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RESEARCH ARTICLE

Abiotrophia and *Granulicatella* Infections in Cancer Patients: A Single-Center Chart Review Study

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ABSTRACT

Objectives: Nutritionally Variant Streptococci (NVS) comprise two primary genera that have been identified from human specimens, particularly the *Abiotrophia* and *Granulicatella* species. These infections are often complicated to manage due to the difficulty identifying these organisms, indolent course of disease, and variable resistance to common antimicrobial agents. The wide breadth of disease presentations involving these organisms has not been fully elucidated, particularly in the immunosuppressed cancer patient population.

Method: We performed a retrospective chart review on 28 patients from an academic cancer center with positive NVS cultures, from January 2012 to July 2018. We reviewed patient characteristics, culture data, immunodeficiency status, response to antibiotic therapy, and outcomes of infection.

Results: Of twenty-eight patients, fifteen patients developed bacteremia from either *Abiotrophia* or *Granulicatella* species, while thirteen patients had positive wound or body fluid cultures. Most patients with bacteremia had underlying hematologic malignancies and neutropenia. Patients with positive wound or body fluid cultures had an invasive procedure at the related site. Intravenous (IV) vancomycin was the most common agent used, and all but two patients were treated with multiple antibiotic regimens.

Conclusions: Infections with NVS have been reported with a variety of clinically infectious presentations and should be considered in cancer patients with neutropenia or in patients who have undergone invasive procedures. Bacteremia was the most common complication, especially in the setting of hematologic malignancy and neutropenia. Focal body site infection was also a common complication related to invasive procedures in immunocompetent patients. Overall mortality was low and related to complications of septic shock. *J Microbiol Infect Dis 2020; 10(2):89-97.*

Keywords: *Abiotrophia, Granulicatella, bacteremia, cancer, neutropenic infection*

INTRODUCTION

Nutritionally Variant Streptococci (NVS) was first described by Frenkel and Hirsch in 1961 as a New Viridans Group Streptococci (VGS) that form satellite colonies around other bacteria [1]. These bacteria depend on other bacteria or enriched media as they do not synthesize pyridoxine, L-cysteine, or other essential nutrients required for growth. Like other VGS, *Abiotrophia* and *Granulicatella* species are part of the normal flora of the oral cavity, urogenital,

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and intestinal tracts [2]. These species are implicated in a variety of clinical infections, the most common being bacteremia and infective endocarditis [3]. Despite being rare, *Abiotrophia* infective endocarditis is associated with increased mortality and serious complications such as rapid valve destruction, heart failure, and embolic events [4,5]. Isolated cases of central nervous system infections [6] and septic arthritis [7] have also been reported. These organisms can cause severe infections in both immunocompetent and immunosuppressed hosts [5,8].

Identifying *Abiotrophia* and *Granulicatella* have been challenging in the past due to their fastidious nature [1,2]. However, with improvement of culture media, these organisms can now be detected in routine blood cultures in 2-3 days. However, there are still challenges to accurately speciating *Abiotrophia* and *Granulicatella* species [9]. In addition, the clinical course can be unfavorable despite the administration of the recommended antibiotic regimens [10]. We aimed to identify and analyze all cases of *Abiotrophia* and *Granulicatella* infections at an academic cancer center from January 2012 to July 2018 to better characterize the presentation and susceptibility of *Abiotrophia* and *Granulicatella* in patients with underlying malignancy.

METHODS

We retrospectively reviewed all cases of positive *Abiotrophia* or *Granulicatella* cultures occurring from January 2012 to July 2018 at H. Lee Moffitt Cancer Center and Research Institute. The computerized epidemiology report provided by the microbiology laboratory identified 28 patients with positive *Abiotrophia* or *Granulicatella* cultures. Positive isolates were identified by the presence of a satellite using the Pyridoxal Disk. Further speciation to distinguish *Granulicatella* and *Abiotrophia* species was done using the VITEK 2 system upon request by physician. Susceptibility testing was done upon request through ARUP Laboratory in Salt Lake City, Utah.

