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## **Influence of the healthcare pathway on the outcome of patients with infective endocarditis**

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1 **Influence of the health-care pathway on the outcome of patients with infective**  
2 **endocarditis**

3

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25

1 **Abstract**

2 **Aims:** To determine the prognosis of patients treated for infective endocarditis (IE) according  
3 to their health-care pathway. To assess how the ESC guidelines are implemented concerning  
4 the performance of transesophageal echocardiography (TEE), the use of antibiotic therapy, and  
5 the performance of valve surgery; and to compare the epidemiological profile of IE according  
6 to the type of centers in which the patients are hospitalized.

7 **Methods and results:** In a prospective multicentric study including 22 hospitals in the South-  
8 East of France, 342 patients were classified in three groups according to their health-care  
9 pathway: 119 patients diagnosed and taken care entirely in a reference center or hospital with  
10 cardiac surgery (Referral Center (RC) group), 111 patients diagnosed and initially taken care  
11 in a non-referral center (NRC) , then referred in a center including cardiac surgery (Transferred  
12 to Referral Center (TRC) group) and 112 patients totally taken care in NRC (NRC group). One-  
13 year mortality was 26% (88 deaths) and was not significantly different between groups 1 and 2  
14 (20% vs 21%,  $p = 0.83$ ). Patients in NRC group had a higher mortality (37%) compared to  
15 patients in RC and TRC groups ( $p < 0.001$ ). ESC guidelines were not implemented similarly  
16 depending on the health-care pathway ( $p = 0.04$ ). Patients in NRC group were significantly older  
17 ( $p < 0.001$ ) and had more comorbidities ( $p < 0.001$ ) than patients treated in referral centers.

18 **Conclusion:** Prognosis of patients with IE is influenced by their health-care pathway. Patients  
19 treated exclusively in NRC have a worse prognosis than patients treated in referral or surgical  
20 centers.

21

22 **Keywords :** endocarditis, mortality, health-care pathway, referral center

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## 1 **Introduction**

2           Epidemiologic profile of infective endocarditis (IE) has changed over the past twenty  
3 years,<sup>1 2 3</sup> but mortality remains high<sup>4 5 6</sup> despite diagnostic improvement and access to surgery  
4 in up to 50% of cases.<sup>7</sup> This persistent severity has justified the development of new diagnostic  
5 and therapeutic strategies to improve prognosis.<sup>8 9</sup> Management by a specialized  
6 multidisciplinary team within a referent medical-surgical center seems to be a key factor in  
7 improving patients prognosis,<sup>10 11</sup> and is recommended by the ESC guidelines.<sup>8 9</sup>

8           However, few studies have compared the prognosis and management of patients with  
9 IE according to their health-care pathway. Indeed, three situations are usually observed: patients  
10 for whom the diagnosis and management are carried out entirely in a referral center and/or  
11 having a cardiac surgery department, patients secondarily referred to a referral hospital or  
12 surgical center by another care center, patients for whom the entire care is provided within a  
13 non-referral care center. In addition, application of European guidelines remains difficult to  
14 assess in daily clinical practice outside the major referral centers. Published epidemiological  
15 data only represent part of the IE, most often not taking into account patients hospitalized in  
16 non-referral centers and therefore introducing a significant bias in the knowledge of this  
17 pathology.<sup>12</sup> Finally, although the ESC guidelines suggest that patients with uncomplicated IE  
18 can be managed in a non-reference center<sup>9</sup>, if all patients with IE<sup>13</sup> or only the sickest patients  
19<sup>14</sup> should be referred to reference centers is still a matter of debate.

20           The main objective of this study was to determine the prognosis of patients treated for  
21 IE according to their health-care pathway. The secondary objectives were to assess how the  
22 ESC guidelines are implemented concerning the performance of transesophageal  
23 echocardiography (TEE), the use of antibiotic therapy, and the performance of valve surgery,  
24 and to compare the epidemiological profile of IE according to the type of centers in which the  
25 patients are hospitalized.

## 1 **Methods**

### 2 **Study design and patients**

3           This was a prospective multicentric study including patients consecutively admitted for  
4 suspicion of IE in 22 hospitals in South-East of France between January 2014 and June 2017.  
5 These hospitals were both tertiary centers with cardiac surgery and second-level community  
6 hospitals. Inclusion criteria were a diagnosis of definite IE based on Duke modified criteria <sup>15</sup>  
7 on native, prosthetic or pacemaker/implantable automatic defibrillator. Non-inclusion criteria  
8 were age < 18 years and patients already included in the study and presenting with a new IE  
9 diagnosis. Patients were screened in the echocardiography lab of each institution and were  
10 prospectively included by local investigators.

11

### 12 **Patient and Public involvement**

13 All patients hospitalized for suspected IE were accepted on admission to participate in this  
14 research protocol. However, they were not involved in the design, conduct, reporting or  
15 dissemination plans of our research. The study complies with the Declaration of Helsinki.  
16 Written consent was waived by La Timone Institutional Review Board, which gave its approval  
17 for this study.

18

### 19 **Data collected at the time of inclusion and during hospitalization**

20           The following clinical data were collected: age, sex, previous cardiac and non-cardiac  
21 diseases, Charlson index score, date of first clinical signs, body temperature, presence of cardiac  
22 murmur, congestive heart failure, neurological complications, septic or cariogenic shock or  
23 atrio-ventricular block on electrocardiogram at time of admission and during hospitalization.

1 Biological data were collected, including hemoglobin level, platelet count, leukocytes count,  
2 C-Reactive Protein serum level, creatinine level, rheumatoid factor. Microbiological data  
3 included: positive or negative blood cultures, type of microorganism and antibiogram.

4 Echocardiographic data collected were: presence of vegetation and its maximal length,  
5 presence of periannular lesion (defined as the presence of abscess and/or pseudoaneurysm  
6 and/or fistula), presence of valvular regurgitation, quantified according to current  
7 recommendations.<sup>16 17</sup>

8 Type and date of the following complications were collected: congestive heart failure,  
9 peripheral embolism, neurological complications (including symptomatic and silent), mycotic  
10 aneurysm, acute kidney failure (>26 $\mu$ mol/L increase of serum creatinine in 48 hours or >50%  
11 increase in 7 days) , glomerulonephritis, uncontrolled infection (fever and/or positive blood  
12 cultures after 7 days of appropriate antibiotic therapy and unlinked to an extracardiac cause).

13 Moreover, type, dose and length of antibiotic therapy was reported. Antibiotic therapy  
14 was considered appropriate if drugs used and full duration of treatment were in accordance with  
15 ESC guidelines (taking into account patients terminating antibiotics prematurely due to death).  
16 Analysis of antibiotic treatment was conducted retrospectively by the Endocarditis team of the  
17 investigator center (CHU La Timone, Marseille).

18 During hospitalization or follow-up the indication (according to ESC guidelines) and  
19 date of surgery was also collected. Finally, surgical risk was evaluated using the Euroscore II.<sup>18</sup>

20

## 21 **Classification of patients according to health-care pathway**

22 Patients were classified in three groups according to their health-care pathway:

- 23 - Referral Center group (RC), including patients diagnosed and taken care entirely in a  
24 reference center or hospital with cardiac surgery (4 hospitals). These centers were the  
25 only surgical centers of this region of France.

- 1 - Transferred to Referral Center group (TRC), including patients diagnosed and initially  
2 taken care in a non-referral center, then referred in a center including cardiac surgery  
3 - Non-Referral Center group (NRC), including patients totally taken care in non-referral  
4 centers (18 centers)

5

## 6 **Follow-up**

7 Patients had a one-year follow-up with a clinical evaluation or if not possible, phone contact.

8

## 9 **Primary and secondary endpoints**

10 Primary endpoint was death from all cause at one-year follow-up. Secondary endpoints  
11 were:

12 - the evaluation of the implementation of European guidelines <sup>8 9</sup> in the three patients groups  
13 regarding: the use of TEE, the choice and duration of antibiotic therapy, and the performance  
14 of valvular surgery and/or extraction of pacemaker or implantable automatic defibrillator when  
15 indicated

16 - comparison of demographical and microbiological data among the three groups.

