Antimicrobial Susceptibility Patterns among a Large, Nationwide Cohort of *Abiotrophia* and *Granulicatella* Clinical Isolates

Kunatum Prasidhthathsint, Mark A. Fisher

Associated Regional and University Pathologists Laboratories and Department of Pathology, University of Utah, Salt Lake City, Utah, USA

ABSTRACT Antimicrobial susceptibility patterns from 599 *A. defectiva*, *G. adiacens*, and *G. elegans* clinical isolates were determined by broth microdilution. We observed significant differences in susceptibility across species, particularly to penicillin and ceftriaxone, and across geographical regions. *A. defectiva* was the least susceptible species overall to penicillin. All isolates were susceptible to vancomycin and >90% were susceptible to levofloxacin.

KEYWORDS *A. defectiva*, *G. adiacens*, *G. elegans*, NVS, nutritionally variant streptococci, susceptibility

The nutritionally variant streptococci (NVS) were first described in 1961 as fastidious Gram-positive cocci that grew as satellite colonies around other bacteria (1). They required supplemental L-cysteine or pyridoxal hydrochloride to promote growth in culture media (2). Over the past 4 decades, the taxonomy of these organisms has continued to evolve. The species that have been identified in human specimens are now classified as *Abiotrophia defectiva*, *Granulicatella adiacens*, and *Granulicatella elegans* based on 16S rRNA sequencing (3). An additional proposed species, "*Abiotrophia para-adiacens*," has also been isolated from human specimens, while the remaining valid species, *Granulicatella balaenopterae*, has not, to date (3, 4).

The NVS are commensal oral and intestinal flora in humans but can also cause significant infections such as endocarditis and septicemia or bacteremia (5). Other reported infections include keratitis, postneurosurgical brain abscess, pancreatic abscess, and infections of bone and joints, including prosthetic joints (5–10). Infections with NVS have high treatment failure rates, including high rates of relapse, complications such as heart failure, embolism, and perivalvular abscess, and high mortality rates (11, 12). Due to their stringent growth requirements and relatively infrequent recovery from clinical specimens, susceptibility testing of these organisms is not routinely performed in clinical microbiology laboratories. Most susceptibility data in the literature, as well as NVS treatment recommendations such as those published in the American Heart Association (AHA) endocarditis guidelines (13), were based on studies with small numbers of isolates. These studies often failed to identify NVS isolates to the species level, and different susceptibility breakpoints were used due to lack of standardized testing methods and interpretive criteria prior to the publication of the Clinical and Laboratory Standards Institute's (CLSI) M45 guidelines for fastidious organisms (14). Not surprisingly, there have been discrepancies among the reported susceptibility patterns of NVS (15–21). These limitations can lead to the use of empirical penicillin and gentamicin without susceptibility testing, which could lead to the unnecessary risk of gentamicin toxicity. In 2006, the CLSI published guidelines for antimicrobial susceptibility testing (AST) of fastidious bacteria, including *Abiotrophia*

Received 5 October 2016 Returned for modification 13 October 2016 Accepted 30 December 2016

Accepted manuscript posted online 11 January 2017

Citation Prasidhthathsint K, Fisher MA. 2017. Antimicrobial susceptibility patterns among a large, nationwide cohort of *Abiotrophia* and *Granulicatella* clinical isolates. J Clin Microbiol 55:1025–1031. <https://doi.org/10.1128/JCM.02054-16>.

Editor Robin Patel, Mayo Clinic

Copyright © 2017 American Society for Microbiology. All Rights Reserved.

Address correspondence to Mark A. Fisher, mark.fisher@path.utah.edu.

and *Granulicatella* species (14, 22–24). Using these standardized guidelines to interpret AST data from a large collection of *Abiotrophia* and *Granulicatella* species isolated across the United States, we identified differences in susceptibility patterns across species, in temporal trends of nonsusceptibility, and in the geographic distribution of penicillin susceptibility. These data may aid in determining appropriate empirical therapy and influence future guidelines for *in vitro* AST and treatment of NVS infections.

