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## **Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study.**

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# Current Features of Infective Endocarditis in Elderly Patients

## Results of the International Collaboration on Endocarditis Prospective Cohort Study

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**Background:** Elderly patients are emerging as a population at high risk for infective endocarditis (IE). However, adequately sized prospective studies on the features of IE in elderly patients are lacking.

**Methods:** In this multinational, prospective, observational cohort study within the International Collaboration on Endocarditis, 2759 consecutive patients were enrolled from June 15, 2000, to December 1, 2005; 1056 patients with IE 65 years or older were compared with 1703 patients younger than 65 years. Risk factors, predisposing conditions, origin, clinical features, course, and outcome of IE were comprehensively analyzed.

**Results:** Elderly patients reported more frequently a hospitalization or an invasive procedure before IE onset. Diabetes mellitus and genitourinary and gastrointestinal cancer were the major predisposing conditions. Blood culture yield was higher among elderly patients with IE. The leading causative organism was *Staphylococcus aureus*, with a higher rate of methicillin resistance. *Streptococcus bovis* and enterococci were also significantly more prevalent. The

clinical presentation of elderly patients with IE was remarkable for lower rates of embolism, immune-mediated phenomena, or septic complications. At both echocardiography and surgery, fewer vegetations and more abscesses were found, and the gain in the diagnostic yield of transesophageal echocardiography was significantly larger. Significantly fewer elderly patients underwent cardiac surgery (38.9% vs 53.5%;  $P < .001$ ). Elderly patients with IE showed a higher rate of in-hospital death (24.9% vs 12.8%;  $P < .001$ ), and age older than 65 years was an independent predictor of mortality.

**Conclusions:** In this large prospective study, increasing age emerges as a major determinant of the clinical characteristics of IE. Lower rates of surgical treatment and high mortality are the most prominent features of elderly patients with IE. Efforts should be made to prevent health care-associated acquisition and improve outcomes in this major subgroup of patients with IE.

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**I**NFECTIONAL ENDOCARDITIS (IE) IS ON the rise in all western countries and in all age groups, and its epidemiologic characteristics have changed significantly in past decades.<sup>1</sup> Despite the great progress in diagnosis and treatment, mortality rates remain high.<sup>2</sup>

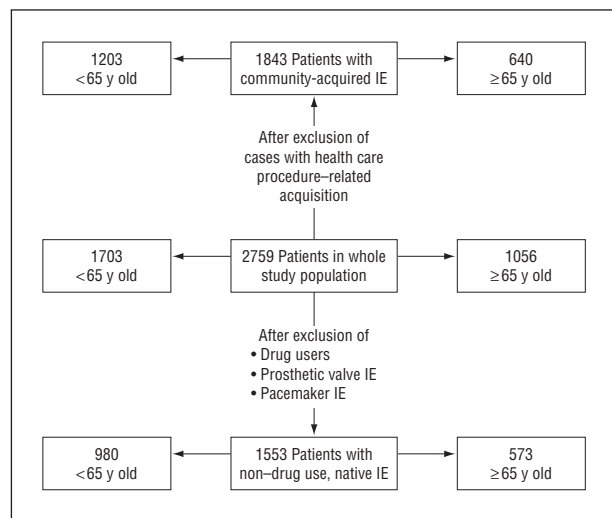
According to recent reports,<sup>3</sup> the largest relative increase in the incidence of IE was found in the elderly population (ie, those 65 years or older). It has been found that elderly patients carry a risk of endocarditis 4.6 times higher than the general population.<sup>4</sup> Factors that account for this increase in incidence in elderly patients

have not been investigated in a prospective fashion. Such factors might include the high prevalence of undiagnosed degenerative valve disease and the increased use of invasive procedures and implanted medical devices.<sup>3,5</sup> These factors could also influence the outcome of elderly patients with IE (hereinafter referred to as IE patients).

