Frontiers in Bioscience Elite

Front. Biosci. (Elite Ed) **2022**; 14(3): 23
https://doi.org/10.31083/j.fbe1403023

Original Research

Abiotrophia spp. and *Granulicatella* spp. Infective Endocarditis: A Contemporary Perspective

Agustín Estévez[1,2,*,†], Mercedes Marín[1,2,3,4], Carlos Sánchez-Carrillo[1], Marina Machado[1,2], Luís Alcalá[1], Blanca Pinilla[5], Antonia Delgado[6,7], Víctor González-Ramallo[5], Álvaro Pedraz[8], Manuel Martínez-Sellés[6,7,9], Emilio Bouza[1,2,3,4], Maricela Valerio[1,2,3,4,*,†], Patricia Muñoz[1,2,3,4], on behalf of GAME-HGUGM[§]

[1]Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón (HGUGM), 28007 Madrid, Spain
[2]Instituto de Investigación Sanitaria Gregorio Marañón, 28007 Madrid, Spain
[3]Medicine Department, Faculty of Medicine, Universidad Complutense de Madrid, 28040 Madrid, Spain
[4]Centro de Investigación Biomédica en Red (CIBER) de Enfermedades Respiratorias-CIBERES (CB06/06/0058), 28029 Madrid, Spain
[5]Internal Medicine Department, HGUGM, 28007 Madrid, Spain
[6]Cardiology Department, HGUGM, 28007 Madrid, Spain
[7]CIBER Enfermedades Cardiovasculares-CIBERCV, 28029 Madrid, Spain
[8]Cardiac Surgery Department, HGUGM, 28007 Madrid, Spain
[9]Universidad Europea de Madrid, Universidad Complutense de Madrid, 28670-28040 Madrid, Spain
*Correspondence: agustin.estevez.prieto@gmail.com (Agustín Estévez); maricela.valerio@salud.madrid.org (Maricela Valerio)
[†]These authors contributed equally.
[§]GAME-HGUGM: Grupo de Apoyo al Manejo de la Endocarditis Infecciosa of Hospital General Universitario Gregorio Marañón. GAME-HGUGM group members are listed in the acknowledgments.

Academic Editor: Suresh G. Joshi
Submitted: 27 June 2022 Revised: 6 July 2022 Accepted: 18 July 2022 Published: 18 August 2022

Abstract

Background: *Abiotrophia* spp. and *Granulicatella* spp. are Gram-positive cocci, formerly known as nutritionally variant or deficient *Streptococcus*. Their role as causative agents of infective endocarditis (IE) is numerically uncertain, as well as diagnostic and clinical management of this infection. The aim of our study is to describe the clinical, microbiological, therapeutic, and prognosis of patients with IE caused by these microorganisms in a large microbiology department. **Methods**: Retrospective analysis of all the patients with *Abiotrophia* spp. and *Granulicatella* spp. IE registered in our centre in the period 2004–2021. **Results**: Of the 822 IE in the study period, 10 (1.2%) were caused by *Abiotrophia* spp. (7) or *Granulicatella* spp. (3). The species involved were *A.defectiva* (7), *G.adiacens* (2) and *G.elegans* (1). Eight patients were male, their mean age was 46 years and four were younger than 21 years. The most frequent comorbidities were congenital heart disease (4; 40%) and the presence of intracardiac prosthetic material (5; 50%). IE occurred on 5 native valves and 5 prosthetic valve or material. Blood cultures were positive in 8/10 patients, within a mean incubation period of 18.07 hours. In the other two patients, a positive 16SPCR from valve or prosthetic material provided the diagnosis. Surgery for IE was performed in seven patients (70%) and in all cases positive *16S rRNA* PCR and sequencing from valve or prosthetic material was demonstrated. Valves and/or prosthetic removed material cultures were positive in four patients. Nine patients received ceftriaxone (4 in monotherapy and 5 in combination with other antibiotics). The mean length of treatment was 6 weeks and IE-associated mortality was 20% at one year follow-up. **Conclusions**: *Abiotrophia* spp. or *Granulicatella* spp. IE were infrequent but not exceptional in our environment and particularly affected patients with congenital heart disease or prosthetic material. Blood cultures and molecular methods allowed the diagnosis. Most of them required surgery and the associated mortality, in spite of a mean age of 46 years, was high.

