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MAJOR ARTICLE

Infective Endocarditis Related to Unusual Microorganisms: A Prospective Population-Based Study

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Background. Increased access to heart valves through early surgery and progress in molecular microbiology have reduced the proportion of infective endocarditis (IE) with no microbiological documentation and increased the proportion of IE associated with unusual microorganisms.

Methods. We performed an ancillary study of a large prospective population-based survey on IE. Unusual-microorganism IE was defined as definite IE (Duke-Li criteria) due to microorganisms other than streptococci, staphylococci, or enterococci.

Results. Of 471 cases of documented IE, 46 (9.8%) were due to unusal microorganisms; the following were involved in >1 case: *Candida albicans* (n = 4), *Cutibacterium acnes* (n = 4), *Pseudomonas aeruginosa* (n = 3), *Cardiobacterium hominis* (n = 3), and *Coxiella burnetii* (n = 2). Cases were documented with blood cultures (n = 37, 80.4%), heart valve polymerase chain reaction (PCR; n = 5), heart valve culture (n = 2), PCR on vertebral biopsy (n = 1), or serology (n = 1). As compared with IE due to staphylococci, streptococci, or enterococci (n = 420), IE due to unusual microorganisms occurred more frequently in patients with previously known heart disease (69.0% vs 44.3%; P = .002), prosthetic valve (40.5% vs 18.1%; P = .0006), longer duration of fever (mean, 35.1 ± 46.8 days vs 12.5 ± 17.8; P = .003), and who were more often nosocomial (38.1% vs 20.2%; P = .02).

Conclusions. In this population-based study, 9.8% of IE cases were due to unusual microorganisms, with a predominance of anaerobes, yeast, and gram-negative bacilli. As compared with IE related to staphylococci, streptococci, or enterococci, IE cases related to unusual microorganisms were associated with previously known heart disease, prosthetic valve, longer duration of fever, and nosocomial acquisition.

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Keywords. *Candida* sp.; *Cutibacterium acnes*; endocarditis; HACEK; *Pseudomonas aeruginosa*.

Infective endocarditis (IE) is a life-threatening disease, mostly related to staphylococci, streptococci, and enterococci, altogether responsible for 80%–90% of IE cases in large cohort studies from Europe, North America, or Oceania [1, 2]. In the recent European guidelines [3], empirical treatment of IE in acutely ill patients targets these gram-positive cocci, although other microorganisms are found in 5%–10% of IE. Unusual microorganisms, defined as those "other than staphylococci, streptococci, and enterococci," include (i) bacteria with documented tropism for cardiac valves, but accounting for a small proportion of IE cases (eg, HACEK group, *Coxiella burnettii, Bartonella* sp., *Tropheryma whipplei*); (ii) pathogens commonly encountered in other sites, but with very low propensity to affect cardiac valves (eg, Enterobacteriaceae, *Pseudomonas* spp., strict anaerobes).

Unusual microorganisms have attracted limited attention to date and have mostly been reported as "miscellaneous" in cohort studies because of their heterogeneity and their low prevalence [4, 5]. However, better awareness of the risk factors for and the characteristics of these unusual microorganisms would be of interest, as some of them may not be susceptible to commonly used empiric antimicrobial regimens. We performed an ancillary study of a large prospective population-based survey on definite IE to better characterize IE due to unusual microorganisms.

Received 3 February 2020; editorial decision 6 April 2020; accepted 10 April 2020.

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DOI: 10.1093/ofid/ofaa127

METHODS

For this study, we analyzed the database created for the purpose of the French population-based epidemiological survey on IE in 2008, whose methods and results have been published elsewhere [6]. In brief, this survey was conducted in 7 regions of France (Paris, Lorraine, Rhône-Alpes, Franche-Comte, Marne, Ille-et-Vilaine, Languedoc-Roussillon), representing a population pool of 16 million inhabitants, 31.9% of the whole French population. All IE cases diagnosed in adults during the study period were reported. A standardized case report form (CRF) was prospectively filled out, and each case was validated by an adjudication committee, including screening for Duke-Li criteria, and confirmation of the causative pathogen. All IE cases that were not classified as definite according to the Duke-Li criteria [7] were excluded from further analysis.