In the past decade, reports of either single-center experiences<sup>6-9</sup> or retrospective analyses<sup>10</sup> have tried to delineate the characteristics of IE in elderly patients, but conflicting data have ensued. On the basis of the results of some of these studies,<sup>3,11,12</sup> IE in elderly persons is currently assumed to have unique clinical characteristics. An

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**Group Information:** The members of the International Collaboration on Endocarditis Prospective Cohort Study Group are listed on pages 2101-2102.



**Figure.** Details of the patient subgroups studied. IE indicates infective endocarditis.

increased frequency of certain predisposing risk factors in older adults seems to influence the etiology of IE.<sup>10</sup> Some studies<sup>8,9</sup> have shown that IE in elderly patients more often involves prosthetic valves or devices and has a lower rate of embolic complications. Transesophageal echocardiography (TEE) was found to increase significantly the diagnostic sensitivity for IE in elderly patients.<sup>9,10</sup> Moreover, most studies<sup>8-10</sup> have observed an excess of mortality and a limited use of surgical treatment in elderly IE patients. In contrast to these data, it has also been suggested that epidemiologic factors and not age may play a greater role in influencing clinical presentation, echocardiographic features, frequency of complications, or need for surgery.<sup>6,7</sup> Therefore, it appears that there is no consensus for an atypical form of IE in elderly persons. In this study, we analyzed data from a large, multicenter, prospective cohort,<sup>2</sup> with the aim of evaluating clinical features and outcome of IE in relation to age.

## METHODS

Included in this study were 2759 consecutive patients enrolled in the International Collaboration on Endocarditis Prospective Cohort Study from June 15, 2000, to December 1, 2005. Details regarding participating centers, patient enrollment, and data collection within the study have already been published.<sup>2,13</sup> Institutional review boards at each participating center approved the study protocol and procedures.

### DEFINITION OF PATIENT SUBGROUPS

The IE patients were stratified into 2 groups by age: those 65 years or older were considered elderly and those 18 to 64 years old were defined as young. All patients were also stratified by presumed site of acquisition in health care–associated IE, community-acquired IE, or unknown acquisition IE. Health care–associated IE was defined as previously suggested.<sup>14</sup> A subgroup of IE patients consuming illicit drugs by inhalation or the intravenous route was referred to as drug users. Another subgroup of patients was defined as having IE on prosthetic intracardiac material, such as implantable cardiac devices and mechanical or bioprosthetic valves.

## TYPE OF AND RATIONALE FOR THE ANALYSES

In the first crude data analysis, the elderly IE group was compared with the young IE group for each of the variables considered. Subsequently, to evaluate the effect of age on the clinical characteristics of IE, we censored subgroups of IE that might introduce bias into the overall analysis. For instance, IE in drug users is primarily seen in young patients, whereas prosthetic IE is more commonly observed in elderly patients, and the clinical characteristics of those entities are unique. We therefore excluded drug users and patients with prosthetic devices from analysis. Hence, this second analysis included only patients with endocarditis on native heart structures in non–drug users. Furthermore, we evaluated the differences between elderly and younger IE patients with community-acquired IE (ie, those forms where no evidence of health care–associated origin was available) to reduce bias due to increased prior hospitalization rates and use of medical procedures in older persons. Details of each of these subgroup analyses are presented in the **Figure**. Finally, an analysis was performed after stratification of patients into 3 age groups, namely, younger than 50 years, 50 to 69 years, and 70 years or older, to evaluate the modification of the different variables as a function of increasing age.

## VARIABLES INCLUDED IN THE STUDY

A number of variables were considered and incorporated in the analysis, including demographic data, predisposing conditions, possible sources of bacteremia, causative pathogens, medications taken, and preexisting medical conditions. Further variables considered were presenting signs and symptoms, echocardiographic findings, treatment strategies, disease complications, and outcome.