Variables observed included patient demographics such as age and sex, clinical symptoms, underlying malignancy, immune status, culture, immunosuppressant medications, treatment of infection, and outcome of infection. Data was recorded from the Infectious Disease consultation reports, discharge summaries, lab results, cultures, and medication profiles using Power Chart/Cerner at Moffitt Cancer Center. Resolution of the infection was defined as repeated negative blood cultures and clinical resolution of signs and symptoms of infected sites. Quantitative description was used for summarizing the data. Microsoft Excel (California, USA) was used to summarize data in mean (± standard deviation) or number (percentage). A table containing these data was made and analyzed for any trends or details.

Informed consent was not necessary due to the retrospective nature of this work and de-identification of data collected from chart review. The methods of this study were approved by the University of South Florida Institutional Review Board (Approval #Pro00034405). The study has been performed in accordance with the 1964 Declaration of Helsinki and its lateral amendments.

RESULTS

Overall Characteristics

There were 28 patients with cultures positive for *Abiotrophia* or *Granulicatella* species during the study period. The mean age of patients affected was 63.7 years, of which 15 (54%) were male, and 13 (46%) were female. Hematologic cancers, particularly AML, were the most common underlying malignancy. Colon cancer was the most common solid tumor malignancy. More details of the underlying malignancies are listed in Table 1. There were fifteen positive blood cultures and thirteen positive wound or other body fluid cultures as shown in Figure 1.

Characteristics and Treatment of Bacteremia

The clinical presentation and treatments used in patients with bacteremia are shown in Table 2. Fever was the most common clinical presentation, followed by gastrointestinal symptoms (abdominal pain) and mucositis. Most patients with bacteremia had an underlying hematologic malignancy (87%) and most were

neutropenic (73%). The average duration of neutropenia at the time of positive culture was 14.3 days (neutropenia was defined as ANC <500 cell/mm3). Twelve patients were on corticosteroids, chemotherapy agents, or other medications that may have contributed to their immunocompromised state which are further detailed in Table 2. The most common agents for empiric antibiotic therapy prior to culture results were ciprofloxacin, cefepime, and piperacillin-tazobactam. All patients with bacteremia were ultimately treated with multiple antibiotic regimens (average 3.2), with most common being vancomycin IV (average duration 6.8 days) and cefepime IV (average duration of 4.2 days.). Thirteen patients with bacteremia survived (87%), and the resolution of infection was confirmed by repeat negative blood cultures and clinical resolution of signs and symptoms. Two patients with bacteremia expired due to complications related to septic shock.

Characteristics and Treatment of Focal Body Site Infections

The clinical presentation and treatments used in patients with wound or body fluid positive cultures are shown in Table 3. Most wound/body fluid positive cultures (85%) were related to a procedure site or recent surgical site, and cultures were ordered due to nonspecific symptoms of infected wound, including fever and redness or drainage from wound site. Two patients had no significant symptoms and had cultures collected during an operation. The most common prophylactic or prior empiric antibiotic therapy agents were cefepime, ceftriaxone, or cefoxitin. Eleven patients were treated with multiple antibiotic regimens (average 2.3), with the most common being cefepime IV (average duration 12.8 days), ciprofloxacin PO (average duration 7 days), or vancomycin IV (average duration 5 days). Twelve patients survived with resolution of infection, while one patient with positive G. elegans urine culture expired due to complications related to septic shock.

Susceptibility

Susceptibility report showed that NVS species were most susceptible to vancomycin and meropenem, with variable susceptibility to penicillin G, ceftriaxone, cefepime, levofloxacin, and ceftazidime. There was resistance to clindamycin and erythromycin, as further detailed in Table 4.

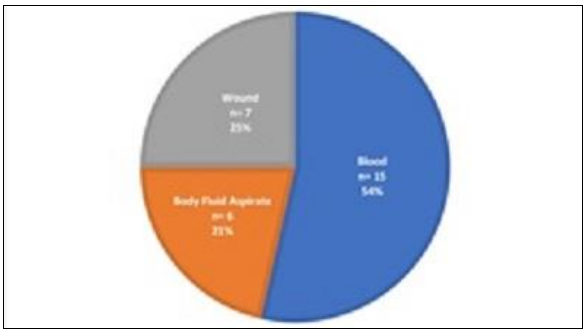

Figure 1. The Sources of isolated bacteria.

Table 1. Underlying malignancy of the cases.