RESULTS AND DISCUSSION

AST was performed on 599 NVS isolates identified as *G. adiacens* (427 isolates), *A. defectiva* (152 isolates), or *G. elegans* (20 isolates). Identification of 73% (436/599) of isolates was performed by Associated Regional and University Pathologists (ARUP) Laboratories, including 70% of *G. adiacens* (298/427), 78% (119/152) of *A. defectiva*, and 95% (19/20) of *G. elegans* isolates. The majority of isolates were recovered from blood (71%), followed by wounds (8.2%), body fluids (6.5%, including unspecified body fluid [2.3%], peritoneal/abdominal fluid [2%], pleural fluid [0.8%], urine [0.7%], cerebrospinal fluid [CSF; 0.5%], and pericardial fluid [0.2%]), tissue (5.7%), joint fluid and bone (5.2%), eye (2.8%), and unspecified sources (0.5%).

Only 14% (21/152) of *A. defectiva* and 39% (168/426) of *G. adiacens* isolates were susceptible to penicillin (Table 1). Interestingly, *G. elegans* was significantly more susceptible to penicillin (80%, 16/20) than *G. adiacens* and *A. defectiva* ($P < 0.001$). Among the penicillin-susceptible *G. adiacens* isolates, 167 had ceftriaxone susceptibility performed, and we found that only 65% (109) were susceptible. However, the vast majority of penicillin-susceptible *A. defectiva* isolates (95%) remained susceptible to ceftriaxone, which is similar to what was seen in recent studies (25, 26). Of the penicillin-resistant *G. adiacens* isolates, 95% (40/42) were also resistant to ceftriaxone, whereas 97% of penicillin-resistant *A. defectiva* isolates remained susceptible to ceftriaxone (Fig. 1; see also Table S1 in the supplemental material). In contrast to what was reported by Alberti et al., we did encounter ceftriaxone-nonsusceptible *A. defectiva*, although not to the extent described by Mushtaq et al., who saw 8% nonsusceptibility (25, 26). Overall, the majority of *A. defectiva* (98%, 148/151) and *G. elegans* (90%, 18/20) isolates were susceptible to ceftriaxone (Table 1), but *G. adiacens* had a significantly lower proportion of susceptible isolates (47%, 201/426, $P < 0.001$). Importantly, there was no significant decrease over the 8 years of data (2007 to 2014) in the rates of susceptibility to penicillin or ceftriaxone for *G. adiacens* and *A. defectiva* using the Mann-Kendall test, although *G. adiacens* showed a nonsignificant trend toward decreased susceptibility to ceftriaxone ($P = 0.386$) (see Fig. S1 in the supplemental material).

The AHA infective endocarditis guidelines recommend different treatment strategies based on penicillin MIC: highly penicillin-susceptible isolates ($\text{MIC} \leq 0.12$) generally do not require addition of gentamicin; for relatively penicillin-resistant isolates ($\text{MIC}, >0.12$ to <0.5), a combination of penicillin and gentamicin is reasonable; and for penicillin-resistant isolates ($\text{MIC} \geq 0.5$), combination therapy with penicillin and gentamicin is recommended (13). It is important to note that these categories differ from the CLSI penicillin susceptibility categories ($\text{MIC} \leq 0.12$, susceptible; $\text{MIC} = 0.25$ to 2, intermediate; $\text{MIC} \geq 4$, resistant) (23). Because there have been differences in penicillin susceptibility reported in the literature (15–21, 24–26), we evaluated the geographic distribution of penicillin susceptibility across different U.S. Census regions using the AHA infective endocarditis guidelines' penicillin MIC categories (Table 2). We found that the Northeast region had the highest proportion of penicillin-susceptible *G. adiacens* isolates (57.5%), while the Midwest had the highest percentage of isolates with a penicillin MIC of >0.12 (69.2%). It is interesting that *A. defectiva* isolates were largely of the penicillin-resistant phenotype (78 to 85%) across the country, without any significant regional bias. We were unable to perform a complete geographical analysis for *G. elegans*, as none of the isolates were from the Northeast.

