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## Original articles

# New trends in the epidemiological and clinical features of infective endocarditis: results of a multicenter prospective study

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*Key words:*

Clinical course;  
Diagnosis; Endocarditis;  
Epidemiology;  
Prognosis.

**Background.** The clinical and epidemiological profiles of infective endocarditis (IE) are continuously evolving. We report the results of a 2-year multicenter prospective survey that investigated new trends in the epidemiology, microbiological and clinical features and the prognosis of IE.

**Methods.** From January 2000 through December 2001, a prospective multicenter survey on IE was conducted in the region of Piedmont, Italy (4.2 million inhabitants).

**Results.** A total of 267 patients with suspected IE were enrolled, of whom 147 received a definite diagnosis of IE, as confirmed by pathology or follow-up data. The annual estimated incidence of IE was 36 cases per 1 million inhabitants in urban Turin and 30 cases per 1 million inhabitants in the province of Turin. A predisposing heart disease was detected in 70.8% of cases, with prosthetic valve involvement in 27 (18%). The incidence of injection drug use was 10%. Twenty-two cases (15%) were related to invasive procedures. Causative microorganisms included: streptococci 37.4% (oral streptococci 17.7%, group D streptococci 9.5%, pyogenic streptococci 3.4%, enterococci 6.8%), staphylococci 34%, other pathogens 28.5%. Blood cultures were negative in 25% of cases. The mean time between symptom onset and hospital admission was 39.7 days; this interval was shorter and associated with a poorer prognosis in cases of IE due to *Staphylococcus aureus* infection ( $p < 0.001$ ). The delay in carrying out echocardiographic and blood culture evaluation often led to a late diagnosis as defined by the Duke criteria ( $8.2 \pm 7.4$  days after admission). Valve surgery was performed in 31% of patients. The in-hospital mortality was 14% and that at 3 months 18%.

**Conclusions.** In Piedmont, the incidence of IE is similar to the rates reported in other recent series. Still, the diagnosis and management of IE remain a challenge. The variegated clinical manifestations of IE and its changing epidemiology require constant surveillance.

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Previous studies on infective endocarditis (IE) reported an incidence ranging from 15 to 60 cases per 1 million inhabitants. The incidence of IE is stable, as are the related morbidity and mortality rates. Still, changes in the epidemiology of IE have emerged<sup>1-5</sup>. Historically, IE was common in patients with rheumatic valvular heart disease following community-acquired bacteremia and most cases (60 to 80%) were due to viridans streptococci<sup>6,7</sup>. During the past 20 years, the incidence of rheumatic heart disease in developed countries has declined<sup>8</sup>. But as more and more patients are hospitalized in intensive care units or undergo invasive procedures for chronic and acute disease, the incidence of nosocomial bacteremia is increasing. Bacteremia is also increasing among injection drug

users, who are now considered at risk for developing IE<sup>1-5,9,10</sup>.

These new trends in the epidemiology of IE need to be monitored in order to provide a timely diagnosis and care. We report the results of a 2-year multicenter prospective survey conducted in Piedmont, Italy, on the epidemiology, the microbiological and clinical features, and the prognosis of IE.

## Methods

From January 2000 through December 2001, a prospective, multicenter survey on IE was conducted in the region of Piedmont, Italy (4.2 million inhabitants). Of the 90 departments of medicine, infectious dis-

eases, cardiology and cardiac surgery contacted, 36 (41%) agreed to participate in the survey. A monitor at each center was responsible for data collection and interaction with the coordinating center. The coordinating center was the Cardiology Department of the Maria Vittoria Hospital, Turin, which is the referring Cardiology Department of the Amedeo di Savoia Hospital, the regional tertiary care hospital for infectious diseases.

The centers received a copy of the study protocol and standard guidelines on blood culture samples<sup>11</sup>, medical treatment of IE<sup>11,12</sup>, transthoracic and transesophageal echocardiography<sup>11-14</sup>, laboratory analysis and Duke University diagnostic criteria<sup>11-15</sup>. Uniform methods for applying diagnostic criteria and collecting data were explained at two meetings. Informed consent forms of the patients participating in the survey were collected.

For each case of suspected IE, the peripheral centers informed the coordinating center and completed a data collection form. The collected data (including echocardiographic findings) were reviewed by two experts. The diagnosis, based on the Duke criteria and 3-month follow-up data, was validated at the coordinating center. The coordinating center was also responsible for data analysis and echocardiographic examination review. Echocardiographic data were available for review in over 90% of cases.