Keywords: *Abiotrophia*; *Granulicatella*; infective endocarditis

1. Introduction

Abiotrophia spp. and *Granulicatella* spp. are Gram-positive cocci that were first described in 1961 as nutritionally variant or deficient *Streptococcus* (NVS) [1], due to their need for enriched culture requirements or their characteristic growth as satellite colonies around other microorganisms. They were later reclassified into different species (*Streptococcus defectivus*, *Streptococcus adjacens*, *Abiotrophia elegans* or *Abiotrophia balaenopterae*) [2–5]. Finally, and thanks to the use of *16S ribosomal RNA* gene (16SPCR) and sequencing, Collins *et al.* [6] classified these microorganisms into two distinct genera; *Abiotrophia* (with the only species *A.defectiva*) and *Granulicatella* (composed of the three species *G.adiacens*, *G.elegans* and *G.balaenopterae*).

Although their role as causative agents of IE is known [7–11], their incidence, diagnostic and clinical management is not completely defined. Most data published in the literature report single clinical cases, with heterogeneous char-

acteristics [12–15], and data on the real impact of this entity are very scarce. Case series described focus on clinical aspects, providing scarce information on the role of microbiological diagnosis [16,17]. The aim of our study is to describe the prevalence, clinical and microbiological characteristics, treatment and outcome of patients with IE caused by these microorganisms in a series of cases from our institution over the past 18 years, with a special focus on microbiological diagnosis, analysing in detail the diagnostic method used in each of the episodes, taking into account both traditional culture and molecular methods.

2. Materials and Methods

2.1 Study Design

The Hospital General Universitario Gregorio Marañón (HGUGM) is a tertiary care institution, one of the largest hospitals in Spain, serving a population of 700,000 inhabitants, with more than 1200 hospitalization beds. HGUGM belongs to the "Spanish Collaboration on Endocarditis—Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España (GAMES)". GAMES study group maintain a nationwide registry of 45 Spanish hospitals that prospectively follow all IE episodes with a common preestablished protocol. Internally, our institution has its own GAME-HGUGM group where all IE cases are discussed. A multidisciplinary group of experts evaluates all patients and review the cases. This is a retrospective descriptive study that analyses the total number of patients with IE by *Abiotrophia* spp. and *Granulicatella* spp. diagnosed in our centre in the period 2004–2021 (18 years).

2.2 Patients

Demographics, underlying conditions, clinical manifestations at IE presentation, affected valves and prosthetic material, microbiological diagnosis, complications, surgical treatment and outcome (until one year of follow up) were analyzed. In order to define IE we used the modified Duke criteria [18]. Place of acquisition of IE was defined following International Collaboration on Endocarditis-Prospective Cohort Study (ICE) and 2015 European Society of Cardiology Guidelines for the management of infective endocarditis recommendations [19,20].

2.3 Microbiological Diagnosis

At our center all the valves and surgical material extracted from patients with IE are process by conventional cultures and molecular methods. Identification of the microorganisms was performed by 16SPCR and sequencing from blood culture isolates and direct valve/prosthetic material at the time of sample processing, as previously described [21]. Identification was also successfully performed by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics, Bremen, Germany) from blood culture colonies from 2019. Three sets of aerobic and anaerobic blood cultures, collected from different sites (peripheral veins +/– catheters) were performed for each patient, in accordance with our hospital practices. Bottles for blood cultures were incubated in an automated system (BACTECTM Plus Aerobic/F and BACTECTM Anaerobic/F, Becton Dickinson). Isolates from valve and blood cultures grew correctly on Columbia Agar 5% Sheep Blood (aerobic conditions), Brucella Blood Agar with Hemin and Vitamin K1 (anaerobic conditions) and Chocolate Agar with Vitox (CO_2 enrichment conditions) without additional nutritional supplementation of the media. Antimicrobial susceptibility (MIC) was performed by microdilution method using *Haemophilus* and *Streptococcus* Sensititre™ AST HPB1 Plate (Thermo Fisher Scientific, Hampshire, United Kingdom) supplemented with 5% lysed horse blood.

2.4 Statistics

The resulting different data was incorporated into a Microsoft® Excel 2016 database for Windows. The qualitative variables were described as absolute and relative frequencies and the quantitative variables as median and interquartile range (IQR). All statistical analysis was performed using the IBM SPSS Statistics® version 18.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Clinical Features

A total of 822 Infective Endocarditis episodes were diagnosed during the 18 years of the study period (From January 2004 to December 2021). Among them, 10 were caused by *Abiotrophia* spp. (7) or *Granulicatella* spp. (3), representing 1.22% of all the IE cases. In terms of demographic characteristics, eight patients were males and two females. The mean age was 46 years (18–67 IQR). In four out of ten cases (40%), the age of the patients was under 21 years, with a mean of 13.5 years (8–19 IQR). Regarding previous comorbidities, 4 patients (40%) had congenital heart disease (1 interatrial communication, 1 Tetralogy of Fallot, 1 complex congenital heart disease with major aortopulmonary collateral arteries (MAPCAs), pulmonary branch hypoplasia, pulmonary atresia and ventricular septal defect, and 1 congenital aortic stenosis) and 5 had intracardiac prosthetic material (50%). Other comorbidities included hypertension (4), ischaemic or vascular heart disease (2), dyslipidemia (2) and diabetes mellitus (1).