Primary Diagnosis	No. Cases (%)
Hematologic	14 (50%)
AML	11 (39%)
ALL	2 (7%)
MDS	1 (3.5%)
Adenocarcinoma of esophagus	1 (3.5%)
Breast cancer	1 (3.5%)
Cholangiocarcinoma	1 (3.5%)
Colon Cancer	3 (11%)
GIST[4]	1 (3.5%)
Lipoma	1 (3.5%)
Melanoma	1 (3.5%)
Osteosarcoma	1 (3.5%)
Renal cell carcinoma	2 (7%)
Squamous cell carcinoma of RLL	1 (3.5%)
Urothelial carcinoma	1 (3.5%)

AML: Acute Myeloid Leukemia
ALL: Acute Lymphoblastic Leukemia
MDS: Myelodysplastic Syndrome
GIST: Gastrointestinal Stromal Tumor

Table 2. Characteristics of the patients diagnosed with bacteremia.

Case	Underlying Malignancy	Underlying Cardiac Conditions	Chemotherapy/ immunosuppressive therapy	Days of Neutropenia (ANC < 500 cells/mm3)	Presentation/ Clinical Symptoms	Treatment	Isolation	Outcome
1	AML	none	CYT, idarubicin, etoposide/DXM	5	F, pain and swelling to tooth extraction site	CFX IV[8] 7 d, VA IV n/a, PTZ IV n/a	*NVS*[6]	SR
2	APML	none	Idarubicin	15	F, mucositis	VA IV n/a, CEP IV n/a	*NVS*	SR
3	Colon cancer	none	Fluorouracil	1	F, abdominal pain, jaundice	CFX IV 2d, MER IV 5 d ERT IV 15 d	*NVS*	SR
4	ALL	none	Fludarabine, Busulfan Etoposide, Methotrexate/ DXM	21	F, nausea and vomiting, mucositis, diarrhea	VA IV 14 d, CFX IV 2 d LEV PO[9] 7d	*NVS*	SR
5	AML	Atrial fibrillation	None	14	F, mucositis, hypotension, altered mental status	CEP IV 4 d, VA IV 11 d	*NVS*	EX
6	AML	none	Idarubicin, CYT/ MP	n/a[10]	F, mucositis, rash, respiratory distress	VA IV 5 d, CEP IV 5 d	*NVS*	SR
7	Renal mass	Chronic heart failure	None	0	F	VA IV 9 d, AMC PO 5 d CEP PO 5d	*G. adiacens*	SR
8	AML	Heart murmur	Idarubicin, CYT Cladribine/ MP, DXM	7	GI bleed, productive cough	LEV PO 2d, MER IV 6d VA IV 2d	*G. adiacens*	SR
9	AML	none	Idarubicin, CYT hydrocortisone	3	F, fatigue, hematuria	CLN IV 8d, VA 10d IV	*G. adiacens*	SR
10	AML	none	CYT	14	F, cellulitis (wrist), abdominal pain, chest pain	VA IV 14 d, CEP IV 2 d PTZ IV 9d	*G. adiacens*	SR
11	APML	none	CYT, idarubicin	15	F, respiratory failure, rash, weight loss, gingivitis/poor dentition	VA IV 14 d, CIP PO 2 d CEF IV 8 d, CEP IV 4 d	*G. adiacens*	SR
12	ALL	none	Vincristine, cyclophosphamide Dasatinib, doxorubicin/ DXM	21	F, chest pain, abdominal pain, night sweats	VA IV 12 d , CEP IV 2 d MER IV 4 d	*G. adiacens*	SR
13	AML	none	CYT, idarubicin, etoposide/ DXM	0	F	VA IV n/a, DOX intrapleural	*G. adiacens*	SR
14	AML	none	Sirolimus, tacrolimus MP, prednisone	0	F, rash (SJS/TEN[5])	VA IV 15 d, CEP IV 4 d	*G. adiacens*	SR
15	MDS	none	Melphalan, cetuximab, fluorouracil, irinotecan/ sirolimus, DXM, MP	31	F, respiratory failure, hypotension	VA IV 1 d, CEP IV 3 d DOX PO 14 d	*G. adiacens*	EX