## STATISTICAL ANALYSIS

Categorical variables are represented as frequencies and percentages of the specified group. Univariate comparisons were made with the Wilcoxon rank sum test or the  $\chi^2$  test as appropriate. A generalized estimating equation method was used to determine factors associated with in-hospital death, embolic complications, and surgical treatment. Variables found to have a simple association with the outcome of interest ( $P < .10$ ) were considered for the final model using backward selection. The variables included in the final adjusted regression models were selected on the basis of a combination of statistical significance ( $P < .05$ ) and clinical judgment. The generalized estimating equation method produces consistent variable estimates that measure association between the outcome of interest and clinical covariates while accounting for the correlation in outcomes of patients from the same hospital. Final variable estimates were converted to odds ratios (ORs) with corresponding 95% Wald confidence intervals (CIs). For all tests, statistical significance was determined at the .05 level. All statistical analyses were performed using SAS statistical software (version 8.2; SAS Institute Inc, Cary, North Carolina).

## RESULTS

### EPIDEMIOLOGY

There were 2759 patients with a diagnosis of definite IE according to the modified Duke criteria. A total of 1703 patients were younger than 65 years and constituted the younger group with IE, whereas the remaining 1056 patients constituted the elderly group with IE (Figure). The

**Table 1. Distribution of Predisposing Clinical Conditions for IE According to Age and Different Patient Subgroups<sup>a</sup>**

Clinical Condition	Unselected Patients (N=2759)			Non-Drug Use, Native IE (n=1553)			Community-Acquired IE (n=1843)		
	Younger (n=1703)	Elderly (n=1056)	P Value	Younger (n=980)	Elderly (n=573)	P Value	Younger (n=1203)	Elderly (n=640)	P Value
Diabetes mellitus	11.9	22.9	<.001	13.1	21.5	<.001	8.9	20.5	<.001
GI cancer	0.8	3.2	<.001	1.0	3.1	<.001	0.5	2.5	<.001
GU cancer	0.6	4.7	<.001	1.1	6.4	<.001	0.5	4.5	<.001
Immunosuppression	6.1	5.5	.48	8.6	5.6	.03	2.8	5.3	.007
Hemodialysis	8.7	6.9	.09	10.6	8.3	.10	0	0	NA
Other chronic illnesses	43.9	54.1	<.001	41.3	52.2	<.001	38.1	49.5	<.001
IVDU	15.4	0.4	<.001	0	0	NA	18.7	0.6	<.001
HIV infection	3.1	0.4	<.001	1.0	0.2	.05	3.4	0.6	<.001

Abbreviations: GI, gastrointestinal; GU, genitourinary; HIV, human immunodeficiency virus; IE, infective endocarditis; IVDU, intravenous drug user; NA, not applicable.

<sup>a</sup>Numbers denote percentage prevalence in individual patient groups. Elderly patients are those 65 years or older; younger patients are those 18 through 64 years old.

proportion of female patients was higher (35.8% vs 29.5%;  $P = .001$ ), and more prosthetic IE cases occurred (26% vs 16%;  $P < .001$ ) among elderly patients. Health care-related cases were more prevalent in the elderly group (39.4% vs 29.3%;  $P < .001$ ), and this remained true after exclusion of patients with IE on a prosthetic device (26.8% vs 19.5%;  $P < .001$ ).

#### PREDISPOSING CONDITIONS AND RISK FACTORS

Nearly half of the 2759 patients enrolled in the study were affected by at least 1 chronic illness before IE onset (data not shown). Elderly IE patients were more likely to have diabetes mellitus, a gastrointestinal or genitourinary cancer, or another chronic illness, whereas drug users were almost exclusively in the younger group (**Table 1**).

The higher prevalence of chronic illnesses was paralleled by the greater use of medications that inhibit platelet aggregation or clot formation in elderly patients. In particular, older patients were significantly more likely to be taking aspirin (25% vs 10%) or oral anticoagulants (23% vs 14%) than were younger IE patients ( $P < .001$  for both comparisons). After exclusion of IE cases on prosthetic devices, use of antiplatelet or anticoagulant medications remained significantly more common among elderly patients (22% vs 9% and 11% vs 4%, respectively;  $P < .001$ ).