The data collection form included patient demographics (date of birth, gender, address), clinical data (information from medical charts, including hospitalization data, initial symptoms, predisposing factors such as heart disease, injection drug use or invasive procedures, IE prophylaxis) and other clinical features useful for applying the Duke criteria and timing, including associated diseases, medical and surgical treatment, and course of the disease.

Blood cultures were usually performed at the laboratory of the peripheral study center. In complex or particular cases, blood samples could also be sent to the two central laboratories (the Infectious Disease Center Laboratory, Amedeo di Savoia Hospital and the Molinette Hospital Microbiology Laboratory, Turin). Blood cultures and *Coxiella burnetii* were considered positive on the basis of the Duke modified criteria<sup>15</sup>.

As described previously<sup>16</sup>, elevated erythrocyte sedimentation rates and C-reactive protein levels were considered abnormal.

An embolic event was defined as the acute onset of organ system dysfunction consistent with ischemia, on the basis of objective changes in the physical examination and confirmed by serial laboratory and radiological studies.

**Statistical analysis.** Continuous variables are expressed as mean  $\pm$  SD whereas categorical variables are expressed as proportions and percentages. Comparisons between patient groups were performed using the unpaired Student's t-test for continuous variables and

the  $\chi^2$  analysis for categorical variables. A p value  $< 0.05$  was considered as statistically significant.

Descriptive statistical analysis included only definite cases of IE according to the Duke criteria after confirmation by autopsy, pathology or surgery data or 3-month follow-up information.

## Results

In the study period, 267 patients with suspected IE were enrolled, of whom 147 (55%) received a definite diagnosis of IE as confirmed by pathology and/or the Duke criteria. These cases constituted the sample population for the purposes of this study.

**Epidemiology.** The age distribution showed a higher incidence of IE after the age of 50, particularly between 70 and 79 years (Fig. 1). The sample cannot be considered representative of the entire region because, except for sporadic cases, no cases were reported from the provinces of Novara, Vercelli, Asti or Biella. This obviously modified the provincial distribution of the disease. Where the survey was highly representative, however, was the city (estimated incidence of 36 cases per 1 million population) and the province of Turin (30 cases per 1 million inhabitants). Moreover, the epidemiological and clinical features of the Turin province were not statistically different from those of the entire population.

**Clinical features.** The main epidemiological and clinical characteristics are reported in table I. A predisposing heart disease was found in 104 of 147 cases (70%); the incidence of injection drug use was 10%; HIV infection was present in 5 patients (3.4%).

Only 18 patients (12%) had received dental care within 50 days of symptom onset (14 tooth extractions, 2 devitalizations, 1 abscess, 1 treatment for a decayed tooth). Twenty-two cases (15%) were related to invasive procedures with a high risk of bacteremia (11 after receiving a percutaneous device, 3 previous surgery, 3 after cardiac surgery, 2 after cardiac catheterization, 1 with chronic hemodialysis, 1 after a prolonged stay in intensive care following a multiple trauma, and 1 case of pacemaker pocket infection).

**Physical examination and diagnostic data.** A previously undetected heart murmur was discovered in 38 cases (26%). A body temperature  $> 38^\circ\text{C}$  was found in 140 (95%).

Elevated erythrocyte sedimentation rates were found in 125 patients (85%); high C-reactive protein levels in 120 (82%). A major echocardiographic criterion as described by the Duke criteria was detected in 132 cases (90%) (Table I). Transesophageal echocardiography was performed in 103 cases (70%). Vegetations were discovered in 121 cases (82%), in 92 of

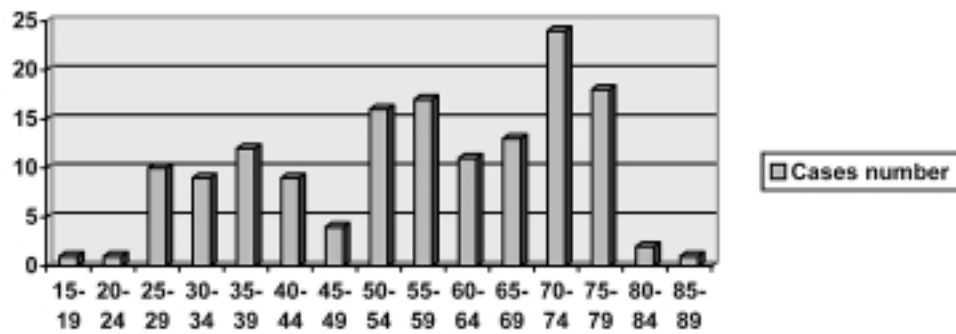


Figure 1. Age distribution of infective endocarditis cases.

