MAJOR ARTICLE

Preeminence of *Staphylococcus aureus* in Infective Endocarditis: A 1-Year Population-Based Survey

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Background. Observational studies showed that the profile of infective endocarditis (IE) significantly changed over the past decades. However, most studies involved referral centers. We conducted a population-based study to control for this referral bias. The objective was to update the description of characteristics of IE in France and to compare the profile of community-acquired versus healthcare-associated IE.

Methods. A prospective population-based observational study conducted in all medical facilities from 7 French regions (32% of French individuals aged ≥18 years) identified 497 adults with Duke-Li–definite IE who were first admitted to the hospital in 2008. Main measures included age-standardized and sex-standardized incidence of IE and multivariate Cox regression analysis for risk factors of in-hospital death.

Results. The age-standardized and sex-standardized annual incidence of IE was 33.8 (95% confidence interval [CI], 30.8–36.9) cases per million inhabitants. The incidence was highest in men aged 75–79 years. A majority of patients had no previously known heart disease. Staphylococci were the most common causal agents, accounting for 36.2% of cases (*Staphylococcus aureus*, 26.6%; coagulase-negative staphylococci, 9.7%). Healthcare-associated IE represented 26.7% of all cases and exhibited a clinical pattern significantly different from that of community-acquired IE. *S. aureus* as the causal agent of IE was the most important factor associated with in-hospital death in community-acquired IE (hazard ratio [HR], 2.82 [95% CI, 1.72–4.61]) and the single factor in healthcare-associated IE (HR, 2.54 [95% CI, 1.33–4.85]).

Conclusions. *S. aureus* became both the leading cause and the most important prognostic factor of IE, and healthcare-associated IE appeared as a major subgroup of the disease.

In industrialized countries, the profile of infective endocarditis (IE) has been changing significantly over the past decades [1]. First, the decrease in rheumatic heart disease and the increase in degenerative heart diseases have led to an increase in patients' age and frequency of comorbidities [2, 3]. Second, the use of prosthetic valves among patients has increased steadily [3]. More recently, it has been suggested that a growing proportion of cases of IE were hospital acquired [4] and/or healthcare related [5], especially cases involving *Staphylococcus aureus* [6]. Finally, injection drug use [7] and hemodialysis [6, 8] may also have contributed to changes in the presentation of IE. Moreillon and Que first pointed out that these changes resulted in a shift in causative microorganisms, with staphylococci surpassing streptococci as the most common causative

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pathogens in cases of IE [9]; these findings were later confirmed by different observational studies [1, 6]. However, most of these findings were from referral center–based studies rather than population–based studies, which may have introduced a bias toward an overestimation of the proportion of staphylococcal IE. When controlling for this referral bias by reviewing only population-based observational studies, Tleyjeh et al confirmed a significant increase in cases of IE among patients with a prosthetic valve but failed to find evidence of significant temporal trends in causative organisms [10]. Two of the 14 studies retained in the review by Tleyjeh et al originated from our group. These 2 population-based observational studies, conducted in 1991 and 1999, used the same methods [11, 12] and showed that the overall incidence of IE was stable, that the incidence of oral streptococcal IE decreased significantly, and that the incidence of staphylococcal IE increased.

In 2008, we performed a third population-based observational study of IE in France, to update the description of characteristics of IE, to compare the profile of community-acquired versus healthcare-associated IE, and to assess prognostic factors of IE.

METHODS

This study was conducted in 2008 in 7 French administrative areas: greater Paris, Lorraine, Rhône-Alpes, Franche-Comté, Marne, Ille-et-Vilaine, and Languedoc-Roussillon. The adult population in these areas (15.3 million inhabitants) encompassed 31.9% of the French population ≥18 years of age. Adult patients living in the study area with a first hospitalization for IE from 1 January through 31 December 2008 were included in this analysis.

The study was announced by mail to all physicians from all hospitals—public and private—in these regions who were likely to be involved in the diagnosis and care of patients with IE. Physicians and microbiologists were asked to send a notification form to the study coordinating center for each suspected case of IE. They were reminded of the study by mail on a regular basis throughout the study period.

A case report form was filled out for each patient aged ≥18 years who was living in one of the study regions and was treated for potential IE. Data were collected on site by a trained clinical research assistant in cooperation with the patient's attending physician, using a set of standard definitions for all variables.

The following information was collected: sex, date of birth, residence, dates of first symptoms and first hospitalization, transfer from/to another facility, history of heart disease, comorbidities (including diabetes mellitus, cancer, dialysis, and immunosuppressive therapy), Charlson comorbidity index [13], procedures and other risk factors for IE, signs and symptoms of IE, echocardiographic data, microbiological data, laboratory and imaging findings, medical and surgical treatment, and outcome. Location of IE was determined by echocardiographic findings and was updated by surgical findings, as needed.