The following information was collected: sex, age, previously known heart disease, comorbidities (including diabetes mellitus, cancer, dialysis, and immunosuppressive therapy), Charlson comorbidity index [8], procedures and other risk factors for IE, date of first symptoms, date of hospital admission, IE diagnosis, and treatment, signs and symptoms of IE, echocardiography, microbiology, imaging studies, treatment, and outcome. Location of IE was determined by echocardiographic findings and could be updated by surgical findings. The mode of IE acquisition was categorized on the basis of 3 mutually exclusive classes: (i) injection drug use–associated IE; (ii) community-acquired IE; and (iii) health care–associated IE, which included nosocomial and non-nosocomial IE, according to prior definitions [6]. Community-acquired IE was considered in patients whose symptoms had started before or within 48 hours of admission and who did not meet criteria for health care–associated infection. Health care–associated IE was considered nosocomial if the first symptoms developed >48 hours after admission and up to 30 days after discharge from the hospital (up to 1 year after implantation of valve prostheses and up to 3 years for coagulase-negative staphylococci-infected intracardiac devices). Health care–associated IE was considered non-nosocomial if the patient had developed signs or symptoms consistent with IE before hospitalization and had undergone health care procedures (intravenous therapy, wound care, specialized nursing care at home, hemodialysis, or intravenous chemotherapy) outside a hospital within the 30 days before the onset of IE.

Microbiological data included the total number of blood culture samples, the number of blood cultures with positive results, results of valve culture, results of serological tests, results of polymerase chain reaction (PCR) analysis of resected material, and causative microorganisms identified using classical culture methods, molecular biology, and/or serology. Unusual-microorganism IE was defined as IE due to microorganisms other than streptococci, staphylococci, or enterococci. For the comparison between IE due to unusual microorganisms and IE due to usual microorganisms, we excluded polymicrobial IE. The study was approved by an institutional review board (Comité de Protection des Personnes, Besançon, France). Patients were informed about the study but did not have to provide individual consent, in accordance with French legal standards.

Quantitative variables were expressed as mean ± SD or as median and interquartile range (IQR). Qualitative variables were described as number (%). Continuous variables were compared using the Student test, and categorical variables were compared using the χ^2 or the Fisher exact test, as appropriate. The level of significance α was set at .05. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

From January 1 to December 31, 2008, 497 patients were diagnosed with definite IE, with 471 cases (94.8%) being microbiologically documented: streptococci and other *Streptococcaceae*, n = 188 (37.8%), staphylococci, n = 180 (36.2%), enterococci, n = 52 (10.5%), other microorganisms, n = 42 (8.5%), and polymicrobial, n = 9 (1.8%). Among the 9 polymicrobial IE, 4 included at least 1 unusual microorganism: *Stenotrophomonas maltophilia* and *Candida pelliculosa* (formerly *Pichia anomala*), *Candida albicans* and *Candida glabrata, Bacillus cereus* and *Staphylococcus capitis, Haemophilus* spp., and *Streptococcus gordonii*. The characteristics of the 42 cases of definite nonpolymicrobial IE involving unusual microorganisms are summarized in Table 1, and the list of these unusual

Table 1. Characteristics of Infective Endocarditis due to Unusual Microorganisms (n = 42, Polymicrobial Cases Excluded)

	Patients
Age, y	62 (51–70)
Male sex	32 (76.2)
Comorbidity(ies)	21 (50.0)
Previously known heart disease	29 (69.0)
Prosthetic valve	17 (40.5)
Pacemaker or intracardiac defibrillator	9 (21.4)
Location of infective endocarditis	
Aortic	16 (38.1)
Mitral	13 (30.9)
Aortic and mitral	5 (11.9)
Cardiac lesions	
Vegetation	32 (76.2)
Abscess	6 (14.3)
Dehiscence	6 (14.3)
Complications	
Embolic events (extracerebral)	11[a] (26.2)
Septic shock	6 (14.3)
Spondylodiscitis or septic arthritis	4 (9.5)
Treatment	
Duration of anti-infective treatment, d	45.5 (36.5–72)
Cardiac surgery	19 (45.2)
Time between anti-infective treatment start and surgery, d	4 (1.5–14)

Data are expressed as number (%) or median (interquartile range).