Table I. Main clinical features of the study population (147 patients).

|  |           |
|--|-----------|
| Predisposing heart disease             | 104 (70%) |
| Injection drug use                     | 15 (10%)  |
| HIV infection                          | 5 (3.4%)  |
| Dental care                            | 18 (12%)  |
| Nosocomial bacteremia                  | 22 (15%)  |
| In-hospital mortality                  | 21 (14%)  |
| Overall mortality*                     | 28 (19%)  |
| Pathological confirmation              | 54 (37%)  |
| Diagnostic echocardiogram**            | 132 (90%) |
| Compatible echocardiogram**            | 11 (7.4%) |
| Positive blood cultures**              | 98 (67%)  |
| Negative blood cultures                | 37 (25%)  |
| Intermittent positive blood cultures** | 12 (8%)   |
| Typical infective agent**              | 70 (48%)  |
| Vascular phenomena**                   | 45 (31%)  |
| Immunologic phenomena**                | 25 (17%)  |

\* after 3-month follow-up; \*\* according to the Duke criteria.

which at transthoracic echocardiography and in 29 at transesophageal echocardiography only. Abscesses were detected in 5 cases, in 2 of which also at transthoracic echocardiography. New prosthetic heart valve dehiscence was present in 11 cases, in 5 of which the diagnosis was established only at transesophageal echocardiography.

Clubbing was found in 5 cases (3.4%), splenomegaly in 20 (14%), splinter hemorrhage in 6 (4%), and microscopic hematuria in 72 (49%).

The presence of at least one vascular phenomenon was detected in 45 cases (31%), of which: 26 were systemic emboli, 10 septic pulmonary infarctions, 2 mycotic aneurysms, 5 cerebral hemorrhages, and 2 Janeway's lesions. Systemic emboli were found in the central nervous system in 15 cases (58%), the retina in 4, the major joints in 2, the spleen in 2, the limbs in 2, and in the coronary artery with myocardial infarction in 1. The sources of the emboli in the central nervous system were mitral valve IE in 7 cases (47%, 13% of all mitral valve IE), aortic and mitral valve IE in 5 (42% of all aortic and mitral valve IE), and aortic valve IE in 3 (7.5% of all aortic valve IE).

Systemic emboli were associated with mitral valve IE in 12 cases (23% of all mitral valve IE), with aortic valve IE in 8 (20% of all aortic valve IE), and with aortic and mitral valve IE in 6 (50% of all aortic and mitral valve IE).

Septic pulmonary infarction subsequent to tricuspid valve involvement was present in all cases of injection drug use or nosocomial bacteremia; an embolic complication occurred in 90% of the cases of this subgroup.

Immunological phenomena were present in 25 patients (17%), of whom 15 (60%) had a positive rheumatoid factor, 7 (28%) glomerulonephritis, 2 (8%) Osler's nodes, and 1 (4%) Roth spot.

The in-hospital mortality was 14% and that at 3 months 18%. The diagnosis of IE was confirmed at histology or at autopsy in 54 patients (37%).

**Predisposing heart disease.** A predisposing heart disease was detected in 104 of 147 patients (70.8%) (Table II), of whom 37 (35.6%) had a prosthetic device (18 with a mechanical valve, 17 with a bioprosthesis, 1 with a prosthetic conduit, and 1 with a pacemaker).