17

## 18 **Statistical analysis**

19 Continuous variables were described by their mean, standard deviation, minimum and  
20 maximum value, 1st and 3rd quartile. Continuous variables were compared using the Mann-  
21 Whitney non parametric U test or Student's t test, depending on the application conditions.  
22 Categorical variables were compared using the chi-square test or the Fisher test, depending on  
23 the application conditions. The event-free survival distributions were estimated with the  
24 Kaplan-Meier method. The log-rank test was used to compare survival distributions for  
25 categorical variables. The effect of continuous variables on the risk of an event occurring was

1 estimated and tested using a Cox model. The surgery variable, which is a time dependent  
2 variable, was estimated using a Poisson approach.

3         Multivariate analyzes were tested using a Cox model. Multivariate analyzes were tested  
4 using a Cox model. Inclusion of variables in the fitted model was carried out according to the  
5 following criteria : result in univariate analysis with statistical significance  $p < 0.20$ , number of  
6 missing values  $< 10\%$  for this variable, effective presence in both categories of a bivariate  
7 variable  $> 10\%$ , as well as according to their clinical relevance. The final models were selected  
8 using the Akaike Information Criteria (AIC).

9         The comparison tests of group 1 to group 2, group 1 to group 3, group 1 + 2 to group 3  
10 were performed in bilateral situation using Bonferroni correction and were considered  
11 statistically significant for  $p < 0.017$ . For all other tests, they were performed bilaterally and  
12 were considered statistically significant for  $p < 0.05$ . Statistical analysis was performed with R  
13 software (version 3.6.2) and RStudio (v 1.2.5).

14

15

16

## 17 **Results**

### 18 **Patient population**

19         Between January 2014 and June 2017, a total of 342 patients with definite IE were  
20 included. Among them, 119 were diagnosed and entirely managed in a reference center or  
21 hospital with cardiac surgery (RC group), 111 were diagnosed and initially managed in a non-  
22 referral center, then referred in a center including cardiac surgery (TRC group) and 112 were  
23 totally managed in non-referral centers (NRC group). Clinical, demographical, biological, and  
24 microbiological characteristics of patients are presented in **Table 1**.

25



1 *Overall population*

2 In the overall population, mean age was 68 +/- 15 years. IE were mainly community-  
3 acquired (83% of cases), *S. aureus* was the most frequent bacteria involved (26% of cases).  
4 Negative blood culture IE represented 17% of cases. Left-sided IE counted for 85% of all cases  
5 and aortic (43%) and mitral (42%) localization were almost equally represented. Perivalvular  
6 complications were observed in 16% of cases. 33% of cases were prosthetic valve IE. More  
7 than half IE cases (58%) showed theoretical indication for valvular surgery or intracardiac  
8 device removal but only 35% had such interventions.

9

10 *Characteristics according to health-care pathway (Table 1)*

11 Patients in NRC group were significantly older and had higher Charlson index. Sources  
12 of infection did not differ between the three groups and microbiological profile of IE cases was  
13 not significantly different. Echocardiographic findings showed more severe lesions in RC group  
14 and TRC group: longer vegetations, more peri-valvular complications, and more severe  
15 valvular regurgitation. Concerning IE complications, there was no significant difference  
16 between groups in embolic events, however more silent embolisms were diagnosed in RC group  
17 and TRC group. Spondylodiscitis was more frequent in NRC group.

18 Patients in RC and TRC groups had more frequent surgical indication, but surgery or  
19 intracardiac device removal was performed in only 52 patients (44%) in RC group, 60  
20 patients (55%) in TRC group and 6 patients (5%) in NRC group,  $p < 0.001$ . In RC group, 81  
21 patients had an indication for intervention and 29 were not operated and in TRC group, 91  
22 patients had an indication for intervention and 31 were not operated. Reasons for absence of  
23 intervention were: deaths before surgery (6 patients in RC group and 2 patients in TRC group  
24 ), patient's refusal (2 patients in RC group and 1 patient in TRC group) and decision of the  
25 endocarditis team due to comorbidities (21 patients in RC group and 28 patients in TRC

1 group). Patients who benefited from surgery were significantly younger (69.4 +/- 13 years vs  
2 62.4 +/- 12 years,  $p=0.01$ ), had lower Charlson index (3.9 +/- 1.9 vs 2.8 +/- 2.7,  $p=0.007$ ),  
3 had more frequently vegetations (86 patients (73%) vs 95 patients (85%),  $p=0.002$ ) and severe  
4 valvular regurgitation (41 patients (35%) vs 68 patients (61%),  $p<0.001$ ) but less renal failure  
5 (29 patients (25%) vs 5 patients (4%),  $p<0.001$ ) and diabetes (39 patients (33%) vs 20 patients  
6 (18%),  $p=0.01$ ).

7 Time from diagnosis to intervention did not significantly differ between RC group and  
8 TRC group (mean time 30+/-32 days vs 22+/-29 days,  $p=0.36$ ). In our cohort, mean time for  
9 right-sided IE was 17+/-18 days and 25+/-28 days for left-sided IE.

10

### 11 **Prognosis of patients according to their health-care pathway**

12 Among the 342 patients, one year mortality was 26% (88 deaths), hospital mortality was  
13 13% (44 deaths) and one year recurrence rate was 4% (13 patients). **Figure 1** shows survival  
14 probability according to health-care pathway.

15 Hospital mortality was 11% (13 deaths) in RC group, 8% (9 patients) in TRC group and  
16 20% (22 patients) in NRC group,  $p=0.03$ . One year mortality was 20% (24 deaths) in RC group,  
17 21% (23 deaths) in TRC group and 37% (41 deaths) in NRC group,  $p=0.003$ . One year mortality  
18 was not significantly different between RC and TRC groups ( $p=0.83$ ), however it was  
19 significantly higher in NRC group compared to RC and TRC groups ( $p<0.001$ ).

20

### 21 **Characteristics of patients only treated in non-referral centers**

22 During the study period, 112 patients were managed only in a NRC. Among them, 28  
23 patients (25%) had indication for valvular surgery or intracardiac device removal. These  
24 patients had a mean age of 76+/-11 years and were at high surgical risk (mean Euroscore 17+/-  
25 16%). Reasons for absence of transfer and surgery included: death before surgery for 16 patients

1 (14%), medical choice for 14 patients (13%), patient's refusal in 3 cases (3%) and high surgical  
2 risk (comorbidities) for 16 patients (14%). 6 patients (5%) had intracardiac device removal  
3 (pacemaker lead or catheter) in the NRC. Among these 28 patients, one year mortality was 50%  
4 (14 deaths). 84 patients (75%) had indication for medical treatment of IE. One year mortality  
5 among them was 29% (24 deaths).

6

### 7 **Prognostic factors of mortality**

8 Results of univariate analysis of prognostic factors of one year mortality are shown in  
9 **Table S1. Table 2** shows prognostic factors of mortality among the 342 patients in multivariate  
10 analysis. Belonging to NRC group was associated with higher risk of death (HR 2.56; 95% CI  
11 1.44-4.55,  $p=0.001$ ). Heart failure (HR 2.4; 95% CI 1.52-3.78,  $p<0.001$ ) and peri-valvular  
12 involvement (HR 3.25; 95% CI 1.86-5.68,  $p<0.001$ ) were IE complications predictive of  
13 mortality.

14

### 15 **Evaluation of European guidelines application according to health-care pathway**

16 **Table 3** shows the implementation of ESC guidelines in the three groups regarding use  
17 of TEE, valvular surgery or intracardiac device removal and antibiotic therapy. In overall  
18 population, ESC guidelines were correctly implemented in 52% of patients. TEE was  
19 performed in most IE cases (92%); however it was significantly less frequently used in NRC  
20 group as compared to the two other groups ( $p<0.001$ ). Guidelines concerning surgery or  
21 intracardiac device extraction were correctly implemented in 78% of cases and there was no  
22 significant difference between the three groups. Antibiotic therapy was in accordance with  
23 guidelines in 72% of cases and there was no significant difference between patients taken care  
24 entirely or partially in RC ( $p=0.66$ ). However, treatment was less frequently in agreement with  
25 guidelines in patients in NRC group compared to the others ( $p<0.001$ ).

