Journal of Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Original Article

Clinical characteristics and outcome of infective endocarditis due to *Abiotrophia* and *Granulicatella* compared to *Viridans* group streptococci

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ARTICLE INFO

Article history:
Accepted 19 May 2022
Available online xxx

Keywords:
Infective endocarditis
Abiotrophia, *Granulicatella*
Viridans group streptococci
International collaboration on endocarditis

SUMMARY

Objective: To describe the clinical characteristics and outcome of *Abiotrophia* and *Granulicatella* infective endocarditis and compare them with Viridans group streptococci infective endocarditis.
Methods: All patients in the International Collaboration on Endocarditis (ICE) - prospective cohort study (PCS) and the ICE-PLUS cohort were included ($n = 8112$). Data from patients with definitive or possible IE due to *Abiotrophia* species, *Granulicatella* species and Viridans group streptococci was analyzed. A propensity score (PS) analysis comparing the ABI/GRA-IE and VGS-IE groups according to a 1:2 ratio was performed.
Results: Forty-eight (0.64%) cases of ABI/GRA-IE and 1,292 (17.2%) VGS-IE were included in the analysis. The median age of patients with ABI/GRA-IE was lower than VGS-IE (48.1 years vs. 57.9 years; $p = 0.001$). Clinical features and the rate of in-hospital surgery was similar between ABI/GRA-IE and VGS-IE (52.1% vs. 45.4%; $p = 0.366$). Unadjusted in-hospital death was lower in ABI/GRA-IE than VGS-IE (2.1% vs. 8.8%; $p = 0.003$), and cumulative six-month mortality was lower in ABI/GRA-IE than VGS-IE (2.1% vs. 11.9%; $p < 0.001$). After PS analysis, in-hospital mortality was similar in both groups, but six-month mortality was lower in the ABI/GRA IE group (2.1% vs. 10.4%; $p = 0.029$).

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https://doi.org/10.1016/j.jinf.2022.05.023
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Please cite this article as: A. Téllez, J. Ambrosioni, M. Hernández-Meneses et al., Clinical characteristics and outcome of infective endocarditis due to Abiotrophia and Granulicatella compared to Viridans group streptococci, Journal of Infection, https://doi.org/10.1016/j.jinf.2022.05.023

Conclusions: Patients with ABI/GRA-IE were younger, had similar clinical features and rates of surgery and better prognosis than VGS-IE.
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Introduction

Abiotrophia (ABI) and *Granulicatella* (GRA) are gram-positive cocci previously described as nutritionally variant *Streptococcus* (NVS) [1] because of the complex media needed for its isolation [2]. Since the initial identification of these microorganisms, they have undergone multiple changes in their nomenclature up to the current taxonomy from 2000 [3–7], which includes one *Abiotrophia* species (*A. defectiva*) and three *Granulicatella* species (*G. adiacens*, *G elegans* and *G. balaenopterae*).

Infective endocarditis (IE) due to ABI and GRA represents between 1–3% of all IE cases [8–10] and typically presents with a subacute clinical course. The clinical features and outcome of IE due to *Abiotrophia* and *Granulicatella* (ABI/GRA-IE) genera are derived mainly from retrospective studies [8–10] and a comparison with IE due to oral pathogens with similar clinical course, such as Viridans group streptococci (VGS), is currently lacking.

The largest case series from the literature and institutional cases of IE due to ABI and GRA was recently published [8]. In this single center study, ABI/GRA-IE was more prevalent than HACEK-IE and approximately one-tenth as frequent as Viridans group streptococci (VGS) IE, periannular complication were more common in ABI/GRA-IE. ABI and GRA-IE share similar clinical features and outcomes. Overall mortality was low and related to age and development of heart failure [8]. However, this study had several limitations, including a publication bias, which could lead to publishing cases with better outcomes and consequently a lower mortality previously not reported in IE due to ABI/GRA [10,11].

This multicenter study aimed to describe ABI/GRA-IE features and compare it with the VGS-IE in patients included in the International Collaboration on Endocarditis (ICE) - prospective cohort study (PCS) and the ICE-PLUS cohorts.

Methods

Study population and clinical data

This observational multicenter prospective cohort study is based on data within the ICE-PCS and the ICE-PLUS cohorts. Both are multi-national prospective registries of consecutives cases of IE, ICE-PCS include data from 61 sites from 28 countries between 2000 and 2006 [12] and the ICE-PLUS include data from 34 centers from 18 countries between 2008 and 2012 [13].

Patients with definite or possible IE according to the modified Duke criteria were included [14]. The microorganism identification was made in each center where the patients were included. Data were prospectively recorded using standard definitions during the index hospitalization and six months after through national death records, medical records, and/or patient contact as available [15].

Data on patients with definitive or possible IE due to *Abiotrophia* species, *Granulicatella* species and Viridans group streptococci were extracted from the ICE-PCS and ICE-PLUS database (see sample acquisition in Fig. 1).