[a]Nine splenic, 1 pulmonary, 1 peripheral.

microorganisms is presented in Table 2. The following species accounted for >1 case: *Candida albicans* (n = 4), *Cutibacterium acnes* (formerly *Propionibacterium acnes,* n = 4), *Pseudomonas aeruginosa* (n = 3), *Cardiobacterium hominis* (n = 3), and *Coxiella burnetii* (n = 2). Seven patients had HACEK IE due to *C. hominis* (n = 3), *Haemophilus* spp. (n = 3), and *Aggregatibacter* spp. (n = 1). Four patients had Enterobacteriaceae IE (*Escherichia coli, Klebsiella pneumoniae, Serratia marcescens*, *Proteus mirabilis,* 1 case each). Most cases were diagnosed with blood cultures (n = 37, 80.4%). The 9 cases of blood culture–negative IE were diagnosed by cardiac valve PCR (n = 5), valve culture (n = 2), PCR on vertebral biopsy (n = 1), and serology (n = 1).

The mean age of patients with nonpolymicrobial IE related to unusual microorganisms was 60.7 ± 14.2 years (median [IQR], 62 [51–70] years), and 32 patients (76.2%) were men. As compared with patients with nonpolymicrobial IE related to staphylococci, streptococci, or enterococci (Table 3), IE related to unusual microorganisms was more common in patients with previously known heart disease (69.0% vs 44.3%; *P* = .002), prosthetic valve (40.5% vs 18.1%; *P* = .0006), nosocomial IE (38.1% vs 20.2%; *P* = .02), and prolonged fever (mean ± SD, 35.1 ± 46.8 days vs 12.5 ± 17.8; *P* = .003). Comparison of staphylococci IE, streptococci/enterococci IE, and unusual-microorganism IE is presented in Supplementary table 1.

Table 2. Unusual Microorganisms Documented by Culture, Serology, or PCR in Definite IE Cases (n = 46, Including 4 Polymicrobial Cases)

Microorganisms[a]	Total	Blood Culture	Valve or Other Site (Culture/PCR)
HACEK			
Aggregatibacter actinomycetemcomitans (i)	1	1	0
Cardiobacterium hominis (i)	3	2	1 (valve PCR)
Haemophilus spp. (i)	2	2	0
Haemophilus parainfluenzae (i)	1	0	1 (valve PCR)
Gram-negative bacilli			
Acinetobacter ursingii (ii)	1	1	0
Campylobacter fetus (i)	1	1	0
Escherichia coli (i)	1	1	0
Francisella tularensis (ii)	1	1	0
Klebsiella pneumonia (i)	1	1	1 (valve culture)
Proteus mirabilis (i)	1	1	0
Pseudomonas aeruginosa (ii)	3	3	0
Serratia marcescens (i)	1	1	0
Stenotrophomonas maltophilia (ii)	1	1	1
Gram-negative cocci			
Moraxella catarrhalis (i)	1	1	0
Neisseria elongata (i)	1	1	0
Gram-positive bacilli			
Bacillus cereus (ii)	1	0	1 (pacemaker culture)
Corynebacterium jeikeium (i)	1	1	0
Corynebacterium mucifaciens (i)	1	1	0
Erysipelothrix rhusiopathiae (ii)	1	1	0
Gordonia bronchialis (i)	1	1	0
Lactobacillus rhamnosus (i)	1	0	1 (PCR on vertebral biopsy)
Lactobacillus spp. (i)	2	2	2 (valve culture)
Listeria monocytogenes (ii)	1	1	0
Anaerobes			
Catabacter honkongensis (i)	1	1	0
Cutibacterium acnes (i)	4	2	2 (valve culture)
Veillonella spp. (i)	1	1	0
Other bacteria			
Bartonella quintana (ii)	1	0	1 (valve PCR)
Coxiella burnetii (ii)	2[b]	0	1 (valve PCR)
Tropheryma whipplei (ii)	1	0	1 (valve PCR)
Yeasts			
Candida albicans (i)	4	4	1 (valve culture)
Candida parapsilosis (i)	2	2	0
Candida glabrata (i)	1	1	0
Candida spp. (i)	1	1	0
Candida pelliculosa (i)	1	0	1 (valve culture)

Abbreviations: IE, infective endocarditis; PCR, polymerase chain reaction.

