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Practical clinical reviews

Prevalence of extracardiac vascular complications in *Abiotrophia* spp. and *Granulicatella* spp. infective endocarditis: Two case reports and a systematic review

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ABSTRACT

Objectives: Infective endocarditis (IE) caused by *Abiotrophia* spp. and *Granulicatella* spp. share an increased risk of extracardiac vascular complications (EVC). The current work aims to assess the prevalence of EVC in IE due to these microorganisms.
Methods: This was a study with mixed design, consisting in a single center experience combined with a systematic review of multiple databases. We included studies enrolling adults >18 years old with a diagnosis of *Abiotrophia* spp. and *Granulicatella* spp. IE. We collected data regarding the presence and the description of EVC in IE along with clinical and microbiological details. Risk of bias assessment was performed using the Newcastle-Ottawa Scale for comparative observational studies, and a dedicated tool for single-arm non-comparative studies. The review was registered in PROSPERO (CRD42023433130).
Results: The cohort study identified 2 patients. The systematic review included 83 studies, involving 228 cases of *Abiotrophia* spp. (n = 103), *Granulicatella* spp. (n = 94), and unspecified nutritionally variant streptococci (n = 31) IE. EVC occurred in 101/230 (44 %) patients, central nervous system involvement occurred in 66/101 (66 % of total embolisms), and pseudoaneurysm or peripheral vascular embolization occurred in 11/101 (11 %).
Conclusions: Considering the observed prevalence of EVC a proactive approach in the diagnosis of such a complication is warranted.

Introduction

Nutritionally variant streptococci (NVS) are Gram-positive bacteria, firstly described in 1961 (Frenkel and Hirsch, 1961) and later reclassified as *Abiotrophia* spp. (*A. defectiva*) and *Granulicatella* spp. *(G. adiacens, G. elegans, and G. balaenopterae)* (Kawamura et al., 1995; Collins and Lawson, 2000). NVS are found in oral, gastroenteric, and urogenital flora, causing invasive infections as bacteremia and infective endocarditis (IE), associated with high rates of complications such as intracranial aneurysms, osteomyelitis, and valvular destruction (Christensen and Facklam, 2001). The isolation of these bacteria proves challenging, necessitating specialized culture media and potentially leading to negative IE diagnoses (Baddour et al., 2015). These difficulties complicate estimating the frequency of NVS IE, with some studies proposing it constitutes 5–6 % of all streptococcal IE cases (Brouqui and Raoult, 2001). Despite its rarity, NVS IE may pose a heightened risk of extracardiac vascular complications (EVC) compared to viridans streptococci (Roberts et al., 1979; Adam et al., 2015). This is possibly due to delayed diagnosis and treatment (Delgado et al., 2023).

In situations like this, when the evidence is expected to be very

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sparse, a recommended approach is to retrieve data from multiple sources, such as electronic medical records of a health system and bibliographic databases (Lin et al., 2020). Therefore, we searched the electronic medical record of a tertiary healthcare system and conducted a systematic review of the literature on IE caused by *Abiotrophia* spp. and *Granulicatella* spp., aiming to assess the prevalence of EVC associated with these specific microorganisms.

Methods

We conducted a study with mixed design, which consists of two case reports and a systematic review of records including patients affected by IE caused by *Abiotrophia* spp. and *Granulicatella* spp.

Medical record search

The electronic medical record of a tertiary healthcare system (Sacco Hospital in Milan, Northern Italy) was queried between January 2017 and May 15th, 2023, to identify cases of IE due to *Abiotrophia* spp. and *Granulicatella* spp. To ensure comprehensive and transparent reporting, we report identified cases using the CARE (CAse REport) guidelines (Riley et al., 2017).

Systematic review search

Data sources and search strategies

A comprehensive search of several databases from 1995 (date of the first distinction of the genus *Abiotrophia* (Kawamura et al., 1995) to May 15th, 2023, was conducted. There was no restriction on language. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with inputs from the study's investigators. The actual search strategy is available in the Supplementary Table S1. The International Prospective Register of Systematic Reviews (PROSPERO) registration number is CRD42023433130.