## 1 **Discussion**

2 This prospective study carried out in 22 hospitals in the South-East of France including  
3 342 IE cases divided into three groups according to their health-care pathway shows that:

4 - The prognosis of patients is influenced by their health-care pathway

5 - The number of patients managed in non-referral centers is high. They are older, have more  
6 comorbidities, and less severe cardiac lesions than the others.

7 - Surgery or device removal is less frequently performed in those patients

8 - European recommendations on the management of these patients are not followed similarly  
9 depending on their health-care pathway

10 - Both in-hospital and long-term mortalities are higher in non-referral centers.

11

## 12 **General population**

13 By including patients treated in NRC, our study has the advantage of providing global  
14 epidemiological information concerning the cases of IE within the south-eastern region,  
15 reflecting the management of this pathology in "real life" and not only in RC. Almost a third of  
16 the patients treated for IE during the inclusion period were treated in a NRC.

17 Consistent with known data <sup>19 20</sup>, there was a predominance of IE cases in males (69%).

18 The mean age of diagnosis of IE was 68 years in our study. This age seemed more advanced in  
19 comparison to other French (average age of 59 +/- 17 years in 1999 <sup>2</sup>, 62 +/- 16 years in 2008  
20 <sup>21</sup>) or European studies (57 +/- 16 years in 2001 <sup>3</sup>, 59 +/- 18 years in the Euro-Endo registry <sup>20</sup>).

21 Concerning microbiological data, *S. aureus* was the predominant germ (26% of IE), which was  
22 in agreement with previous studies <sup>21 22</sup>. There was a majority of left-sided IE (85%). An  
23 embolic event was observed in 38% of cases. This rate was comparable to other studies that  
24 describe the occurrence of an embolic event in 20 to 50% of cases <sup>21 23 24</sup>

25

## 1 **Mortality according to health-care pathway**

2           In our cohort, hospital mortality was 13% and one-year mortality was 26%. Few studies  
3 have compared the prognosis of patients with IE according to their health-care pathway. A  
4 study by Fernandez-Hidalgo et al. <sup>25</sup>, compared the hospital mortality of 223 patients treated in  
5 a RC with cardiac surgery with 144 patients taken care in a NRC and secondarily referred to  
6 the RC. This study did not show any significant difference in terms of hospital mortality  
7 between the two groups. Likewise, an international multicenter study <sup>12</sup> carried out in RC in the  
8 management of IE did not show difference in hospital mortality between 1,164 patients  
9 transferred from NRC and 1,596 patients treated directly within the RC. However, these studies  
10 have some limitations: by considering only patients treated in RC they are not representative of  
11 epidemiology of patients treated in NRC. The originality of our study is to compare three  
12 groups, including a group of patients treated exclusively in NRC, these patients usually being  
13 not included in previous studies. Our main findings is a significantly higher hospital (20%) and  
14 one year mortality (37%) in patients treated only in NRC. Belonging to NRC group was an  
15 independent risk factor in multivariate analysis of one-year mortality in the total cohort of  
16 patients. This excess of mortality observed in NRC group could be explained by various factors:  
17 epidemiological differences compared to other groups, recommendations on the management  
18 of IE that are less implemented and a higher absence of surgery rate in patients with a theoretical  
19 surgical indication.

20

## 21 **Implementation of European guidelines**

22           In our study, we observed a more frequent use of TEE (92% of patients) than in other  
23 multicenter studies (60-75% <sup>3 20</sup>). However, within NRC group, TEE was significantly less  
24 frequently performed compared to the other groups. TEE has a key role in the diagnostic  
25 process of IE and in particular in the detection of peri-annular complications and should be

1 performed systematically, in accordance with current recommendations <sup>8 9 26</sup>. Thus, it is  
2 possible that these complications, often requiring surgery, have not been diagnosed in some  
3 patients, especially in NRC group.

4       Regarding valve surgery or the extraction of intracardiac material, there was no  
5 significant difference in application of recommendations between the three groups. However,  
6 we noted within each group patients with a theoretical indication for surgery for who surgery  
7 was finally not performed. Within NRC group, 25% of patients presented a theoretical  
8 indication and only 5% received interventional management. Conversely, in RC and TRC  
9 groups, 65% of patients with theoretical surgical indication benefited from intervention.  
10 Different studies have already shown the poor prognosis of patients with a theoretical indication  
11 for surgery and not operated <sup>20 27</sup>, which may in part explain the higher mortality of patients in  
12 NRC group. In addition, the main multicenter studies carried out over the last few years  
13 highlight a surgery rate close to 50% (52% in Euro Heart Survey <sup>3</sup>, 51% in the EuroEndo  
14 register <sup>20</sup>, 48% in the ICE register <sup>4</sup>). Among the patients treated exclusively in RC, the rate of  
15 surgery or extraction of intracardiac material was 44%, close to previous published data. On  
16 the other hand, if we considered all the patients for whom the diagnosis of IE was made in a  
17 non-referral center (TRC and NRC groups), the overall rate of valve surgery or extraction of  
18 intracardiac material was only 30 %. Several factors could explain this discrepancy with the  
19 pre-existing studies. Indeed, most studies on IE focused on patients treated in RC with a cardiac  
20 surgery department. It is possible that a referral bias may cause an overestimation of the rate of  
21 cardiac surgery in this pathology, by not considering many IE of "medical" management and  
22 treated exclusively in NRC. On the other hand, it is also possible that among the patients  
23 diagnosed in a NRC, surgical indications were sometimes not identified, especially in NRC  
24 group in which, unlike TRC group, it was not possible to re-evaluate the surgical indications  
25 by a multidisciplinary team in a reference center. In a same way, a Spanish study by Lopez-

1 Dupla et al. <sup>28</sup> in a university center without a cardiac surgery department showed that the  
2 establishment of a multidisciplinary team including a cardiac surgeon was associated with an  
3 increase in the rate of surgical indication identified (14.5% vs 34.5% ). Finally, the European  
4 guidelines concerning the antibiotic treatment were significantly less applied among patients in  
5 group 3 with 35% of inappropriate antibiotic therapy. Here again, few studies concerning the  
6 antibiotic treatment used in non-referral centers are available. Fernandez-Hidalgo et al. <sup>25</sup>  
7 showed that among the patients diagnosed in a NRC and referred secondarily to a surgical  
8 center, the antibiotic treatment initiated in the non-referral center was inadequate in 54% of  
9 cases. In this study, inadequate treatment was associated with an increased risk of in-hospital  
10 mortality in multivariate analysis. The goal of our study was to evaluate the implementation of  
11 ESC guidelines in “real life”. It is however important to highlight that in some cases, there may  
12 be logical reasons why patients do not undergo an indicated procedure such as TEE, for instance  
13 when a patient is not operable, or surgery.

14

### 15 **Epidemiological characteristics of IE according to health-care pathway**

16 The epidemiological profile of patients in RC and TRC groups was comparable. These  
17 were patients with more severe IE than in NRC group with more hemodynamic complications,  
18 a higher rate of vegetations, more peri-annular complications. These elements partly explain  
19 the higher surgical indication rate in these two groups. The patients in NRC group were  
20 significantly older, presented more comorbidities, and a greater operative risk. Some studies  
21 focusing on IE cases in the elderly have shown, including during treatment in a RC, limited  
22 access to surgery and significant mortality in these patients when surgery, although indicated,  
23 was not performed <sup>29 30</sup>.

24

25

## 1 **Limitations**

2           Some data could not be recorded, such as the reason for the transfer of patients to a  
3 referral center, the time between diagnosis and the transfer of patients, and some factors who  
4 could have influenced transfer decision (such as cirrhosis or poor nutritional status). Due to the  
5 large number of participating non-referral centers, the reasons for transferring patients may  
6 have differed from one center to another. Moreover, modified Duke criteria were used for  
7 diagnosis of IE and have limited sensitivity. This study reflects the epidemiology and practices  
8 used in the south-eastern region of France and cannot be generalized to all the other centers.  
9 Finally, the study design was meant to compare prognosis of patients according to the health-  
10 care pathway but reasons explaining the different prognosis observed could only be  
11 hypothesized.