The mode of IE acquisition was categorized on the basis of 3 mutually exclusive classes: (1) injection drug use–associated IE, (2) community-acquired IE, and (3) healthcare-associated IE, which included nosocomial and nonnosocomial IE, according to prior definitions [6, 14–16] described in detail in the supplementary materials.

Microbiological data included the total number of blood samples cultured, the number of blood cultures with positive results, results of valve cultures, results of serological tests, results of polymerase chain reaction (PCR) analysis of resected material, and causative microorganisms identified. Microbiologists were asked to send all strains of streptococci and staphylococci to the corresponding national reference centers, where identification was confirmed on the basis of phenotypic and molecular microbiology techniques [17–19].

Cardiac surgery was considered to be part of IE treatment if it was performed during antibiotic treatment or ≤30 days after the completion of antibiotic therapy.

After completion of case report forms, their contents were validated by an expert team in each region. This process also included the validation of the diagnosis according to the Duke criteria modified by Li [20]. Only Duke-definite cases of IE were included in the study.

The study was approved by an institutional review committee (Comité de Protection des Personnes, Besançon, December 2007). Patients were informed of the study but did not have to provide individual consent, in accordance with French legal standards.

Statistical Analysis

Incidence rates, expressed as the number of cases per million inhabitants, were calculated by dividing the number of cases recorded during the study year by the number of persons residing in the study regions who were aged ≥18 years. Population references were obtained from the estimation made by the National Institute of Statistics and Economic Studies on 1 January 2008, using data from the nationwide 2007 census. The in-hospital mortality rate was defined as the number of patients who died during the initial hospital stay, whatever the cause of death, divided by the study population size.

Quantitative variables are described as mean (SD) except for time variables, which are described as median (interquartile range [IQR]). For intergroup comparison, we used ad hoc methods (1-way analysis of variance and the Pearson χ^2 test), and .05

Table 1. Main Characteristics of Patients With Infective Endocarditis (IE), Overall and According to Mode of Acquisition and Type of Underlying Disease

Variable	Whole Population	Mode of Acquisition[a]			Underlying HD			
		Community-Acquired Cases	Healthcare-Associated Cases	*P*	Prosthetic Valve	Previously Known HD	No Previously Known HD	*P*
Patient characteristics								
Total	497 (100)	335 (73.3)	122 (26.7)	…	104 (20.9)	131 (26.4)	262 (52.7)	…
Age, years, mean (SD)	62.3 (15.9)	62.9 (15.4)	67.4 (12.4)	.01	66.0 (14.7)	62.9 (16.1)	60.6 (16.1)	.01
Age ≥70 years	192 (38.6)	130 (38.8)	58 (47.5)	.09	52 (50.0)	56 (42.7)	84 (32.1)	.003
Male sex	369 (74.2)	260 (77.6)	78 (63.9)	.003	77 (74.0)	96 (73.3)	196 (74.8)	.95
Charlson comorbidity index, mean (SD)	1.9 (2.2)	1.7 (2.0)	2.9 (2.5)	<.0001	1.9 (2.0)	2.1 (2.2)	1.9 (2.3)	.52
≥1 Comorbidity	237 (47.7)	145 (43.3)	73 (59.8)	.002	48 (46.2)	58 (44.3)	131 (50.0)	.53
Diabetes mellitus	113 (22.7)	71 (21.2)	40 (32.8)	.01	25 (24.0)	28 (21.4)	60 (22.9)	.89
Cancer	89 (17.9)	55 (16.4)	32 (26.2)	.02	17 (16.3)	26 (19.8)	46 (17.6)	.77
Dialysis	11 (2.2)	0 (0)	10 (8.2)	<.0001	1 (1.0)	5 (3.8)	5 (1.9)	.33
IDU	29 (5.8)	0 (0)	0 (0)	…	3 (2.9)	2 (1.5)	24 (9.2)	.003
Cardiac history								
Underlying HD				.5				…
Prosthetic valve	104 (20.9)	69 (20.6)	30 (24.6)	…	… …	… …	… …	…
No previously known HD	262 (52.7)	168 (50.1)	62 (50.8)	…	… …	… …	… …	…
Previously known HD without prosthetic valve	131 (26.4)	98 (29.3)	30 (24.6)	…	… …	… …	… …	…
Previous IE	32 (6.4)	23 (6.9)	4 (3.3)	.15	17 (16.3)	13 (9.9)	2 (0.8)	<.0001
Intracardiac device (PM or ICD)	66 (13.3)	23 (6.9)	42 (34.4)	<.0001	11 (10.6)	14 (10.7)	41 (15.6)	.26
Clinical and biological features								
Fever	424/493 (86.0)	284/333 (85.3)	101/120 (84.2)	.77	86 (82.7)	104/129 (80.6)	234/260 (90.0)	.02
Heart failure	168 (33.8)	114 (34.0)	41 (33.6)	.93	32 (30.8)	58 (44.3)	78 (29.8)	.01
NYHA class 3 or 4	100/455 (22.0)	68/307 (22.1)	25/112 (22.3)	.97	18/95 (18.9)	37/116 (31.9)	45/244 (18.4)	.01
Vascular phenomena	235 (47.3)	163 (48.7)	39 (32.0)	.002	51 (49.0)	60 (45.8)	124 (47.3)	.88
Cerebral embolism	102 (20.5)	79 (23.6)	12 (9.8)	.001	29 (27.9)	25 (19.1)	48 (18.3)	.11
Cerebral hemorrhage	29 (5.8)	20 (6.0)	5 (4.1)	.44	8 (7.7)	14 (10.7)	7 (2.7)	.004
Other embolism	165 (33.2)	110 (32.8)	29 (23.8)	.06	29 (27.9)	40 (30.5)	96 (36.6)	.21
Immunologic phenomena	58/487 (11.9)	46/329 (14.0)	8/120 (6.7)	.04	11/103 (10.7)	13/128 (10.2)	34/259 (13.2)	.63
Serum creatinine level ≥180 μmol/L	141/488 (28.9)	80/331 (24.2)	43/119 (36.1)	.01	30/102 (29.4)	31/130 (23.8)	80/256 (31.3)	.31
Location of IE				<.0001				<.0001
Aortic	153 (30.8)	113 (33.7)	32 (26.2)	…	51 (49.0)	33 (25.2)	69 (26.3)	…
Mitral	172 (34.6)	127 (37.9)	38 (31.1)	…	24 (23.1)	61 (46.6)	87 (33.2)	…
Aortic and mitral	60 (12.1)	46 (13.7)	7 (5.7)	…	14 (13.5)	12 (9.2)	34 (13.0)	…
Tricuspid	41 (8.2)	10 (3.0)	18 (14.8)	…	3 (2.9)	6 (4.6)	32 (12.2)	…
Bilateral	14 (2.8)	9 (2.7)	2 (1.6)	…	2 (1.9)	3 (2.3)	9 (3.4)	…