Overall, 50% of IE occurred on native valves (2 aortic and 3 mitral), and 50% on prosthetic valves or intracardiac prosthetic material (1 biological mitral prosthetic valve, 1 mechanical prosthetic aortic valve, 1 prosthetic conduit and Melody® transcatheter pulmonary valve (TPV), 1 Contegra® conduit (Medtronic Inc, Minneapolis, MN, USA) and 1 polytetrafluoroethylene (PTFE, Goretex®) patch over the atrial septal defect. For patients with a prosthetic valve or prosthetic material, the median time between surgery and the onset of IE was one year. No embolic events or cen-

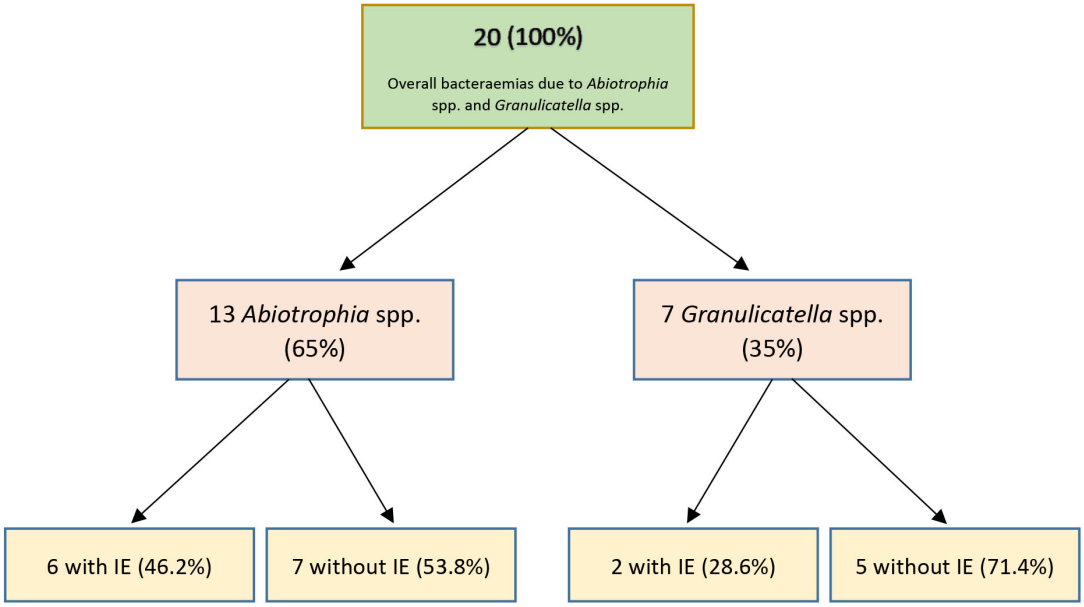

Fig. 1. Distribution of bacteraemias by *Abiotrophia* spp. and *Granulicatella* spp.

tral nervous system involvement were reported in any patient. Regarding cardiac involvement associated with IE, patient #3 presented with ruptured chordae with severe mitral insufficiency, and patient #8 developed a heart failure decompensation in the context of IE. The clinical characteristics, treatment and outcome of the patients are presented in Table 1.

3.2 Microbiological Features

In the seven cases where surgery was performed, the valve and/or prosthetic material was analyzed by 16SPCR and sequencing, being positive in all cases. Conventional culture of the valves and/or prosthetic material after surgery was positive in only four cases. Blood cultures were positive in eight patients, in the other two cases (#5 and #10), they were sterile, but they had received empirical broad-spectrum antibiotic therapy prior to blood culture extraction. These patients had positive 16SPCR from valve or prosthetic material.

The mean minimum time to positivity for blood cultures was 18.07 hours, being 18.07 hours in bottles under aerobic conditions, and 27.77 hours in bottles under anaerobic conditions. Colony identification was successfully performed in all cases by 16SPCR and sequencing. In those cases where preliminary MALDI-TOF identification was performed (cases 6, 7 and 9), it was correct. Both *Abiotrophia* spp. and *Granulicatella* spp. were isolated from positive blood cultures on Columbia Blood Agar (low growth and after re-incubation for several days), on Chocolate Agar (optimal growth), and on Brucella Agar (optimal growth), therefore, additional nutritional enrichment of the media was not necessary for the growth of the isolates. The mean time to negative blood cultures after initiation of antibiotic therapy was 10.5 days, but we must consider that in some cases control blood cultures were performed more than 7–10 days after the first positive blood cultures. The microbiological characteristics of *Abiotrophia* spp. and *Granulicatella* spp. IE are listed in Table 2.