Among the acquired predisposing cardiac conditions, mitral regurgitation and nonrheumatic aortic stenosis were significantly more common in elderly IE patients (57% vs 38% and 28% vs 10%, respectively;  $P < .001$  for both comparisons). In contrast, congenital heart disease, mostly bicuspid aortic valve and ventricular or atrial septal defects, was significantly less frequent (2.7% vs 16.2%;  $P < .001$ ).

Within the 6 months before IE onset, elderly patients reported significantly more often at least 1 invasive procedure (56.2% vs 38.5% of younger IE patients;  $P < .001$ ). In addition, elderly IE patients were significantly more likely to have a pacemaker or an automatic implantable cardioverter defibrillator (19.5% vs 7.1% in younger IE

patients;  $P < .001$ ). However, the proportion of persons with intracardiac devices who had evidence of IE that involved the device itself did not differ between the 2 groups (44% vs 36%;  $P = .54$ ).

#### ETIOLOGY

*Staphylococcus aureus* was the most common causative pathogen in both patient groups (**Table 2**). Elderly IE patients showed a higher prevalence of coagulase-negative staphylococci, enterococci, and *Streptococcus bovis* and lower rates of infection by viridans group streptococci. Methicillin resistance was significantly more prevalent in elderly patients as a consequence of increased nosocomial acquisition because its prevalence decreased by 30% after exclusion of health care-related cases (Table 2). Enterococci and *S bovis* were 2 to 3 times more prevalent, whereas viridans group streptococci were consistently less prevalent among elderly IE patients.

#### CLINICAL PRESENTATION

Clinical evidence of IE was found less often in elderly patients than in younger patients: in particular, vascular and immune-mediated phenomena, such as embolic events, splenomegaly, Osler nodes, Roth spots, Janeway lesions, and conjunctival hemorrhages, were all observed less commonly among elderly IE patients ( $P < .001$ ) (**Table 3**). The overall incidence of vascular embolic events was 18.9%, with a lower incidence in elderly patients (14.7% vs 21.4% in younger patients;  $P < .001$ ). Elderly IE patients showed significantly lower rates of complications, such as septic pulmonary infarcts, intracranial hemorrhages, and mycotic aneurysms (data not shown). These differences did not translate into a diagnostic delay.

#### DIAGNOSIS

Table 3 indicates the prevalence of the Duke diagnostic criteria fulfillment in the 2 age groups. Blood cultures were more likely to grow bacteria when obtained from elderly patients, even though there was an equal rate of

**Table 2. Prevalence of the Major Causative Pathogens of Infective Endocarditis (IE) According to Age and Different Patient Subgroups<sup>a</sup>**

Causative Pathogens	Unselected Patients (N=2759)			Non-Drug Use, Native IE (n=1553)			Community-Acquired IE (n=1843)		
	Younger (n=1703)	Elderly (n=1056)	P Value	Younger (n=980)	Elderly (n=573)	P Value	Younger (n=1203)	Elderly (n=640)	P Value
Gram positive	81.1	88.1	<.001	81.8	89.4	<.001	80.4	88.6	<.001
Gram negative	4.1	2.7		4.4	2.3		4.4	2.8	
Fungi or yeasts	1.5	1.5		1.2	0.5		0.6	0.8	
Others or culture negative	13.2	7.5		12.5	7.7		14.5	7.7	
<i>Staphylococcus aureus</i>	33.2	28.3	<.001	27.2	27.4	.95	28.7	19.4	<.001
Methicillin resistant	21.1	35.8	<.001	26.0	35.0	.05	10.8	14.4	.26
Coagulase-negative staphylococci	9.1	14.0	<.001	7.3	9.7	.09	6.4	10.8	<.001
Viridans group streptococci	18.6	14.2	<.001	22.6	18.7	.06	23.8	19.5	.03
<i>Streptococcus bovis</i>	4.4	8.3	<.001	5.8	10.1	.002	5.4	12.5	<.001
Enterococci	6.3	16.5	<.001	7.6	16.2	<.001	4.5	17.5	<.001

<sup>a</sup>Numbers denote percentage prevalence in individual patient groups. Elderly patients are those 65 years or older; younger patients are those 18 through 64 years old.