Table 1 continued.

Variable	Whole Population		Mode of Acquisition[a]				Underlying HD					
			Community-Acquired Cases		Healthcare-Associated Cases	*P*	Prosthetic Valve		Previously Known HD		No Previously Known HD	*P*
Pacemaker	26	(5.2)	7	(2.1)	19	(15.6)	…	4	(3.8)	5	(3.8)	17	(6.5)	…
Other location	2	(0.4)	2	(0.6)	0	(0)	…	0	(0)	2	(1.5)	0	(0)	…
Unknown	29	(5.8)	21	(6.3)	6	(4.9)	…	6	(5.8)	9	(6.9)	14	(5.3)	…
Cardiac lesions of IE														
Positive echocardiography	460	(92.6)	307	(91.6)	116	(95.1)	.22	95	(91.3)	119	(90.8)	246	(93.9)	.48
Vegetation	435	(87.5)	289	(86.3)	110	(90.2)	.27	79	(76.0)	114	(87.0)	242	(92.4)	.0001
Dehiscence	19/104	(18.3)	12/69	(17.4)	6/30	(20.0)	.76	19	(18.3)	0	(0)	0	(0)	…
Severe regurgitation	194/492	(39.4)	149/331	(45.0)	30	(24.6)	<.0001	19/102	(18.6)	68/129	(52.7)	107/261	(41.0)	<.0001
Cardiac abscess (echo and surgery)	101	(20.3)	71	(21.2)	18	(14.8)	.12	37	(35.6)	27	(20.6)	37	(14)	<.0001
Microorganisms							<.0001							.01
Streptococci	180	(36.2)	163	(48.7)	9	(7.4)	<.0001	23	(22.1)	50	(38.2)	107	(40.8)	.003
Oral streptococci	93	(18.7)	83	(24.8)	5	(4.1)	<.0001	12	(11.5)	30	(22.9)	51	(19.5)	.08
Group D streptococci	62	(12.5)	57	(17.0)	4	(3.3)	.0001	9	(8.7)	15	(11.5)	38	(14.5)	.29
Pyogenic streptococci	25	(5.0)	23	(6.9)	0	(0)	.003	2	(1.9)	5	(3.8)	18	(6.9)	.11
Enterococci	52	(10.5)	36	(10.7)	13	(10.7)	.98	17	(16.3)	14	(10.7)	21	(8.0)	.06
Other Streptococcaceae	8	(1.6)	7	(2.1)	1	(0.8)	.69	1	(1.0)	6	(4.6)	1	(0.4)	.006
Staphylococcus aureus	132	(26.6)	69	(20.6)	40	(32.8)	.007	22	(21.2)	31	(23.7)	79	(30.2)	.15
Coagulase-negative staphylococci	48	(9.7)	14	(4.2)	32	(26.2)	<.0001	13	(12.5)	9	(6.9)	26	(9.9)	.34
Other microorganisms	42	(8.5)	26	(7.8)	16	(13.1)	.08	17	(16.3)	12	(9.2)	13	(5.0)	.002
≥2 Microorganisms	9	(1.8)	2	(0.6)	4	(3.3)	.04	1	(1.0)	2	(1.5)	6	(2.3)	.76
No microorganism identified	26	(5.2)	18	(5.4)	7	(5.7)	.88	10	(9.6)	7	(5.3)	9	(3.4)	.06
Outcome														
Cardiac surgery	223	(44.9)	165	(49.3)	37	(30.3)	.0003	41	(39.4)	61	(46.6)	121	(46.2)	.45
In-hospital death	113	(22.7)	68	(20.3)	38	(31.1)	.02	27	(26.0)	26	(19.8)	60	(22.9)	.54
Length of hospitalization, days, median (IQR)														
Whole population	43.0	(27.5–67.0)	41.0	(25.0–62.0)	49.0	(30.0–81.0)	.03	43.0	(25.0–59.5)	44.0	(26.0–71.0)	42.0	(29.0–68.0)	.80
Operated patients	47.0	(31.0–71.0)	45.0	(31.0–67.0)	52.0	(32.0–81.0)	.35	51.0	(35.0–79.0)	51.0	(35.0–81.0)	43.0	(31.0–62.0)	.17
Nonoperated patients	38.0	(24.0–62.0)	35.0	(22.0–55.0)	46.0	(30.0–80.5)	.009	36.0	(24.0–50.0)	38.0	(23.0–53.0)	40.0	(27.0–72.0)	.36
Dead patients	26.0	(11.0–44.0)	18.5	(10.5–42.5)	33.0	(22.0–52.0)	.04	19.0	(11.0–42.0)	25.5	(13.0–47.0)	27.0	(11.5–46.0)	.77
Survivors	47.0	(32.0–72.0)	44.0	(31.0–68.0)	54.0	(36.0–94.0)	.008	47.0	(34.0–68.0)	46.5	(32.0–79.0)	45.5	(32.0–72.0)	.99