Two different analyses were made: the first included the whole cohort of both groups, ABI/GRA-IE and VGS-IE with a follow-up at six-months. In the second, a propensity score (PS) analysis was performed between the ABI/GRA-IE group and the VGS-IE group with a 1:2 ratio also with a follow-up at six-months. The matching criteria for cases and controls included: year of diagnosis, age and gender, type of IE (native or prosthetic), and valve involvement where possible [16].

Definitions

Definitions of the variables included in the ICE-PCS AND ICE-PLUS case report form have been previously reported [15,17]. Time to diagnosis was considered as the interval between the first clinical manifestations or medical contact and the diagnostic echocardiography. Microorganisms were recorded according to the taxonomy existing at the time of inclusion in the ICE cohort. The microorganisms with the previous taxonomy [3–5] for the period between 2000 and 2006 were reclassified according to the current taxonomy [7]. ABI/GRA-IE group corresponds to IE due to *Abiotrophia* spp., *A. defectiva, Granulicatella* spp., *G. adiacens* and *G. elegans*. The VGS-IE group included all cases of IE due to *Streptococcus mitis* group, *Streptococcus sanguinis* group, *Streptococcus anginosus* group, *Streptococcus mutans* group, *Streptococcus salivarius* group as well as Viridans group streptococci that could not be further identified to the species level. Three groups of antibiotic regimens were defined, β-lactam in monotherapy (penicillin, ampicillin, amoxicillin, cefazolin, cephalothin, ceftriaxone, cefuroxime or imipenem), β-lactam plus aminoglycosides (gentamicin) or other antibiotics (regimen where β-lactams were not included).

Statistical analysis

The qualitative variables were described as absolute and relative frequencies, and the quantitative variables as median and inter-quartile range (IQR). The comparisons of qualitative variables between groups were done with χ^2. The comparisons between groups in the quantitative variables were performed using the Mann-Whitney test. Values of $p < 0.05$ were considered statistically significant. Kernel density estimate was used to analyze time-to-diagnosis distribution [18].The odds were estimated with a 95% confidence interval (CI) to evaluate the association between binary variables and in-hospital mortality or six-month mortality. The multivariate analysis of prognostic factors of in-hospital and six-month mortality was performed for the whole cohort of Abiotrophia/Granulicatella and Viridans group streptococci. The analysis was performed using Stata version 14.0 software.

Ethics

The Hospital Clínic IRB approved the ICE-PCS and the ICE-PLUS protocols on April 20th, 2004 and December 11th, 2008, respectively, following the principles outlined in the Declaration of Helsinki. Informed consent (oral/written) was obtained from all patients according to local institutional review boards or ethic committee guidelines at all sites.

Results

Cases identified

During the two study periods, there were a total of 8112 cases of definite or possible IE: 5668 from ICE-PCS and 2444 from ICE-PLUS. In 610 cases, the infective etiology was unknown and in 7502 cases the etiology was reported. Forty-eight (0.64%) cases

