

Review

Granulicatella infection: diagnosis and management

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Granulicatella species, along with the genus *Abiotrophia*, were originally known as 'nutritionally variant streptococci'. They are a normal component of the oral flora, but have been associated with a variety of invasive infections in man and are most noted as a cause of bacterial endocarditis. It is often advised that *Granulicatella* endocarditis should be treated in the same way as enterococcal endocarditis. We review here the published data concerning diagnosis and treatment of *Granulicatella* infection, and include some observations from local cases, including four cases of endocarditis.

Introduction

Nutritionally variant streptococci (NVS), first described in the early 1960s from cases of endocarditis (Frenkel & Hirsch, 1961), were transferred to a separate genus, *Abiotrophia*, in the mid-1990s (Kawamura *et al.*, 1995). Since then, this genus has been divided into the genera *Abiotrophia* and *Granulicatella* on the basis of 16S rRNA gene sequencing (Collins & Lawson, 2000). We review here the published data concerning diagnosis and treatment of *Granulicatella* infection. The PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>) was searched for 'Granulicatella' and individual references were reviewed for relevant clinical data. The reference lists of these publications were also reviewed. For specific infections, e.g. infective endocarditis, searches for 'Abiotrophia' were also undertaken: the species identification was reviewed and relevant cases were included. We also include some observations from local cases, including four cases of endocarditis, two cases of infection of prosthetic materials, and two cases considered to be either transient bacteraemias or contamination of blood cultures at the point of collection. Both of these final cases were also associated with the presence of prosthetic materials. Of the six active infections, successful therapy was possible in four.

Granulicatella species are catalase-negative and oxidase-negative, facultatively anaerobic, Gram-positive cocci (Collins & Lawson, 2000), and belong to the *Carnobacteriaceae* (Ludwig *et al.*, 2008). The *Streptococcaceae* (including the genus *Streptococcus*), *Enterococcaceae* (including *Enterococcus*) and *Aerococcaceae* (including *Abiotrophia*) are related families

within the order *Lactobacilliales* (Ludwig *et al.*, 2008). *Granulicatella* and *Abiotrophia* were known as NVS because of their requirement for pyridoxal or other additional agents to be incorporated into standard media for successful laboratory isolation (Frenkel & Hirsch, 1961; Ruoff, 1991). Recovery of NVS from blood samples can be achieved using thiol broths (Ruoff, 1991).

Three species of *Granulicatella* have been described: *G. adiacens*, *G. elegans* and *G. balaenopterae* (Collins & Lawson, 2000). A further species, *Abiotrophia para-adiacens*, related to *Abiotrophia adiacens*, was proposed prior to separation of the *Granulicatella* and *Abiotrophia* genera (Kanamoto *et al.*, 2000), and is occasionally reported (Dowd *et al.*, 2008; Senn *et al.*, 2006a, b), but the name is not currently validly published (Garrity *et al.*, 2004). *G. balaenopterae* has not been described from human samples (Collins & Lawson, 2000).

Granulicatella species are a normal component of the oral flora (Aas *et al.*, 2005; Sato *et al.*, 1999), are found in dental plaque (Mikkelsen *et al.*, 2000), endodontic infection (Siqueira & Rôças, 2006) and dental abscesses (Robertson & Smith, 2009), but can also cause a variety of serious infections.

Frequency

Granulicatella species are uncommon clinical isolates, with the majority of reported isolates recovered from blood culture. In the largest series to include the clinical source of isolates, 39 of 43 *G. adiacens* isolates with a known source were isolated from blood, with the remainder isolated from sinus, bone marrow, abscesses and eye samples (Christensen & Facklam, 2001). The NVS as a group have been estimated

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to cause between 5 and 6% of all cases of streptococcal endocarditis (Brouqui & Raoult, 2001; Roberts *et al.*, 1979), although this is often over-reported as 5% of all cases of endocarditis (Facklam, 2002; Ruoff, 1991; Wijetunga *et al.*, 2002). A review of local cases revealed eight episodes of possible bloodstream infection caused by *G. adiacens* between 2005 and 2009. For comparison, a total of six episodes caused by *Abiotrophia* species were identified during the same time period.