12

## 13 **Conclusion**

14           Prognosis of patients with IE is influenced by their health-care pathway. Patients treated  
15 exclusively in NRC have a worse prognosis than patients treated in RC. These patients are often  
16 fragile and their management difficult. Given the difference in mortality between patients  
17 managed in referral vs non-referral centers, the current recommendations of treating patients  
18 with non-complicated IE in non-referral centers should be questioned. IE is a deadly disease  
19 with a better prognosis when managed in RC.

20

## 21 **Supplementary data**

22           Supplementary material is available online.

23

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2 Clinique Inter-régional 2012)

3

#### 4 **Conflict of interest**

5 None declared

6

#### 7 **Data availability**

8 The data underlying this article will be shared on reasonable request to the corresponding  
9 author.

10

11

12

13

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11 **Figure legend**

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13 **Figure 1 : Probability of survival according to health-care pathway**

14 A: Comparison of survival between the three groups

15 B: Comparison of survival between Referral Centers (RC) and Transferred to Referral Centers  
16 (TRC) groups

17 C: Comparison of survival between RC and Non-Referral Centers (NRC) groups

18 D: Comparison of survival between groups RC and TRC together and NRC group

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1           **Influence of the health-care pathway on the outcome of patients with infective**  
2   **endocarditis**

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1 **Abstract**

2 **Aims:** To determine the prognosis of patients treated for infective endocarditis (IE) according  
3 to their health-care pathway. To assess how the ESC guidelines are implemented concerning  
4 the performance of transesophageal echocardiography (TEE), the use of antibiotic therapy, and  
5 the performance of valve surgery; and to compare the epidemiological profile of IE according  
6 to the type of centers in which the patients are hospitalized.

7 **Methods and results:** In a prospective multicentric study including 22 hospitals in the South-  
8 East of France, 342 patients were classified in three groups according to their health-care  
9 pathway: 119 patients diagnosed and taken care entirely in a reference center or hospital with  
10 cardiac surgery (**Referral Center (RC) group**), 111 patients diagnosed and initially taken care  
11 in a non-referral center (NRC) , then referred in a center including cardiac surgery (**Transferred  
12 to Referral Center (TRC) group**) and 112 patients totally taken care in **NRC (NRC) group**). One-  
13 year mortality was 26% (88 deaths) and was not significantly different between groups 1 and 2  
14 (20% vs 21%,  $p = 0.83$ ). Patients in **NRC** group had a higher mortality (37%) compared to  
15 patients in **RC and TRC** groups ( $p < 0.001$ ). ESC guidelines were not implemented similarly  
16 depending on the health-care pathway ( $p = 0.04$ ). Patients in **NRC** group were significantly older  
17 ( $p < 0.001$ ) and had more comorbidities ( $p < 0.001$ ) than patients treated in referral centers.

18 **Conclusion:** Prognosis of patients with IE is influenced by their health-care pathway. Patients  
19 treated exclusively in NRC have a worse prognosis than patients treated in referral or surgical  
20 centers.

21

22 **Keywords :** endocarditis, mortality, health-care pathway, referral center

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## 1 **Introduction**

2           Epidemiologic profile of infective endocarditis (IE) has changed over the past twenty  
3 years,<sup>1 2 3</sup> but mortality remains high<sup>4 5 6</sup> despite diagnostic improvement and access to surgery  
4 in up to 50% of cases.<sup>7</sup> This persistent severity has justified the development of new diagnostic  
5 and therapeutic strategies to improve prognosis.<sup>8 9</sup> Management by a specialized  
6 multidisciplinary team within a referent medical-surgical center seems to be a key factor in  
7 improving patients prognosis,<sup>10 11</sup> and is recommended by the ESC guidelines.<sup>8 9</sup>

8           However, few studies have compared the prognosis and management of patients with  
9 IE according to their health-care pathway. Indeed, three situations are usually observed: patients  
10 for whom the diagnosis and management are carried out entirely in a referral center and/or  
11 having a cardiac surgery department, patients secondarily referred to a referral hospital or  
12 surgical center by another care center, patients for whom the entire care is provided within a  
13 non-referral care center. In addition, application of European guidelines remains difficult to  
14 assess in daily clinical practice outside the major referral centers. Published epidemiological  
15 data only represent part of the IE, most often not taking into account patients hospitalized in  
16 non-referral centers and therefore introducing a significant bias in the knowledge of this  
17 pathology.<sup>12</sup> Finally, although the ESC guidelines suggest that patients with uncomplicated IE  
18 can be managed in a non-reference center<sup>9</sup>, if all patients with IE<sup>13</sup> or only the sickest patients  
19<sup>14</sup> should be referred to reference centers is still a matter of debate.

20           The main objective of this study was to determine the prognosis of patients treated for  
21 IE according to their health-care pathway. The secondary objectives were to assess how the  
22 ESC guidelines are implemented concerning the performance of transesophageal  
23 echocardiography (TEE), the use of antibiotic therapy, and the performance of valve surgery,  
24 and to compare the epidemiological profile of IE according to the type of centers in which the  
25 patients are hospitalized.

## 1 **Methods**

### 2 **Study design and patients**

3 This was a prospective multicentric study including patients consecutively admitted for  
4 suspicion of IE in 22 hospitals in South-East of France between January 2014 and June 2017.  
5 These hospitals were both tertiary centers with cardiac surgery and second-level community  
6 hospitals. Inclusion criteria were a diagnosis of definite IE based on Duke modified criteria <sup>15</sup>  
7 on native, prosthetic or pacemaker/implantable automatic defibrillator. Non-inclusion criteria  
8 were age < 18 years and patients already included in the study and presenting with a new IE  
9 diagnosis. Patients were screened in the echocardiography lab of each institution and were  
10 prospectively included by local investigators.

11

### 12 **Patient and Public involvement**

13 All patients hospitalized for suspected IE were accepted on admission to participate in this  
14 research protocol. However, they were not involved in the design, conduct, reporting or  
15 dissemination plans of our research. The study complies with the Declaration of Helsinki.  
16 Written consent was waived by La Timone Institutional Review Board, which gave its approval  
17 for this study.

18

### 19 **Data collected at the time of inclusion and during hospitalization**

20 The following clinical data were collected: age, sex, previous cardiac and non-cardiac  
21 diseases, Charlson index score, date of first clinical signs, body temperature, presence of cardiac  
22 murmur, congestive heart failure, neurological complications, septic or cariogenic shock or  
23 atrio-ventricular block on electrocardiogram at time of admission and during hospitalization.

1 Biological data were collected, including hemoglobin level, platelet count, leukocytes count,  
2 C-Reactive Protein serum level, creatinine level, rheumatoid factor. Microbiological data  
3 included: positive or negative blood cultures, type of microorganism and antibiogram.

4 Echocardiographic data collected were: presence of vegetation and its maximal length,  
5 presence of periannular lesion (defined as the presence of abscess and/or pseudoaneurysm  
6 and/or fistula), presence of valvular regurgitation, quantified according to current  
7 recommendations.<sup>16 17</sup>

8 Type and date of the following complications were collected: congestive heart failure,  
9 peripheral embolism, neurological complications (including symptomatic and silent), mycotic  
10 aneurysm, acute kidney failure (>26 $\mu$ mol/L increase of serum creatinine in 48 hours or >50%  
11 increase in 7 days) , glomerulonephritis, uncontrolled infection (fever and/or positive blood  
12 cultures after 7 days of appropriate antibiotic therapy and unlinked to an extracardiac cause).

13 Moreover, type, dose and length of antibiotic therapy was reported. Antibiotic therapy  
14 was considered appropriate if drugs used and full duration of treatment were in accordance with  
15 ESC guidelines (taking into account patients terminating antibiotics prematurely due to death).  
16 Analysis of antibiotic treatment was conducted retrospectively by the Endocarditis team of the  
17 investigator center (CHU La Timone, Marseille).

18 During hospitalization or follow-up the indication (according to ESC guidelines) and  
19 date of surgery was also collected. Finally, surgical risk was evaluated using the Euroscore II.<sup>18</sup>

20

## 21 **Classification of patients according to health-care pathway**

22 Patients were classified in three groups according to their health-care pathway:

23 - Referral Center group (RC), including patients diagnosed and taken care entirely in a  
24 reference center or hospital with cardiac surgery (4 hospitals). These centers were the  
25 only surgical centers of this region of France.