3.3 Significance of Abiotrophia spp. and Granulicatella spp. Bacteraemia

A total of 20 bacteraemias due to *Abiotrophia* spp. or *Granulicatella* spp. were detected in our microbiology department during the study period. Eight of these bacteraemias corresponded to patients with IE. Distribution of the number of bacteraemias by microorganism in relation to whether or not they correspond to IE is shown in Fig. 1. A detailed description of the patients with bacteraemia without IE is available in the **Supplementary Material** section.

3.4 Treatment and Outcome

Regarding the antibiotic treatment received, ceftriaxone was administered in all patients in a targeted regimen once the antibiogram of the microbiological isolates was known (patient #8 received 3 weeks of daptomycin prior to ceftriaxone as the isolate had a high MIC to ceftriaxone and the clinical situation was severe). In four out of eight patients, ceftriaxone was administered as monotherapy, with a favorable evolution in all of them. In four patients, ceftriaxone was administered in combination with gentamicin. No adverse effects to the antibiotic treatments were reported in any case. The average duration of intravenous antibiotic

Table 1. Clinical characteristics, treatment and outcome of patients with infective endocarditis due to *Abiotrophia* spp. and *Granulicatella* spp. at HGUGM.

Patient	Age	Gender	Underlying conditions	Valve prosthesis or prosthetic material, and year of surgery	Year of IE diagnosis	Affected valve or material	Surgery	Species	Antibiotic treatment	Treatment duration (weeks)	IE recur-rence	Exitus after 12 months
# 1	67	M	HBP, DM, dyslipidemia, aortic stenosis	No	2004	Native aortic valve	Yes	*Abiotrophia defectiva*	Ceftriaxone and Gentamicin	6	No	No
# 2	55	M	HBP, dyslipidemia	No	2009	Native mitral valve	Yes	*Abiotrophia defectiva*	Ceftriaxone	6	No	No
# 3	54	M	HCM, MM	No	2011	Native mitral valve	No	*Abiotrophia defectiva*	Vancomycin, Gentamicin and Rifampicin	*	No	Yes
# 4	81	M	Ischaemic and valvular heart disease, AF, dyslipidemia, HBP	Yes (biological mitral valve) 2010	2012	Biological mitral prosthetic valve	Yes	*Abiotrophia defectiva*	Ceftriaxone	8	No	No
# 5	1	M	IAC, Transverse arch hypoplasia with associated aortic coarctation	Yes (Goretex® patch) 2016	2017	Pericardial fluid, surgical wound and Goretex® patch	Yes	*Abiotrophia defectiva*	Ceftriaxone	5	No	No
# 6	15	F	Tetralogy of Fallot, DiGeorge syndrome	Yes (Melody® TPV) 2018	2019	Prosthetic duct (RV-PA) and Melody® pulmonary valve	Yes	*Abiotrophia defectiva*	Ceftriaxone and Gentamicin	Ceftriaxone (6), and Gentamicin (4)	No	No
# 7	20	M	Congenital heart disease	Yes (Contegra® pulmonary prosthetic lung conduit) 2001	2021	Contegra® pulmonary prosthetic lung conduit	No	*Abiotrophia defectiva*	Ceftriaxone, Gentamicin and Levofloxacin	Ceftriaxone (6), Gentamicin (1), and Levofloxacin from 10/1/22	No	No**
# 8	86	M	Aortic stenosis, COPD, HBP, CKD	Yes (mechanical prosthetic aortic valve) 2010	2011	Mechanical prosthetic aortic valve	No	*Granulicatella adiacens*	Daptomycin, Ceftriaxone and Levofloxacin	Daptomycin (3), Ceftriaxone (6) and Levofloxacin (12)	No	Yes
# 9	63	F	Dyslipidemia, gastritis, hysterectomy, polymyalgia rheumatica	No	2019	Native mitral valve	Yes	*Granulicatella adiacens*	Ceftriaxone	5	No	No
# 10	18	M	Congenital aortic stenosis	No	2016	Native aortic valve	Yes	*Granulicatella elegans*	Ceftriaxone, Gentamicin, Piperacillin/tazobactam and Vancomycin	3	No	Yes

HBP, high blood pressure; DM, diabetes mellitus; AF, atrial fibrillation; IAC, interatrial communication; RV-PA, right ventricle-pulmonary artery; HCM, hypertrophic cardiomyopathy; MM, multiple myeloma; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease, *patient only received antibiotic therapy for 1 day due to acute exitus; ** that patient has been followed for 7 months at the time of publication of this paper.