In contrast to the findings of Alberti et al. (25) but similar to the data from Mushtaq et al. (26), we found that not all NVS were susceptible to meropenem. In fact,

TABLE 1 Antimicrobial susceptibility of *G. adiacens*, *G. elegans*, and *A. defectiva*

Antimicrobial agent and species (no. of isolates)	MIC ($\mu\text{g/ml}$)			Interpretive breakpoint ($\mu\text{g/ml}$) ^a or % of isolates		
	Range	MIC ₅₀	MIC ₉₀	Susceptible	Intermediate	Resistant
Penicillin						
<i>G. adiacens</i> (426)	≤ 0.03 to ≥ 16	0.25	2	≤ 0.12 39.4 ^b	0.25–2 50.7 ^b	≥ 4 9.9
<i>G. elegans</i> (20)	≤ 0.03 –8	≤ 0.03	0.25	80 ^c	15 ^c	5
<i>A. defectiva</i> (152)	≤ 0.03 –8	0.5	8	13.8 ^d	63.2 ^d	23 ^d
Ceftriaxone						
<i>G. adiacens</i> (426)	≤ 0.06 to ≥ 32	2	≥ 16	≤ 1 47.2 ^b	2 24.4	≥ 4 28.4 ^b
<i>G. elegans</i> (20)	≤ 0.06 to ≥ 16	0.12	1	90	5	5
<i>A. defectiva</i> (151)	0.12 to ≥ 16	0.5	1	98 ^d	1.3 ^d	0.7 ^d
Erythromycin						
<i>G. adiacens</i> (413)	≤ 0.12 to ≥ 8	≥ 8	≥ 8	≤ 0.25 44.6	0.5 0.2	≥ 1 55.2
<i>G. elegans</i> (19)	≤ 0.12 to ≥ 8	≤ 0.12	≥ 8	52.6		47.4
<i>A. defectiva</i> (143)	≤ 0.12 to ≥ 8	≥ 8	≥ 8	39.9	0.7	59.4
Clindamycin						
<i>G. adiacens</i> (414)	≤ 0.03 to ≥ 32	0.06	≥ 4	≤ 0.25 77.3	0.5 2.9	≥ 1 19.8
<i>G. elegans</i> (19)	≤ 0.03 to ≥ 4	0.12	0.5	89.4	5.3	5.3
<i>A. defectiva</i> (143)	≤ 0.03 –4	0.12	0.25	92.3 ^d	5.6	2.1 ^d
Meropenem						
<i>G. adiacens</i> (425)	≤ 0.06 to ≥ 16	0.12	0.5	≤ 0.5 91.3	1 6.4	≥ 2 2.4
<i>G. elegans</i> (20)	≤ 0.06 –1	≤ 0.06	0.25	95	5	
<i>A. defectiva</i> (150)	0.12–2	0.5	1	80.7 ^d	18.7 ^d	0.6
Levofloxacin						
<i>G. adiacens</i> (414)	≤ 0.25 to ≥ 16	1	2	≤ 2 91.6	4 0.7	≥ 8 7.7
<i>G. elegans</i> (19)	≤ 0.25 –1	0.5	1	100		
<i>A. defectiva</i> (144)	0.25–4	≤ 0.25	0.5	99.3 ^d	0.7	0 ^d
Vancomycin						
<i>G. adiacens</i> (423)	≤ 0.5 –1	1	1	≤ 1 100		
<i>G. elegans</i> (20)	≤ 0.5 –1	1	1	100		
<i>A. defectiva</i> (152)	≤ 0.5 –1	0.5	1	100		
Daptomycin						
<i>G. adiacens</i> (343)	≤ 0.25 to ≥ 8	4	≥ 8			
<i>G. elegans</i> (19)	≤ 0.25 to ≥ 8	0.5	2			
<i>A. defectiva</i> (119)	≤ 0.25 –4	2	4			
Linezolid						
<i>G. adiacens</i> (413)	≤ 0.25 –2	1	1			
<i>G. elegans</i> (19)	0.5–1	0.5	1			
<i>A. defectiva</i> (143)	≤ 0.25 –2	1	1			
Gentamicin						
<i>G. adiacens</i> (414)	≤ 0.12 to ≥ 16	2	4			
<i>G. elegans</i> (19)	0.25–2	1	2			
<i>A. defectiva</i> (143)	≤ 0.12 to ≥ 16	2	4			
TMP/SMX						
<i>G. adiacens</i> (391)	$\leq 0.12/2.4$ to $\geq 8/152$	0.25/4.8	4/76			
<i>G. elegans</i> (18)	0.25/4.8–4/76	0.25/4.8	4/76			
<i>A. defectiva</i> (128)	$\leq 0.12/2.4$ to $\geq 4/76$	0.25/4.8	0.25/4.8			
Doxycycline						
<i>G. adiacens</i> (410)	≤ 0.06 to ≥ 16	≤ 0.12	8			
<i>G. elegans</i> (19)	≤ 0.12 –8	≤ 0.12	8			
<i>A. defectiva</i> (144)	≤ 0.06 –8	≤ 0.12	2			
Rifampin						
<i>G. adiacens</i> (387)	≤ 0.5 to ≥ 8	≤ 0.5	≤ 0.5			
<i>G. elegans</i> (18)	≤ 0.5	≤ 0.5	≤ 0.5			
<i>A. defectiva</i> (126)	≤ 0.5 –1	≤ 0.5	≤ 0.5			

