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Characteristics and regional variations of group D streptococcal endocarditis in France

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ABSTRACT

The proportion of infective endocarditis (IE) caused by group D streptococci (GDS; formerly *Streptococcus bovis*) increased markedly in France, to account for 25% of all cases of IE by 1999. In an attempt to explain this phenomenon, a comparative analysis of GDS and oral streptococci (OS) causing IE was performed. This study was based on data collected from a large cross-sectional population-based survey that was conducted in 1999. In total, 559 cases of definite IE were recorded, of which 142 involved GDS and 79 involved OS. Patients with GDS IE were older (62.7 vs. 56.6 years, p 0.01) and had a history of valve disease less frequently than did patients with OS IE (33.8% vs. 67.1%, p <0.0001). At-risk procedures for IE were performed less frequently in patients with GDS than in patients with OS (14.8% vs. 24.1%, p 0.08), but co-morbidities were more frequent in the GDS group (59.9% vs. 32.9%, p 0.0001). Diabetes, colon diseases and cirrhosis were also more frequent in the GDS group (p 0.006, p <0.0001 and p 0.08, respectively). Rural residents accounted for 31.0% of the GDS group, but for only 15.2% of the OS group (p 0.001). Likewise, the proportion of GDS IE was higher in regions with mixed (urban and rural) populations (Franche-Comté 81.8%, Marne 68.7%, Lorraine 70.3% and Rhône-Alpes 65.3%) than in exclusively urban regions (Paris and Ile de France 58.0%). Further investigations are required to elucidate the link in France between the incidence of GDS IE, rural residency and nutritional factors.

Keywords Bacteraemia, endocarditis, group D streptococci, incidence, nutritional factors, oral streptococci

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INTRODUCTION

As shown by numerous epidemiological surveys, the profile of infective endocarditis (IE) has changed dramatically in recent decades [1–5]. The proportion of IE caused by *Staphylococcus aureus* and other nosocomial pathogens is increasing, while the frequency of IE caused by oral streptococci (OS) is decreasing, particularly in northern Europe and the USA [6–8]. OS remain the primary cause of IE in southern Europe and South America [9]. Analysis of regional variations as part of the International Collaboration on Endocarditis study [10] revealed that group D streptococci (GDS) are an emerging cause of IE, especially in European countries, and particularly in France, Spain and Italy [9].

GDS formerly included two species named *Streptococcus bovis* and *Streptococcus equinus*, which were distinct from enterococci [11]. New species have now been described within the *Strep. bovis–Strep. equinus* complex [12–17], and the taxonomy of the related species has been clarified [17,18]. The term GDS is used in the present study to designate the different species

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belonging to the *Strep. bovis–Strep. equinus* complex.

Clinical and epidemiological features of GDS IE reported in the literature include a higher age at onset, an increased frequency of co-morbid conditions, the development of IE despite the absence of a history of valve disease, and multivalvular involvement [9,19]. In addition to an association of GDS IE with colonic tumours [20,21], evidence of a correlation with chronic liver disease has been presented [22]. However, risk-factors for acquisition of GDS IE have not yet been clearly identified. The high frequency of GDS IE in France [2] might be attributed, in part, to nutritional or other environmental factors. Nutritional habits in France, such as frequent consumption of uncooked meat and fresh milk products, might have an impact on GDS intestinal colonisation and subsequent GDS bacteraemia and IE. In order to examine this hypothesis, a comparative analysis of cases of OS IE and GDS IE was performed.