Table 2. Microbiological characteristics of infective endocarditis due to *Abiotrophia* spp. and *Granulicatella* spp. at HGUGM.

Patient	Species	Penicillin (MICs/S, I or R)	Cefotaxime (MICs/S, I or R)	Erythromycin (MICs/S, I or R)	Clindamycin (MICs/S, I or R)	Vancomycin (MICs/S, I or R)	Rifampicin (MICs/S, I or R)	Levofloxacin (MICs/S, I or R)	Microbiological diagnosis*	Time to blood culture positivity (hours)	Total number of positive blood culture bottles over the total
# 1	*Abiotrophia defectiva*	<0.03 (S)	0.25 (S)	<0.5 (S)	NA	<0.5 (S)	NA	NA	Blood cultures and 16SPCR from valve	NA	6/6
# 2	*Abiotrophia defectiva*	0.12 (S)	0.25 (S)	<0.25 (S)	<0.25 (S)	1 (S)	NA	NA	Blood cultures, 16SPCR and valve culture	9.72	6/6
# 3	*Abiotrophia defectiva*	0.25 (S)	0.5 (S)	<0.25 (S)	<0.25 (S)	0.5 (S)	NA	<0.5 (S)	Blood cultures	15.58	3/6
# 4	*Abiotrophia defectiva*	0.12 (S)	0.5 (S)	<0.25 (S)	<0.25 (S)	1 (S)	<1 (S)	<0.5 (S)	Blood cultures and 16SPCR from valve	14.15	3/6
# 5	*Abiotrophia defectiva*	1 (I)	1 (S)	>32 (R)	>0.5 (R)	0.5 (S)	NA	<0.5 (S)	Culture and 16SPCR from pericardial fluid and goretex patch	NA	NA
# 6	*Abiotrophia defectiva*	<0.03 (S)	0.12 (S)	<0.25 (S)	<0.25 (S)	<0.25 (S)	<0.25 (S)	<0.5 (S)	Blood cultures, 16SPCR and culture from prosthetic conduit and pulmonary Melody valve	15.98	4/6
# 7	*Abiotrophia defectiva*	1 (I)	<0.06 (S)	<0.25 (S)	<0.25 (S)	<0.25 (S)	<0.25 (S)	<0.5 (S)	Blood cultures	48.16	3/6
# 8	*Granulicatella adiacens*	0.25 (I)	2 (I)	<0.25 (S)	>0.5 (R)	0.5 (S)	NA	<0.5 (S)	Blood cultures	10.95	6/6
# 9	*Granulicatella adiacens*	0.25 (I)	0.25 (S)	<0.25 (S)	>0.5 (R)	0.5 (S)	<0.25 (S)	<0.5 (S)	Blood cultures, 16SPCR and culture from valve	11.97	6/6
# 10	*Granulicatella elegans*	NA	NA	NA	NA	NA	NA	NA	16SPCR from valve	NA	NA

NA, not available; I, susceptible to high doses and/or extended perfusion; MIC, minimum inhibitory concentration, * only those microbiological tests with positive results are mentioned in the table.

treatment was 6 weeks. Patient #3 only received antibiotic therapy for 1 day due to acute exitus the day after hospital admission. Patient #7 received 6 weeks of ceftriaxone, the first week in combination with gentamicin. After completing treatment with ceftriaxone, he was started on suppressive long-term treatment with oral levofloxacin, due to the impossibility of performing surgery for IE. Patient #10 temporarily received piperacillin/tazobactam and vancomycin for other infectious complications during hospital admission.

Surgery for IE was indicated in all cases, but could be performed in seven patients (70%). The description of the non-surgical patients is detailed in the **Supplementary Material** section.

At one-year follow-up, no patient had recurrence of IE due to *Abiotrophia* spp. or *Granulicatella* spp. Patient #9, who had presented with an IE due to *G.adiacens* on native mitral valve in 2019, underwent valve replacement surgery and presented with another IE on prosthetic mitral valve due to methicillin-sensitive *Staphylococcus aureus* in 2021. IE-associated mortality was 20% (patients #3 and #10). Another patient died due to another infectious complication five months after IE. A detailed description of the patients who died can be found in the **Supplementary Material** section.

4. Discussion

Here we present one of the largest case series of *Abiotrophia* spp. or *Granulicatella* spp. IE diagnosed in a single institution (10 cases), over 18 years. Most of the previous reports are based on a review of previously published individual cases with one or a few cases of their own [22–24]. Although the percentage of IE due to *Abiotrophia* spp. or *Granulicatella* spp. is low compared to the total number of IE diagnosed in our hospital in the same period (1.22%), it is not an exceptional entity, especially if we compare it with the percentage of IE caused by microorganisms from the HACEK group (1.58%) or the *Streptococcus viridans* group (14.84%) in our institution.