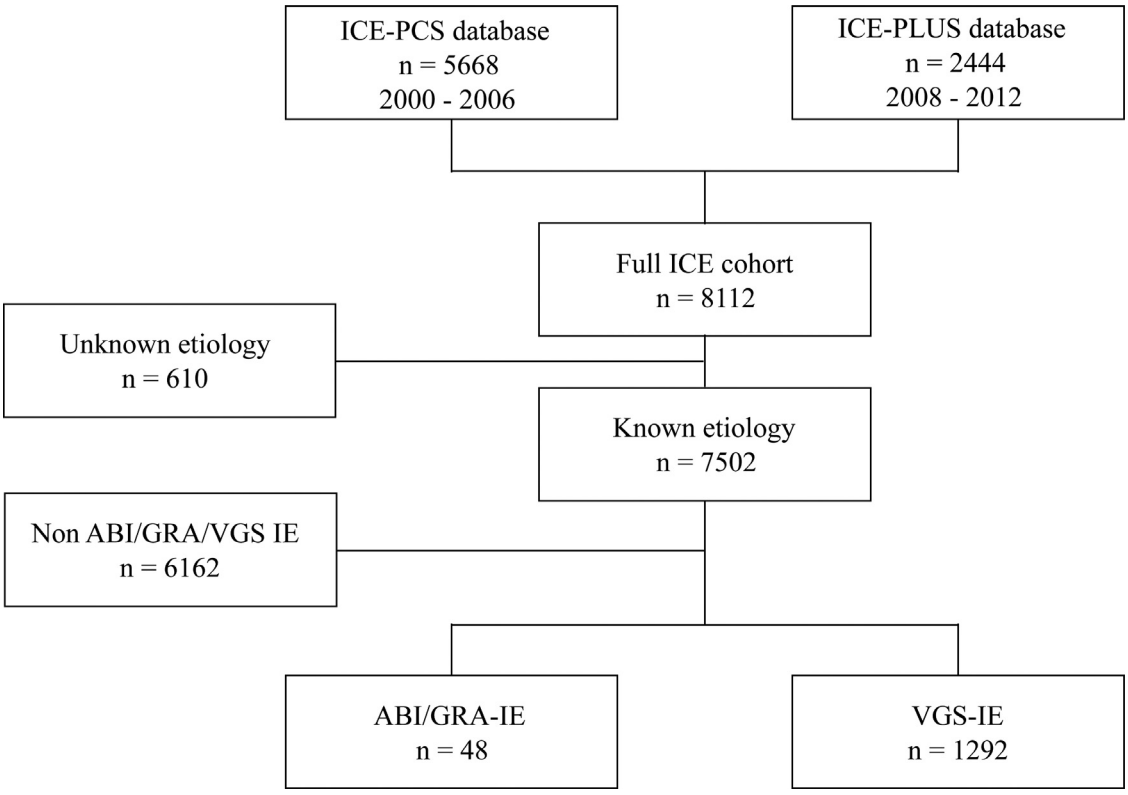

Fig. 1. Selection of cases Flowchart illustrating the selection of cases of *Abiotrophia* or *Granulicatella* and Viridans group streptococci infective endocarditis from the International Collaboration on Endocarditis (ICE) – prospective cohort study and the ICE-PLUS cohort. Definitive and possible infective endocarditis were included in the analysis. ABI = *Abiotrophia*; GRA = *Granulicatella*; VGS Viridans group streptococci; IE = infective endocarditis.

of ABI/GRA-IE and 1292 (17.2%) VGS-IE were included in the final analysis according to the selection criteria (Fig. 1).

The ABI/GRA group is composed of 24 species from the *Abiotrophia* genus (14 *A. defectiva* and 10 *Abiotrophia* spp.) and 24 species from the *Granulicatella* genus (15 *Granulicatella adiacens,* two *G. elegans* and seven *Granulicatella* spp). Only three cases were included in a previous publication [8]. Forty-one definite (85%) and seven possible (15%) ABI/GRA-IE were included.

The VGS-IE group is composed of 398 *Streptococcus mitis* group, 97 *Streptococcus mutans* group, 59 *Streptococcus salivarius* group, 54 *Streptococcus anginosus* group, and 684 Viridans group streptococci that could not be further identified to the species level. Included in the VGS-IE group were 1153 definite (89%) and 139 possible (11%) cases.

Abiotrophia *and* Granulicatella *infective endocarditis*

The incidence of IE due to *Abiotrophia* or *Granulicatella* was lower in the first ICE-PCS period than in the second ICE-PLUS period (4.84 vs. 10.36 per 1000 cases of IE, $p = 0.007$) (see Supplementary Fig. 1 and supplementary Table 1). Supplementary Tables 2, 3 and 4 summarize the demographics, baseline comorbidities, clinical, echocardiographic findings, complications, surgery and mortality of both genera. Clinical characteristics and outcomes (surgery, mortality) were similar between both genera. As outcomes were similar, we have analyzed both genera together and compared them with VGS-IE group.

Demographic features, comorbidities and type of infective endocarditis

Table 1 summarizes the demographics and baseline comorbidities of both groups. The majority of cases were men in both groups, 30 (62,5%) in ABI/GRA-IE and 907 (70.2%) in VGS-IE ($p = 0.28$). Patients in the ABI/GRA-IE were younger, the median age in the ABI/GRA-IE was 48.1 years (interquartile range [IQR], 35.4–58.8) and 57.9 (IQR, 41.5–72.2) in the VGS-IE group ($p = 0.001$). In the full cohort, some comorbidities were less frequent among ABI/GRA-IE group. Native valves were more frequently affected in ABI/GRA-IE (42 [89.4%]) than VGS-IE (945 [76.5%]) ($p = 0.006$) and less frequently than prosthetic valves ($p = 0.026$). Most cases were community acquired in both groups ($p = 0.72$).

Clinical presentation and echocardiographic findings

Table 2 summarizes the clinical and echocardiographic findings of both cohorts. The majority of patients were diagnosed within one month of the first clinical manifestation in both groups ($p = 0.72$). Time to diagnosis was shorter in ABI/GRA-IE (5 days, IQR, 1.5–22.5) than in VGS-IE (9 days, IQR, 3.0–24.0) ($p = 0.01$). However, the Kernel density estimate showed both early and late distribution peaks in ABI/GRA-IE and only an early peak in VGS-IE (see Supplementary Figs. 2 and 3). Most clinical manifestations reported were similar between groups.

The echocardiographic findings were comparable between groups. As a group, paravalvular complications (abscess, valve perforation and fistula) were equally distributed among both types of IE. Paravalvular prosthetic valve complications as dehiscence or new paravalvular regurgitation were similar in both groups.

Complications, antibiotic treatment and outcomes

Table 3 summarizes complications, antibiotic treatment and outcomes of both cohorts. More CHF and less new conduction abnormality (NCA) were observed in patients with ABI/GRA-IE, al-

Table 1
Demographics, baseline comorbidity and type of infective endocarditis of the full cohort and Propensity Score–Matched Cohort.