Clinical significance

Endocarditis

Seventeen cases of *Granulicatella* endocarditis (rather than nutritionally variant streptococcal endocarditis) have been described in the literature since 1997 (see Table 1). Cases have been reported for both *G. adiacens* (Chang *et al.*, 2008; Christensen *et al.*, 1999; Jeng *et al.*, 2005; Lin & Hsu, 2007; Perkins *et al.*, 2003; Hernando Real *et al.*, 2007; Rosenthal *et al.*, 2002; Schwede *et al.*, 2007; Vandana *et al.*, 2010; Woo *et al.*, 2003) and *G. elegans* (Al-Tawfiq *et al.*, 2007; Casalta *et al.*, 2002; Ohara-Nemoto *et al.*, 2005; Roggenkamp *et al.*, 1998). These include infections of prosthetic valves (Christensen *et al.*, 1999; Jeng *et al.*, 2005; Schwede *et al.*, 2007) and of pacemaker leads (Rosenthal *et al.*, 2002). Locally, four cases of endocarditis were identified, in two of which the patients had known cardiac abnormalities. In each case, between two and six sets of blood cultures were positive for *G. adiacens* after less than 24 h incubation (Bactec 9240 automated blood culture system; Becton Dickinson). It has been suggested that *Granulicatella* may be under-reported and diagnosed as 'culture-negative' endocarditis (Brouqui & Raoult, 2001); however, the largest case series of culture-negative endocarditis cases identified only one case (0.3%; *G. elegans*; Houpikian & Raoult, 2005).

Endocarditis caused by *G. adiacens* is more common than that caused by *Abiotrophia* species, with *G. elegans* being comparatively rare (Christensen & Facklam, 2001). Strains of *G. adiacens* from endocarditis have been reported to display fibrinonectin binding, unlike those not associated with endocarditis or *G. elegans* (Dowd *et al.*, 2008; Okada *et al.*, 2000). This difference between *G. adiacens* and *G. elegans* may account for the different prevalence in endocarditis. Mixed valvular disease is not uncommon (5 of 21 cases; Lin & Hsu, 2007; Schwede *et al.*, 2007), and many cases have required surgical intervention (Al-Tawfiq *et al.*, 2007; Casalta *et al.*, 2002; Chang *et al.*, 2008; Christensen *et al.*, 1999; Lin & Hsu, 2007; Roggenkamp *et al.*, 1998). Combinations of either benzylpenicillin (penicillin G) (Christensen *et al.*, 1999; Lin & Hsu, 2007; Ohara-Nemoto *et al.*, 2005; Schwede *et al.*, 2007) or amoxicillin (Casalta *et al.*, 2002; Perkins *et al.*, 2003) with gentamicin are the most frequent antibiotic interventions. The British Society for Antimicrobial Chemotherapy (BSAC), American Heart Association (AHA) and the European Society for Cardiology (ESC) all make recommendations for the

treatment of NVS or *Granulicatella* in their endocarditis guidelines (Baddour *et al.*, 2005; Gould *et al.*, 2012; Habib *et al.*, 2009). The AHA guidelines explicitly recommend that NVS endocarditis should be treated as for enterococci (Baddour *et al.*, 2005); the BSAC guidelines previously contained the same explicit recommendation (Elliott *et al.*, 2004), although the latest guidelines no longer make this link between treatments (Gould *et al.*, 2012). Locally, therapeutic success has been achieved with both vancomycin (1 g 12-hourly) and amoxicillin (2 g 4-hourly), with the addition of gentamicin (1 mg kg⁻¹ to a maximum of 80 mg 12-hourly) when the isolates were provisionally identified. Three patients were treated with 6 weeks of antibiotic therapy, although one required aortic and mitral valve replacement after 4 weeks.

NVS endocarditis has been considered to have a high relapse rate (Stein & Nelson, 1987), and relapses following treatment have been reported for *Granulicatella* endocarditis (Christensen *et al.*, 1999; Schwede *et al.*, 2007). To date, no relapses are known for our local patients who survived the initial episode. Complications, which may necessitate surgery, are not uncommon, and include valvular damage (Al-Tawfiq *et al.*, 2007; Roggenkamp *et al.*, 1998), heart failure (Lin & Hsu, 2007), distal embolization (Lin & Hsu, 2007; Vandana *et al.*, 2010), cerebral mycotic aneurysm (Chang *et al.*, 2008; Lin & Hsu, 2007) and extension of vegetations to the atrial wall (Al-Tawfiq *et al.*, 2007; Jeng *et al.*, 2005). One of our local cases required surgery following the development of cardiac failure. The overall mortality for reported cases of *Granulicatella* endocarditis (rather than NVS endocarditis) is 9.5%, with two deaths (see Table 1).