AML: Acute Myeloid Leukemia, APML: Acute Promyelocytic Leukemia, ALL: Acute Lymphoblastic Leukemia, MDS: Myelodysplastic Syndrome, SJS/TEN: Stevens-Johnson/toxic epidermal necrolysis, NVS: Nutritionally Variant Streptococci, *G. adiacens*: *Granulicatella adiacens,* IV: Intravenous, PO: by mouth, MP: methylprednisolone, DXM: dexamethasone, CYT: Cytarabine, F: Fever, CFX: Ceftriaxone, VA: Vancomycin, PTZ: Piperacillin-Tazobactam, CEP: Cefepime, MER: Meropenem, ERT: Ertapenem, AMC: Amoxicillin-clavulanate, DOX: Doxycycline, LEV: Levofloxin, CIP: Ciprofloxacin, CEF: Ceftazidim, CEP: Cephalexin, CLN: Clindamycin, SR: Survived, EX: Deceased, n/a: data not available,

Table 3. Characteristics of the patients with wound or body fluid aspirate positive cultures

Case	Underlying Malignancy	Prior Procedures	Presentation/ Clinical Symptoms	Treatment	Source	Isolation	Outcome
1	Cholangiocarcinoma	biliary stent exchange	decreased bilirubin	CFX IV4 2 PTZ IV 1 d	body fluid aspirate (bile)	G. adiacens	SR
2	Colon cancer	hemicolectomy	fever, chills, abscess (abdominal wall)	VA IV 4 d, CFX IV 5 d, AMC PO 9 d	body fluid aspirate (Abdominal abscess)	*NVS*[2]	SR
3	Adenocarcinoma (esophagus)	Ivor Lewis esophagectomy	respiratory failure	CEP IV 3 d, PTZ IV 11 d, LVQ PO 7 d	body fluid aspirate (pleural)	*NVS*	SR
4	Melanoma (metastatic to lung)	thoracotomy	Air leak from thoracotomy chest tube	VA IV 12 d CFD PO 5 d CIP PO 5 d	body fluid aspirate (pleural)	*NVS*	SR
5	Melanoma (left thigh)	biopsy (left thigh lesion)	cellulitis (left groin)	SFT PO 7 d catheter exchange	body fluid aspirate (thigh seroma)	*NVS*	SR
6	Urothelial carcinoma, Colon cancer	none	lethargy, altered mental status, nausea, vomiting, abdominal pain	CEP IV 3 d CFX IV 2 d PTZ IV n/a AMC PO 14 d	Urine	*G. elegans*	EX
7	Colon cancer	colectomy (right)	pus from Wound site	SFT PO 14 d, CIP IV 5 d	Wound (abdominal)	*NVS*	SR
8	Breast cancer	breast implant	fever, cellulitis (left breast)	VA IV 2 d, PTZ IV 4 d, LEV PO 10 d CIP PO 15 d	Wound (left breast capsule)	*G. adiacens*	SR
9	Lipoma (left thigh)	left thigh drain placement	fever, decreased drain output, swelling, redness	CIP PO n/a	Wound (left thigh)	*G. adiacens*	SR
10	Acute myeloid leukemia	none	fever, diarrhea, molar cavity	CHL mouth wash CEP IV 35 d, CLN IV 28 days, MER IV 6 d, CFD PO 15 d	Wound (molar)	*A. defectivus*	SR
11	Osteosarcoma (left thigh)	distal femoral replacement (left)	hematoma and quadriceps tear	VA IV 2 d, CEP IV 12 d, DAP IV 1 d, Wound irrigation debridement	Wound (knee swab)	*G. adiacens*	SR
12	Gastrointestinal stromal tumor	flexible sigmoidoscopy	GI bleed (melena)	None	Wound (pelvis swab)	*G. adiacens*	SR
13	Squamous cell carcinoma (right lower lobe lung)	none	secondary empyema of right lung w/ abscess fever, diarrhea	CEP IV 11 d TOB inhaled 13 d CIP IV 3 d LN IV n/a	Wound (pleural fluid)	*NVS*	SR

G. adiacens: *Granulicatella adiacens,* NVS: Nutritionally Variant Streptococci, *G.elegans*: *Granulicatella elegans, A. defectiva*: *Abiotrophia defective,* IV: Intravenous, PO: by mouth, CFX: Ceftriaxone, VA: Vancomycin, CEP: Cefepime, MER: Meropenem, PTZ: Piperacillin-Tazobactam, AMC: Amoxicillin-clavulanate, SFT: sulfamethoxazole-trimethoprim, DOX: Doxycycline, LEV: Levofloxacin, CIP: Ciprofloxacin, LN: Linezolid, CEF: Ceftazidim, CEP: Cephalexin, CLN: Clindamycin, LVQ: Levaquin, TOB: Tobramycin, CFD: Cefdinir, CIP: Ciprofloxacin, DAP: Daptomycin, CHL: Chlorhexidine, SR: Survived

Table 4. Most Common Antibiotic Regimen Used and Susceptibility Report.

