%)
<i>Streptococcus oralis</i>	18 (11.7%)	8 (9.6%)
<i>Streptococcus parasanguis</i>	1 (0.6%)	1 (1.2%)
<i>Streptococcus salivarius</i>	4 (2.6%)	3 (3.6%)
<i>Streptococcus sanguinis</i>	5 (3.2%)	4 (4.8%)
<i>Streptococcus sp.</i>	0 (0%)	2 (2.4%)
Staphylococcaceae	Early-diagnosed IE n=153 (86.9%)	Late-diagnosed IE n=23 (13.1%)
<i>Staphylococcus aureus</i>	119 (77.8%)	11 (47.8%)
<i>Coagulase negative staphylococci</i>	34 (22.2%)	12 (52.2%)
<i>Staphylococcus capitis</i>	2 (1.3%)	1 (4.3%)
<i>Staphylococcus epidermidis</i>	24 (15.7%)	9 (39.1%)
<i>Staphylococcus haemolyticus</i>	1 (0.7%)	1 (4.3%)
<i>Staphylococcus lugdunensis</i>	3 (2.0%)	1 (4.3%)
<i>Staphylococcus sp.</i>	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)