Table II. Predisposing heart disease.

|                                   |          |
|-----------------------------------|----------|
| Prosthetic valves                 | 37 (25%) |
| Mechanical                        | 18       |
| Biological                        | 17       |
| Prosthetic conduit                | 1        |
| Pacemaker                         | 1        |
| Native valves                     | 67 (45%) |
| Mitral valve prolapse             | 25       |
| Aortic stenosis                   | 5        |
| Aortic stenosis and insufficiency | 6        |
| Mitral stenosis                   | 2        |
| Mitral stenosis and insufficiency | 3        |
| Aortic insufficiency              | 6        |
| Mitral insufficiency              | 3        |
| Mitral and aortic insufficiency   | 5        |
| Bicuspid aortic valve             | 8        |
| Interventricular septal defect    | 1        |
| Previous mitral valvuloplasty     | 2        |
| Aortic valve sclerosis            | 2        |

Rheumatic valve disease (mitral and/or aortic) was present in 8 cases. A mitral valve prolapse was detected in 25 cases. A bicuspid aortic valve was diagnosed in 8 cases and suspected in another 10. A history of previous IE was disclosed in 7 patients, 5 of whom (71.4%) had a prosthetic valve. In 43 cases (29.2%), no predisposing heart disease was discernible.

**Initial clinical presentation.** The initial presentation was variable. Fever was the most frequent sign (about 90% of cases). The symptoms at the time of presentation are reported in table III. The mean time between symptom onset and hospital admission was 39.7 days; in 71 patients (48%) symptoms were present 30 days prior to admission and in 18 patients 90 days before admission. Among these 18 patients (15 males), the aortic valve was involved in 7, the mitral valve in 5, and the mitral and aortic valves in 3. Streptococcal IE was present in 7 cases (3 streptococci viridans, 4 streptococci bovis), staphylococcal IE in 6 (no *Staphylococcus aureus* cases), enterococcal IE in 3, *Candida albicans* in 1. The interval between symptom onset and hospital admission was shorter in patients with *Staphylococcus aureus* IE than in those with IE due to other microorganisms (10.1 ± 9.8 vs 44.1 ± 4.2 days, respectively, p < 0.001).

**Valvular involvement.** The IE valvular involvement is reported in table IV. Native valves were involved in 118 cases (80.2%) and a prosthetic heart valve in 27 (18.4%). The most frequently involved heart valves were the mitral valve (45% of all native valve IE) and the aortic valve (34%). Concomitant involvement of the mitral and aortic valves was found in 12 cases (8.2%); the tricuspid valve was involved in 11 injection drug users (7.5%).

**Table III.** Initial symptoms and signs of infective endocarditis.

|                                   |             |
|-----------------------------------|-------------|
| Fever                             | 132 (89.7%) |
| Asthenia                          | 9 (6.1%)    |
| Dyspnea                           | 8 (5.4%)    |
| Arthralgia and myalgia            | 8 (5.4%)    |
| Cough                             | 5 (3.4%)    |
| Hemiparesis, hyposthenia, aphasia | 3 (2%)      |
| Weight loss                       | 3 (2%)      |
| Nausea and vomiting               | 2 (1.3%)    |
| Angina pectoris                   | 2 (1.3%)    |
| Flu-like symptoms                 | 2 (1.3%)    |
| Syncope                           | 1 (0.6%)    |
| Palpitations                      | 1 (0.6%)    |
| Acute renal insufficiency         | 1 (0.6%)    |
| Headache                          | 1 (0.6%)    |
| Jaundice                          | 1 (0.6%)    |
| Abdominal pain                    | 1 (0.6%)    |

The total number of symptoms and signs exceeds the overall number of cases because the symptoms/signs were multiple; only relevant symptoms/signs are reported.

**Table IV.** Valve involvement in infective endocarditis.

|                                |             |
|--------------------------------|-------------|
| Native valves                  | 118 (80.2%) |
| Mitral valve                   | 53 (36%)    |
| Aortic valve                   | 40 (27.2%)  |
| Mitral and aortic valve        | 12 (8.2%)   |
| Tricuspid valve                | 11 (7.5%)   |
| Aortic and tricuspid valve     | 1 (0.6%)    |
| Pulmonic valve                 | 1 (0.6%)    |
| Pacemaker                      | 1 (0.6%)    |
| Interventricular septal defect | 1 (0.6%)    |
| Prosthesis                     | 27 (18.4%)  |
| Bioprosthesis                  | 16 (10.9%)  |

**Etiologic agents.** Blood cultures were persistently positive in 98 cases (67%), intermittently positive in 12 (8%), and negative in 25% of cases. *Coxiella burnetii* serology was positive in 1 case. The etiologic agent was detected from biologic specimens (valves, septic emboli) in 5 cases. The etiologic agent remained unknown in 29 cases (19.7%), about 80% of which had received a previous course of antibiotic therapy. A detailed list of the etiologic agents is reported in table V.