^aInterpretive breakpoints are shown in bold for each antibiotic.

^bP value shows significant differences ($P < 0.05$) between *G. adiacens* and *G. elegans*.

^cP value shows significant differences ($P < 0.05$) between *G. elegans* and *A. defectiva*.

^dP value shows significant differences ($P < 0.05$) between *A. defectiva* and *G. adiacens*.

(A) *G. adiacens* (N = 426) (B) *G. elegans* (N = 20) (C) *A. defectiva* (N = 151)

FIG 1 Scattergram comparisons of ceftriaxone and penicillin MICs for *G. adiacens* (A), *G. elegans* (B), and *A. defectiva* (C). Shading indicates the relative frequency of observations.

significantly more *A. defectiva* isolates were susceptible to ceftriaxone than meropenem ($P < 0.001$). Meropenem nonsusceptibility among NVS has been described (16, 18, 26), suggesting that this difference could be due to the evaluation of different populations, as the Alberti et al. study was based on isolates from a single county whereas our isolates were referred from hospitals in 42 states. Another possible reason for this difference is that Alberti et al. used lower concentrations of lysed horse blood (LHB; 2.5% versus 5% in this study) and pyridoxal HCl (1 µg/ml versus 10 µg/ml) than those used in our study. The CLSI currently recommends 2.5 to 5% LHB and 10 µg/ml pyridoxal HCl for NVS AST. Although we saw substantially more nonsusceptibility to meropenem than did Alberti et al., most nonsusceptible isolates (84%) were intermediate rather than resistant. Further, our MIC₅₀ values were identical, and our MIC₉₀ values were the same for *G. adiacens* and differed by only 1 dilution for *A. defectiva*.