- 1 - Transferred to Referral Center group (TRC), including patients diagnosed and initially  
2 taken care in a non-referral center, then referred in a center including cardiac surgery  
3 - Non-Referral Center group (NRC), including patients totally taken care in non-referral  
4 centers (18 centers)

5

## 6 **Follow-up**

7 Patients had a one-year follow-up with a clinical evaluation or if not possible, phone contact.

8

## 9 **Primary and secondary endpoints**

10 Primary endpoint was death from all cause at one-year follow-up. Secondary endpoints  
11 were:

12 - the evaluation of the implementation of European guidelines<sup>8 9</sup> in the three patients groups  
13 regarding: the use of TEE, the choice and duration of antibiotic therapy, and the performance  
14 of valvular surgery and/or extraction of pacemaker or implantable automatic defibrillator when  
15 indicated

16 - comparison of demographical and microbiological data among the three groups.

17

## 18 **Statistical analysis**

19 Continuous variables were described by their mean, standard deviation, minimum and  
20 maximum value, 1st and 3rd quartile. Continuous variables were compared using the Mann-  
21 Whitney non parametric U test or Student's t test, depending on the application conditions.  
22 Categorical variables were compared using the chi-square test or the Fisher test, depending on  
23 the application conditions. The event-free survival distributions were estimated with the  
24 Kaplan-Meier method. The log-rank test was used to compare survival distributions for  
25 categorical variables. The effect of continuous variables on the risk of an event occurring was

1 estimated and tested using a Cox model. The surgery variable, which is a time dependent  
2 variable, was estimated using a Poisson approach.

3 Multivariate analyzes were tested using a Cox model. Multivariate analyzes were tested  
4 using a Cox model. Inclusion of variables in the fitted model was carried out according to the  
5 following criteria : result in univariate analysis with statistical significance  $p < 0.20$ , number of  
6 missing values  $< 10\%$  for this variable, effective presence in both categories of a bivariate  
7 variable  $> 10\%$ , as well as according to their clinical relevance. The final models were selected  
8 using the Akaike Information Criteria (AIC).

9 The comparison tests of group 1 to group 2, group 1 to group 3, group 1 + 2 to group 3  
10 were performed in bilateral situation using Bonferroni correction and were considered  
11 statistically significant for  $p < 0.017$ . For all other tests, they were performed bilaterally and  
12 were considered statistically significant for  $p < 0.05$ . Statistical analysis was performed with R  
13 software (version 3.6.2) and RStudio (v 1.2.5).

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## 17 **Results**

### 18 **Patient population**

19 Between January 2014 and June 2017, a total of 342 patients with definite IE were  
20 included. Among them, 119 were diagnosed and entirely managed in a reference center or  
21 hospital with cardiac surgery (RC group), 111 were diagnosed and initially managed in a non-  
22 referral center, then referred in a center including cardiac surgery (TRC group) and 112 were  
23 totally managed in non-referral centers (NRC group). Clinical, demographical, biological, and  
24 microbiological characteristics of patients are presented in **Table 1**.

25



## 1 *Overall population*

2 In the overall population, mean age was 68 +/- 15 years. IE were mainly community-  
3 acquired (83% of cases), *S. aureus* was the most frequent bacteria involved (26% of cases).  
4 Negative blood culture IE represented 17% of cases. Left-sided IE counted for 85% of all cases  
5 and aortic (43%) and mitral (42%) localization were almost equally represented. Perivalvular  
6 complications were observed in 16% of cases. 33% of cases were prosthetic valve IE. More  
7 than half IE cases (58%) showed theoretical indication for valvular surgery or intracardiac  
8 device removal but only 35% had such interventions.

9

## 10 *Characteristics according to health-care pathway (Table 1)*

11 Patients in NRC group were significantly older and had higher Charlson index. Sources  
12 of infection did not differ between the three groups and microbiological profile of IE cases was  
13 not significantly different. Echocardiographic findings showed more severe lesions in RC group  
14 and TRC group: longer vegetations, more peri-valvular complications, and more severe  
15 valvular regurgitation. Concerning IE complications, there was no significant difference  
16 between groups in embolic events, however more silent embolisms were diagnosed in RC group  
17 and TRC group. Spondylodiscitis was more frequent in NRC group.

18 Patients in RC and TRC groups had more frequent surgical indication, but surgery or  
19 intracardiac device removal was performed in only 52 patients (44%) in RC group, 60  
20 patients (55%) in TRC group and 6 patients (5%) in NRC group,  $p < 0.001$ . In RC group, 81  
21 patients had an indication for intervention and 29 were not operated and in TRC group, 91  
22 patients had an indication for intervention and 31 were not operated. Reasons for absence of  
23 intervention were: deaths before surgery (6 patients in RC group and 2 patients in TRC group  
24 ), patient's refusal (2 patients in RC group and 1 patient in TRC group) and decision of the  
25 endocarditis team due to comorbidities (21 patients in RC group and 28 patients in TRC

1 group). Patients who benefited from surgery were significantly younger (69.4 +/- 13 years vs  
2 62.4 +/- 12 years,  $p=0.01$ ), had lower Charlson index (3.9 +/- 1.9 vs 2.8 +/- 2.7,  $p=0.007$ ),  
3 had more frequently vegetations (86 patients (73%) vs 95 patients (85%),  $p=0.002$ ) and severe  
4 valvular regurgitation (41 patients (35%) vs 68 patients (61%),  $p<0.001$ ) but less renal failure  
5 (29 patients (25%) vs 5 patients (4%),  $p<0.001$ ) and diabetes (39 patients (33%) vs 20 patients  
6 (18%),  $p=0.01$ ).

7 Time from diagnosis to intervention did not significantly differ between RC group and  
8 TRC group (mean time 30+/-32 days vs 22+/-29 days,  $p=0.36$ ). In our cohort, mean time for  
9 right-sided IE was 17+/-18 days and 25+/-28 days for left-sided IE.

10

### 11 **Prognosis of patients according to their health-care pathway**

12 Among the 342 patients, one year mortality was 26% (88 deaths), hospital mortality was  
13 13% (44 deaths) and one year recurrence rate was 4% (13 patients). **Figure 1** shows survival  
14 probability according to health-care pathway.

15 Hospital mortality was 11% (13 deaths) in RC group, 8% (9 patients) in TRC group and  
16 20% (22 patients) in NRC group,  $p=0.03$ . One year mortality was 20% (24 deaths) in RC group,  
17 21% (23 deaths) in TRC group and 37% (41 deaths) in NRC group,  $p=0.003$ . One year mortality  
18 was not significantly different between RC and TRC groups ( $p=0.83$ ), however it was  
19 significantly higher in NRC group compared to RC and TRC groups ( $p<0.001$ ).

20

### 21 **Characteristics of patients only treated in non-referral centers**

22 During the study period, 112 patients were managed only in a NRC. Among them, 28  
23 patients (25%) had indication for valvular surgery or intracardiac device removal. These  
24 patients had a mean age of 76+/-11 years and were at high surgical risk (mean Euroscore 17+/-  
25 16%). Reasons for absence of transfer and surgery included: death before surgery for 16 patients

1 (14%), medical choice for 14 patients (13%), patient's refusal in 3 cases (3%) and high surgical  
2 risk (comorbidities) for 16 patients (14%). 6 patients (5%) had intracardiac device removal  
3 (pacemaker lead or catheter) in the **NRC**. Among these 28 patients, one year mortality was 50%  
4 (14 deaths). 84 patients (75%) had indication for medical treatment of IE. One year mortality  
5 among them was 29% (24 deaths).

6

### 7 **Prognostic factors of mortality**

8 Results of univariate analysis of prognostic factors of one year mortality are shown in  
9 **Table S1. Table 2** shows prognostic factors of mortality among the 342 patients in multivariate  
10 analysis. Belonging to **NRC** group was associated with higher risk of death (HR 2.56; 95% CI  
11 1.44-4.55,  $p=0.001$ ). Heart failure (HR 2.4; 95% CI 1.52-3.78,  $p<0.001$ ) and peri-valvular  
12 involvement (HR 3.25; 95% CI 1.86-5.68,  $p<0.001$ ) were IE complications predictive of  
13 mortality.