Values are expressed as no. or proportion (%) of patients, unless otherwise indicated.

Abbreviations: HD, heart disease; ICD, implantable cardiovertor defibrillator; IDU, injection drug use; IE, infective endocarditis; IQR, interquartile range; NYHA, New York Heart Association; PM, pacemaker; SD, standard deviation.

[a] After exclusion of IDU-associated IE and IE of unknown origin.

was the level of statistical significance. On the basis of 500 cases of IE, 75% of which being community acquired, and a 2-sided alpha risk of 5%, we calculated that a 15% difference between community-acquired and healthcare-associated IE could be detected with a power of 90%.

In-hospital prognostic factors were determined using bivariable and multivariable Cox proportional hazards models. The following variables were evaluated for their potential impact on prognosis: age, sex, underlying heart disease, Charlson comorbidity index, diabetes mellitus, dialysis, mode of IE acquisition, time to diagnosis, *S. aureus* as the causative agent, heart failure, cerebral complication, intracardiac abscess, and cardiac surgery. Although it has been demonstrated that the best option for assessing the impact of cardiac surgery on outcome is to assign the variable a time-dependent format, this is true only when the prognosis analysis includes time after hospitalization [21]. Therefore, we assigned the cardiac surgery variable a binary format. For multivariable analysis, variables entered into the model were those with a P value of $\leq .1$ in bivariable analysis. A forward stepwise variable selection was then performed, with a P value of .1 required for entering the variable into the model and a P value of .05 required for removing the variable. The assumption of proportionality was tested and met. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

All statistical analyses were performed using SAS (version 9.2) software (SAS Institute).

RESULTS

Population

A total of 938 notifications led to the identification of 845 patients with a putative diagnosis of IE. Of these, 213 were excluded for the following reasons: hospitalization outside the study period (n = 86), living outside the study regions (n = 104), missing data (n = 17), and age of <18 years (n = 6). Of the remaining 632 patients, 135 did not fulfill the criteria for definite IE (IE was probable in 105 cases and excluded in 30). The present report is based on the remaining 497 cases of definite IE.

A total of 369 cases (74.2%) were in men. The patients' mean age was 62.3 years (SD, 15.9 years; range, 18–96 years) overall, 61.4 years (SD, 15.6 years) among men, and 65.0 years (SD, 16.6 years) among women (P = .03). Table 1 compares characteristics of IE according to the mode of acquisition and type of underlying heart disease. Injection drug use was associated with 29 cases of IE, and the mode of acquisition could not be ascertained in 11. These 40 cases were excluded from the comparison between the 335 cases of community-acquired IE (73.3%) and 122 cases (108 nosocomial and 14 nonnosocomial) of healthcare-associated IE (26.7%).

Incidence

The crude annual incidence of IE was 32.4 cases per million inhabitants (95% CI, 29.6–35.4), with 50.7 cases per million inhabitants in men (95% CI, 45.6–56.1) and 15.9 cases per million inhabitants in women (95% CI, 13.3–18.9). The age-standardized and sex-standardized annual incidence was 33.8 cases per million inhabitants (95% CI, 30.8–36.9). The incidence increased in patients aged ≥50 years and peaked at 194 cases per million inhabitants in men aged 75–79 years (Figure 1). Interestingly, most of the increased incidence of IE in male patients aged ≥50 years was attributable to healthcare-associated IE (Figure 2).