TABLE 2 Geographic distribution of highly penicillin-susceptible (MIC, ≤ 0.12), relatively penicillin-resistant (MIC, >0.12 to <0.5), and penicillin-resistant (MIC, ≥ 0.5) isolates (American Heart Association endocarditis treatment categories) of *G. adiacens* and *A. defectiva*

U.S. census region	% (no.) of <i>G. adiacens</i> isolates			% (no.) of <i>A. defectiva</i> isolates		
	Highly penicillin susceptible	Relatively penicillin resistant	Penicillin resistant	Highly penicillin susceptible	Relatively penicillin resistant	Penicillin resistant
Midwest	30.8 (32) ^a	24 (25)	45.2 (47)	5.9 (2)	8.8 (3)	85.3 (29)
South	37.6 (41) ^b	15.6 (17)	46.8 (51) ^b	12.5 (4)	3.1 (1)	84.4 (27)
Northeast	57.5 (23)	15 (6)	27.5 (11)	21.1 (4)		78.9 (15)
West	41.6 (72)	22.5 (39)	35.8 (62)	16.4 (11)	6 (4)	77.6 (52)

^aP value shows significant differences ($P < 0.05$) in isolate susceptibility between Midwest and Northeast.

^bP value shows significant differences ($P < 0.05$) in isolate susceptibility between South and Northeast.

(Table 1). Our data were essentially identical to the meropenem values reported by Mushtaq et al., suggesting that large and broad isolate collections reveal modal MICs for meropenem that overlap the current susceptible breakpoint. Even larger multi-center studies may be required to fully resolve the normal meropenem MIC distribution for these organisms. As with penicillin and ceftriaxone, there was no significant decrease in meropenem susceptibility over the course of the study, although there was a trend for *A. defectiva* ($P = 0.095$).

Erythromycin was the least active of all tested drugs across the NVS group, especially for *G. adiacens* and *A. defectiva*, which had MIC₅₀ values of ≥ 8 $\mu\text{g/ml}$ (25, 26). Only 39 to 53% of NVS species were susceptible to erythromycin, which is consistent with data from Alberti et al. (25). Among the erythromycin-resistant isolates, 63% (144/228) of *G. adiacens* isolates were susceptible to clindamycin (Table 3). A similar pattern, although with even higher clindamycin susceptibility rates, was also seen in *A. defectiva* (91%, 76/84 susceptible) and *G. elegans* (89%, 8/9 susceptible). The rate of clindamycin nonsusceptibility among erythromycin-resistant isolates of *G. adiacens* was similar to that previously described for NVS and other streptococci in the United States (Table 3) but was considerably lower for *A. defectiva* and *G. elegans*. The erythromycin-resistant/clindamycin-susceptible pattern has been associated with macrolide efflux and may suggest this rather than ribosomal methylation as a predominant mechanism of erythromycin resistance among *A. defectiva* and *G. elegans* isolates (15, 17). Zheng et al. found that five of eight erythromycin-resistant NVS contained the *mef(A)* gene, encoding macrolide efflux, whereas the remaining three contained the *erm(B)* gene, encoding ribosomal methylation leading to the constitutive macrolide-lincosamide-streptogramin B (cMLS_B) phenotype (15). There is currently no evidence for inducible MLS_B among NVS, likely due to the lack of reliable, standardized testing methods for the phenotype in these fastidious organisms. As with the beta-lactams, there was no significant change over time in erythromycin or clindamycin susceptibility among *G. adiacens* isolates ($P = 0.266$ and $P = 0.711$, respectively) or *A. defectiva* isolates ($P = 0.174$ and $P = 0.803$, respectively). Levofloxacin showed very good activity across all three species with $>90\%$ susceptibility, although roughly 8% of *G. adiacens* isolates tested resistant, similar to what was seen in recent studies (25, 26). All isolates were susceptible to vancomycin, also similar to what was seen in other studies (15–18, 25, 26).

We examined MIC distributions for several antibiotics that do not have CLSI inter-

TABLE 3 Clindamycin interpretations among erythromycin-resistant NVS

Clindamycin interpretive categories	% (no.) of NVS species:		
	<i>G. adiacens</i> (n = 228)	<i>G. elegans</i> (n = 9)	<i>A. defectiva</i> (n = 84)
Susceptible	63.2 (144) ^a	88.9 (8)	90.5 (76)
Intermediate	3.5 (8)		7.1 (6)
Resistant	33.3 (76) ^a	11.1 (1)	2.4 (2)

^aP < 0.0001 for differences with *A. defectiva*.