	Full Cohort			Propensity Score–Matched Cohort		
	ABI/GRA ($n=48$)	VGS ($n=1292$)	*P* Value	ABI/GRA ($n=48$)	VGS ($n=96$)	*P* Value
Demographics						
Male	30 (62.5)	907 (70.2)	0.278	30 (62.5)	60 (62.5)	1
Age, yrs.	48 (35–59)	58 (42–72)	0.001	48 (35–59)	47 (34–59)	0.703
Geographical distribution						
Asia/Middle east	2 (4.3)	81 (6.5)	0,459	2 (4.3)	8 (8.5)	0.303
Australia/New Zealand/ Africa	9 (19.1)	235 (18.8)	0.959	9 (19.1)	13 (13.8)	0.432
Europe	27 (57.4)	646 (51.8)	0.443	27 (57.4)	55 (58.5)	0.904
North America	2 (4.3)	102 (8.2)	0.198	2 (4.3)	8 (8.5)	0.303
South America	7 (14.9)	183 (14.7)	0.967	7 (14.9)	10 (10.6)	0.486
Comorbidities						
CCI	1 (0–2)	2 (0–3)	0,003	1 (0–2)	1 (0–2)	0.802
CHD	8 (18.2)	228 (18.3)	0.990	8 (18.2)	24 (30.4)	0.120
Previous IE	6 (12.5)	131 (10.2)	0.631	6 (12.5)	10 (10.4)	0.715
MI	0 (0)	27 (3.8)	<0.001	0 (0)	0 (0)	1
CHF	3 (10)	96 (13.4)	0.543	3 (10)	3 (4.8)	0.393
PVD	0 (0)	24 (3.3)	<0.001	0 (0)	1 (1.6)	0.316
Stroke	0 (0)	36 (5.0)	<0.001	0 (0)	3 (4.8)	0.079
COPD	2 (6.5)	62 (8.6)	0.630	2 (6.5)	4 (6.3)	0.985
Diabetes	1 (2.1)	148 (11.6)	<0.001	1 (2.1)	8 (8.4)	0.074
CKD	1 (3.2)	43 (5.8)	0.431	1 (3.2)	0 (0)	0.312
Dialysis	1 (3.0)	15 (1.4)	0.590	1 (3.0)	1 (1.5)	0.645
Liver Disease	0 (0)	22 (3.0)	0.152	0 (0)	2 (3.2)	0.152
Cancer	4 (8.5)	105 (8.2)	0.948	4 (8.5)	4 (4.3)	0.354
HIV-infection	2 (4.3)	14 (1.1)	0.289	2 (4.3)	1 (1.1)	0.309
IVDU	1 (2.2)	55 (4.3)	0.338	1 (2.2)	2 (2.1)	0.979
Place of acquisition						
Community	41 (93.2)	1185 (94.6)	0.718	41 (93.2)	91 (97.8)	0.255
Nosocomial	0 (0)	33 (2.6)	<0.001	0 (0)	2 (2.2)	0.155
Nosohusial	3 (6.8)	35 (2.8)	0.293	3 (6.8)	0 (0)	0.075
Type of IE						
Native	42 (89.4)	945 (76.5)	0.006	42 (89.4)	84 (89.4)	1
Prosthetic	5 (10.6)	259 (21.0)	0.026	5 (10.6)	10 (10.6)	1
Other	0 (0)	31 (2.5)	<0.001	0 (0)	0 (0)	1
Valve involved						
– Aortic	12 (28.6)	441 (39.9)	0.113	12 (28.6)	29 (32.6)	0.640
– Mitral	16 (38.1)	421 (38.1)	0.997	16 (38.1)	37 (41.6)	0.704
– Aortic plus mitral	12 (28.6)	199 (18.0)	0.135	12 (28.6)	19 (21.3)	0.381
– Tricuspid	1 (2.4)	34 (3.1)	0.774	1 (2.4)	3 (3.4)	0.745
– Pulmonary	1 (2.4)	11 (1.0)	0.559	1 (2.4)	1 (1.1)	0.630

Epidemiological, geographical distribution, place of acquisition and type of infective endocarditis due to *Abiotrophia*/*Granulicatella* or Viridans groups streptococci. Values are n (%) or median (interquartile range). Patients with missing data were excluded from the analyses.
CCI = Charlson comorbidity index; COPD = Chronic obstructive pulmonary disease; CHD = congenital heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; IE = infective endocarditis; IVDU = intravenous drug user; MI = myocardial infarction; PVD = peripheral vascular disease.

though not statistically significant. Stroke, systemic embolization and persistent bacteremia were comparable in both groups.

No statistically significant differences in the antibiotic regimen (β-lactam in monotherapy, β-lactam plus aminoglycoside or other antibiotics) were observed between both groups, although there was a trend of lower use of β-lactams as monotherapy in the ABI/GRA-IE.

In-hospital surgery was performed in 25 (52.1%) patients with ABI/GRA-IE and in 583 (45.4%) patients with VGS-IE ($p=0.37$). In-hospital death was reported as 2.1% in ABI/GRA-IE group and 8.8% in VGS-IE group ($p=0.003$) (Table 3). Cumulative six-month mortality was 2.1% in ABI/GRA-IE group and 11.9% in VGS-IE group ($p < 0.001$) (Graphical abstract).