14

### 15 **Evaluation of European guidelines application according to health-care pathway**

16 **Table 3** shows the implementation of ESC guidelines in the three groups regarding use  
17 of TEE, valvular surgery or intracardiac device removal and antibiotic therapy. In overall  
18 population, ESC guidelines were correctly implemented in 52% of patients. TEE was  
19 performed in most IE cases (92%); however it was significantly less frequently used in **NRC**  
20 group as compared to the two other groups ( $p<0.001$ ). Guidelines concerning surgery or  
21 intracardiac device extraction were correctly implemented in 78% of cases and there was no  
22 significant difference between the three groups. Antibiotic therapy was in accordance with  
23 guidelines in 72% of cases and there was no significant difference between patients taken care  
24 entirely or partially in **RC** ( $p=0.66$ ). However, treatment was less frequently in agreement with  
25 guidelines in patients in NRC group compared to the others ( $p<0.001$ ).

## 1 Discussion

2 This prospective study carried out in 22 hospitals in the South-East of France including  
3 342 IE cases divided into three groups according to their health-care pathway shows that:

4 - The prognosis of patients is influenced by their health-care pathway

5 - The number of patients managed in non-referral centers is high. They are older, have more  
6 comorbidities, and less severe cardiac lesions than the others.

7 - Surgery or device removal is less frequently performed in those patients

8 - European recommendations on the management of these patients are not followed similarly  
9 depending on their health-care pathway

10 - Both in-hospital and long-term mortalities are higher in non-referral centers.

11

## 12 General population

13 By including patients treated in **NRC**, our study has the advantage of providing global  
14 epidemiological information concerning the cases of IE within the south-eastern region,  
15 reflecting the management of this pathology in "real life" and not only in **RC**. Almost a third of  
16 the patients treated for IE during the inclusion period were treated in a **NRC**.

17 Consistent with known data <sup>19 20</sup>, there was a predominance of IE cases in males (69%).

18 The mean age of diagnosis of IE was 68 years in our study. This age seemed more advanced in  
19 comparison to other French (average age of 59 +/- 17 years in 1999 <sup>2</sup>, 62 +/- 16 years in 2008  
20 <sup>21</sup>) or European studies (57 +/- 16 years in 2001 <sup>3</sup>, 59 +/- 18 years in the Euro-Endo registry <sup>20</sup>).

21 Concerning microbiological data, *S. aureus* was the predominant germ (26% of IE), which was  
22 in agreement with previous studies <sup>21 22</sup>. There was a majority of left-sided IE (85%). An  
23 embolic event was observed in 38% of cases. This rate was comparable to other studies that  
24 describe the occurrence of an embolic event in 20 to 50% of cases <sup>21 23 24</sup>

25

## 1 **Mortality according to health-care pathway**

2           In our cohort, hospital mortality was 13% and one-year mortality was 26%. Few studies  
3 have compared the prognosis of patients with IE according to their health-care pathway. A  
4 study by Fernandez-Hidalgo et al. <sup>25</sup>, compared the hospital mortality of 223 patients treated in  
5 a **RC** with cardiac surgery with 144 patients taken care in a NRC and secondarily referred to  
6 the **RC**. This study did not show any significant difference in terms of hospital mortality  
7 between the two groups. Likewise, an international multicenter study <sup>12</sup> carried out in **RC** in the  
8 management of IE did not show difference in hospital mortality between 1,164 patients  
9 transferred from NRC and 1,596 patients treated directly within the RC. However, these studies  
10 have some limitations: by considering only patients treated in RC they are not representative of  
11 epidemiology of patients treated in NRC. The originality of our study is to compare three  
12 groups, including a group of patients treated exclusively in **NRC**, these patients usually being  
13 not included in previous studies. Our main findings is a significantly higher hospital (20%) and  
14 one year mortality (37%) in patients treated only in NRC. Belonging to **NRC** group was an  
15 independent risk factor in multivariate analysis of one-year mortality in the total cohort of  
16 patients. This excess of mortality observed in **NRC** group could be explained by various factors:  
17 epidemiological differences compared to other groups, recommendations on the management  
18 of IE that are less implemented and a higher absence of surgery rate in patients with a theoretical  
19 surgical indication.

20

## 21 **Implementation of European guidelines**

22           In our study, we observed a more frequent use of TEE (92% of patients) than in other  
23 multicenter studies (60-75% <sup>3 20</sup>). However, within **NRC group**, TEE was significantly less  
24 frequently performed compared to the other groups. TEE has a key role in the diagnostic  
25 process of IE and in particular in the detection of peri-annular complications and should be

1 performed systematically, in accordance with current recommendations <sup>8 9 26</sup>. Thus, it is  
2 possible that these complications, often requiring surgery, have not been diagnosed in some  
3 patients, especially in **NRC group**.

4 Regarding valve surgery or the extraction of intracardiac material, there was no  
5 significant difference in application of recommendations between the three groups. However,  
6 we noted within each group patients with a theoretical indication for surgery for who surgery  
7 was finally not performed. Within **NRC** group, 25% of patients presented a theoretical  
8 indication and only 5% received interventional management. Conversely, in **RC and TRC**  
9 groups, 65% of patients with theoretical surgical indication benefited from intervention.  
10 Different studies have already shown the poor prognosis of patients with a theoretical indication  
11 for surgery and not operated <sup>20 27</sup>, which may in part explain the higher mortality of patients in  
12 **NRC** group. In addition, the main multicenter studies carried out over the last few years  
13 highlight a surgery rate close to 50% (52% in Euro Heart Survey <sup>3</sup>, 51% in the EuroEndo  
14 register <sup>20</sup>, 48% in the ICE register <sup>4</sup>). Among the patients treated exclusively in **RC**, the rate of  
15 surgery or extraction of intracardiac material was 44%, close to previous published data. On  
16 the other hand, if we considered all the patients for whom the diagnosis of IE was made in a  
17 non-referral center (**TRC and NRC** groups), the overall rate of valve surgery or extraction of  
18 intracardiac material was only 30 %. Several factors could explain this discrepancy with the  
19 pre-existing studies. Indeed, most studies on IE focused on patients treated in **RC** with a cardiac  
20 surgery department. It is possible that a referral bias may cause an overestimation of the rate of  
21 cardiac surgery in this pathology, by not considering many IE of "medical" management and  
22 treated exclusively in **NRC**. On the other hand, it is also possible that among the patients  
23 diagnosed in a **NRC**, surgical indications were sometimes not identified, especially in **NRC**  
24 group in which, unlike **TRC** group, it was not possible to re-evaluate the surgical indications  
25 by a multidisciplinary team in a reference center. In a same way, a Spanish study by Lopez-

1 Dupla et al. <sup>28</sup> in a university center without a cardiac surgery department showed that the  
2 establishment of a multidisciplinary team including a cardiac surgeon was associated with an  
3 increase in the rate of surgical indication identified (14.5% vs 34.5% ). Finally, the European  
4 guidelines concerning the antibiotic treatment were significantly less applied among patients in  
5 group 3 with 35% of inappropriate antibiotic therapy. Here again, few studies concerning the  
6 antibiotic treatment used in non-referral centers are available. Fernandez-Hidalgo et al. <sup>25</sup>  
7 showed that among the patients diagnosed in a NRC and referred secondarily to a surgical  
8 center, the antibiotic treatment initiated in the non-referral center was inadequate in 54% of  
9 cases. In this study, inadequate treatment was associated with an increased risk of in-hospital  
10 mortality in multivariate analysis. The goal of our study was to evaluate the implementation of  
11 ESC guidelines in “real life”. It is however important to highlight that in some cases, there may  
12 be logical reasons why patients do not undergo an indicated procedure such as TEE, for instance  
13 when a patient is not operable, or surgery.

14

### 15 **Epidemiological characteristics of IE according to health-care pathway**

16 The epidemiological profile of patients in RC and TRC groups was comparable. These  
17 were patients with more severe IE than in NRC group with more hemodynamic complications,  
18 a higher rate of vegetations, more peri-annular complications. These elements partly explain  
19 the higher surgical indication rate in these two groups. The patients in NRC group were  
20 significantly older, presented more comorbidities, and a greater operative risk. Some studies  
21 focusing on IE cases in the elderly have shown, including during treatment in a RC, limited  
22 access to surgery and significant mortality in these patients when surgery, although indicated,  
23 was not performed <sup>29 30</sup>.