pretive breakpoints (Table 1) and found similar MIC₅₀ and MIC₉₀ values for linezolid, gentamicin, and rifampin across the three species. *A. defectiva* showed substantially lower MIC₉₀ values for trimethoprim-sulfamethoxazole (TMP-SMX) and doxycycline than either *Granulicatella* species. We did not find any gentamicin MIC₉₀ greater than 4 in our study. Daptomycin MIC_{50/90} values were similar to those seen by Alberti et al. and Mushtaq et al., with *G. adiacens* and *A. defectiva* showing MIC₉₀s of 4 µg/ml or greater when sufficiently high concentrations were tested (25, 26), whereas *G. elegans* tended to have slightly lower daptomycin MICs (Table 1).

Among this large, well-defined collection of NVS isolates, there were significant differences in susceptibility profiles across species, particularly for penicillin and ceftriaxone. This demonstrates that identification to the species level and routine susceptibility testing may help in narrowing and improving empirical therapy of NVS infections. The high penicillin MIC phenotype was significantly more common in *A. defectiva* across all U.S. Census regions but was also substantial among *G. adiacens* isolates. Because only 14% of *A. defectiva* and 39% of *G. adiacens* isolates have penicillin MICs of ≤0.12 and these two species account for approximately 97% of all NVS isolates, these data suggest that the empirical addition of gentamicin (until penicillin MICs are determined) may be reasonable if penicillin was considered for the treatment of endocarditis. Unfortunately, there is no consensus on treatment of nonendocarditis NVS infections. By expanding our understanding of the activity of a broad selection of drugs against a large collection of isolates, these data may contribute to improved treatment of NVS infections.

MATERIALS AND METHODS

AST was performed on 879 NVS isolates received from across the United States between September 2006 and August 2015. Data from the 599 nonredundant isolates that were identified to the species level as *A. defectiva*, *G. adiacens*, and *G. elegans* were included for analysis. Isolates of the same species from different body sites or those collected from the same site but ≥45 days from the 1st collection date were included. Only the first result from duplicate submissions on the same patient or the first of multiple morphotypes in a culture was included. Identification was performed at ARUP Laboratories by 16S rRNA gene sequencing or matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS; Bruker Biotyper, Billerica, MA) or prior to submission for AST by client laboratories. The identification of 20 client-identified isolates was confirmed at ARUP, and MIC distributions for all isolates identified by clients were analyzed by Fisher's exact and Welch's *t* tests and were found to be substantially equivalent to those from isolates identified by ARUP. Antimicrobial susceptibility testing was performed using custom-made broth microdilution panels (Trek, Oakwood Village, OH) in cation-adjusted Mueller-Hinton broth supplemented with 5% lysed horse blood and 0.001% pyridoxal HCl (Sigma-Aldrich, St. Louis, MO) according to CLSI M45 guidelines for fastidious organisms (14, 23). Daptomycin wells were supplemented with calcium to a final concentration of 50 µg/ml. MIC values and susceptibility interpretations were determined for penicillin, ceftriaxone, vancomycin, clindamycin, erythromycin, levofloxacin, and meropenem according to CLSI M45 (23), and MICs alone were determined for daptomycin, linezolid, gentamicin, TMP-SMX, doxycycline, and rifampin. Quality control (QC) was performed in accordance with CLSI guidelines using *Streptococcus pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212 (23, 27), and results were reported only if QC values were in range. MIC_{50/90} values were calculated using WHONET software (v. 5.6; World Health Organization [WHO] Collaborating Centre for Surveillance of Antimicrobial Resistance [<http://www.who-net.org/software.html>]). Statistical analyses were performed using Fisher's exact test to compare differences in susceptibility prevalence across species, among antimicrobial agents, and across geographic regions. The Mann-Kendall test was used to analyze trends for *G. adiacens* and *A. defectiva* over the eight full calendar years in the study (2007 to 2014) in susceptibility to penicillin, ceftriaxone, meropenem, clindamycin, erythromycin, and levofloxacin.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/JCM.02054-16>.