Other bloodstream infection

Bacteraemia has been reported in the absence of endocarditis (Abdul-Redha *et al.*, 2007; Christensen & Facklam, 2001; Senn *et al.*, 2006a; Woo *et al.*, 2003). *G. adiacens* bacteraemia has also been reported in association with early onset neonatal sepsis, with maternal vaginal carriage also identified (Bizzarro *et al.*, 2011). Infected aortic atheroma, with an associated dissection, has also been reported (Woo *et al.*, 2003). This patient did not survive their infection. Two episodes of probable transient bacteraemia were identified locally. In both episodes, a single blood culture taken from an arterial line grew *G. adiacens*, and both cases were considered to be either colonizers of the lines or coincidental transient bacteraemia.

Other infection

Two patients were identified locally with a probable focus of infection involving prosthetic material. The first had radiological evidence of infection of an abdominal aortic graft. One of six sets of blood cultures grew *G. adiacens*. The patient did not survive attempted surgical repair of the infected graft and targeted antimicrobial therapy was never started. The second patient had four sets of blood cultures

Table 1. Case reports of *G. adiacens* or *G. elegans* endocarditis

| Organism | Sex | Age (years) | Valve* | Cardiac risk factors† | Isolated‡ | Antibiotic therapy§ | Surgery† | Outcome | Reference |
|--------------------|-----|-------------|-----------|--|--------------|---------------------|------------------------------|----------|------------------------------------|
| <i>G. adiacens</i> | M | 58 | M | None | BC | VAN, GEN | None | Survived | This paper |
| <i>G. adiacens</i> | M | 63 | M and A | Mitral valve prolapse | BC, valvelli | AMOX, GEN | AVR, MVR | Survived | This paper |
| <i>G. adiacens</i> | F | 38 | T | VSD | BC | AMOX, GEN | None | Survived | This paper |
| <i>G. adiacens</i> | F | 63 | M and T | None | BC | AMOX, GEN | None | Died | This paper |
| <i>G. adiacens</i> | F | 71 | A | Previous AVR and aortic prosthesis | BC | PEN, GEN | AVR | Survived | Christensen <i>et al.</i> (1999) |
| <i>G. adiacens</i> | M | 31 | M | None reported | BC | OXA, GEN | Valvuloplasty | Survived | Chang <i>et al.</i> (2008) |
| <i>G. adiacens</i> | M | 18 | P | Congenital heart disease (surgically corrected, including PVR) | BC | VAN, GEN, RIF | None | Survived | Jeng <i>et al.</i> (2005) |
| <i>G. adiacens</i> | F | 18 | M | Rheumatic heart disease | NS | PEN, GEN | MVR | Survived | Lin & Hsu (2007) |
| <i>G. adiacens</i> | M | 61 | M and T | None reported | NS | PEN, GEN | MVR, TVR | Survived | Lin & Hsu (2007) |
| <i>G. adiacens</i> | M | 30 | M | None reported | NS | PEN, GEN, CTR | MVR | Survived | Lin & Hsu (2007) |
| <i>G. adiacens</i> | F | 28 | M and A | None reported | NS | PEN, GEN, VAN, TEI | AVR, MVR | Survived | Lin & Hsu (2007) |
| <i>G. adiacens</i> | M | 57 | Unknown¶ | Mitral regurgitation | BC | AMOX, GEN | None | Survived | Perkins <i>et al.</i> (2003) |
| <i>G. adiacens</i> | F | 77 | A | Aortic stenosis and mitral regurgitation | BC | VAN, AMP, GEN | None | Survived | Hernando Real <i>et al.</i> (2007) |
| <i>G. adiacens</i> | M | 68 | Pacemaker | Pacemaker for atrial fibrillation | BC | PEN, GEN, RIF | None | Survived | Rosenthal <i>et al.</i> (2002) |
| <i>G. adiacens</i> | M | 41 | M and A¶ | AVR for aortic stenosis | BC | PEN, GEN | None | Survived | Schwede <i>et al.</i> (2007) |
| <i>G. adiacens</i> | M | 85 | NR | Aortic regurgitation | NR | NR | NR | Died | Woo <i>et al.</i> (2003) |
| <i>G. adiacens</i> | M | 71 | M | None reported | BC | AMP, GEN | Embolectomy | Survived | Vandana <i>et al.</i> (2010) |
| <i>G. elegans</i> | M | 47 | M | Mitral valve prolapse | BC | NS | Annuloplasty and debridement | Survived | Al-Tawfiq <i>et al.</i> (2007) |
| <i>G. elegans</i> | M | 29 | A | Bicuspid aortic valve | Valvelli | AMOX, GEN | AVR | Survived | Casalta <i>et al.</i> (2002) |
| <i>G. elegans</i> | F | 53 | NS | None reported | BC | PEN, GEN | NS | Survived | Ohara-Nemoto <i>et al.</i> (2005) |
| <i>G. elegans</i> | NR | 38 | A | None reported | BC | PTA, GEN, VAN | AVR | Survived | Roggenkamp <i>et al.</i> (1998) |