Streptococci were the most frequent etiologic agents (55 patients); only 24 cases were caused by *Streptococcus viridans* (21% of all positive blood cultures). Fifty patients had staphylococcal IE. *Staphylococcus aureus* was the etiologic agent in 28 cases. Streptococcal and staphylococcal IE accounted for the bulk of cases (89.6%) with a discernible etiology. Staphylococci were more frequent in nosocomial than in overall cases (57 vs 34% respectively, p < 0.05). Among injection drug users, *Staphylococcus aureus* was the etiologic agent in 8 out of 16 cases (50%); other pathogens included *Streptococcus viridans* (3 cases) and *Neisseria B species* (1 case).

**Table V.** Etiologic agents in infective endocarditis.

|                     |            |
|---------------------|------------|
| Streptococci        | 55 (37.4%) |
| Oral*               | 26 (17.7%) |
| Group D             | 14 (9.5%)  |
| Pyogenic            | 5 (3.4%)   |
| Enterococcal        | 10 (6.8%)  |
| Staphylococcal      | 50 (34%)   |
| Aureus              | 28 (19%)   |
| Epidermidis         | 12 (8.2%)  |
| Others              | 10 (6.8%)  |
| Escherichia coli    | 2 (1.4%)   |
| Candida albicans    | 2 (1.4%)   |
| HACEK               | 2 (1.4%)   |
| Corynebacterium     | 1 (0.6%)   |
| Klebsiella oxytoca  | 1 (0.6%)   |
| Pseudomonas         | 1 (0.6%)   |
| Coxiella burnetii** | 1 (0.6%)   |
| Neisseria           | 1 (0.6%)   |

HACEK = Hemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella. \* include: *S. salivarius* 13, *S. sanguinis* 11, *S. vestibularis* 1, *S. mitis* 1; \*\* based on positive serology.

The main clinical features according to etiologic agents are reported in table VI. Older patients more frequently had IE caused by non-oral streptococci (enterococci and group D streptococci), while younger patients more often had *Staphylococcus aureus* IE. The male to female ratio decreased progressively for non-oral streptococcal, staphylococcal and oral streptococcal IE. A predisposing heart disease was more common in cases of oral streptococcal IE, while injection drug use was more frequent in case of staphylococcal IE. Aortic valve involvement was common in non-oral streptococcal IE, while mitral valve involvement was usual for oral streptococcal IE. Staphylococcal IE carried a poorer prognosis because of the increased associated incidence of heart failure and mortality; 11 of 19 deaths (58%) were due to staphylococci (*Staphylococcus aureus* in 9 cases); other deaths were due to group D streptococci (2 cases), streptococci viridans (1 case), *Candida albicans* (1 case), and unknown pathogens in 4.

**Clinical course.** The mean length of hospital stay was  $35.5 \pm 28.1$  days. On the basis of the Duke criteria, the diagnostic delay was  $8.2 \pm 7.4$  days after admission, and  $39.7 \pm 42.9$  days after the onset of symptoms. The delay in diagnosis was  $> 90$  days in 18 cases. The delay in obtaining blood cultures after the onset of symptoms was  $< 7$  days in about 34% of cases, 7-14 days in 15%, 15-28 days in 21%, and  $> 28$  days in 30% of cases. For the same time scale, the delay between the onset of symptoms and transthoracic echocardiography was 25, 22, 22 and 31% respectively, while the delay to transesophageal echocardiography was 21, 14, 29 and 36% respectively.

Direct etiologic evidence was collected from pathologic and bacteriologic specimens in 54 cases, in 44 of

which after cardiac surgery, in 9 of which at autopsy, and in 1 of which after central nervous system surgery.

Cardiac surgery was necessary in 45 cases (31%), in 30 of which it was performed during hospitalization and in 15 of which after discharge. Percutaneous extraction of an infected pacemaker electrode was performed in 1 case. During the follow-up period, 28 deaths (19%) occurred, of which 21 (14%; 2 after cardiac surgery) occurred during hospitalization and 7 (5%) after discharge. Forty-three patients (29%) presented with heart failure during hospitalization.