PATIENTS AND METHODS

Cases of IE analysed in this study were collected during a cross-sectional prospective multi-regional population-based survey that was conducted in France during 1999. This survey included seven geographical areas: Lorraine, Ile-de France, Franche-Comté, Marne, Rhône-Alpes, Nouvelle–Calédonie and Gironde. The methods and main results of this survey have been published previously [2]. In brief, the survey was conducted between 1 December 1998 and 31 March 2000. During this period, 653 cases of IE were entered into the database. All case report forms were checked and validated by two expert investigators who had not been involved in the care of the corresponding patients. These investigators were responsible for validating the diagnosis of IE according to the Duke criteria [23]. This process excluded 94 cases; the remaining 559 cases of definite IE were included in the study [2]. Standard variables, e.g., demographical and predisposing factors, clinical picture and outcome, were investigated, as well as variables such as residence (rural or urban residency at the time of IE diagnosis), nutritional habits (consumption of milk, unprotected water, meat, fish and shellfish) and animal contacts (cattle, rodents and pets). Predisposing factors for IE included pre-existing valvulopathy (i.e., valve prolapse, regurgitation, stenosis, bicuspid aortic valve), injecting drug use and the presence of a prosthetic valve. At-risk medical or surgical procedures for IE were also recorded. Co-morbidities recorded included diabetes mellitus, cardiovascular disease (i.e., arterial hypertension, coronary heart disease, stroke, dyslipidaemia), respiratory disorders, renal failure, immunodeficiency (i.e., treatment with corticosteroids or other immunosuppressive agents, human immunodeficiency virus infection, splenectomy), malignancies, cirrhosis and colon diseases (i.e., diverticulosis, adenoma, adenocarcinoma, ischaemic or inflammatory lesions). Clinical characteristics of IE included fever, cardiac murmurs, vascular manifestations (i.e., Janeway lesions, cerebral and/or conjunctival haemorrhage), purpura, immunological manifestations (i.e., Roth spots, Osler nodes, rheumatoid factor), embolic events and metastatic infectious foci resulting from bacteraemia (i.e., vertebral osteomyelitis and septic arthritis). Multi-valvular involvement was defined as echocardiography findings consistent with IE in more than one valve. Severe cardiac failure was defined as grades III–IV of the New York Heart Association definitions [24].

Microbiologists were asked to complete a form that requested information concerning the identification and antibiotic susceptibilities of the causative microorganism (total number and number of positive blood cultures, results of valve cultures and serological tests). Almost half (46.6%) of the streptococcal isolates were submitted to the Centre National de Référence des Streptocoques (Paris, France) and were identified to the species and subspecies levels according to the current classification of GDS and OS. All isolates were Gram-positive catalase-negative cocci arranged in pairs or chains, and were identified as streptococci according to their phenotypic characteristics. α-Haemolysis, or the absence of haemolysis, was observed around colonies grown on Columbia sheep blood agar. Gas was not produced in de Man, Rogosa and Sharpe broth, the pyrrolidonyl-arylamidase rapid test was negative, and the isolates were susceptible to vancomycin. The isolates were also tested for growth on bile-aesculin agar and in Todd–Hewitt broth containing NaCl 6.5% w/v. Biochemical traits were determined using the Rapid ID32 STREP identification system (bioMérieux, Marcy l'Etoile, France). When the isolate could not be assigned to an individual species because of atypical results, a 1500-bp fragment of the 16S rRNA gene was amplified with primers 27f and 1525r, according to the method of Tee *et al*. [25], and 16S rRNA gene sequence analysis was performed [26].

According to the current taxonomy [18], isolates identified as *Streptococcus mitis*, *Streptococcus oralis*, *Streptococcus sanguinis*, *Streptococcus gordonii*, *Streptococcus parasanguinis*, *Streptococcus mutans* or *Streptococcus salivarius* were included in the OS group, and those identified as *Streptococcus gallolyticus*, *Streptococcus pasteurianus*, *Streptococcus infantarius* or *Strep. bovis* were included in the GDS group. Streptococci belonging to the *Streptococcus anginosus* group (formerly the milleri group), which includes *Strep. anginosus*, *Streptococcus constellatus* and *Streptococcus intermedius*, were not included in the present study.

Continuous variables were calculated as means ± SD, while categorical variables were calculated as percentages. Mann–Whitney rank sum and chi-square tests were used to evaluate quantitative and qualitative variables, respectively, with $p < 0.05$ considered to be statistically significant. All statistical analyses were performed using BMDP software (BMDP Statistical Software, Los Angeles, CA, USA).

RESULTS

Of the 559 cases of IE, there were 142 and 79 cases of GDS and OS IE, respectively (Table 1). Most GDS isolates were identified as *Strep. gallolyticus*, or had been identified as *Strep. bovis* if they had not been sent for further identification at the Centre National de Référence des Streptocoques.

Table 1. Identification of group D streptococci (GDS) and oral streptococci (OS) isolates responsible for cases of infective endocarditis

Isolates	*n*	%
Total GDS	142	64
Identified GDS[a]	79	56
Streptococcus gallolyticus	71	50
Streptococcus infantarius	5	4
Streptococcus pasteurianus	3	2
Unspeciated GDS[b]	63	44
Total OS	79	36
Streptococcus sanguinis	14	18
Streptococcus mitis	27	34
Streptococcus salivarius	2	3
Streptococcus mutans	7	9
Streptococcus oralis	23	29
Streptococcus parasanguinis	2	3
Streptococcus gordonii	4	5

[a]Isolates of GDS were identified according to the current taxonomy.
[b]Isolates identified as *Streptococcus bovis*, but not further identified according to the current taxonomy.

Strep. mitis and *Strep. oralis* were the OS isolated most frequently.