Antibiotic Treatment, n (%)	Route, Duration	Susceptibility Report*	Susceptible, n	Susceptible, n	Resistant, n
VA, 18 (64)	IV, 7.6 days	VA	6		
CEP, 13, (46)	IV, 6.8 days	MER, PEN G	6	1	
PTZ, 6, (28)	IV, 4.2 days	CEP	4	2	
CFX, 4 (14)	IV, 4 days	CFX	3	1	
		LEV	1		1
		CEF		1	
		CLN			1
LEV 3, (11)	PO^2, 9.3 days	ERT			1

IV: Intravenous PO: by mouth, VA:Vancomycin, MER: Meropenem, PTZ: Piperacillin-Tazobactam, PEN G: Penicillin G, CFX: Ceftriaxone, CEP: Cefepime, LEV: Levofloxacin, CEF: Ceftazidime, CLN: Clindamycin, ERT: Erythromycin

DISCUSSION

We collected the data of patients with positive *Abiotrophia* and *Granulicatella* cultures spanning a six-year period (Jan 2012-July 2018). Most *Granulicatella* and *Abiotrophia* infections present as bacteremia, which was consistent with our findings [3, 5]. G. elegans has the lowest incidence in human specimens, as reflected in this study; their low infectivity is presumed to be due to its low frequency of colonization and low binding capacity [12-14].

Low granulocyte and neutrophil count, mucosal damage, and invasive procedures or foreign body material may increase the risk of infectious complications. Chemotherapy associated mucositis and neutropenia have been identified as risk factors for *Granulicatella* infections [8, 15-16]. Most patients with bacteremia had an underlying hematologic malignancy (87%), and most of these patients were neutropenic for a significant amount of time (average 14.3 days). All but two patients with bacteremia were on cytotoxic chemotherapy agents or immunosuppressive agents as further listed in Table 2. Immune defects due to hematologic malignancies combined with immunosuppression from chemotherapy may put patients at increased risk for infectious complications. In addition, chemotherapy agents may induce mucositis or disrupt the integrity of mucosal lining, which may play a role in endogenous flora, such as NVS species, seeding into bloodstream [16].

Both A. defectiva and G. adiacens have shown high capacity to bind fibronectin and extracellular matrix proteins, which may contribute to their infectivity, especially in association with foreign body material [11]. These species have been reported in breast implants and hip arthroplasty [17,18]. The incidence of these species in association with foreign body material may rise due to the diagnostic improvements in molecular medicine and increasing use of foreign body material [17-19]. Almost all patients in this study with wound or body fluid positive cultures had infections that were related to a site of a recent procedure or surgery. These findings suggest invasive procedures may predispose to *Abiotrophia* or *Granulicatella* infections in wound or body fluids, even in the absence of neutropenia or immunocompromised state. Symptoms for foreign body infections with these species are noted to present years later after implantation [17-19]. In contrast, patients in our study presented with symptoms within a much shorter period, an average of four months post-procedure. Regarding wound infections, appropriate use of antibiotics and removing any foreign body is reported to result in good clinical outcomes [17-19]. In our study, patients with infections related to foreign bodies recovered without recurrent infection after treatment with appropriate antibiotics and/or debridement of infected tissue and removal of the prosthesis.

Current guidelines do not reflect the susceptibility profiles of *Abiotrophia* and

Granulicatella spp. For instance, the recommendations by the American Heart Association 2015 are that infective endocarditis caused by *Granulicatella* spp. be treated with a combination regimen of ampicillin or penicillin plus gentamicin [20]. However, according to Prasidthrathsint K. et al, clinical isolates of A. defectiva and G. adiacens have shown variable susceptibility to penicillin. A. defectiva was most susceptible to vancomycin, levofloxacin, ceftriaxone, clindamycin, and meropenem in vitro. G. adiacens showed similar susceptibility to vancomycin, levofloxacin, meropenem, but lower susceptibility to clindamycin and ceftriaxone [21]. These differences in susceptibility profiles may explain why positive cultures persisted in some patients despite prophylactic or prior empiric antibiotic therapy. The susceptibility reports in our study showed that vancomycin and piperacillin-tazobactam are useful agents for G. adiacens. However, unlike susceptibility profiles reported in the literature, G. adiacens showed resistance to agents such as meropenem, ceftriaxone, and levofloxacin. The susceptibility report for A. defectiva was limited as there was only data available for one patient. Our findings demonstrate how these organisms can show variable susceptibility to broad-spectrum agents that are reported to be effective in the literature.