Our study shows that isolation of these microorganisms do not require special media supplementation or the prolongation of the incubation time as previously described [1,25], something that should lead us away from the old idea that these microorganisms are difficult to culture. MALDI-TOF preliminary identification was correct in the three cases in which it was performed, as our group described before [26], and was verified by subsequent 16SPCR and sequencing. We routinely performed 16SPCR and sequencing on all isolates from blood cultures or valve/prosthetic material. In addition, we performed 16SPCR and sequencing directly on all surgical material (valves and/or prosthetic material) in IE, the role of which was previously described by Marin *et al*. [27]. In cases in which blood cultures were negative, 16SPCR on valve or prosthetic material provided the diagnosis. This work highlights the role of molecular methods in the diagnosis of endocarditis, and reinforces the idea that they should be implemented in routine practice in the diagnosis of this entity.

MICs to penicillin and cefotaxime were generally low, with some resistance to erythromycin and clindamycin. MICs to vancomycin, rifampicin and levofloxacin were low in all isolates tested, with 100% susceptibility. These data are in accordance with the susceptibility profile published in the literature for these microorganisms [28].

Information on the literature available on the role of *Granulicatella* spp. and *Abiotrophia* spp. infection outside of IE is very limited [29–31]. In this work, we reviewed all the bacteraemias due to *Abiotrophia* spp. or *Granulicatella* spp. in our institution in the study period (2004–2021). We detected 20 *Abiotrophia* spp. or *Granulicatella* spp. bacteraemias during the study period, of which 8 episodes were IE. In our opinion, the presence in blood of these microorganisms requires the exclusion of IE.

Téllez *et al*. [16] published the largest case series available to date of IE caused by these microorganisms (12 cases of their own), and review the literature of IE collected until 2015. In their review, focused on clinical aspects, the lower rate of congenital heart disease (10.5%) compared to ours (40%) is remarkable. Our data suggest that IE due to *Abiotrophia* spp. or *Granulicatella* spp. should be especially considered in patients with any type of cardiac structural damage, and that it is exceptional in patients without previous cardiac disease. Regarding the species involved, most of their cases were due to the genera *Granulicatella* (9/12), while in our cases, the genera *Abiotrophia* was predominant (7/10). No specific predisposing factors for IE due to these particular microorganisms have been described, although some authors suggest that previous oral colonization could be considered [32].

In absence of comparative studies, ceftriaxone seems to be the treatment of choice, with a good safety profile and early negative blood cultures. The association of gentamicin to ceftriaxone therapy did not seem to provide an evident benefit in terms of mortality or cure of IE. The high need for surgery in these patients (70%) in our case series is also very remarkable, which probably is well explained by the frequency of prosthetic material and underlying heart disease.

The main limitations of our study lie in the small number of cases available, probably due to the rare condition of this entity. Another aspect to be taken into account is that this is a descriptive study carried out in a single centre, and our results should be treated with caution when extrapolating them to other cases of IE due to *Abiotrophia* spp. or *Granulicatella* spp. in different patient profiles with other characteristics than ours.

It is essential to keep studying the role of *Abiotrophia* spp. and *Granulicatella* spp. IE, which, although uncommon, is not exceptional. Further analysis of larger case series, ideally in a multicentre manner, is needed to better un-

derstand this infection and to improve the management of these patients in clinical practice.

5. Conclusions

IE due to *Abiotrophia* spp. or *Granulicatella* spp. are infrequent, representing around one-percent of all IE cases in our series. It mainly affects patients with previous heart disease (congenital or acquired) and/or carriers of intracardiac prosthetic material, occurring in younger patients compared with IE due to other aetiologies, mainly due to the role of congenital cardiopathy. Blood cultures and 16SPCR and sequencing allowed the diagnosis. The antimicrobial therapy of choice was ceftriaxone. Most of them required surgery and the IE-associated mortality was considerable.

Author Contributions

AE, MV—formal analysis, conceptualization, data curation, writing-original draft and editing. MeM, CS—microbiological methodology, data curation. MaM, LA, BP, AD, VG, AP, MMS, EB, PM—conceptualization, data curation, formal analysis, clinical methodology, writing and editing.

Ethics Approval and Consent to Participate

The study and the common case report form were approved by the local and national institutional review boards and ethics committees (Comité ético de Investigación Clínica Regional de la Comunidad de Madrid CEIC-R; EC 18/07; date 11/01/2008). Informed consent was not required as this was a retrospective study with data extracted from the hospital's official medical records, anonymized at the time of writing this paper.