Demographics and risk-factors for GDS IE and OS IE are summarised in Table 2. GDS IE predominated among the elderly, and both GDS IE and OS IE affected males more frequently than females. There was a significant difference between the GDS and OS groups in the mean weight of patients, but not in body mass index values (Table 2). Residency in a rural area was significantly more frequent for patients with GDS IE (31.0 vs. 15.2%, p 0.001). Unfortunately, the role of nutritional habits could not be assessed because of numerous missing data. Animal contacts were as frequent in the GDS as in the OS group (23.9% vs. 25.3%, p 0.6). The proportion of cases of GDS IE was higher in Franche-Comté (81.8%), Marne (68.7%), Rhône-Alpes (65.3%) and Lorraine (70.3%) than in Ile de France (58.3%), an exclusively urban area (Fig. 1). However, comparison of the standardised incidences of GDS IE was not as demonstrative. Thus, although the highest incidence was observed in a rural region (Marne, 23.9 cases/million), the incidence observed in Ile de France (11.4 cases/million), which is an industrialised and urban region, was intermediate compared

Table 2. Demographics, risk-factors and clinical/echocardiographical data for cases of infective endocarditis (IE) caused by group D streptococci (GDS) and oral streptococci (OS)

Variables	GDS IE (*n* = 142)	OS IE (*n* = 79)	p
Demographics/risk-factors			
Age, mean ± SD	62.7 ± 13.3	56.6 ± 16.1	0.01
Male, *n* (%)	116 (81.7)	60 (75.9)	0.3
Body mass index, mean ± SD	24.2 ± 4.8	24.2 ± 3.9	0.8
Cigarette smoker, *n* (%)	32 (22.5)	23 (29.1)	0.2
Rural residency, *n* (%)	44 (31.0)	2 (15.2)	0.001
Pre-existing valvulopathy[a], *n* (%)	48 (33.8)	53 (67.1)	<0.0001
Co-morbidities[b], *n* (%)	85 (59.9)	26 (32.9)	0.0001
Diabetes mellitus	23 (16.2)	1 (1.3)	0.006
Cirrhosis	12 (8.5)	2 (2.5)	0.08
Colon diseases[c]	71 (50)	9 (11.4)	<0.0001
Clinical and echocardiographical data, *n* (%)			
Murmur	117 (82.4)	73 (92.4)	0.04
Fever	124 (87.3)[j]	68 (86.1)	0.5
Embolism[d]	47 (33.1)	25 (31.6)	0.8
Vascular manifestations[e]	55 (38.7)	28 (35.4)	0.6
Immunological manifestations[f]	36 (25.4)	25 (31.6)	0.3
Metastatic infectious foci[g]	10 (7.0)	1 (1.3)	0.1
Congestive heart failure[h]	41 (19.0)[j]	16 (15.2)[j]	0.1
Location of IE[i]			
Mitral valve	54 (38.0)	49 (62.0)	0.0006
Aortic valve	103 (72.5)	36 (45.6)	0.0001
Multi-valvular involvement	36 (27.9)	15 (20.5)	0.2
Intra-cardiac lesions on echocardiography			
Vegetations	123 (86.6)	70 (88.6)	0.6
Abscess	22 (15.5)	15 (19)	0.5
Valve regurgitation	133 (93.7)	70 (88.6)	0.1
Outcome			
Surgical treatment	73 (51.4)	46 (58.2)	0.6
In-hospital mortality	18 (12.7)	5 (6.3)	0.1

[a]Defined as valve prolapse, regurgitation, or stenosis and bicuspid aortic valve.
[b]Including cardiovascular disease, diabetes mellitus, malignancy, colon disease, cirrhosis, respiratory disorder, renal failure and immunodeficiency.
[c]Including diverticulosis, adenoma, adenocarcinoma, and ischaemic or inflammatory lesions of the bowel.
[d]Including stroke, and ocular, hepatic, splenic, coronary, pulmonary, peripheral or renal embolism.
[e]Including Janeway lesions, cerebral haemorrhage and conjunctival haemorrhage.
[f]Including Roth spots, Osler nodes, rheumatoid factor and glomerulonephritis.
[g]Including vertebral osteomyelitis and septic arthritis.
[h]Defined as New York Heart Association grade ≥III [24].
[i]Valvular location was not confirmed on echocardiography in 13 cases of GDS and six cases of OS.
[j]Data were missing concerning congestive heart failure for 27 cases of GDS and 12 cases of OS, and concerning fever for two cases of GDS.