Underlying Heart Disease

The distribution of underlying heart disease is summarized in Table 1. Of note, 262 patients (52.7%) had no previously known heart disease. Sixty-six patients (13.3%) had an intracardiac device (8 had implantable cardiovertor defibrillators, and 58 had pacemakers). At least 1 prosthetic valve was present in 104 patients (20.9%; 116 prostheses were present, of which 66 were mechanical, 47 were biological, and 3 were homografts). The time between the last surgical procedure and IE was <1 year in 23 cases (22.1%). Thirty-four patients (6.8%) had congenital heart disease, of whom 18 (52.9%) had undergone surgical repair for this condition.

Clinical and Laboratory Characteristics of IE

For 493 patients, fever was absent in 69 (14.0%). Heart failure was common (in 168 patients [33.8%]), reaching New York Heart Association class 3 or 4 in 100 of 455 patients (21.9%). Eighteen of 429 patients (4.2%) had a Glasgow coma scale score of ≤8 during the course of the disease. An imaging procedure (cerebral, thoracic, or abdominal) was performed for 434 (87.3%) patients, as part of routine screening in 310 (71.4%) patients for any imaging, in 256/349 (73.4%) patients for cerebral CT/MRI, and in 323/337 (95.8%) patients for abdominal CT or ultrasonography. At least 1 vascular phenomenon was evidenced in 235 patients (47.3%) and consisted of embolism (in 224 patients [45.1%]) (Table 2), intracranial hemorrhage (in 29 [5.8%]), mycotic aneurysm (in 19 [3.8%]), and Janeway lesion (in 8 [1.6%]). Immunologic manifestations were observed in 58 of 487 patients (11.9%) and included glomerulonephritis (in 11 of 473 [2.3%]), Osler nodes (in 13 of 484 [2.7%]), Roth spots (in 3 of 439 [0.7%]), and positive rheumatoid factor (in 35 of 129 [27.1%]).

Echocardiographic Data and Location of IE

Transthoracic echocardiography was performed for 497 patients (100%), and transesophageal echocardiography was performed for 437 (87.9%). A major echocardiographic criterion was present in 460 patients (92.6%): 435 (87.5%) had vegetations (in 148 of the 348 patients [42%] whose vegetation size was recorded, vegetations were ≥15 mm long), 80 (16.1%) had an

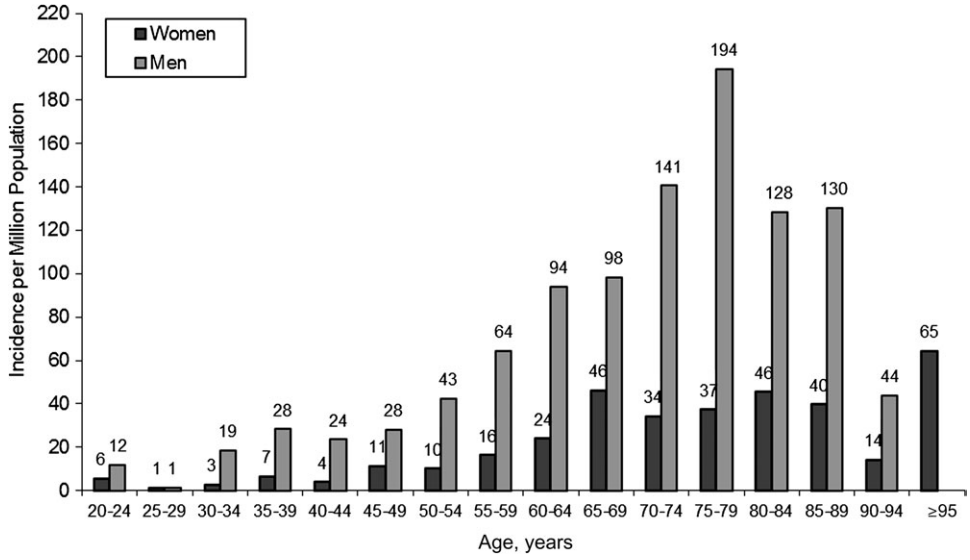

Figure 1. Incidence of infective endocarditis in the study population, by age and sex.

abscess, and of the 104 patients with a valve prosthesis, 19 (18.3%) had prosthesis dehiscence. The distribution of the locations of IE is summarized in Table 1. In the 66 patients with intracardiac stimulation devices, IE was located on leads only in 26 (39.4%), on tricuspid valve and/or leads in 21 (31.8%), on leads and left heart valves in 2 (3.0%), and on left heart valves only without evidence of lead involvement in 13 (19.7%); the location of IE remained uncertain in 4 patients (6.1%).