**Table 3. Prevalence of Modified Duke Criteria Fulfillment in Younger and Older Patients With Infective Endocarditis<sup>a</sup>**

Duke Criteria	Unselected Patients (N=2759)		
	Younger (n=1703)	Elderly (n=1056)	P Value
Major criteria			
Positive blood culture	86.4	92.2	<.001
Vegetation	88.0	83.9	.001
Abscess	14.0	15.4	.007
Dehiscence of prosthesis or new prosthesis regurgitation	6.6	10.9	<.001
Serologic test results	2.2	2.3	.83
Minor criteria			
Predisposing native cardiac condition	29.7	34.9	.004
Drug abusers	15.4	0.4	<.001
Fever	94.4	94.6	.82
Embolic events	21.4	14.7	<.001
Osler nodes, Roth spots, or Janeway lesions	6.8	2.6	.001

<sup>a</sup>Numbers denote percentage prevalence in individual patient groups. Elderly patients are those 65 years or older; younger patients are those 18 through 64 years old.

antecedent antibiotic use (data not shown). The TEE provided a major diagnostic gain mostly in elderly IE patients. Elderly patients less often had evidence of valve regurgitation and intracardiac vegetations.

Mitral regurgitation was the predominant form of valve dysfunction in elderly IE patients (63% vs 44%;  $P < .001$ ), whereas aortic and tricuspid disease prevailed in younger patients (52% and 18% vs 43% and 9%, respectively;  $P < .001$ ). Significantly more mitral and less aortic and tricuspid vegetations were found in the elderly patients compared with the younger patients (50%, 41%, and 7% vs 45%, 44%, and 17%, respectively;  $P < .001$ ). Intracardiac device infection represented a significant subset of IE in the elderly patients (10%) compared with the younger group (3%) ( $P < .001$ ).

### COMPLICATIONS, THERAPEUTIC APPROACH, AND OUTCOME

Elderly patients had lower rates of complications and in particular fewer strokes and significantly less peripheral emboli, despite exclusion of patients with IE on prosthetic devices who underwent long-term anticoagulation (**Table 4**). Elderly IE patients underwent cardiac surgery less often than their younger counterparts (38.9% vs 53.5%;  $P < .001$ ). Severe embolism, valve regurgitation, and large vegetations less often represented the reason for surgery, and intraoperatively elderly patients showed fewer vegetations (74% vs 84%) or valve perforation (24% vs 29%).

Despite lower rates of clinical complications, the rate of in-hospital death among elderly IE patients was twice as high as in younger patients, with a mortality rate approaching 25% (Table 4). This difference did not change among patient subgroups.

Multivariate analysis was performed to identify independent predictors of in-hospital death, embolic complications, and surgical treatment. Age older than 65 years was confirmed to be a strong independent risk factor for in-hospital death in both the whole study population (OR, 2.04; 95% CI, 1.62-2.56;  $P < .001$ ) and the different patient subgroups considered ( $P < .001$  in each case). Moreover, age older than 65 years was independently associated with a reduced risk of embolic events in the whole study population (OR, 0.72; 95% CI, 0.60-0.85;  $P < .001$ ) and the native IE subgroup with or without drug users ( $P < .001$  in both cases) but not in IE on prosthetic devices. Finally, age older than 65 years was a significant independent predictor of fewer surgical interventions ( $P < .001$  in all cases).