NR, Not reported; NS, not specified.

*M, Mitral; T, tricuspid; A, aortic; P, pulmonary.

†MVR, Mitral valve replacement; TVR, tricuspid valve replacement; AVR, aortic valve replacement; PVR, pulmonary valve replacement; VSD, ventricular septal defect.

‡BC, Blood culture.

§AMOX, amoxicillin; AMP, ampicillin; CTR, ceftriaxone; GEN, gentamicin; OXA, oxacillin; PEN, penicillin; PTA, piperacillin with tazobactam; RIF, rifampicin; TEI, teicoplanin; VAN, vancomycin.

||Detected by PCR only.

¶No echocardiographic lesions.

taken on the same day, both peripherally and from the lumens of a Tesio line, which grew *G. adiacens*, and morphologically identical colonies grew from the Tesio line tip. Transthoracic echocardiography showed no evidence of valvular lesions, and the patient was treated with a short course of vancomycin.

G. adiacens has also been reported to cause infection of the central nervous system. As well as mycotic aneurysms arising from endocarditis (Chang *et al.*, 2008; Lin & Hsu, 2007), *Granulicatella* infections following neurosurgery have been reported to cause both brain abscesses (Biermann *et al.*, 1999) and meningitis with epidural abscess (Cerceo *et al.*, 2004). One case of brain abscess without surgery has been reported; the child had congenital heart defects but no vegetations were seen on imaging (Michelow *et al.*, 2000).

G. adiacens has been reported to cause septic arthritis (Hepburn *et al.*, 2003; Riede *et al.*, 2004), vertebral osteomyelitis (Rosenthal *et al.*, 2002; Fukuda *et al.*, 2010; Heath *et al.*, 1998) and discitis (Heath *et al.*, 1998). There are also reports of infections of breast implants (del Pozo *et al.*, 2008) and of peritoneal dialysis related peritonitis (Altay *et al.*, 2008). Locally, one further *G. adiacens* was isolated from a pericardial fluid sample; this patient was transferred to another centre and no further information was available.

Identification

Locally, *Granulicatella* isolates are identified by either biochemical testing (API Strep; bioMérieux) and/or molecular confirmation. In several cases, identification was delayed as the isolates were thought to be poorly growing streptococci before pyridoxal dependence was considered. In one case, direct antimicrobial susceptibility testing from positive blood cultures was noted to show growth only in the vicinity of the *Staphylococcus aureus* strain used as a control for Stokes' susceptibility testing, and the possibility of *Abiotrophia* species or *Granulicatella* species was then considered. Molecular identification locally is made by an in-house 16S rRNA gene sequencing method using the primers fD1 (Weisburg *et al.*, 1991) and UR (Hendolin *et al.*, 2000).

In all but one case locally, blood cultures became positive within 24 h of incubation; the exception was considered to represent a transient bacteraemia. In all but three cases, both the aerobic and anaerobic blood culture bottles became positive; of the three remaining cases, two were considered transient events. On average, anaerobic blood cultures became positive slightly earlier than the aerobic bottle, but this was not significant or reliable (3.56 h, standard deviation 8.49 h). Where an acceptable API 20 Strep result was not available, isolates seemed to identify as *Gemella* species.

Biochemical testing has been reported to potentially lead to incorrect identification, with *G. elegans* being misidentified

as *Streptococcus acidominimus*, *Gemella morbillorum* and *G. adiacens* (Abdul-Redha *et al.*, 2007; Al-Tawfiq *et al.*, 2007) and *G. adiacens* as *Gemella* as happened locally. Identification of isolates by 16S rRNA gene sequencing of either bacterial isolates (Biermann *et al.*, 1999; Ohara-Nemoto *et al.*, 2005; Hernando Real *et al.*, 2007; Woo *et al.*, 2003) or of valvular tissue (Casalta *et al.*, 2002), or identification by biochemical methods including API (Perkins *et al.*, 2003; del Pozo *et al.*, 2008; Rosenthal *et al.*, 2002) and VITEK (bioMérieux; Altay *et al.*, 2008), or combinations of approaches (Abdul-Redha *et al.*, 2007; Al-Tawfiq *et al.*, 2007; Lin & Hsu, 2007), have been previously reported.