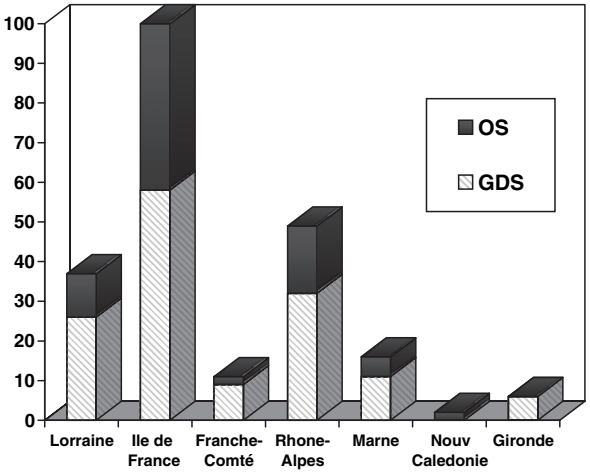

Fig. 1. Regional variations in the number of cases of infective endocarditis caused by group D streptococci (GDS) and oral streptococci (OS) in France.

with that observed in Rhône-Alpes, where the incidence of GDS IE was the lowest (6.9 cases/million).

Pre-existing valvulopathy was detected more frequently in the OS than in the GDS group (Table 2). Several patients with OS and GDS IE (n = 6 and n = 5, respectively) had a history of IE, while 11 patients in each group had a prosthetic valve at the time of onset of IE. Three patients from the OS group and one from the GDS group were injecting drug users. Invasive procedures creating a risk of IE were recorded more often for the OS than for the GDS group (24.1% vs. 14.8%, p 0.08), with a trend towards a higher frequency of dental procedures in the OS group (19% vs. 11.3%, p 0.1).

Co-morbidities, particularly diabetes mellitus, were detected more frequently in GDS than in OS patients (Table 2). Cirrhosis was more prevalent in the GDS group, although the difference was not statistically significant. Colonic disease was significantly more frequent among patients with GDS IE. However, it should be noted that colonoscopy was performed in 64.7% of GDS IE patients, but in only 20.2% of OS patients. Among 92 of 142 patients with GDS IE who underwent colonoscopy, colon disease was detected in 71 (77.1%) cases involving adenomas (n = 55, 77.5%), adenocarcinoma (n = 5, 7%) and diverticulosis (n = 16, 22.5%), with 30% of adenomas presenting with a degree of dysplasia. When only the 46 patients who had *Strep. gallolyticus* IE and who underwent colonoscopy were considered, the distribution of colon abnormalities (n = 32/46, 69.5%) was adenomas n = 24 (75%), adenocarcinoma n = 3 (9.3%), and diverticulosis n = 10 (31.2%), with 20% of adenomas presenting with a certain degree of dysplasia.

Clinical and echocardiographical data, as well as in-hospital outcome, are summarised in Table 2. Cardiac murmur at the time of diagnosis was not detected in 17.6% of GDS and 7.6% of OS IE patients. In addition, a pre-existing murmur was more prevalent in the OS than in the GDS group (35.5% vs. 20.6%, p 0.03). Embolic complications were recorded for one-third of cases in both groups. However, metastatic foci of the disease tended to be more frequent in the GDS group (Table 2). Although vascular manifestations of IE did not differ significantly, purpura tended to be more frequent in the GDS than in the OS group (10.6% vs. 3.8%, respectively, p 0.07). The rates of congestive heart failure did not differ statistically between the two groups. Similarly, laboratory parameters (white blood cell count $>10^9$/L, serum creatinine >180 μmol/L, and C-reactive protein >120 mg/L), as well as the ratio of positive to total blood cultures taken, did not differ between the two groups.

Vegetations were visualised in >85% and abscesses in <20% of the cases in both groups. Valve regurgitation was very common, and was slightly more frequent in the GDS group. The aortic valve was involved more frequently in the GDS group, and the mitral valve in the OS group (p <0.001); multi-valvular involvement was detected in <30% of cases in both groups (Table 2). More than 50% of the patients in both groups underwent surgical treatment, consisting mainly of valve replacement. The in-hospital mortality rate was low in both groups, but there was a trend towards a higher mortality rate in the GDS IE group (p 0.1).

DISCUSSION

In France, the proportion of GDS IE increased during the last 25 years of the 20th century, reaching 25% in 1999 [2,3,27]. This increase has not been fully explained to date. To the best of our knowledge, this is the first investigation of a possible correlation between rural residency and a higher proportion of GDS IE. Regional variations of GDS and OS IE were revealed, with the

lowest proportion of GDS IE being in Ile de France (Paris and suburbs), which is an almost exclusively urban area, while the highest proportions of GDS IE were observed in regions characterised by a rural or mixed urban/rural population. However, factors that may promote GDS IE among rural residents require further elucidation. According to Tripodi *et al*. [28], the selection of sporadic, endemic clones of GDS from the endogenous intestinal flora may play a role in the incidence of GDS bacteraemia and IE, but the factors that might influence this phenomenon are still unknown.