Study selection and data extraction

We followed the PRISMA guidelines for systematic review (Supplementary, PRISMA checklist). We included individual studies which (i) reported at least one case of NVS IE and (ii) provided sufficient details to determine the presence of EVC. We excluded IE in child patients (<18 years) or due to polymicrobial infections. Two reviewers (G.P. and C.M.) screened all titles and abstracts independently. Disagreements were resolved through discussion with a third reviewer (M.P.). We extracted individual data for each report. When this was not possible, we reported the aggregated data. Missing data were handled by contacting study authors. Extracted data included study design, year, country, age, sex, EVCs (which were defined as any vascular complications not involving heart and coronary vessels, such as mycotic aneurysm, ischemic/hemorrhagic stroke, vascular embolus, embolization in spleen/liver/kidney/lung/vertebral tissue), cardiac complications (heart failure, arrhythmias, severe valvular insufficiency, myocardial infarction, cardiogenic shock, perivalvular abscess, pseudoaneurysm, fistula), extracardiac non-vascular complications (kidney injury, septic shock, immunological complications, coma), microbiological agent, diagnosis according to the Duke criteria (Fowler et al., 2023), type of valve involved, vegetation size, cardiac surgery, type and duration of antimicrobial therapy, clinical outcome (relapse/death at 6 months).

Type of outcome measure

The primary outcome was the proportion of EVC. Secondarily, we planned to assess the factors associated with both EVC occurrence and 6-months mortality. Lastly, we aimed to compare the characteristics of IE due to *Abiotrophia* spp. *versus Granulicatella* spp.

Quality assessment and certainty of evidence

Risk of bias assessment was performed using the Newcastle-Ottawa Scale for comparative observational studies (Stang, 2010) and a dedicated tool for single-arm non-comparative studies (Murad et al., 2018).

Certainty of evidence (CoE) was assessed using the GRADE approach (Guyatt et al., 2011).

Summary of statistical analysis and software used

Study characteristics were described using counts and percentages, or medians and interquartile ranges (IQRs), as appropriate. Categorial variables were evaluated using the chi-squared test or Fisher's exact test. To assess factors associated with EVC and 6-months mortality, we extracted individual data, when possible. Therefore, two multivariate logistic regression were performed to assess the variables associated with (i) extracardiac complications, accounting for *a priori* defined variables: age, sex at birth, presence of a valvular vegetation larger than 10 mm, type (mitral, aortic, tricuspid, pulmonary) and nature (native or prosthetic) of the affected valve, and (ii) mortality at 6 months, accounting for age, sex, and nature of the valve (native or prosthetic). A p-value of less than or equal to 0.05 was deemed to indicate statistical significance. For the screening process we used Covidence, for the data extraction Microsoft Excel, and for the data analysis R (version 4.2.1).

Results

Case reports

First case report

A 41-year-old female, with a history of childhood rheumatic disease and recent myocardial infarction, presented with a three-week history of persistent fever. Clinical examination revealed Janeway lesions, a painful swelling in the palm, and a systolic murmur. Laboratory test showed microcytic anemia (Hb 9.9 g/dL – MCV 69 fL) with leukocytosis and elevated CRP (101 mg/L). In transthoracic (TTE) and transesophageal echocardiography (TEE) a large vegetation (20x15 mm) of the mitral valve was found. Abdominal, chest and brain CT revealed an abscess in left encephalic parietal posterior lobe (20 mm), a splenic infarction and a subcapsular liver infarction. Musculotendinous echography of palm of right hand revealed a pseudoaneurysm of third metacarpal artery. All blood cultures collected upon admission were positive to *A. defectiva*. Empiric antibiotic therapy with vancomycin and ceftriaxone was initiated. Mitral valve replacement was performed, leading to clinical and laboratory improvement. The antibiotic regimen transitioned to ceftriaxone. Two weeks later a clinical and laboratory improvement was observed, and a significant reduction of embolization area was documented on the control CT. The patient was discharged after the completion of six weeks of antibiotic therapy. No relapse occurred during the 6-month follow-up.

Second case report

A 21-year-old Chinese male presented with a one-week history of fever, fatigue, and sudden-onset dysarthria. Clinical examination revealed a systolic murmur and a TTE showed a mitral valve with severe regurgitation and two mobile vegetations, (18x16x6 mm and 16x11x5mm). Laboratory exams revealed severe anemia (Hb 6.1 g/dl) and elevated CRP (140 mg/L).

Empiric antibiotic therapy with ceftriaxone and vancomycin was initiated, but the latter was narrowed with ceftriaxone alone following the isolation of *A. defectiva* bloodstream infection.