Prognostic factors

The factors associated with in-hospital mortality in the multivariate analysis were the usual reported for other etiologies. The microorganism involved (ABI/GRA-IE versus VGS-IE) was not associated with mortality (OR, 4.72 [95% CI, 0.64–34.51]). At six months, the same factors were associated with mortality, but male gender was associated with a better prognosis (OR, 0.66 [95% CI, 0.43–0.98]); the microorganism involved was not associated with mortality either (OR, 6.79 [95% CI, 0.93–49.54]). Factors associated with in-hospital and six-months mortality are shown in Tables 4 and 5.

Propensity score analysis

Propensity score matching with a 1:2 ratio was performed, matching every patient of the ABI/GRA-IE group with two patients in the SGV-IE group. Both groups were well balanced in terms of gender, age and type of IE (native or prosthetic). No regional differences were observed between reporting of ABI/GRA-IE versus VGS-IE.

No differences in comorbidities were observed (Table 1), clinical presentation was similar and acute (<1 month) presentation was common between both groups ($p=0.89$).

Intracardiac vegetations were observed in 35 (72.9%) patients with of ABI/GRA-IE and in 89 (92.7%) of patients with VGS-IE. Echocardiographic findings in native and prosthetic IE were also similar in both ABI/GRA-IE group and VGS-IE group (Table 2).

Congestive heart failure was observed in 20 (41.7%) patients in the ABI/GRA-IE group and in 27 (28.4%) patients in the VGS-IE

Table 2
Clinical and echocardiographic findings of the full cohort and Propensity Score–Matched Cohort.

	Full Cohort			Propensity Score–Matched Cohort		
	ABI/GRA ($n=48$)	VGS ($n=1292$)	*P* Value	ABI/GRA ($n=48$)	VGS ($n=96$)	*P* Value
Clinical findings						
Acute presentation (< 1 month)	32 (68.1)	863 (70.6)	0.720	32 (68.1)	63 (69.2)	0.891
Time to diagnosis, days	5 (1.5–22.5)	9 (3–24)	0.01	5 (1.5–22.5)	10 (4–32.5)	0.11
Fever	39 (88.6)	1090 (90)	0.778	39 (88.6)	79 (88.8)	0.983
Osler's nodes	1 (2.1)	34 (2.7)	0.776	1 (2.1)	2 (2.2)	0.979
Conjunctival hemorrhages	0 (0)	48 (3.9)	<0.001	0 (0)	4 (4.3)	0.043
Roth spots	0 (0)	22 (2.0)	<0.001	0 (0)	1 (1.2)	0.316
Splenomegaly	12 (25.5)	175 (14.2)	0.078	12 (25.5)	13 (14.1)	0.122
Janeway lesion	0 (0)	40 (3.2)	<0.001	0 (0)	3 (3.2)	0.081
Splinter hemorrhage	1 (2.1)	84 (7.0)	0.029	1 (2.1)	8 (8.6)	0.073
Vascular embolic event	6 (19.4)	169 (23.4)	0.574	6 (19.4)	17 (27.0)	0.401
Presence of new murmur	19 (48.7)	467 (44.5)	0.603	19 (48.7)	45 (53.6)	0.617
Worsening of pre-existing murmur	15 (44.1)	238 (27.7)	0.058	15 (44.1)	23 (32.9)	0.272
Elevated Rheumatoid factor	6 (20)	86 (11.1)	0.229	6 (20)	10 (19.2)	0.933
Elevated C-reactive protein	37 (84.1)	924 (79.5)	0.418	37 (84.1)	75 (86.2)	0.750
Elevated sedimentation rate	31 (75.6)	724 (72.7)	0.670	31 (75.6)	53 (74.6)	0.910
Hematuria	8 (38.1)	157 (28.2)	0.360	8 (38.1)	11 (23.4)	0.235
Echocardiographic findings						
Intracardiac vegetation	35 (72.9)	1003 (78.7)	0.373	35 (72.9)	89 (92.7)	0.005
Vegetation location						
– Aortic	10 (28.6)	362 (37.4)	0.260	10 (28.6)	28 (32.6)	0.664
– Mitral	15 (42.9)	388 (40.0)	0.741	15 (42.9)	36 (41.9)	0.704
– Aortic plus mitral	9 (25.7)	186 (19.2)	0.385	9 (25.7)	19 (22.1)	0.676
– Tricuspid	0 (0.0)	23 (2.4)	<0.001	0 (0.0)	2 (2.3)	0.155
– Pulmonary	1 (2.9)	10 (1.0)	0.520	1 (2.9)	1 (1.2)	0.579
New moderate or severe regurgitation	33 (70.2)	790 (62.3)	0.243	33 (70.2)	68 (72.3)	0.793
Paravalvular complications	13 (27.7)	282 (22.2)	0.406	13 (27.7)	25 (26.0)	0.838
Perforation	6 (12.8)	141 (11.1)	0.738	6 (12.8)	16 (16.7)	0.529
Abscess	7 (14.6)	166 (13.5)	0.832	7 (14.6)	12 (12.6)	0.751
Fistula	0 (0)	35 (2.8)	<0.001	0 (0)	2 (2.1)	0.155
Prosthetic paravalvular complications	1 (20)	65 (26.0)	0.741	1 (20)	5 (50)	0.231
Dehiscence	1 (20)	31 (12.4)	0.675	1 (20)	3 (30)	0.671
New paravalvular regurgitation	1 (20)	51 (20.6)	0.975	1 (20)	3 (30)	0.671

Clinical manifestations and echocardiographic findings of the current episode of infective endocarditis due to *Abiotrophia*/*Granulicatella* or Viridans groups streptococci. Values are n (%) or median (interquartile range). Patients with missing data were excluded from the analyses.