### SUBGROUP ANALYSES

To corroborate the evidence obtained concerning the features of IE in elderly patients, we further restricted the analysis, looking at data derived from spontaneous, native valve, community-acquired IE cases only (1060 patients), thereby excluding all health care-related cases

**Table 4. Major Complications, Treatment Choices, and Outcome of Infective Endocarditis (IE) According to Age in Different Patient Subgroups<sup>a</sup>**

Variable	Unselected Patients (N=2759)			Non-Drug Use, Native IE (n=1553)			Community-Acquired IE (n = 1843)		
	Younger (n = 1703)	Elderly (n = 1056)	P Value	Younger (n = 980)	Elderly (n = 573)	P Value	Younger (n = 1203)	Elderly (n = 640)	P Value
Congestive heart failure	30.3	33.1	.17	32.7	37.5	.07	30.2	32.5	.38
Stroke	17.8	14.6	<.001	19.8	16.0	.06	17.2	13.1	.02
Systemic embolism	25.9	15.3	<.001	26.5	17.3	<.001	27.3	15.1	<.001
Intracardiac abscess	13.3	15.2	.20	12.9	12.0	.56	13.8	14.5	.74
Persistent bacteremia	9.0	9.2	.10	8.5	7.3	.35	5.8	4.7	.27
New-onset heart block	8.0	7.6	.62	8.8	6.8	.15	8.1	6.8	.36
Treatment received									
Medical only	46.5	61.1	<.001	43.9	67.0	<.001	44.1	61.2	<.001
Medical and surgical	53.5	38.9		56.0	32.9		55.8	38.7	
Mortality rate	12.8	24.9	<.001	12.4	25.1	<.001	9.8	22.2	<.001

<sup>a</sup>Numbers denote percentage prevalence in individual patient groups. Elderly patients are those 65 years or older; younger patients are those 18 through 64 years old.

**Table 5. Clinical Features of IE Showing Close Dynamic Relation With Age<sup>a</sup>**

Feature	Overall (N=2759)	By Age Group			P Value
		<50 y (n=1003)	50-69 y (n=982)	≥70 y (n=773)	
Type of IE					
Native	68.6	75.2	68.5	60.3	<.001
Prosthetic	20.1	13.8	21.6	26.5	
Diabetes mellitus	16.2	6.2	21.4	22.4	<.001
Cancer	8.3	2.9	8.5	14.9	<.001
Aspirin use	16.0	6.8	16.8	27.0	<.001
Warfarin use	17.8	10.3	21.5	22.7	<.001
History of invasive procedures	18.1	11.2	19.9	24.4	<.001
Carriage of endocavitary devices (pacemaker, AICD, or other)	11.8	4.6	11.0	23.2	<.001
IE evidence at history or clinical examination	83.5	88.6	82.3	78.4	<.001
Health care-related acquisition	13.5	6.9	14.9	20.3	<.001
Pathogen					
<i>Staphylococcus aureus</i>	31.3	35.5	29.8	27.8	<.001
Viridans group streptococci	16.9	19.6	16.4	14.1	
<i>Enterococcus</i> species	10.2	5.1	9.6	17.6	
<i>Streptococcus bovis</i>	5.9	2.1	7.6	8.9	
TEE-only evidence of IE	14.6	11.8	13.5	19.8	<.001
Surgical treatment	47.9	54.8	49.8	36.6	<.001
Systemic embolism (other than stroke or TIA)	21.8	26.5	23.0	14.3	<.001
In-hospital mortality	17.4	9.8	18.5	25.8	<.001

Abbreviations: AICD, automatic implantable cardioverter defibrillator; IE, infective endocarditis; TEE, transesophageal echocardiogram; TIA, transient ischemic attack.

<sup>a</sup>Numbers denote percentage prevalence in individual patient groups.

in addition to all cases of IE on prosthetic devices or in drug users. In this subgroup analysis, all major differences between elderly and younger patients observed in epidemiologic and clinical presentation persisted (data not shown). A large reduction in *S aureus* prevalence was seen, and the rate of methicillin resistance was the same in the 2 age groups. In this selected sample, the difference between the 2 age groups in terms of surgical interventions was even greater (32% vs 61%;  $P < .001$ ). Furthermore, the in-hospital mortality rate was nearly 3 times higher among elderly patients (22% vs 6%).