24

25

## 1 **Limitations**

2       Some data could not be recorded, such as the reason for the transfer of patients to a  
3 referral center, the time between diagnosis and the transfer of patients, and some factors who  
4 could have influenced transfer decision (such as cirrhosis or poor nutritional status). Due to the  
5 large number of participating non-referral centers, the reasons for transferring patients may  
6 have differed from one center to another. Moreover, modified Duke criteria were used for  
7 diagnosis of IE and have limited sensitivity. This study reflects the epidemiology and practices  
8 used in the south-eastern region of France and cannot be generalized to all the other centers.  
9 Finally, the study design was meant to compare prognosis of patients according to the health-  
10 care pathway but reasons explaining the different prognosis observed could only be  
11 hypothesized.

12

## 13 **Conclusion**

14       Prognosis of patients with IE is influenced by their health-care pathway. Patients treated  
15 exclusively in NRC have a worse prognosis than patients treated in RC. These patients are often  
16 fragile and their management difficult. Given the difference in mortality between patients  
17 managed in referral vs non-referral centers, the current recommendations of treating patients  
18 with non-complicated IE in non-referral centers should be questioned. IE is a deadly disease  
19 with a better prognosis when managed in RC.

20

## 21 **Supplementary data**

22       Supplementary material is available online.

23

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2 Clinique Inter-régional 2012)

3

#### 4 **Conflict of interest**

5 None declared

6

#### 7 **Data availability**

8 The data underlying this article will be shared on reasonable request to the corresponding  
9 author.

10

11

12

13

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11 **Figure legend**

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13 **Figure 1 : Probability of survival according to health-care pathway**

14 A: Comparison of survival between the three groups

15 B: Comparison of survival between Referral Centers (RC) and Transferred to Referral Centers  
16 (TRC) groups

17 C: Comparison of survival between RC and Non-Referral Centers (NRC) groups

18 D: Comparison of survival between groups RC and TRC together and NRC group

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**Table 1: Characteristics of patients according to their health-care pathway**

	<b>Total (n=342)</b>	<b>RC group (n=119)</b>	<b>TRC group (n=111)</b>	<b>NRC group (n=112)</b>	<b><i>p</i></b>
Male	236 (69)	82 (69)	83 (75)	71 (63)	0.19
Age (mean $\pm$ SD, years)	68 +/- 15	67 +/- 14	66 +/-15	73 +/- 14	<0.001
<b>Medical history</b>					
History of IE	42 (12)	17 (14)	16 (14)	9 (8)	0.25
Intravenous drug abuse	16 (5)	5 (4)	9 (8)	2 (2)	0.08
Cancer	59 (17)	12 (10)	21 (19)	26 (23)	0.03
Renal failure	50 (15)	18 (15)	16 (14)	16 (14)	0.98
Diabetes	85 (25)	28 (24)	31 (28)	26 (23)	0.66
Hypertension	147 (43)	47 (40)	53 (48)	47 (40)	0.38
Atrial fibrillation	116 (34)	48 (40)	33 (30)	35 (31)	0.19
History of valvular surgery	114 (33)	53 (45)	41 (37)	20 (18)	<0.001
Charlson index (mean $\pm$ SD)	3.9 +/- 2	3.4 +/- 2	3.4 +/- 2	4.9 +/- 2	<0.001
Euroscore II (mean $\pm$ SD, %)	9.3 +/- 11	7.2 +/- 6	7.4 +/- 8	13.6 +/- 15	0.004
<b>Treatment before episode</b>					
Oral anticoagulant	126/233 (54)	52/78 (67)	38/72 (53)	36/83 (43)	0.01
VKA	93/227 (40)	40/75 (53)	30/71 (42)	23/81 (28)	0.006
Aspirin	77/227 (34)	23/75 (31)	21/71 (30)	33/81 (41)	0.27
Statin	87/227 (38)	25/75 (33)	33/71 (46)	29/81 (36)	0.23
<b>Source of infection</b>					
Community	284 (83)	97 (82)	97 (87)	90 (80)	
HC related - nosocomial	54 (16)	22 (18)	12 (11)	20 (18)	0.21
HC related - non nosocomial	4 (1)	0	2 (2)	2 (2)	
<b>Biology</b>					
Hemoglobin (mean $\pm$ SD, g/L)	109 +/- 22	111 +/- 20	108 +/- 20	109 +/- 18	0.39
Leukocytes (mean $\pm$ SD, G/L)	11 +/- 5	10 +/- 4	11 +/- 4	11 +/- 6	0.28
Platelets (mean $\pm$ SD, G/L)	240 +/- 132	243 +/- 123	226 +/- 124	254 +/- 148	0.22
CRP (mean $\pm$ SD, mg/L)	106 +/- 99	91 +/- 95	103 +/- 84	127 +/- 117	0.02
Serum cretinine (mean $\pm$ SD, $\mu$ mol/L)	127 +/- 102	131 +/- 91	128 +/- 113	123 +/- 104	0.22
Positive rheumatoid factor	84 (25)	39 (33)	33 (30)	12 (11)	<0.001
<b>Microbiology</b>					
<i>Staphylococcus Aureus</i>	88 (26)	24 (20)	34 (31)	30 (27)	0.18
Coagulase-negative Staphylococci	24 (7)	13 (11)	4 (4)	7 (6)	0.89

Oral Streptococci	53 (15)	14 (12)	21 (19)	18 (16)	0.32
<i>Enterococcus faecalis</i>	53 (15)	17 (14)	19 (17)	17 (15)	0.83
<i>Streptococcus gallolyticus</i>	29 (8)	7 (6)	9 (8)	13 (12)	0.29
Gram negative bacilli	22 (6)	8 (7)	4 (4)	10 (9)	0.27
Others	24 (7)	10 (8)	9 (8)	5 (4)	0.43
Negative blood cultures	58 (17)	28 (24)	16 (14)	14 (13)	0.06
<b>Clinical data</b>					
Heart failure	95 (28)	33 (28)	40 (36)	22 (20)	0.02
Cardiogenic shock	13 (4)	12 (10)	1 (1)	0	<0.001
Septic shock	32 (9)	12 (10)	6 (5)	14 (13)	0.18
Systemic embolism	131 (38)	44 (37)	50 (45)	37 (33)	0.17
Silent embolism	67 (20)	31 (26)	25 (23)	11 (10)	0.01
Intracranial hemorrhage	24 (7)	8 (7)	8 (7)	8 (7)	0.99
Mycotic aneurysm	14 (4)	5 (4)	3 (3)	6 (5)	0.62
Spondylodiscitis	45 (13)	9 (8)	15 (14)	21 (19)	0.04
<b>Echocardiographic data</b>					
IE localization					
Prosthetic valve	113 (33)	53 (45)	40 (36)	20 (18)	<0.001
Aortic	148 (43)	54 (45)	56 (50)	38 (34)	0.04
Mitral	144 (42)	51 (43)	49 (44)	44 (39)	0.75
Tricuspid	23 (7)	11 (9)	8 (7)	4 (4)	0.22
Pulmonary	0	0	0	0	
Pacemaker / ICD	24 (7)	9 (8)	11 (10)	4 (4)	0.17
Vegetation	241 (70)	83 (70)	88 (79)	70 (63)	0.02
Vegetation length (mean, mm)	13 +/- 8	13 +/- 9	16 +/- 8	10 +/- 7	<0.001
Peri-valvular lesion	55 (16)	18 (15)	31 (28)	6 (5)	<0.001
Severe valvular regurgitation	129 (38)	59 (50)	50 (45)	20 (18)	<0.001
LVEF (mean $\pm$ SD, %)	56 +/- 12	56 +/- 12	56 +/- 12	56 +/- 11	0.42
<b>Surgery and outcome</b>					
Indication for surgery / device extraction	200 (58)	81 (68)	91 (82)	28 (25)	<0.001
Surgery / device extraction	118 (35)	52 (44)	60 (55)	6 (5)	<0.001
Hospital mortality	44 (13)	13 (11)	9 (8)	22 (20)	0.03
One-year mortality	88 (26)	24 (20)	23 (21)	41 (37)	0.003
Recurrence at one year	13 (4)	8 (7)	2 (2)	3 (3)	0.16