Acknowledgment

GAME-HGUGM study group: Iván Adán, David Alonso, Juan Carlos Alonso, Ana Álvarez-Uría, Javier Bermejo, Emilio Bouza, Gregorio Cuerpo Caballero, Antonia Delgado Montero, Agustín Estévez, Ramón Fortuny Ribas, Esther Gargallo, Ana González Mansilla, Mª Eugenia García Leoni, Francisco Javier González Moraga, Víctor González Ramallo, Martha Kestler Hernández, Amaia Mari Hualde, Marina Machado, Mercedes Marín, Manuel Martínez-Sellés, Rosa Melero, Patricia Muñoz, Diego Monzón, María Olmedo, Álvaro Pedraz, Blanca Pinilla, Ángel Pinto, Cristina Rincón, Hugo Rodríguez-Abella, Marta Rodríguez-Créixems, Eduardo Sánchez-Pérez, Antonio Segado, Neera Toledo, Maricela Valerio, Pilar Vázquez, Eduardo Verde Moreno, Sofía de la Villa.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.fbe1403023.

References

[1] Frenkel A, Hirsch W. Spontaneous development of L forms of streptococci requiring secretions of other bacteria or sulphydryl compounds for normal growth. Nature. 1961; 191: 728–730.

[2] Bouvet A, Grimont F, Grimont PAD. Streptococcus defectivus sp. nov. and *Streptococcus adjacens* sp. nov., nutritionally variant streptococci from human clinical specimens. International Journal of Systematic and Evolutionary Microbiology. 1989; 39: 290–294.

[3] Kawamura Y, Hou XG, Sultana F, Liu S, Yamamoto H, Ezaki T. Transfer of *Streptococcus adjacens* and *Streptococcus defectivus* to Abiotrophia gen. nov. as *Abiotrophia adiacens* comb. nov. and *Abiotrophia defectiva* comb. nov., respectively. International Journal of Systematic Bacteriology. 1995; 45: 798–803.

[4] Roggenkamp A, Abele-Horn M, Trebesius KH, Tretter U, Autenrieth IB, Heesemann J. *Abiotrophia elegans* sp. nov., a possible pathogen in patients with culture-negative endocarditis. Journal of Clinical Microbiology. 1998; 36: 100–104.

[5] Lawson PA, Foster G, Falsen E, Sjödén B, Collins MD. *Abiotrophia balaenopterae* sp. nov., isolated from the minke whale (*Balaenoptera acutorostrata*). International Journal of Systematic Bacteriology. 1999; 49: 503–506.

[6] Collins MD, Lawson PA. The genus Abiotrophia (Kawamura *et al*.) is not monophyletic: proposal of Granulicatella gen. nov., *Granulicatella adiacens* comb. nov., *Granulicatella elegans* comb. nov. and *Granulicatella balaenopterae* comb. nov. International Journal of Systematic and Evolutionary Microbiology. 2000; 50: 365–369.

[7] Ohara-Nemoto Y, Tajika S, Sasaki M, Kaneko M. Identification of *Abiotrophia adiacens* and *Abiotrophia defectiva* by 16S rRNA gene PCR and restriction fragment length polymorphism analysis. Journal of Clinical Microbiology. 1997; 35: 2458–2463.

[8] Christensen JJ, Gruhn N, Facklam RR. Endocarditis caused by *Abiotrophia* species. Scandinavian Journal of Infectious Diseases. 1999; 31: 210–212.

[9] Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. Clinical Microbiology Reviews. 2001; 14: 177–207.

[10] Senn L, Entenza JM, Greub G, Jaton K, Wenger A, Bille J, *et al*. Bloodstream and endovascular infections due to *Abiotrophia defectiva* and *Granulicatella species*. BMC Infectious Diseases. 2006; 6: 9.

[11] Lin CH, Hsu RB. Infective endocarditis caused by nutritionally variant streptococci. The American Journal of the Medical Sciences. 2007; 334: 235–239.

[12] Miyawaki N, Okada T, Koyama T, Furukawa Y. Right-sided Infective Endocarditis with Ventricular Free Wall Vegetation Caused by *Abiotrophia defectiva* in a Patient with Unrepaired Ventricular Septal Defect: A Case Report. Internal Medicine. 2022. (in press)

[13] Li J, Zhou L, Gong X, Wang Y, Yao D, Li H. *Abiotrophia defectiva* as a Rare Cause of Mitral Valve Infective Endocarditis With Mesenteric Arterial Branch Pseudoaneurysm, Splenic Infarction, and Renal Infarction: A Case Report. Frontiers in Medicine. 2022; 9: 780828.