A variety of molecular techniques have been developed to help accelerate the identification of Gram-positive cocci, including *Granulicatella*. As well as 16S rRNA gene sequencing, sequencing of the *rpoB* gene (Drancourt *et al.*, 2004) and the ribosomal 16S–23S intergenic spacer region (Tung *et al.*, 2007) have been used to identify *Granulicatella*, *Abiotrophia*, *Enterococcus* and *Streptococcus* species. Fluorescence *in situ* hybridization has been used for rapid identification of Gram-positive cocci, including *Granulicatella*, from positive blood cultures (Gescher *et al.*, 2008). Oligonucleotide arrays have also been used, using the ribosomal intergenic spacer region (Tung *et al.*, 2006). The increasing use of molecular methods in the diagnosis of endocarditis, including 16S (Breitkopf *et al.*, 2005) and 23S (Vollmer *et al.*, 2010) rRNA gene sequencing, may mean an increasing recognition of formerly rare organisms in endocarditis. The use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has been reported to identify *G. adiacens* to genus level in one-third of tests only (Neville *et al.*, 2011).

Susceptibilities

Antibiotic susceptibility testing by disc diffusion is not recommended for *Granulicatella* isolates (Jorgensen & Hindler, 2007). Broth microdilution (using a supplemented Mueller–Hinton broth) is suggested (Jorgensen & Hindler, 2007), although a disc diffusion method utilizing *S. aureus* culture supernatants incorporated into the test media has also been reported (Tantimavanich *et al.*, 2002). Etest results have been shown to be similar to broth dilution for penicillin, although there is a higher rate of intermediate susceptibility reported (Douglas *et al.*, 1994). In our isolates, penicillin MICs ranged from 0.016 to 1.0 mg l⁻¹ by Etest (AB Biodisk/bioMérieux). Four of the five local isolates with MIC data were susceptible to benzylpenicillin by EUCAST streptococcal breakpoint values (European Committee on Antimicrobial Susceptibility Testing, 2011). Resistance to β -lactam antibiotics has been reported in both *G. adiacens* (susceptibility rates of 55–67 % to penicillin, 0–63 % to ceftriaxone, 81 % to amoxicillin and 96 % to meropenem) and *G. elegans* (susceptibility rates of 100 % to penicillin, 0 % to cefuroxime and 33 % to ceftriaxone) (Tuohy *et al.*, 2000; Zheng *et al.*, 2004). Resistance has also been reported to clindamycin, tetracycline, erythromycin and ciprofloxacin,

but not to vancomycin or rifampicin (Tuohy *et al.*, 2000; Zheng *et al.*, 2004). The need for routine susceptibility testing is unclear as many infections may be managed without such results (Jorgensen & Hindler, 2007).

Summary

Granulicatella species are an uncommon cause of infection. We suggest that *Granulicatella* (and *Abiotrophia*) species should be considered in patients where slow-growing α -haemolytic streptococci are isolated from blood cultures or other sterile sites. For isolates which are showing poor growth after 48 h, we suggest that a presumptive identification should be made by examining for satellitism around an *S. aureus* strain if pyridoxal-supplemented blood agar is not available (Reimer & Reller, 1981). Where antimicrobial susceptibilities will affect clinical management, centres should consider using reference facilities to confirm the results of local laboratory testing. It has been advised that NVS endocarditis should be treated in the same way as enterococcal endocarditis, using combinations of benzylpenicillin (Baddour *et al.*, 2005; Gould *et al.*, 2012; Habib *et al.*, 2009), ampicillin (Baddour *et al.*, 2005)/amoxicillin (Gould *et al.*, 2012; Habib *et al.*, 2009) or vancomycin (Baddour *et al.*, 2005; Habib *et al.*, 2009) alongside gentamicin (Baddour *et al.*, 2005; Gould *et al.*, 2012; Habib *et al.*, 2009). Reviewing the cases of specific *Granulicatella* endocarditis shows that these antimicrobial combinations are clinically effective in practice.

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