[a]Microorganisms were categorized as (i) endogenous; (ii) exogenous (environment, zoonosis).

[b]In 1 case, diagnosis relied on serology.

Table 3. Comparison of Endocarditis due to Staphylococci, Streptococci, or Enterococci (n = 420) and Endocarditis Due to Unusual Microorganisms (n = 42), Polymicrobial Cases Excluded

	Staphylococci, Streptococci, or Enterococci IE (n = 420)	Unusual Microorganisms IE (n = 42)	*P* Value
Patients' characteristics			
Age, y	62.8 ± 16.0	60.7 ± 14.2	.42
Male sex	317 (75.5)	32 (76.2)	.92
Charlson comorbidity index	1.9 ± 2.2	2.3 ± 2.7	.52
≥1 comorbidity	196 (46.7)	21 (50.0)	.68
Cardiac history			
Previously known heart disease	186 (44.3)	29 (69.0)	**.002**
Prosthetic valve	76 (18.1)	17 (40.5)	**.0006**
Intracardiac device (PM or ICD)	53 (12.6)	9 (21.4)	.11
Mode of acquisition			**.018**
Community-acquired IE	313 (73.6)	26 (61.9)	
Nosocomial IE	83 (20.2)	16 (38.1)	
Health care–associated, non-nosocomial IE	14 (3.4)	0	
Clinical and biological features			
Time to IE diagnosis <4 d after admission	200 (47.7)	15 (35.7)	.14
Vegetation(s)	375 (89.3)	32 (76.2)	.13
Fever	367 (87.8)	32 (76.2)	.77
Fever duration, d	12.5 ± 17.8	35.1 ± 46.8	**.003**
Outcome			
Cardiac surgery	182 (43.3)	19 (45.2)	.81
In-hospital death	101 (24.0)	6 (14.3)	.15

Data are expressed as number (%) of patients or mean ± SD. In bold: *P* values < 0.05.

Abbreviations: ICD, implantable cardioverter defibrillator; IE, infective endocarditis; PM, pacemaker.

DISCUSSSION

To the best of our knowledge, this is the first population-based prospective study on IE due to unusual mircrooganisms. We found that 9.8% of documented IE involved unusual microorganisms, with *C. albicans* (n = 4), *C. acnes* (n = 4), *P. aeruginosa* (n = 3), *C. hominis* (n = 3), and *C. burnetii* (n = 2) being the most common unusual microorganisms. Previously known heart disease, prosthetic valve, nosocomial acquisition, and prolonged fever were more common in endocarditis due to unusual microorganisms, as compared with staphylococci, streptococci, or enterococci. In our study, most cases of IE related to unusual microorganisms were diagnosed by blood cultures (n = 37, 80.4%).

Contrary to recent series of blood culture–negative endocarditis, largely dominated by 2 zoonotic pathogens, that is, *C. burnettii* and *Bartonella* sp. [5, 9–12], the spectrum of unusual microorganisms potentially responsible for IE appears broad, distributed in gram-negative bacilli (n = 11), gram-positive bacilli (n = 9), yeasts (n = 9), HACEK group (n = 7), anaerobes (n = 6), gram-negative cocci (n = 2), and others (n = 4). The proportion of IE related to strict anaerobes in our cohort (6/497, 1.2%) is in line with a recent prospective cohort in Spain [13], in which 0.9% of IE cases were due to strict anerobes, primarily *C. acnes* [14], as in our cohort. Likewise, the proportion of IE related to HACEK bacteria (7/497, 1.4%), Enterobacteriaceae (4/497, 0.8%), and *P. aeruginosa* (3/497, 0.6%) in our study is in the usual range for large cohort studies, such as the International Collaboration on Endocarditis (ICE), that is, 0.5%–3% of all IE cases [15–17].