[14] Lancaster I, Patel D, Tamboli C, Chun P, Sethi V, Namey J. *Abiotrophia defectiva* Infective Endocarditis: A Rare and Dangerous Cause of Endocarditis. Case Reports in Infectious Diseases. 2022; 2022: 7050257.

[15] Mosca AM, Mané F, Marques Pires C, Medeiros P. Infective endocarditis by a rare and fastidious agent: *Abiotrophia defectiva*. BMJ Case Reports. 2021; 14: e241964.
[16] Tellez A, Ambrosioni J, Llopis J, Pericas JM, Falces C, Almela M, *et al*. Epidemiology, clinical features and outcome of infective endocarditis due to *Abiotrophia* spp. and *Granulicatella* spp.: Report of 76 cases (2000-2015). Clinical Infectious Diseases. 2018; 66: 104–111.
[17] Téllez A, Ambrosioni J, Hernández-Meneses M, Llopis J, Ripa M, Chambers ST, *et al*. Clinical characteristics and outcome of infective endocarditis due to *Abiotrophia* and *Granulicatella* compared to Viridans group streptococci. Journal of Infection. 2022. (in press)
[18] Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr, Ryan T, *et al*. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clinical Infectious Diseases. 2000; 30: 633–638.
[19] Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG, Jr, Bayer AS, *et al*. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. JAMA Internal Medicine. 2009; 169: 463–473.
[20] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, *et al*. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). European Heart Journal. 2015; 36: 3075–3128.
[21] Marín M, Garcia-Lechuz JM, Alonso P, Villanueva M, Alcalá L, Gimeno M, *et al*. Role of universal 16S rRNA gene PCR and sequencing in diagnosis of prosthetic joint infection. Journal of Clinical Microbiology. 2012; 50: 583–589.
[22] Rhodes HM, Hirigoyen D, Shabnam L, Williams DN, Hansen GT. Infective endocarditis due to *Abiotrophia defectiva* and *Granulicatella* spp. complicated by infectious intracranial cerebral aneurysms: a report of three cases and review of the literature. Journal of Medical Microbiology. 2016; 65: 493–499.
[23] Carleo MA, Del Giudice A, Viglietti R, Rosario P, Esposito V. Aortic Valve Endocarditis Caused by *Abiotrophia defectiva*: Case Report and Literature Overview. In Vivo. 2015; 29: 515–518.
[24] Giuliano S, Caccese R, Carfagna P, Vena A, Falcone M, Venditti M. Endocarditis caused by nutritionally variant streptococci: a case report and literature review. InfezMed. 2012; 20: 67–74.
[25] George RH. The isolation of symbiotic streptococci. Journal of Medical Microbiology. 1974; 7: 77–83.
[26] Rodríguez-Sánchez B, Marín M, Sánchez-Carrillo C, Cercenado E, Ruiz A, Rodríguez-Créixems M, *et al*. Improvement of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry identification of difficult-to-identify bacteria and its impact in the workflow of a clinical microbiology laboratory. Diagnostic Microbiology and Infectious Disease. 2014; 79: 1–6.
[27] Marin M, Muñoz P, Sanchez M, Del Rosal M, Alcala L, Rodriguez-Creixems M, *et al*. Molecular diagnosis of infective endocarditis by real time broad-range polymerase chain reaction (PCR) and sequencing directly from heart valve tissue. Medicine. 2007; 86: 195–202.
[28] Alberti MO, Hindler JA, Humphries RM. Antimicrobial Susceptibilities of *Abiotrophia defectiva*, *Granulicatella adiacens*, and *Granulicatella elegans*. Antimicrobial Agents and Chemotherapy. 2015; 60: 1411–1420.
[29] Wan J, Larsen MP, Panwalkar P, Mofidi A. Simultaneous bilateral revision total knee arthroplasty following *Abiotrophia defectiva* infection. BMJ Case Reports. 2020; 13: e237116.
[30] Onorati I, Guiraudet P, Billard-Pomares T, Martinod E. A recurrent lung abscess caused by delayed diagnosis of unique co-infection with *Abiotrophia defectiva*. Interactive CardioVascular and Thoracic Surgery. 2020; 31: 909–911.
[31] Bakhsh W, Childs S, Ikpeze T, Mesfin A. Lumbar Spine Infection by *Granulicatella* and *Abiotrophia* Species. World Neurosurgery. 2017; 108: 997.e1–997.e3.
[32] Sasaki M, Shimoyama Y, Ishikawa T, Kodama Y, Tajika S, Kimura S. Contribution of different adherent properties of *Granulicatella adiacens* and *Abiotrophia defectiva* to their associations with oral colonization and the risk of infective endocarditis. Journal of Oral Science. 2020; 62: 36–39.