GDS IE affects the elderly more frequently than does OS IE or staphylococcal IE [29–31]. The results of the present study are in accordance with these previous findings, and with recent relevant observations within the merged International Collaboration on Endocarditis database [9]. Increased age may explain, in part, the increased incidence of co-morbidities identified in this group of patients [19,30]. In the present study, diabetes mellitus was also more frequent in the GDS group, as reported previously in one study [9].

The clinical characteristics of patients with GDS IE in the present series were consistent with previous observations that pre-existing valvulopathy was not characteristic of GDS IE [32]. The results also confirmed the already reported predilection of GDS IE for the aortic valve [33,34]. It remains controversial whether multi-valvular involvement is more frequent in GDS IE, as reported by Kupferwasser *et al*. [31] and Hoen *et al*. [9], but the present study demonstrated a lower incidence of multi-valvular GDS IE in accordance with the findings of Duval *et al*. [32]. Data concerning embolic manifestations of GDS IE are also conflicting. Some studies have reported that embolic complications and metastatic foci are more frequent in GDS IE [22,29,32], and that both GDS and *Staph. aureus* IE are associated with higher rates of embolisation [35]. However, these findings were discounted by Kupferwasser *et al*. [31], and the incidence of embolisation in the present study did not differ between OS and GDS IE, in line with other recent data [9]. Cardiac failure, surgical treatment for IE, and in-hospital mortality rates were similar for the GDS and OS groups in the current analysis, as well as in most previous studies [29]. Taking into account the fact that GDS IE affects primarily the elderly and individuals with co-morbidities, in-hospital mortality rates were relatively low (<13%), i.e., far lower than those for *Staph. aureus* IE [36], although higher than those for OS IE.

As established previously, GDS bacteraemia is more likely to occur in patients with underlying colon disease, especially adenomas and cancer [22,32,37]. Tripodi *et al*. [22] reported a 60% rate of chronic liver disease in patients with GDS IE, and a 46.7% rate of colonic adenoma. Colonic cancer has been clearly associated with GDS IE, and other colonic lesions, e.g., diverticulosis and adenomas, which are detected more often in the elderly, are also associated strongly with GDS IE [22]. The ability of GDS to bind to epithelial cells via cell-wall proteins, promoting bacterial colonisation of the intestine and systemic infection of the host, has been reported [37]. Furthermore, experimental models have demonstrated a potential role for GDS in the pathogenesis of colonic cancer [39,40]. The relatively increased frequency of adenomas with dysplastic features (>30%) in patients with GDS IE, as revealed by the present study, supports this hypothesis. The possible link between GDS intestinal colonisation and carcinogenesis requires further investigation. The high prevalence of colonic disease (69.5%) in the *Strep. gallolyticus* subgroup highlights this association and the need for further investigation of potential correlations between some GDS and colonic disease, including cancer. Unfortunately, only half of the clinical GDS isolates were fully speciated in the present analysis.

A major strength of the present study was the use of a large, prospectively collected group of well-defined cases of IE from seven regions in France, together representing >25% of the French population. Data collection was satisfactory and there was no evidence of under-reporting by the participating physicians during the period of the study. Single-centre studies frequently analyse a small number of cases [29,32] and are prone to referral bias. In the present study, the proportion of GDS IE cases (25%) is one of the highest described to date [2]. The analysis compared variables between two streptococcal groups (OS and GDS) that are similar in terms of virulence and susceptibility to penicillin [41]. Identification of the GDS isolates according to the new classification criteria revealed *Strep. gallolyticus* (formerly *Strep. bovis* biotype I) to be the most frequent GDS species involved in IE (Table 1). In a 16-year prospective study, *Strep. bovis* type I bacteraemia

was found previously to be associated more often with colon tumours and with IE (57% and 74%, respectively) than was *Strep. salivarius* and *Strep. bovis* type II [42].

To the best of our knowledge, the present study is the first to investigate the role of environmental factors in the incidence of GDS IE. However, a major limitation of the study was the fact that it was not feasible to investigate the possible association between food and alcohol consumption and the incidence of GDS IE because of important missing data concerning nutritional habits within the study population. Further investigations are required to examine the potential role of nutritional factors and rural residence in GDS intestinal colonisation.

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