Microbiological documentation of IE has dramatically improved over the last decades in developed countries, thanks to (i) the development of cardiac surgery during the acute phase of IE, which provides access to heart valves in up to half of patients with IE [6]; (ii) molecular biology, especially 16S rDNA PCR—the so-called "universal bacterial PCR"—which allows the identification of almost any bacteria encountered in IE, even when antibiotics have been initated before sampling [5, 11, 18]. These developments have reduced the proportion of IE with no microbiological documentation to <5% in contemporary cohort studies [6], while physicians and microbiologists are increasingly confronted with unexpected organisms identified by 16S rDNA on heart valves [18]. As about 20% of the unusual microorganisms were yeasts in our study, additional molecular tools targeting fungi, such as 18S and 28S rDNA PCR, may be of value.

We found that unusual microorganisms are more commonly encountered in patients with previously known heart disease, prosthetic valve, or nosocomial IE. This reflects that specific predisposing conditions as well as nosocomial acquisition enlarge the spectrum of pathogens potentially associated with IE. *Candida* spp. and *P. aeruginosa*, both closely associated with nosocomial bloodstream infections, were among the top 4 pathogens identified in our study. Patients with IE related to unusual microorganisms had longer duration of fever compared with patients with staphylococci, streptococci, or enterococci IE. This may reflect (i) delayed diagnosis, due to longer time to positivity for blood cultures [19], or the need to wait for PCR on excised heart valves in patients with blood culture–negative IE; (ii) inactive empirical treatment, as most empirical treatment do not target unusual microorganisms; (iii) slower clinical response, even with appropriate anti-infective treatment, as may be expected with fastidious (ie, difficult-to-grow) microorganisms [4], or *Candida* spp. [20]. HACEK IE has been associated with prolonged fever and delayed diagnosis, as compared with IE related to other pathogens [15]. In our study, early diagnosis, as defined by time to diagnosis <4 days after hospital admission, tended to be more common for IE related to staphylococci, streptococci, or enterococci, as compared with IE related to unusual microorganisms (47.7% vs 35.7%; $P = .14$).

Our study has limitations. First, as the study was performed in 1 country, during a single year, its findings may not be generalizable, given that the epidemiology of infectious diseases, including IE, may vary with time and geographical areas [21]. Second, due to the limited sample size, our study was not powered to describe rare causes of IE. In addition, the comparison of IE related to staphylococci, streptococci, or enterococci and unusual microorganisms could only be performed on a limited set of variables and probably missed significant risk factors. Third, unusual microorganisms responsible for IE were highly heterogeneous, merging IE cases classically associated with a protracted disease course, and good prognosis (eg, HACEK group or *C. acnes* IE) [4] with IE cases of dismal prognosis (eg, Enterobacteriaceae [17] or fungal IE [20]), which complicates the interpretation of our findings. Finally, as our cohort was restricted to definite IE according to modified Duke criteria, some cases of IE related to unusual microorganisms may have been missed, as blood culture criteria are more stringent for unusual microorganisms. However, this is, to our knowledge, the first population-based study on IE due to unusual microorganisms that has avoided the selection biases associated with studies originating from referral centers [22]. Our study provides original data on the characteristics of IE related to unusual microorganisms and risk factors.

In conclusion, we found that 9.8% of documented IE involves unusual microorganisms, with a predominance of strict anaerobes, yeast, and gram-negative bacilli. As compared with IE related to staphylococci, streptococci, or enterococci, IE related to unusual microorganisms is associated with previously known heart disease, prosthetic valve, nosocomial acquisition, and longer duration of fever.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility

of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Financial support. This work was funded by a research grant from the French Ministry of Health and the support of the Société Française de Cardiologie, the European Society of Clinical Microbiology and Infectious Diseases, Novartis France. The sponsor was the Hôpital Universitaire de Besançon. The study was supported by the following professional organizations: Association Pour l'enseignement de la Thérapeutique, Société de Pathologie Infectieuse de Langue Française, Société Française de Microbiologie, Société Nationale Française de Médecine Interne, Société de Réanimation de Langue Française, Société Française de Gérontologie, Société Française de Cardiologie, Société Française de Chirurgie Thoracique et Cardiovasculaire, Société Française d'Anesthésie-Réanimation, and Fédération Française de Cardiologie.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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APPENDIX

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