Table 3
Complications, antibiotic treatment, surgery and outcomes of the full cohort and Propensity Score–Matched Cohort.

	Full Cohort			Propensity Score–Matched Cohort		
	ABI/GRA ($n=48$)	VGS ($n=1292$)	*P* Value	ABI/GRA ($n=48$)	VGS ($n=96$)	*P* Value
Complications						
Stroke	7 (14.6)	191 (15.1)	0.928	7 (14.6)	14 (14.7)	0.980
Systemic embolization (non-stroke)	6 (12.5)	256 (20.1)	0.119	6 (12.5)	20 (21.1)	0.180
Congestive heart failure	20 (41.7)	362 (28.4)	0.067	20 (41.7)	27 (28.4)	0.121
Persistent positive blood cultures	2 (4.3)	29 (2.4)	0.536	2 (4.3)	4 (4.5)	0.937
New conduction abnormality	1 (4.5)	35 (9.4)	0.062	1 (4.5)	2 (4.7)	0.971
Antibiotic treatment						
β-lactam in monotherapy	4 (12.9)	192 (23.5)	0.088	4 (12.9)	21 (30.4)	0.035
β-lactam plus aminoglycoside	22 (71.0)	526 (64.4)	0.429	22 (71.0)	429 (60.9)	0.317
Other antibiotics	5 (16.1)	99 (12.1)	0.550	5 (16.1)	6 (8.7)	0.319
Outcomes						
In-hospital surgery	25 (52.1)	583 (45.4)	0.366	25 (52.1)	51 (53.7)	0.857
In-hospital death	1 (2.1)	113 (8.8)	0.003	1 (2.1)	5 (5.2)	0.321
Relapse	0 (0)	11 (1,5)	0.001	0 (0)	1 (1,7)	0.316
6-month surgery	3 (7.0)	42 (4.1)	0.471	3 (7.0)	2 (2.5)	0.291
6-month mortality	1 (2.1)	154 (11.9)	<0.001	1 (2.1)	10 (10.4)	0.029

Complications, surgery and outcomes of infective endocarditis due to *Abiotrophia*/*Granulicatella* or Viridans Group streptococci. Values are n (%) or median (interquartile range). Patients with missing data were excluded from the analyses.

group ($p=0.12$). Stroke, persistent positive blood cultures and new conduction abnormality were observed in similar ratios between both groups.

β-lactams as monotherapy were less used in the ABI/GRA-IE group (4, 12.9% vs. 21, 30.4%; $p=0.035$). The use of β-lactam plus aminoglycoside or other antibiotics was comparable between both groups.

In-hospital surgery was performed in 25 (52.1%) cases of ABI/GRA-IE and in 51 (53.7%) cases of VGS-IE ($p=0.86$) and six-month surgery was similar in both groups (Table 3). In-hospital death was similar in both groups, but six-month mortality was lower in the ABI/GRA IE group, where only one death (2.1%) was reported compared with 10 (10.4%) in the VGS-IE group ($p=0.029$) (Graphical abstract).

Table 4
Univariate and multivariate analysis for predictors of in-hospital mortality.

	Univariate				Multivariate			
		95% CI				95% CI		
Predictors	OR	Lower	Upper	*P* Value	OR	Lower	Upper	*P* Value
Age > 60 years	2.00	1.35	2.97	<0.001				
Gender (Male)	0.68	0.46	1.02	0.07				
PVE	1.95	1.27	2.99	0.002	1.75	1.05	2.93	0.03
Hemodialysis	0.81	0.10	6.22	0.84				
Diabetes Mellitus	2.38	1.46	3.89	<0.001				
IVDU	1.64	0.72	3.73	0.23				
Cancer	1.20	0.62	2.32	0.58				
CHD	0.42	0.21	0.81	0.01				
Community acquisition	1.60	0.57	4.49	0.37				
VGS-IE vs ABI/GRA-IE	4.72	0.64	34.51	0.13				
Intracardiac vegetation	1.09	0.67	1.77	0.73				
Stroke	2.92	1.88	4.52	<0.001	3.52	2.08	5.95	<0.001
CHF	4.35	2.91	6.50	<0.001	4.87	3.03	7.85	<0.001
PPBC	1.69	0.58	4.92	0.34				
Paravalvular complications	2.75	1.83	4.14	<0.001	2.30	1.41	3.74	0.001
In-hospital surgery	0.94	0.64	1.38	0.75				
CCI	1.30	1.18	1.42	<0.001	1.32	1.10	1.59	0.002

ABI/GRA-IE = *Abiotrophia* or *Granulicatella* infective endocarditis; CCI = Charlson comorbidity index; CHD = Congenital heart disease; CHF = Congestive heart failure; IVDU = Intravenous drug user; PPBC = Persistent positive blood cultures; PVE = Prosthetic valve endocarditis; VGS-IE = Viridans group streptococci infective endocarditis.