A mechanical prosthesis valve replacement surgery was then urgently performed while valve biopsy cultures were negative. After surgery, a doppler ultrasound revealed pseudoaneurysms in the left humeral artery and left leg, prompting a surgical by-pass. The patient was discharged after the completion of 4 weeks of antibiotic treatment.

No relapse occurred during the 6-month follow-up.

Systematic review

A total of 83 studies were included in the final analysis of the systematic review (Fig. 1). Among them, 10 were IE registries, 8 case series of consecutive patients, 3 case series of non-consecutive patients, and 62 single case reports (Supplementary, Table S2 and Bibliography). Seventy-six studies reported individual data for a total of 130 IE cases, while seven studies reported aggregated data for additional 98 IE cases. Therefore, the total number of the cases including our center experience was 230.

Description of the included cases and proportion of EVC

The characteristics of the 230 *Abiotrophia* spp. or *Granulicatella* spp. IE included in our study are depicted in Table 1. One hundred and three (45 %) were IE cases specifically due to *Abiotrophia* spp., 94 (41 %) to *Granulicatella* spp., and 33 (14 %) to a not defined NVS species. Overall, the patients were predominantly male (131/179, 73 %) and their median age was 55 (36–65). EVC were observed in 101/230 (44 %) cases, predominantly involving the central nervous system (66/101, 66 % of total embolisms). Pseudoaneurysm or peripheral vascular embolization was found in 11 cases (11 %), and spleen and vertebral involvement were noted in 33 (33 %) and 12 (12 %) cases, respectively. Cardiac complications occurred in 132/205 (64 %) cases, while extracardiac non-vascular complications occurred in 20/162 (12 %) cases. The 6-month mortality rate was 14 % (27/198), with a 3 % (4/128) observed relapse proportion.