TEXT S1, PDF file, 0.3 MB.

TEXT S2, PDF file, 0.2 MB.

ACKNOWLEDGMENTS

We thank Promporn Suksaranjit, Elisabeth Malmberg, Melody Ollerton, and Andy Wilson for assistance with statistical analyses and David Davis for generating custom reports to aggregate the susceptibility data.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

M.A.F. has received research funding for unrelated projects from Thermo-Fisher.

REFERENCES

- Frenkel A, Hirsch W. 1961. Spontaneous development of L forms of streptococci requiring secretions of other bacteria or sulphhydryl compounds for normal growth. *Nature* 191:728–730. <https://doi.org/10.1038/191728a0>.
- George RH. 1974. The isolation of symbiotic streptococci. *J Med Microbiol* 7:77–83. <https://doi.org/10.1099/00222615-7-1-77>.
- Collins MD, Lawson PA. 2000. The genus *Abitrophia* (Kawamura et al.) is not monophyletic: proposal of *Granulicatella* gen. nov., *Granulicatella adiacens* comb. nov., *Granulicatella elegans* comb. nov. and *Granulicatella balaenopterae* comb. nov. *Int J Syst Evol Microbiol* 50(Part 1): 365–369. <https://doi.org/10.1099/00207713-50-1-365>.
- Kanamoto T, Sato S, Inoue M. 2000. Genetic heterogeneities and phenotypic characteristics of strains of the genus *Abitrophia* and proposal of *Abitrophia para-adiacens* sp. nov. *J Clin Microbiol* 38:492–498.
- Christensen JJ, Facklam RR. 2001. *Granulicatella* and *Abitrophia* species from human clinical specimens. *J Clin Microbiol* 39:3520–3523. <https://doi.org/10.1128/JCM.39.10.3520-3523.2001>.
- Biermann C, Fries G, Jehnichen P, Bhakdi S, Husmann M. 1999. Isolation of *Abitrophia adiacens* from a brain abscess which developed in a patient after neurosurgery. *J Clin Microbiol* 37:769–771.
- Ince A, Tiemer M, Gille J, Boos C, Russlies M. 2002. Total knee arthroplasty infection due to *Abitrophia defectiva*. *J Med Microbiol* 51:899–902. <https://doi.org/10.1099/0022-1317-51-10-899>.
- Riede U, Graber P, Ochsner PE. 2004. *Granulicatella* (*Abitrophia*) *adiacens* infection associated with a total knee arthroplasty. *Scand J Infect Dis* 36:761–764. <https://doi.org/10.1080/00365540410021009a>.
- Hepburn MJ, Fraser SL, Rennie TA, Singleton CM, Delgado B, Jr. 2003. Septic arthritis caused by *Granulicatella adiacens*: diagnosis by inoculation of synovial fluid into blood culture bottles. *Rheumatol Int* 23: 255–257. <https://doi.org/10.1007/s00296-003-0305-4>.
- Carey RB, Gross KC, Roberts RB. 1975. Vitamin B6-dependent *Streptococcus mitior* (*mitis*) isolated from patients with systemic infections. *J Infect Dis* 131:722–726. <https://doi.org/10.1093/infdis/131.6.722>.
- Stein DS, Nelson KE. 1987. Endocarditis due to nutritionally deficient streptococci: therapeutic dilemma. *Rev Infect Dis* 9:908–916. <https://doi.org/10.1093/clinids/9.5.908>.
- Adam EL, Siciliano RF, Gualandro DM, Calderaro D, Issa VS, Rossi F, Caramelli B, Mansur AJ, Strabelli TM. 2015. Case series of infective endocarditis caused by *Granulicatella* species. *Int J Infect Dis* 31:56–58. <https://doi.org/10.1016/j.ijid.2014.10.023>.
- Baddour LM, Wilson WR, Bayer AS, Fowler VG, Jr, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O’Gara P, Taubert KA, American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. 2015. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation* 132:1435–1486. <https://doi.org/10.1161/CIR.0000000000000296>.