Values are n(%). RC: Referral Center; TRC : Transferred to Referral Center; NRC: Non-Referral Center; HC: health-care. CRP: C-Reactive Protein. LVEF: left ventricular ejection fraction. ICD implantable cardioverter defibrillator

**Table 2: Predictive factors of mortality in multivariate analysis**

<b>Multivariate analysis</b>		
	<b>HR 95 %-CI</b>	<b><i>p</i> value</b>
RC Group*	1	-
TRC Group	0.95 (0.53-1.69)	0.857
NRC Group	2.56 (1.44-4.55)	0.001
Age (per one year)	1.03 (1.01-1.05)	0.002
Heart failure - No*	1	-
Yes	2.4 (1.52-3.78)	<0.001
Peri-valvular lesion - No*	1	-
Yes	3.25 (1.86-5.68)	<0.001
LVEF (per one %)	0.97 (0.95-0.99)	0.001

\*Reference category

RC : Referral Center ; TRC: Transferred to Referral Center; NRC: Non-Referral Center;

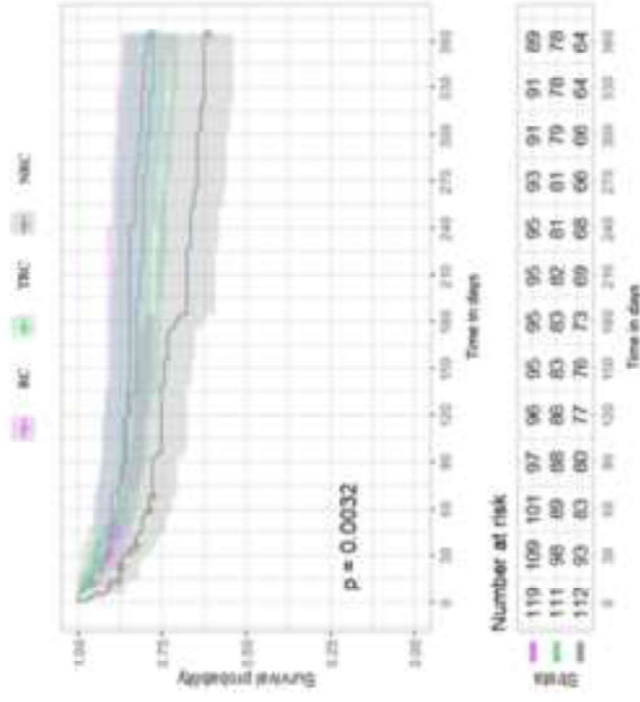
LVEF : Left Ventricular Ejection Fraction

**Table 3: Implementation of European guidelines according to health-care pathway**

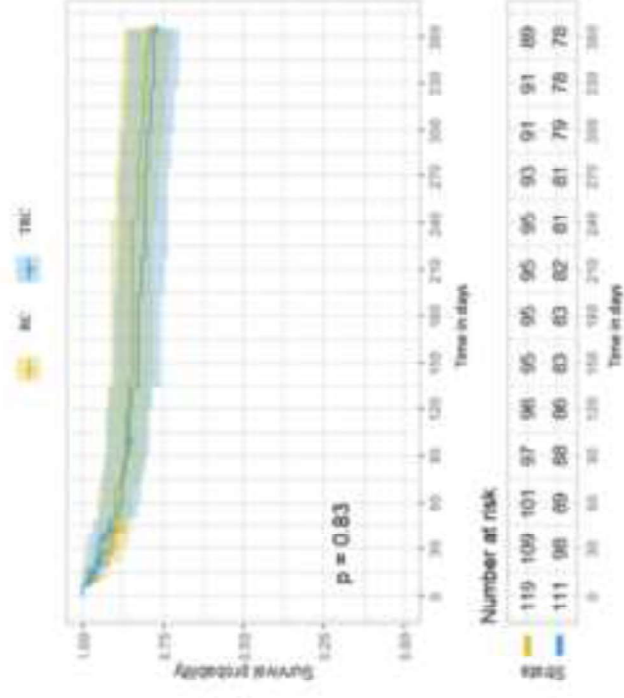
	<b>Total</b>	<b>RC group</b>	<b>TRC group</b>	<b>NRC group</b>	<b><i>p</i></b>	<b><i>p</i> RC vs TRC</b>	<b><i>p</i> RC vs NRC</b>	<b><i>p</i> RC+TRC vs NRC</b>
ESC guidelines implementation	178 (52)	67 (61)	65 (60)	46 (46)	0.04	0.91	0.03	0.04
TEE	313 (92)	115 (97)	107 (96)	91 (81)	<0.001	1	<0.001	<0.001
Surgery / device explantation	267 (78)	92 (77)	81 (73)	94 (84)	0.14	0.45	0.20	0.14
Antibiotic therapy	246 (72)	92 (84)	90 (87)	64 (65)	<0.001	0.66	0.001	<0.001

RC : Referral Center, TRC : Transferred to Referral Center; NRC: Non-Referral Center; TEE : Trans-Esophageal Echocardiography

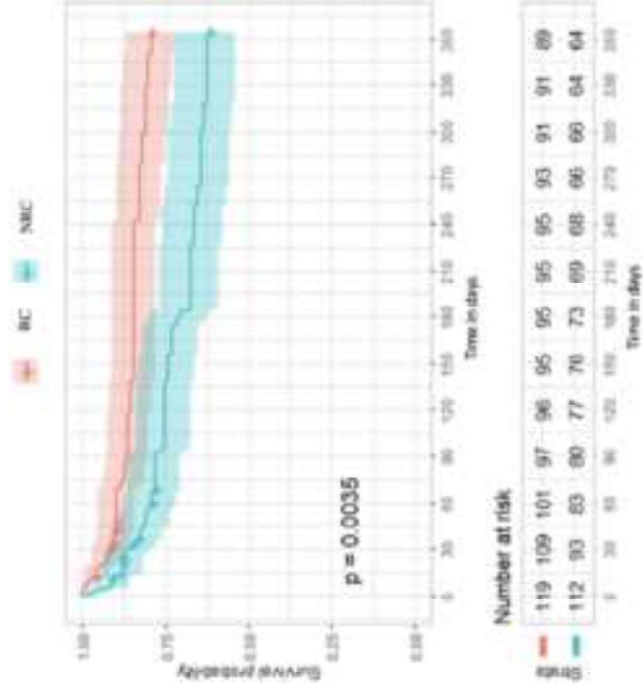
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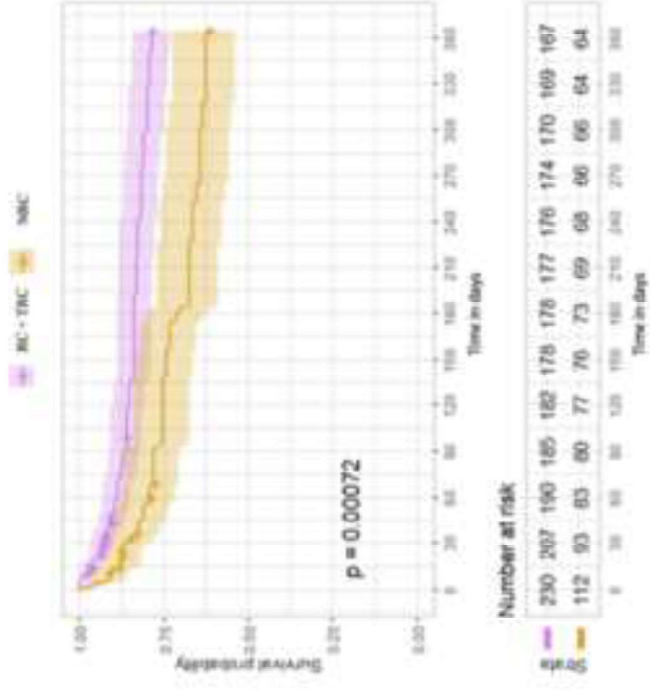
B.



C.



D.



Supplemental Data File (.doc, .tif, pdf, etc.)



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