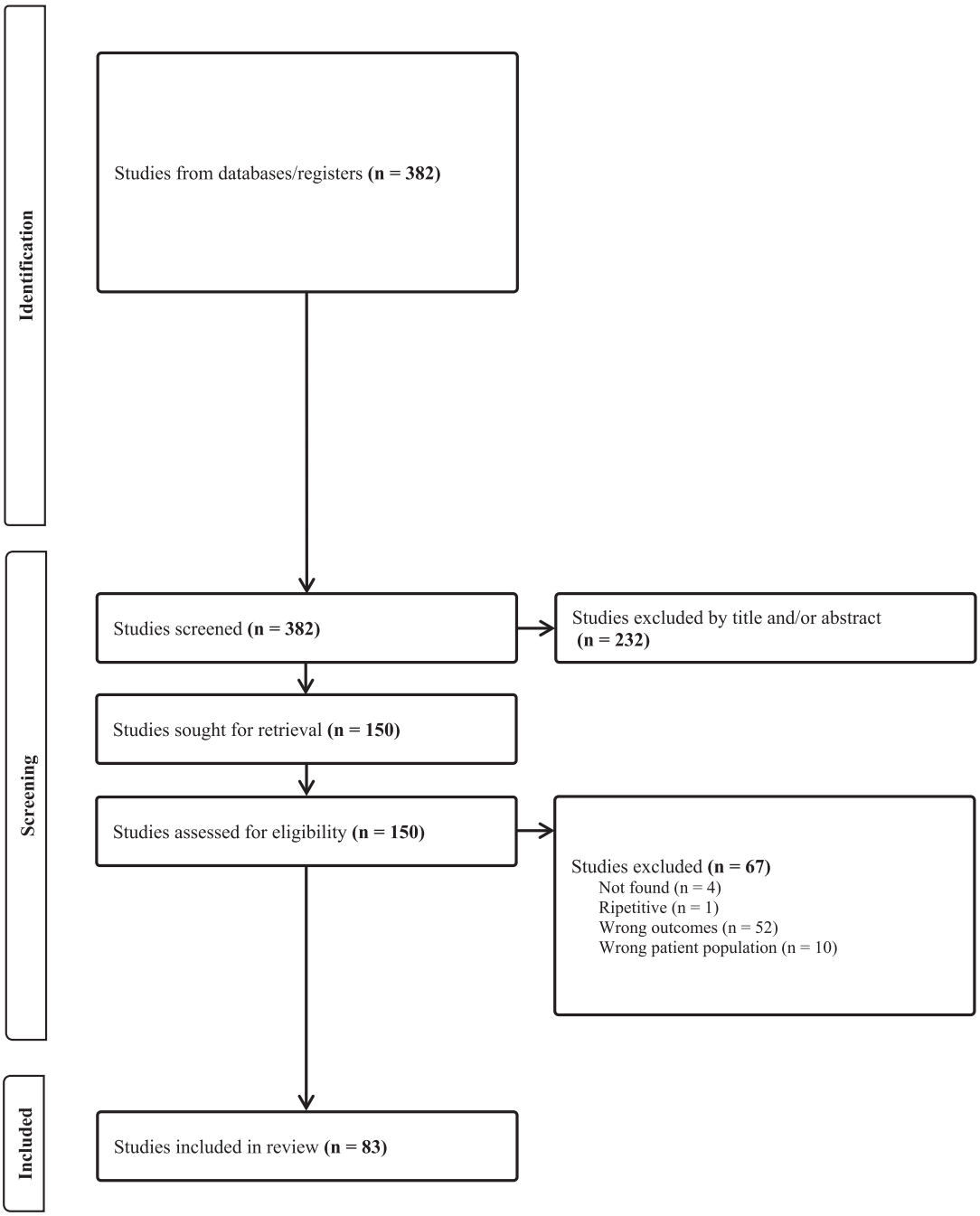

Fig. 1. PRISMA flow diagram of the included studies.

Table 1
Characteristics and description of extracardiac vascular complications, treatment and outcomes of the study population. Acronyms: IQR, interquartile range; IE, infective endocarditis; NVS, nutritionally-variant streptococci not determinate; nd, not determinate; NA, not applicable. *Total phenomena: 136. **Total phenomena: 180. ***Total phenomena: 24. °Diagnosis in line with 2023 Duke-ISCVID Criteria (Riley et al., 2017). °°Antibiotic therapy regimen combination in ESC guidelines (Delgado et al., 2023): penicillin G/ceftriaxone or vancomycin plus gentamicin.

Characteristics of population	Total 230
Age, median (IQR)	55 (35–65)
Sex at birth, n (%)	
Male	131/179 (73)
Female	48/179 (27)
Risk factors, n (%)	
No	86/204 (42)
Recent dental procedure or periodontitis	17/204 (8)
Congenital cardiac disease	25/204 (12)
Prosthetic valve/device	21/204 (10)
Previous IE	1/204 (0)
Valvulopathy	52/204 (25)
IVDU	6/204 (3)
Immunosuppression	2/204 (1)
Rheumatic heart disease	7/204 (3)
Vegetation > 10 mm, n (%)	53/71 (75)
First valve involved, n (%)	
Aortic	94/211 (45)
Mitral	111/211 (52)
Pulmonary	2/211 (1)
Tricuspid	2/211 (1)
Device	2/211 (1)
Valve type, n (%)	
Native	147/180 (82)
Prosthetic	33/180 (18)
Second valve involved, n (%)	32/187 (17)
Third valve involved, n (%)	2/129 (1)
Agent, n (%)	
Abiotrophia spp.	103/230 (45)
Granulicatella spp.	94/230 (41)
NVS nd	33/230 (14)
Diagnosis, n (%)	
Definite	146/151 (97)
Possible	5/151 (3)
Echocardiogram positive, n (%)	119/122 (97)
Blood culture positive, n (%)	137/141 (97)
Valve culture positive, n (%)	22/24 (92)
Extracardiac vascular complications*, n (%)	101/230 (44)
Mycotic aneurism	15/101 (15)
Ischemic stroke	38/101 (38)
Haemorrhagic stroke	15/101 (15)
Vascular embolus/pseudoaneurysm	11/101 (11)
Spleen	33/101 (33)
Liver	3/101 (3)
Kidney	5/101 (5)
Lung	2/101 (2)
Vertebral	12/101 (12)
NA	2/101 (2)
Cardiac complications**, n (%)	132/205 (64)
Heart failure	45/132 (34)
Arrhythmia	7/132 (5)
Severe valve insufficiency	91/132 (69)
Pseudoaneurysm	3/132 (2)
Paravalvular abscess	24/132 (18)
Fistula	3/132 (2)
Cardiogenic shock	5/132 (4)
Myocardial infarction	1/132 (1)
Extracardiac nonvascular complications***, n (%)	20/162 (12)
Acute kidney injury	8/20 (40)
Septic shock	9/20 (45)
Immune phenomena	6/20 (30)
Coma	1/20 (5)
Antibiotic therapy (targeted), n (%)	
Monotherapy	19/129 (15)
Combination	110/129 (85)
Duration of antibiotic therapy, median	6
Cardiac surgery, n (%)	148/202 (73)
Relapse, n (%)	4/128 (3)
Death at 6 months, n (%)	27/198 (14)
Combination beta-lactams/glycopeptides + amynoglicoside°°, n (%)	143/186 (77)