- Clinical and Laboratory Standards Institute. 2006. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria; approved guideline M45-A. Clinical and Laboratory Standards Institute, Wayne, PA.
- Zheng X, Freeman AF, Villafranca Shortridge D, Beyer J, Kabat W, Dembkowski K, Shulman ST. 2004. Antimicrobial susceptibilities of invasive pediatric *Abitrophia* and *Granulicatella* isolates. *J Clin Microbiol* 42: 4323–4326. <https://doi.org/10.1128/JCM.42.9.4323-4326.2004>.
- Tuohy MJ, Procop GW, Washington JA. 2000. Antimicrobial susceptibility of *Abitrophia adiacens* and *Abitrophia defectiva*. *Diagn Microbiol Infect Dis* 38:189–191. [https://doi.org/10.1016/S0732-8893\(00\)00194-2](https://doi.org/10.1016/S0732-8893(00)00194-2).
- Liao CH, Teng LJ, Hsueh PR, Chen YC, Huang LM, Chang SC, Ho SW. 2004. Nutritionally variant streptococcal infections at a university hospital in Taiwan: disease emergence and high prevalence of beta-lactam and macrolide resistance. *Clin Infect Dis* 38:452–455. <https://doi.org/10.1086/381098>.
- Murray CK, Walter EA, Crawford S, McElmeel ML, Jorgensen JH. 2001. *Abitrophia* bacteremia in a patient with neutropenic fever and antimicrobial susceptibility testing of *Abitrophia* isolates. *Clin Infect Dis* 32(10):E140–E142. <https://doi.org/10.1086/320150>.
- Giuliano S, Caccese R, Carfagna P, Vena A, Falcone M, Venditti M. 2012. Endocarditis caused by nutritionally variant streptococci: a case report and literature review. *Infez Med* 20:67–74.
- Ruoff KL. 1991. Nutritionally variant streptococci. *Clin Microbiol Rev* 4:184–190. <https://doi.org/10.1128/CMR.4.2.184>.
- Cooksey RC, Swenson JM. 1979. In vitro antimicrobial inhibition patterns of nutritionally variant streptococci. *Antimicrob Agents Chemother* 16: 514–518. <https://doi.org/10.1128/AAC.16.4.514>.
- Clinical and Laboratory Standards Institute. 2010. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria—2nd ed; approved guideline M45-A2. Clinical and Laboratory Standards Institute, Wayne, PA.
- Clinical and Laboratory Standards Institute. 2015. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria—3rd ed; approved guideline M45, 3rd ed. Clinical and Laboratory Standards Institute, Wayne, PA.
- Jorgensen JH, Hindler JF. 2007. New consensus guidelines from the Clinical and Laboratory Standards Institute for antimicrobial susceptibility testing of infrequently isolated or fastidious bacteria. *Clin Infect Dis* 44:280–286. <https://doi.org/10.1086/510431>.
- Alberti MO, Hindler JA, Humphries RM. 2015. Antimicrobial susceptibilities of *Abitrophia defectiva*, *Granulicatella adiacens*, and *Granulicatella elegans*. *Antimicrob Agents Chemother* 60:1411–1420. <https://doi.org/10.1128/AAC.02645-15>.
- Mushtaq A, Greenwood-Quaintance KE, Cole NC, Kohner PC, Ihde SM, Strand GJ, Harper LW, Virk A, Patel R. 2016. Differential antimicrobial susceptibilities of *Granulicatella adiacens* and *Abitrophia defectiva*. *Antimicrob Agents Chemother* 60:5036–5039. <https://doi.org/10.1128/AAC.00485-16>.
- Clinical and Laboratory Standards Institute. 2016. Performance standards for antimicrobial susceptibility testing; approved guideline M100S, 26th ed. Clinical and Laboratory Standards Institute, Wayne, PA.