## Discussion

In this study, a total of 147 patients with definite IE were enrolled from tertiary and secondary medical care settings throughout the region of Piedmont. Because of its prospective, multicenter design, the survey seems to be representative of the provinces that participated in the survey. In the city of Turin, the most representative population sample in the study, the incidence of IE was 36 cases per 1 million inhabitants. The estimated incidence of IE for the city is comparable with that of recent surveys reporting incidence rates between 17 and 62 cases per 1 million inhabitants<sup>1-5</sup>. Moreover, the main demographic, epidemiological and clinical features of Turin and the other provinces of the region were similar.

This multicenter study cannot be directly compared with a previous single center study conducted in Turin<sup>17</sup>. Even so, we felt it necessary to compare the two in order to point out new trends in the epidemiology and clinical features of IE. Compared with the urban population sample collected in the early 1990s<sup>17</sup>, the

**Table VI.** Main clinical characteristics of infective endocarditis according to etiologic groups.

|                            | Oral streptococci (n=26) | Staphylococcus aureus (n=28) | Other streptococci* (n=24) | p     |
|----------------------------|--------------------------|------------------------------|----------------------------|-------|
| Age (years)                | 57.1 ± 14.0              | 50 ± 18.6                    | 66 ± 9.7                   | 0.002 |
| Males                      | 13                       | 18                           | 20                         | 0.005 |
| Predisposing heart disease | 21                       | 11                           | 13                         | 0.01  |
| Injection drug use         | 0                        | 7                            | 0                          | 0.02  |
| Prosthetic valves          | 3                        | 7                            | 4                          | NS    |
| Mitral valve               | 12                       | 4                            | 5                          | 0.03  |
| Aortic valve               | 9                        | 3                            | 9                          | 0.05  |
| Tricuspid valve            | 0                        | 6                            | 0                          |       |
| Embolic events             | 4                        | 8                            | 3                          | NS    |
| Cerebral hemorrhage        | 2                        | 1                            | 2                          | NS    |
| Cerebral embolus           | 0                        | 3                            | 3                          | NS    |
| Immunologic phenomena      | 4                        | 5                            | 5                          | NS    |
| In-hospital surgery        | 6                        | 4                            | 2                          | NS    |
| Delayed surgery            | 4                        | 1                            | 2                          | NS    |
| In-hospital mortality      | 1                        | 9                            | 2                          | 0.006 |
| Heart failure              | 7                        | 14                           | 3                          | 0.011 |

\* include: group D streptococci and enterococci.

present study population, sampled nearly a decade later, showed a lower number of injection drug users, HIV infection and right-sided IE. The increase in the number of IE cases without a predisposing heart disease and without injection drug use was probably related to the growing proportion of older persons in the general population with unknown degenerative aortic and mitral valve diseases and to an increase in the number of nosocomial and iatrogenic cases<sup>18</sup>. As a direct consequence of less injection drug use, fewer HIV-infected patients with IE were noted.

Presently the mean population age is similar to that reported in other studies<sup>5,19</sup>. Of the predisposing heart diseases, prosthetic heart valve infections is becoming more frequent, accounting for 25% of cases in our study. The most frequent predisposing factor in native valve heart disease is mitral valve prolapse, while bicuspid aortic valve disease is becoming more and rheumatic heart valve disease less common<sup>20</sup>. As reported elsewhere<sup>11,21</sup>, the mitral valve is the most frequently affected heart valve and is the one most often associated with systemic embolization. However, the aortic valve was recently reported<sup>5</sup> to be the most frequently involved native valve in IE. In our study, this held true for non-oral streptococcal IE and in elderly patients.

The symptoms at presentation are variable, sometimes insidious; fever is almost always present. The erythrocyte sedimentation rate is frequently abnormal, but the white blood cell count is often normal<sup>22</sup>. The onset of the disease is often aspecific and may precede the florid phase of the disease or hospitalization or a correct diagnosis for several months often without serious complications. As in other studies<sup>3,19</sup>, so too in our survey this was true for oral and group D streptococcal IE and for staphylococcal IE (excluding *Staphylococcus aureus*-related cases).

Of the etiologic agents, a reduction in streptococci viridans was observed with a similar frequency for *Staphylococcus aureus*, oral and non-oral streptococci including group D streptococci, and enterococci. A French study<sup>5</sup> reported a greater reduction in oral streptococci-related IE. This drop could reflect the changing demographic features of the affected population or the success of antibiotic prophylaxis before invasive dental care or poor attention to other possible sources of bacteremia.