Factors associated with EVC and 6-months mortality

In the multivariable logistic regression model after accounting for a priori chosen potential confounders mitral valve involvement was associated to a higher odd of EVC [adjusted odds ratio (aOR) 4.38; 95 % CI 1.39–15.41; Supplementary Table S3a]. In the multivariable logistic regression model of factors associated with 6-moths mortality only age resulted associated to a higher odds of death (per 1 year more, aOR 1.05; 95 % CI 1–1.1) (Supplementary Table S3b).

Abiotrophia spp. and Granulicatella spp. EVC comparison

For this purpose, a total of 129/130 individual cases (68 *Abiotrophia* spp. *versus* 61 *Granulicatella* spp.) were analyzed, one case of IE was excluded due to undetermined species (Supplementary Table S4). No evidence for a difference was detected regarding demographic characteristics, proportion of EVC, cardiac complications, extracardiac non-vascular complications, type of valve affected, size of vegetations, and 6-months mortality.

Quality assessment and CoE

The methodological quality of the included studies is summarized in Supplementary Table S5. Out of the 83 studies included, 43 (52 %) were deemed to have a high-risk of bias, mostly due to bias in the selection of the patients. The CoE for the primary outcome was deemed to be at very low certainty due to the inclusion of case reports and case series alone.

Discussion

In this systematic review including 230 patients with IE due to *Abiotrophia* spp. or *Granulicatella* spp., we found a high proportion of EVC (45 %). Moreover, EVC occurrence was associated with mitral valve involvement. The IE related 6-months mortality due to *Abiotrophia* spp. or *Granulicatella* spp. was 14 % and a significant association was found with older age.

The proportion of EVC in our study (45 %) was higher when compared to the largest study conducted on *Abiotrophia* spp. or *Granulicatella* with a mixed study design, where the prevalence of EVC was less than 10 % (2/12) in the reported cases, and 30 % (23/76) in the literature review (Téllez et al., 2018). Similar results were showed by another case series mixed with literature review on *Granulicatella* IE (Adam et al., 2015) reporting an embolisms' proportion of 30 % (8/26). The higher prevalence of EVC observed in our study might be related to the inclusion of a higher number of single case reports, accounting for 62 of total studies. It is well-documented that studies reporting positive or unusual findings are more likely to be published in the literature. Therefore, the overrepresentation of these positive findings in our study may have led to an inflated estimation of the prevalence of EVC.

The overall prevalence of EVC complications in all IE is estimated to be 20–50 % (Habib et al., 2015); ranging from 27 % (Murdoch et al., 2009) to 47 % (Thuny et al., 2007).

The risk of EVC is associated with specific microorganisms, such as

Staphylococcus aureus, *Streptococcus bovis, and Candida* spp. (Habib et al., 2015). Among the genus *Streptococcus*, to which *Abiotrophia* and *Granulicatella* belong, *Streptococcus bovis* is associated with an increased risk of EVC.

Pergola et al (Pergola et al., 2001) analyzed the incidence of embolic events in IE caused by *Streptococcus bovis* and other pathogens, highlighting that in *Streptococcus bovis* IE the incidence of at least one embolic event is 55 %, with a high risk of central nervous system (35 %) and peripheral arteries (10 %) embolisms. These data significantly differ from the EVC of IE caused by other streptococci (18 %) or other pathogens (37 %) (Pergola et al., 2001).

As regards NVS, the burden of EVC may be explained by strong ability of *Abiotrophia* to adherence to fibronectin of vascular endothelium in contrast to *Granulicatella,* whose biofilm formation capability can lead to the development of large valvular vegetations (Sasaki et al., 2020), which is a well-known risk factors for EVC (Delgado et al., 2023). The release of extracellular proteins is a vital component of bacterial physiology, holding significant clinical significance. Bacterial pathogens move diverse virulence-related proteins outside their cells, tactically placing them in host environments to aid in colonization and eventual infection. Radhika et al (Bhardwaj et al., 2024) found more than 20 possible proteins in the *A. defectiva* secretome that exhibit potential virulence properties. Another possibility of the high proportion of EVC in these infections is the delay in the diagnosis, given the potential difficulties to grow such bacteria in the media. However, we did not assess in the studies included the time from symptoms onset to diagnosis and any microbiological difficulties in the growth of these microorganisms.