Causative Microorganisms

Causative microorganisms were identified in blood cultures for 451 of 497 patients (90.7%). In patients with negative blood culture results, the causative microorganism was identified by valve culture for 5 patients, by lead culture for 3, by culture of synovial fluid for 2, by PCR of valve material and/or blood for 8, by serology for 1, and by both serology and PCR of valve material for 1. Eventually, 26 patients (5.2%) had no microorganism identified.

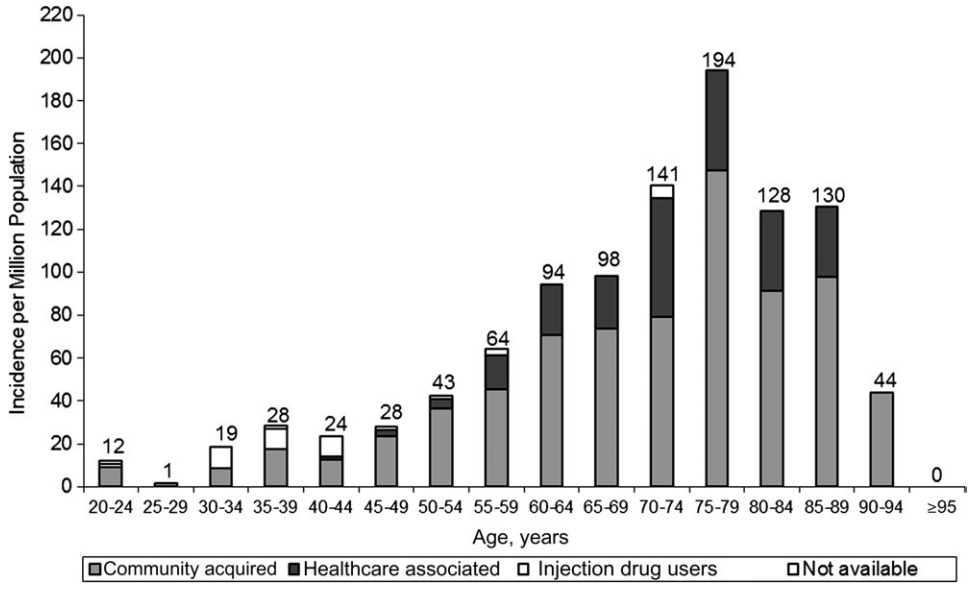

Figure 2. Incidence of infective endocarditis in the male population, by age and by mode of acquisition.

Table 2. Distribution and Characteristics of Cerebral and Embolic Complications in Patients With Infective Endocarditis

Variable	Overall (n = 497)	Symptomatic Events	Before Antibiotic Therapy
Cerebral complications	137 (27.6)	99/493 (20.1)	51/497 (10.3)
Cerebral embolism	102 (20.5)	69/493 (14.0)	29/497 (5.8)
Intracranial hemorrhage	29 (5.8)	24/495 (4.8)	10/497 (2.0)
Cerebral abscess	13 (2.6)	8/496 (1.6)	2/497 (0.4)
Extracerebral embolic events	165 (33.2)	76/486 (15.6)	41/497 (8.2)
Pulmonary	43 (8.7)	27/495 (5.5)	11/497 (2.2)
Splenic	83 (16.7)	10/493 (2.0)	17/497 (3.4)
Renal	45 (9.1)	7/491 (1.4)	8/497 (1.6)
Peripheral	41 (8.2)	36/492 (7.3)	10/497 (2.0)
Hepatic	14 (2.8)	0 (0)	2/497 (0.4)
Coronary	5 (1.0)	3/497 (0.6)	1/497 (0.2)
Any embolic event	224 (45.1)	136/485 (28.0)	76/497 (15.3)

Values are no. or proportion (%) of patients.

Table 3 shows that *S. aureus* was the most frequent single species among IE-causing microorganisms, accounting for >25% of all cases. Resistance to methicillin was observed in 13.6% and 41.7% of *S. aureus* and coagulase-negative staphylococci, respectively.

According to the mode of acquisition, streptococci overall, as well as oral and group D streptococci individually, were more frequently responsible for community-acquired IE, whereas both *S. aureus* and coagulase-negative staphylococci were more frequently responsible for healthcare-associated IE.

Treatment and Outcome

The median durations of hospitalization are reported in Table 1. Cardiac surgery was performed in 223 patients (mean age, 58.2 years [SD, 15.6 years]; male sex, 174 patients [78%]) after a median time of 10.0 days (IQR, 3.0–23.0 days) after the beginning of antibiotic treatment, a median time of 2.0 days (IQR, 0.0–9.0 days) after indication for surgery was established, and ≤2 days after the decision to operate for 94 patients (42.1%). Indications for surgery were hemodynamic for 142 patients (63.7%), uncontrolled infection for 100 (44.8%), and embolic for 116 (52.0%). Surgery was performed significantly more frequently in patients with community-acquired IE than in patients with healthcare-associated IE (49.3% vs 30.3%; $P = .0003$).