Interestingly, when we compared the data of the whole study population after stratification of patients into 3 age

groups (namely, <50, 50-69, and ≥70 years), we found a positive or negative progressive trend as a function of age for most of the variables that were significantly associated with age in the previous analyses (**Table 5**). For instance, before the age of 50 years, health care-associated IE accounted for 6.9% of cases; this figure increased to 14.9% between the ages of 50 and 70 years and to more than 20% in patients older than 70 years. In addition, distribution of pathogens (with methicillin-resistant *S aureus*, *S bovis*, and enterococci prevalence increasing with age); rates of distinctive clinical manifestations, embolism, and use of surgery (decreasing with age); and mortality (progressively increasing with age)

all behaved as a function of age. These data further supported the hypothesis that age per se is a determinant of the different or atypical presentation of elderly IE patients.

## COMMENT

Infective endocarditis is a life-threatening disease that causes significant morbidity among elderly persons.<sup>3,4</sup> We analyzed data from the largest prospective, multicenter cohort of IE patients ever collected, evaluating the impact of advanced patient age on a number of variables that affect epidemiology, etiology, clinical presentation, treatment, and outcome of IE. This study provides a comprehensive outlook of IE in elderly patients and indicates that age is a major determinant of the characteristics of IE. It appears that elderly persons with IE indeed have distinctive features when compared with matched cases of younger age and that IE in elderly patients is often a consequence of medical procedures and medical advances.

In our current cohort of IE patients, elderly patients represent a major subgroup, as opposed to what was observed a few decades ago.<sup>4</sup> Infective endocarditis has a definite predilection for males, but the proportion of females affected progressively increases with patient age. The increasing susceptibility of elderly women to IE resembles the similar epidemiologic trend observed in western countries for other cardiovascular disorders.<sup>15</sup>

Among the medical conditions that seem to be associated and could play a pathogenetic role in elderly IE patients, diabetes mellitus and abdominal neoplasia feature prominently. The higher prevalence of diabetes in elderly IE patients could influence the death rate because diabetes was found to be an independent predictor of mortality in IE.<sup>16,17</sup> We confirm that intestinal neoplasia is a major risk factor for IE in elderly patients, accounting for the higher infection rates with enteric bacteria. Genitourinary tract lesions also appear as a major risk factor for invasion of the bloodstream by pathogenic bacteria. In addition, evaluation of gastrointestinal and genitourinary neoplasia frequently requires invasive procedures, which remain an important risk factor for IE in elderly patients. These findings might affect the IE antibiotic prophylaxis strategy by taking into account patient age in the global risk assessment.

We found that the proportion of IE cases that are deemed to be associated with health care procedures steadily increases with patient age. These data show that health care procedures are currently placing the increasing population of frail, disabled elderly people at a high risk of IE. In this setting, appropriate antibiotic prophylaxis and higher adherence to the aseptic technique should be strongly pursued.

The increase in nosocomial IE cases is associated with a changed microbiological profile.<sup>1</sup> Although the prevalence of *S aureus* decreases with age, the opposite trend is observed for methicillin resistance for both *S aureus* and coagulase-negative staphylococci. Irrespective of prior invasive procedures, enterococci and, especially in southern Europe, *S bovis* are emerging as the major players of spontaneous IE in elderly patients, possibly in relation

to higher rates of occult genitourinary or gastrointestinal tract disorders. These data should be taken into account to optimize the empirical treatment in culture-negative cases, although blood cultures have the highest yields in elderly IE patients.

Our data further confirmed the importance of TEE in elderly IE patients. Because these patients have fewer vegetations and tend to more often have intracardiac abscesses and prosthetic paravalvular complications, TEE should be widely used to increase the diagnostic power in this patient subset, often characterized by significant mitral annular calcification.