We found an association between mitral valve involvement and EVC occurrence. In the literature Vilacosta (Vilacosta et al., 2002) and Shiue (Shiue et al., 2010) highlighted a significant risk of embolism in mitral IE. Furthermore, in the systematic review of overall IEs conducted by Yang et al (Yang et al., 2019 Feb) a similar emphasis on the risk of EVC was evident. However, in comparison to this latest review, our study did not identify significant differences in the incidence of EVC associated with the vegetation size. One plausible explanation for this lack of disparity could be attributed to the unique dynamics of the mitral valve. The anterior leaflet of the mitral valve is required to move more rapidly and forcefully during valve closure, potentially destabilizing attached vegetations. Additionally, the force generated by atrial contraction produces a jet stream across the mitral orifice, generating an area of negative pressure that exerts a suction effect on the valves and the vegetation, thereby increasing the risk of embolism (Rohmann et al., 1992).

EVC may be totally silent in around 20 % of patients with IE, especially those affecting the splenic or cerebral circulation. Embolic complications, especially involving the CNS, worsen the patient's prognosis and management (García-Cabrera et al., 2013). Cerebral imaging often detects lesions that may change the therapeutic strategy, in particular, the indications and timing of cardiovascular surgery (Duval et al., 2010). Therefore, promptly searching for latent and asymptomatic embolic complications enhance the patient outcome and affect clinical decision-making (Cooper et al., 2009).

Despite imaging being useful for detecting embolic foci, the best way to reduce the risk of embolic complications remains the prompt initiation of appropriate antibiotic therapy with a drastic and significant reduction in the risk of embolisms up to 6–21 %. Some previous studies showed that early surgical intervention for patients with indications improves prognosis.

In our systematic review, we presented novel findings regarding the distinctions between *Abiotrophia* spp. and *Granulicatella* spp. IE. Despite our comprehensive analysis, we did not identify significant evidence in either group, highlighting the limitations stemming from the relatively low sample size. As a result, uncertainties persist regarding the precise differences between these two pathogens in the context of IE. ESC guidelines (Delgado et al., 2023), for this reason, consider *Abiotrophia* spp. and *Granulicatella* spp. as a single entity regarding the rates of embolic and cardiac complications.

This review presents some limitations. Firstly, while we included 17 case series or registries with 161 cases, it's important to note that many of the considered studies primarily consist of case reports highlighting positive findings; considering only the case series, the rate of EVC is significantly lower (33 %). Secondly, within some of the studies analyzed, there was either no follow-up conducted or the follow-up duration was less than 6 months. This abbreviated follow-up period may not adequately capture the long-term outcomes or complications associated with infective endocarditis and embolic events. Extending the follow-up duration could offer more comprehensive insights into the natural history and prognosis of these conditions.

Thirdly, our review focused exclusively on the risk factors for IE and did not encompass the broader range of factors that could contribute to a more severe clinical presentation. This limitation may restrict the depth of understanding regarding the determinants of disease severity and treatment outcomes.

Lastly, our inclusion criteria primarily targeted the risk of EVC, which may have led to a partial investigation of other characteristics associated with NVS IE. As a result, certain aspects of NVS IE were not systematically explored, potentially limiting the breadth of our analysis.

Conclusions

In conclusion, *Abiotrophia* and *Granulicatella* infective endocarditis are associated with a high risk of cardiac and extracardiac complications and consequently a very high need to surgery. A proactive approach in the diagnosis of such a complication, with a low threshold for additional imaging, is warranted.

Ethical approval statement

The systematic review did not require ethical approval.

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CRediT authorship contribution statement

Giacomo Pozza: Conceptualization, Investigation, Data curation, Writing – original draft. **Chiara Mariani:** Conceptualization, Investigation, Data curation. **Matteo Passerini:** Conceptualization, Methodology, Software, Writing – review & editing. **Marta Colaneri:** Conceptualization, Methodology, Software, Writing – review & editing. **Andrea Giacomelli:** Conceptualization, Methodology, Software, Writing – review & editing. **Larry J. Prokop:** Methodology, Software, Writing – review & editing. **Mohammad H. Murad:** Methodology, Writing – review & editing. **Monica Schiavini:** Conceptualization, Writing – review & editing. **Andrea Gori:** Conceptualization, Writing – review & editing. **Spinello Antinori:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinpr.2024.100367.

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