A higher frequency of *Staphylococcus aureus* forms has been reported in surveys from the United States<sup>18,21,23</sup>. *Staphylococcus aureus* was also the single most frequent etiologic agent in our study. Our data showed a great reduction in the number of *Staphylococcus aureus* infections related to injection drug use, whereas, as noted in other studies<sup>24-27</sup>, an increasing number of cases was related to nosocomial forms or invasive procedures. Some studies<sup>18,24-26</sup> reported a dramatic increase in the risk of IE in immunodepressed and dialyzed patients, two groups that were scarcely represented in our survey.

The spread of *Staphylococcus aureus* IE in developed countries and its acute onset and poor prognosis<sup>5,18,20</sup> stress the importance of an early diagnosis and treatment of these cases, which represent an emerging challenge in the management of IE. In uncomplicated *Staphylococcus aureus* bacteremia (i.e. without IE), the transesophageal-based approach to guide treatment duration was found to be less cost-effective than empirical treatment for 2 to 4 weeks<sup>28</sup>.

The often very long delay between the onset of symptoms and hospitalization suggests that IE may presently have a subtle progression and go unrecognized for some time, without raising any clinical suspicion. Interdisciplinary awareness campaigns directed at cardiologists, practitioners, internists, neurologists, geriatricians, surgeons and critical care physicians would be very useful in this respect.

The length of hospital stay was long, though shorter than those reported in other series<sup>5,20</sup>. The overall mortality was high, despite the slight decrease compared with previous studies<sup>3</sup>. Mortality could be reduced with an early diagnosis, prompt medical and surgical therapy and, possibly, with reparative surgery. A late diagnosis is often due to the low clinical suspicion of the disease, combined with a delayed request of blood cultures and transthoracic and transesophageal echocardiography examinations.

The high number of negative blood cultures observed in our study was probably due to the frequent use of previous empirical antibiotic therapy and a reduced use of focused microbiological studies. Extending the modern technologies of advanced laboratories may improve the accuracy of blood cultures. It is important to perform *Coxiella burnetii*, *Bartonella* species, *Chlamydia* species, *Legionella* and *Brucella* species serology. The laboratory should also be advised of a suspected diagnosis of IE because of the need of targeted cultures to detect HACEK microorganisms, *Bartonella*, *Brucella*, *Legionella* and *Abiotrophia* species (nutritionally variant streptococci) and fungi.

The presence of *Tropheryma whipplei* should be determined by histological analysis on the specimen or by means of the polymerase chain reaction<sup>20</sup>.

However, the most important diagnostic tool is echocardiography which, on the basis of the major Duke echocardiographic criteria, has a sensitivity of about 90% and a specificity of 97%.

Diagnostic transesophageal echocardiography was performed in 103 cases (about 70%), all patients with a prosthetic heart valve or an uncertain transthoracic echocardiogram. The sensitivity was 90% and the specificity 94%, both rates consistent with those of previous reports<sup>29-32</sup>. The delay to echocardiography was considerable. About 31% of transthoracic echocardiograms and 36% of transesophageal echocardiograms were performed later than 30 days after the onset of symptoms. The delay might have been responsible for the late diagnosis, complications and prolonged hospi-

talization; it was sometimes related to a low clinical suspicion or to organizational problems and the lack of examination availability. Since echocardiography is necessary for an early diagnosis, a good quality transthoracic and/or transesophageal echocardiogram should be available within 48 hours of having posed the clinical suspicion of IE.

In conclusion, in Piedmont, the incidence of IE is similar to the rate reported in other recent series. Because an early diagnosis is difficult to establish, the morbidity and mortality rates associated with the disease remain high. The number of cases related to rheumatic disease and injection drug use has decreased, while nosocomial and iatrogenic cases have increased. That the frequency of *Staphylococcus aureus* IE is on the increase, carries important prognostic implications. In the diagnosis and management of IE many challenges remain open. The variable clinical manifestations of the disease and its changing epidemiology require constant surveillance.

## Appendix

### Author Contributions

- Study concept and design: E. Cecchi, R. Trincherio, A. Brusca
- Data acquisition: E. Cecchi, D. Forno, I. Dal Conte
- Analysis and interpretations: E. Cecchi, R. Gnavi, R. Trincherio
- Drafting of the manuscript: E. Cecchi, M. Imazio
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