As previously observed,<sup>8,18</sup> vascular manifestations of IE, such as embolic events, are less common in elderly patients, despite higher rates of mitral valve involvement<sup>19</sup> and independent of other variables. Factors that may account for this phenomenon may include a more widespread use of both antiplatelet and anticoagulant medications and, possibly, a less pronounced acute-phase response,<sup>18</sup> correlating with lower rates of immune-mediated manifestations. Furthermore, the decline in immunity and hemostatic function in elderly patients<sup>20</sup> may contribute to a reduced rate and efficiency of vegetation formation, as shown by our finding of the relative lack of vegetations by echocardiography and at surgery.

Despite promising experimental results in IE due to *S aureus*, anticoagulants and antiplatelet medications were shown to be ineffective in reducing the rate of embolism in IE and possibly to be deleterious because of the increased risk of intracranial hemorrhage.<sup>21-23</sup> These views are based mostly on retrospective studies or on the de novo addition of such drugs in the acute phase of IE. However, to our knowledge, no one has prospectively studied the effect of a preexisting anticoagulant or antiplatelet treatment on the embolic risk in IE. A recent retrospective study<sup>24</sup> showed that continuous daily antiplatelet therapy was associated with a decreased incidence of embolic events during IE. Our finding that patients who more commonly receive antiplatelet or anticoagulant medications before IE onset also have lower rates of vegetation formation and embolism suggests that this issue should be evaluated further in an ad hoc prospective investigation.

This study confirms a significantly lower rate of cardiac surgical procedures among elderly IE patients.<sup>4,8,25</sup> This finding may be due to the higher operative risk related to advanced age. However, since surgical treatment is a major determinant of a successful outcome in IE,<sup>26</sup> the observed increase in mortality among elderly IE patients could be, at least in part, a consequence of the reduced rate of surgery. Whether the potential benefits of a surgical approach are truly outweighed by an increased operative mortality needs to be assessed.

After exclusion from the analysis of different subgroups of patients (prosthetic IE, health care-related IE) that may carry an intrinsically worse prognosis, the mortality of IE in elderly patients remained approximately twice that of younger patients. Moreover, the rate of death showed a steady and progressive increase as a function of age and was independently associated with age older than 65 years. Therefore, the higher complexity of the frail condition, which predisposes patients to a reduced

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use of surgery, represents the typical feature of IE in elderly patients. This condition could be intrinsically more aggressive because of the reduced ability to dominate bloodstream infection, as shown by higher rates of positive blood cultures. The prevalence of diabetes, cancer, and concomitant chronic illnesses may also play a role.

Our study has some limitations. The enrolling institutions are mostly tertiary care referral centers with cardiac surgical programs, so the results may not be completely applicable to the general IE population. Moreover, 1-year follow-up data were not yet available.

In conclusion, our data show that elderly patients currently account for a major proportion of IE patients. Any substantial progress in the management of this clinical condition will necessarily involve the improvement of IE care in elderly patients. In elderly patients, IE is characterized by common onset in prosthetic device carriers and often has a health care-associated acquisition. Chronic disorders, diabetes mellitus, and genitourinary or gastrointestinal cancer are major predisposing conditions. It is a disease of debilitated persons that typically ensues after medical treatment. The clinical characteristics of IE in elderly patients differ substantially in terms of the pattern of cardiac involvement, the causative microorganisms, and the type and frequency of complications. A high index of suspicion for the presence of IE may be needed because presenting manifestations may not be obvious. Diagnosis is challenging because transthoracic echocardiography has a lower sensitivity and TEE is more often necessary. Age per

se seems to be the most critical factor in determining the unique nature of IE in the elderly population. We also confirm that IE in elderly patients is a severe clinical condition, in which the mortality rate is twice that observed in younger patients. Efforts should be made to significantly reduce the risk of health care-associated acquisition and improve outcomes in these patients.

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