Table 5
Univariate and multivariate analysis for predictors of six-month mortality.

	Univariate				Multivariate			
		95% CI				95% CI		
Predictors	OR	Lower	Upper	*P* Value	OR	Lower	Upper	*P* Value
Age > 60 years	1.97	1.41	2.78	<0.001				
Gender (Male)	0.64	0.46	0.91	0.01	0.66	0.43	0.98	0.04
PVE	1.93	1.33	2.81	0.001	1.70	1.08	2.68	0.02
Hemodialysis	1.99	0.56	7.09	0.29				
Diabetes Mellitus	1.86	1.18	2.93	0.008				
IVDU	1.51	0.73	3.16	0.27				
Cancer	1.80	1.07	3.03	0.03				
CHD	0.35	0.19	0.64	0.001				
Community acquisition	1.45	0.62	3.42	0.39				
VGS-IE vs ABI/GRA-IE	6.79	0.93	49.54	0.06				
Intracardiac vegetation	1.27	0.82	1.97	0.28				
Stroke	2.54	1.71	3.77	<0.001	2.99	1.87	4.79	0.001
CHF	4.18	2.94	5.92	<0.001	4.5	2.99	6.77	0.001
PPBC	1.52	0.57	4.02	0.40				
Paravalvular complications	2.14	1.48	3.08	<0.001	1.92	1.24	2.98	0.003
In-hospital surgery	0.75	0.53	1.06	0.11				
CCI	1.31	1.21	1.43	<0.001	1.48	1.23	1.77	<0.001

ABI/GRA-IE = *Abiotrophia* or *Granulicatella* infective endocarditis; CCI = Charlson comorbidity index; CHD = Congenital heart disease; CHF = Congestive heart failure; IVDU = Intravenous drug user; PPBC = Persistent positive blood cultures; PVE = Prosthetic valve endocarditis; VGS-IE = Viridans group streptococci infective endocarditis.

Discussion

This is the first large multi-national prospective cohort study that provides a greater understanding of the characteristics of ABI/GRA-IE and how it differs from VGS-IE. It confirms the low prevalence of ABI/GRA as the etiology of IE [8–10,15]. The overall clinical characteristics were comparable to VGS-IE, although younger patients with fewer comorbidities were observed in the ABI/GRA-IE group. It is worth highlighting that the intravenous drug users' rate was very low in both cohorts, with only one user (2.2%) in ABI/GRA-IE and 55 users (4.3%) in VGS-IE. The same rate of complications was observed between both groups, however more patients developed CHF, but these differences were not statistically significant. In the whole cohort, patients in the ABI/GRA-IE group had lower in-hospital and 6-month mortality, but in the PS analysis, no differences were observed in-hospital mortality, but 6-month mortality remained lower in the ABI-GRA-IE group.

As with VGS-IE, most cases of ABI/GRA-IE were community-acquired. In this study, only 0.64% of the cases of IE with known etiology were due to ABI/GRA, and ABI/GRA-IE was almost 30 times less frequent than VGS-IE, even less frequent than previously described [8]. The higher incidence (4.84 vs. 10.36 per 1000 cases of IE) of ABI/GRA-IE in the second period compared with the first could probably reflect an improvement in isolation and identification of these bacteria through molecular biology. However, the respective changes in prophylaxis recommendations in 2007 and 2009 in America and Europe [19,20] could have also driven the higher incidence observed in the second period in our study.

According to our results, IE cause by the ABI and GRA genera presents similar clinical features and outcomes, as previously described [8]. However, the highest prevalence of mitral valve involvement [8] in *Abiotrophia* compared with *Granulicatella* was not observed in our study. Only a higher rate of CHF was observed in *Abiotrophia* IE in comparison with *Granulicatella* IE, although rates

of cardiac surgery were similar. The absence of substantial differences in the main outcomes (surgery, mortality) allows us to consider both together as a single group and thus compare it with VGS-IE.