The overall in-hospital mortality rate was 22.7% (113 patients). It was higher among patients with healthcare-associated IE than among those with community-acquired IE (31.1% vs 20.3%; $P = .01$). The mortality rate among patients with prosthetic valve IE was not significantly higher than that among patients with native valve IE.

Prognostic Factors

Table 4 displays the results of Cox regression analyses in the whole population. Multivariable analysis identified 4 parameters as statistically significant and independently associated with a higher risk of in-hospital death. These were greater age, *S. aureus* as the cause of IE, development of cerebral complications, and heart failure.

In the subgroup of patients with community-acquired IE, results remained essentially similar to those observed in the whole population: *S. aureus* as the cause of IE (HR, 2.82 [95% CI, 1.72–4.61]; $P = .0001$), the development of cerebral complications (HR, 2.38 [95% CI, 1.45–3.93]; $P = .0007$), and a greater age (HR, 1.04 [95% CI, 1.02–1.06]; $P = .0001$) were the 3 most significant prognostic factors. By contrast, in the subgroup of patients with healthcare-associated IE, *S. aureus* was the only factor associated with a higher risk of in-hospital death (HR, 2.54 [95% CI, 1.33–4.85]; $P = .005$).

DISCUSSION

The 2 most important results of this study are that (1) *S. aureus* has become the predominant species responsible for IE in France and (2) healthcare-associated IE now represents >25% of all cases of IE.

Overall, *S. aureus* was the predominant species among causative pathogens, accounting for >25% of cases, far ahead of the number of cases caused by oral streptococci. This is particularly striking among healthcare-associated IE cases, but even among community-acquired IE cases staphylococci are as frequent as oral streptococci. Coagulase-negative staphylococci also emerged as frequently responsible for IE, not only in prosthetic valve IE but also in native valve IE, although this was significantly more the case in the subgroup of healthcare-associated IE. Overall, streptococci were more frequently responsible for community-acquired than healthcare-associated IE, but the formerly predominant oral streptococci accounted

Table 3. Distribution of Causative Microorganisms in Patients With Infective Endocarditis

Microorganisms	No. (%) of Patients (n = 497)	
Streptococcaceae	240	(48.3)
Streptococci	180	(36.2)
Oral streptococci[a]	93	(18.7)
Group D streptococci[b]	62	(12.5)
Pyogenic streptococci	25	(5.0)
Enterococci	52	(10.5)
Other Streptococcaceae[c]	8	(1.6)
Staphylococcaceae	180	(36.2)
Staphylococcus aureus	132	(26.6)
Coagulase-negative staphylococci	48	(9.7)
Other microorganisms[d]	42	(8.5)
HACEK group	6	…
Enterobacteriaceae	4	…
Propionibacterium acnes	4	…
Pseudomonas aeruginosa	3	…
Lactobacillus species	2	…
Corynebacterium species	2	…
Coxiella burnetii	2	…
Bartonella quintana	1	…
Tropheryma whipplei	1	…
Candida species	6	…
Miscellaneous[e]	11	…
≥2 Microorganisms[f]	9	(1.8)
No microorganism identified	26	(5.2)

Abbreviations: HACEK, *Haemophilus sp, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae.*

[a] Including 8 strains of *Streptococcus pneumoniae.*

[b] Including 45 strains of *Streptococcus gallolyticus* subspecies *gallolyticus.*

[c] Three strains of *Gemella* species, 3 strains of *Granulicatella adiacens,* 1 strain of *Abiotrophia defectiva,* and 1 strain of *Aerococcus viridans.*

[d] Because of very small numbers, percentages are not reported.

[e] *Gordonia bronchialis, Bacillus* species, *Erysipelothrix rhusiopathiae, Neisseria elongata, Moraxella catarrhalis, Veillonella* species, *Listeria monocytogenes, Acinetobacter ursingii, Campylobacter fetus, Francisella tularensis,* and *Catabacter hongkongensis* (1 strain of each species).

[f] *S. aureus* plus another pathogen (n = 3), 2 different strains of coagulase-negative staphylococci (n = 2), *Staphylococcus capitis* plus *Bacillus cereus* (n = 1), *Streptococcus gordonii* plus *Haemophilus* species (n = 1), *Stenotrophomonas maltophilia* plus *Pichia anomala* (n = 1), and 2 different strains of *Candida* species (n = 1).

for <20% of cases of IE overall. In addition, group D streptococci accounted for 12.5% of all microorganisms. Although this percentage is quite higher than that found in the International Collaboration on Endocarditis (ICE) project [1], it is also much lower than the 25% observed in our previous French survey [12]. These figures clearly illustrate the dramatic change of paradigm in IE: within a few years, this disease shifted from an infectious disease mostly of dental origin to mostly a healthcare-related infection, as previously highlighted by other studies [16, 22–25].