Twenty five (89%) patients survived with no recurrent infections. Vancomycin IV was the most common treatment for these infections in our study, and most patients received multiple antimicrobial agents. Despite *Granulicatella* and *Abiotrophia* being sources of infective endocarditis reported in literature, we found no cases of endocarditis in this study, which may be related to the finding that only two patients had underlying heart conditions, neither of which had bacteremia. In addition, most patients (75%) had prophylactic or prior empiric therapy prior or at the onset of symptoms, which may have precluded more serious infections. While no patients in this study needed central venous catheter removal, there is an increasing body of evidence that suggests that many gram-positive bacterial catheter infections can be successfully treated with the use of antimicrobial agents without catheter removal [22].

While *Abiotrophia* and *Granulicatella* isolates showed susceptibility to vancomycin in vitro, there are reports in literature where treatment failure was still observed [10]. The use of multiple antibiotic therapy in our study may have had a synergistic effect in preventing serious complications while effectively resolving *Abiotrophia* and *Granulicatella* infections. Three patients expired due to sepsis related complications. The single case of G. elegans was unsuccessfully treated with cefepime, ceftriaxone, and piperacillin-tazobactam, and susceptibility data was not available. However, these adverse outcomes cannot be attributed solely to treatment failure of *Abiotrophia* and *Granulicatella*, as these patients had polymicrobial infections.

Accurately identifying these species is important, especially in negative cultures. Phenotyping characterization is considered difficult due to the fastidious nature of these species, and conventional biochemical testing may lead to misidentification [2, 23].The presence of satellitism may be inconsistent, depending on the nutrients in the agar used, which can vary by manufacturer [9]. Although it is generally accepted that all three species grow well on chocolate agar or pyridoxal supplemented agar, there have been cases of G. elegans isolates only being supported by cysteine, and not pyridoxal or chocolate agar [14, 19]. In a study comparing identification of various *Abiotrophia* and *Granulicatella* species using Vitek MS, Bruker MS, and Vitek 2, Vitek MS was the most superior, while the Vitek 2 system showed limitations to correct identification [24]. Especially with negative cultures, 16S rRNA sequencing was recommended for identification [23,24]. Even with improvements in culture media and speciation technology, there are still nuances and challenges to correctly identifying *Abiotrophia* and *Granulicatella* spp. which laboratories need to be aware.

Limitations of Study

Our study has several limitations. First, its retrospective design limited the available data on each patient. Second, we did not have adequate data to further analyze the differences between each species, as further speciation data was done only for patients with more severe clinical presentation or this information was not available in the patients' records. We were thus unable to further analyze an optimal

treatment regimen for each species, as susceptibility reports and speciation data were limited. Finally, the use of Vitek 2 to further speciate NVS in this study may have contributed inaccuracies and limitations of this study despite resolution of infections in most patients. Using 16S rRNA sequencing in the future may improve the accuracy of identifying the different species.

Conclusion

The difficulty of isolation, the potential misidentification, and serious pathogenicity associated with *Granulicatella* and *Abiotrophia* infections highlight how important it is for clinicians and laboratories to be aware of these infections. With the improvement of molecular diagnostics and identification, we can expect the incidence of *Granulicatella* and *Abiotrophia* infections to grow. Improved guidelines on antimicrobial therapy and continued surveillance are still needed for more effective treatment. While IV vancomycin has been shown in literature and our study to be the most effective agent, using multiple antibiotic regimens may have a synergistic effect that can more effectively resolve *Abiotrophia* and *Granulicatella* infections, especially if recommended guidelines do not lead to favorable outcomes. Clinicians need to be aware of the pathogenicity and presentation of these infections, especially in neutropenic patients or patients who have undergone recent procedures. This may be especially relevant in cancer patients, who may be more prone to immunosuppression and neutropenia with anti-cancer therapies, or invasive procedures related to solid tumor removal.

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