The low mortality observed in our study contrasts with earlier reports, where mortality was considered to be higher in patients with ABI/GRA-IE in comparison with other more frequent etiologies of IE such as *Streptococcus* and *Enterococcus spp* [10,11]. A more recent study found a lower mortality (9.2%) rate in ABI/GRA-IE [8] similar to our findings. In this study, in-hospital death was lower in ABI/GRA-IE than in VGS-IE (2.1% vs 8.8%), but these differences were not statistically significant in the PS analysis (2.1% vs 5.2%). However, six-month mortality was statistically significantly lower in ABI/GRA-IE in both analyses. These results confirm the lower mortality for ABI/GRA-IE reported in our previous article [8], having addressed the publication bias of that article. One factor that could contribute to the lower mortality rates observed is the younger age and low comorbidity rates in patients with ABI/GRA-IE (See table for Charlson comorbidity index). Another explanation for the improved outcomes compared with those previously reported is the improvement in the isolation and identification of fastidious microorganisms like *Abiotrophia* and *Granulicatella* [21,22]. These improvements in microbiological diagnosis could lead to a more appropriate antibiotic treatment. Third, complications related to ABI/GRA-IE have been described in other studies [8,11,23]. Congestive heart failure has been reported to be more frequent in ABI/GRA-IE compared with VGS-IE [8]. In this study, CHF was reported at a higher rate in the ABI/GRA-IE group than in the VGS-IE group (42% vs 28%), these differences were observed in the whole cohort and in the PS analysis, without being statistically significant, probably due to the small sample size. Moreover, surgery has been reported to be common in ABI/GRA-IE in contrast with earlier studies in which lower rates of surgery were observed [8,24]. In our study, hospital surgery was performed in 52% of patients with ABI/GRA-IE, and a similar rate of surgery between ABI/GRA-IE and VGS-IE was observed in the PS analysis. The high prevalence of CHF in ABI/GRA-IE could lead to the high mortality rates previously described, but younger age as well as improvements in and better access to cardiac surgery could result in the superior outcomes that we have observed.

One interesting finding was the high rates of combined therapy observed in both groups. This finding may be attributed to a high rate of resistance in both genera; however, it is in line with the guideline recommendations of the time, i.e., some recommended combined therapy even in susceptible strains of VGS [19,20,25–27]. So, it is possible that this finding is related more to the guideline recommendations than to the resistance rate. However, obtaining conclusions in this field is challenging due to the large data gaps in antibiotic use.

As previously reported [28,29], prosthetic valve endocarditis, paravalvular complications, stroke and congestive heart failure were associated with worse prognosis. At six months, the same variables were associated with poor prognosis, but male gender was associated with better prognosis. The etiology of IE (VGS vs. ABI/GRA) was not associated with higher mortality, although a non-significant statistical difference of higher VGS-IE mortality was observed in the univariate analysis both for in-hospital (OR, 4.72 [95% IC 0.64–34.51]) and at six months (OR, 6.79 [95% IC 0.93–49.54]).

Our study has several limitations. First, the addition of 'possible IE' to the analysis could bias the results; however, less than 15% of cases had a possible diagnosis, hence we decided to maintain them in favor of more statistical power. Second, in our study, the microorganism identification in the participating centers without a central repository of strains did not allow us to perform a detailed analysis between the *Abiotrophia* and *Granulicatella* genera (species level identification, antibiotic susceptibility patterns). Third, the low prevalence of ABI/GRA-IE prevented us from matching patients by center and comorbidities in the PS analysis. This may possibly introduce a bias related to center management; however, in terms of comorbidities, both groups were well balanced. Fourth, antimicrobial regimens were not reported in detail and only 31 (65%) patients in the ABI/GRA-IE group and 817 (63%) patients in the VGS-IE group had this information. Besides, as stated before, the antimicrobial susceptibility was not reported in most cases. This is especially important, because several studies [30–32] confirm a lower rate of susceptibility to penicillin in *Abiotrophia defectiva* isolates than in *Granulicatella adiacens*, and a higher rate of susceptibility to ceftriaxone in *A. defectiva* than in GRA. This could explain why beta-lactam monotherapy was less frequently used in patients with ABI/GRA-IE than in VGS-IE. In any case, the rates of relapses and mortality were very low. Fifth, the difficulty identifying the origin of bacteremia prevented us from confirming whether changes in prophylaxis recommendations could have impacted the difference in incidence observed in our study between periods. Finally, given the age of the data, it may be difficult to extrapolate our findings to the current context; however, as these cohorts are the only to address species identification at this level, it is unlikely similar studies will be available in the coming years.

Conclusions

Patients with *Abiotrophia* and *Granulicatella* IE have lower ages, but similar clinical features, rates of surgery and prognosis, when compared with VGS-IE patients. These findings are contrary to previous reports, where ABI/GRA-IE had a higher rate of complications and worse prognosis. These observations may be attributed to improvement in microorganism isolation and identification, early proper antibiotic treatment and better access to surgery.

Transparency declaration

JMM has received consulting honoraria and/or research grants from AbbVie, Bristol-Myers Squibb, Contrafect, Genentech, Jansen, Medtronic, MSD, Novartis, Gilead Sciences, and ViiV Healthcare, outside the submitted work. CWW is a founder of Predigen Inc, and has received honoraria and/or research grants from Roche Molecular Sciences, Biomerieux, Biofire, Giner, IDbyDNA, Janssen, and Sanofi, outside the submitted work. VHC has received consulting honoraria from UpToDate and Theravance, outside of the submitted work. All other authors: no conflicts.

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Funding

This work was supported by the Resident Award "Emili Letang", granted by Hospital Clínic de Barcelona, Research, Innovation and Education Department to AT. JMM received a personal 80:20 research grant from the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–23.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.05.023.

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