Actually, healthcare-associated IE accounted for at least 25% of this series of IE cases, which was not biased toward tertiary-care recruitment. The profile of these healthcare-associated IE cases was different from that of community-acquired IE in many respects. Patients with healthcare-associated IE were older, as reported elsewhere [5]. Not surprisingly, healthcare-associated IE developed more often in patients who had major comorbidities, were undergoing hemodialysis, or had intravascular devices implanted. A total of 11.4% of all healthcare-associated cases of IE were nonnosocomial; this proportion was lower than that in the United States but higher than that outside the United States, as determined in the ICE *S. aureus* IE study by Fowler et al [6]. Interestingly, the distribution of underlying heart diseases did not differ between healthcare-associated and community-acquired IE. Likewise, the proportions of healthcare-associated cases of IE with a complicated disease course were either comparable to (for septic shock and heart failure) or less than (for cerebral embolism, vascular phenomena, or extracardiac complications) the proportions observed for community-acquired IE, which could be attributable to a shorter time to diagnosis. However, the in-hospital mortality rate was significantly higher than that among patients with community-acquired IE. This may be linked to the significantly higher rates of staphylococcal IE and prior comorbidities.

Analyses of prognosis showed that identification of *S. aureus* as the causative organism was the factor with the greatest prognostic weight, overall and in subgroup analyses. In addition, in healthcare-associated IE, the single factor associated with mortality in multivariable analysis was identification of *S. aureus* as the causative organism.

The major strength of this observational study is its population-based design, which minimizes the impact of a potential referral bias, the major limitation of most previous epidemiological studies of IE [10, 26, 27]. Furthermore, the diagnosis in each case of IE was validated by experts on the basis of Duke-Li criteria for definite IE, and identification of streptococci and staphylococci was checked by corresponding reference centers, which was not the case in the 2 most recently published population-based studies [22, 28]. One of these studies was performed in Australia and showed results very close to ours in terms of age of onset, distribution of microorganisms, proportion and severity of healthcare-associated IE, and prognostic factors [22]. The other study, conducted in the Veneto region of Italy, showed that the incidence of IE increased over the study period (2000–2008) and that mortality increased in association with age, Charlson comorbidity index, and staphylococcal origin [28].

This study has 2 limitations. First, although it was population based, it was based on active notification but not on an active search for cases. Therefore, we cannot exclude the possibility that case identification was not exhaustive. Second, because the

Table 4. Factors Associated With In-Hospital Death by Bivariable and Multivariable Cox Regression Models in the Study Population

	Bivariate Cox Regression			Multivariate Cox Regression		
Variable	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Age, per 1-year increment	1.03	(1.01–1.04)	.0001	1.03	(1.02–1.04)	<.0001
Sex			.62			…
Women	1.11	(0.74–1.67)		…	…	
Men	1	(ref)		…	…	
Underlying heart disease			.48			…
No previously known heart disease	1.18	(0.75–1.88)		…	…	
Prosthetic valve	1.40	(0.81–2.40)		…	…	
Previously known heart disease	1	(ref)		…	…	
Mode of acquisition			.13			…
Community	1.85	(0.58–5.88)		…	…	
Healthcare-related	2.56	(0.79–8.32)		…	…	
Intravenous drug use	1	(ref)		…	…	
Staphylococcus aureus vs other pathogens	2.57	(1.78–3.72)	<.0001	2.71	(1.87–3.93)	<.0001
Charlson comorbidity index, per 1-unit increment	1.08	(1.01–1.16)	.02	…	…	…
Diabetes mellitus, yes vs no	1.18	(0.78–1.78)	.44	…	…	…
Dialysis, yes vs no	1.85	(0.75–4.54)	.18	…	…	…
Cerebral complication, yes vs no	2.02	(1.39–2.94)	.0002	2.11	(1.45–3.09)	<.0001
Heart failure, yes vs no	1.37	(0.94–1.99)	.10	1.47	(1.01–2.13)	.04
Cardiac abscess, yes vs no	1.28	(0.80–2.04)	.30	…	…	…
Cardiac surgery, yes vs no	0.63	(0.43–0.92)	.02	…	…	…

Abbreviations: CI, confidence interval; HR, hazard ratio; ref, reference value.

information on the mode of acquisition was not recorded in our 2 previous studies [11, 12], we cannot confirm that the incidence of healthcare-associated IE increased significantly in France. However, we conducted a study that compared age-standardized and sex-standardized incidence rates of IE over the 3 studies and found that the incidence of *S. aureus* IE increased over time [29]. Because *S. aureus* is responsible for the increased incidence of healthcare-associated IE [6, 16], we can reasonably state that our study captured the emergence of healthcare-associated IE that is currently underway.

In summary, the 2 major results of this study are that (1) *S. aureus* is now both the leading cause of IE and the most important prognostic factor in IE and (2) healthcare-associated IE is an emerging facet of the disease, which is a source of concern because of its frequency and severity. If healthcare-associated IE may be viewed as an undesirable effect of healthcare universalization [24], significant efforts should be made to minimize the risk of bacteremia in healthcare facilities.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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