Mediterranean Journal of Hematology and Infectious Diseases

Original Article

Nutritionally Variant Streptococci Bacteremia in Cancer Patients: A Retrospective Study, 1999-2014

Abraham T. Yacoub[1], Jayasree Krishnan[1], Ileana M. Acevedo[2], Joseph Halliday[2] and John N. Greene[1]

[1] H. Lee Moffitt Cancer Center and Research Institute. 12902 Magnolia Drive. Tampa, Florida 33612-9497.
[2] University of South Florida, Morsani College of Medicine, Division of Infectious Disease and International Medicine, 1 Tampa General Circle, G323.

Competing interests: The authors have declared that no competing interests exist.

Abstract. ***Background.*** ***Nutritionally variant Streptococci (NVS), Abiotrophia* and *Granulicatella* are implicated in causing endocarditis and blood stream infections more frequently than other sites of infection. Neutropenia and mucositis are the most common predisposing factors for infection with other pathogens in cancer patients. In this study, we investigated the clinical characteristics of NVS bacteremia in cancer patients and identified risk factors and outcomes associated with these infections.**

Materials and Methods. **We retrospectively reviewed all cases of NVS bacteremia occurring from June 1999 to April 2014 at H. Lee Moffitt Cancer Center and Research Institute. The computerized epidemiology report provided by the microbiology laboratory identified thirteen cancer patients with NVS bacteremia. We collected data regarding baseline demographics and clinical characteristics such as age, sex, underlying malignancy, neutropenic status, duration of neutropenia, treatment, and outcome.**

Results. **Thirteen patients were identified with positive NVS blood stream infection. Ten patients (77%) had hematologic malignancies, including chronic lymphocytic leukemia (CLL)(1), multiple myeloma (MM)(1), acute myelogenous leukemia (AML)(4), and non-Hodgkin's lymphoma (NHL)(4). The non-hematologic malignancies included esophageal cancer(2) and bladder cancer (1).**

Conclusion. **NVS should be considered as a possible agent of bacteremia in cancer patients with neutropenia and a breach in oral, gastrointestinal and genitourinary mucosa (gingivitis/mucositis).**

Citation: Yacoub A.T., Krishnan J., Acevedo I.M., Halliday J., Greene J.N. Nutritionally Variant Streptococci Bacteremia in Cancer Patients: A Retrospective Study, 1999-2014. Mediterr J Hematol Infect Dis 2015, 7(1): e2015030, DOI: http://dx.doi.org/10.4084/MJHID.2015.030

Published: April 20, 2015 **Received: December 21, 2014** **Accepted: March 3 , 2015**

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Correspondence to: John N. Greene, M.D., F.A.C.P. Chief, Infectious Diseases and Hospital Epidemiologist. H. Lee Moffitt Cancer Center and Research Institute. Professor of Internal Medicine & Interdisciplinary Oncology. University of South Florida College of Medicine. 12902 Magnolia Drive, Tampa, Florida 33612-9497. E-mail: john.greene@moffitt.org

Introduction. *Nutritionally Variant Streptococci (NVS)* (*Abiotrophia* and *Granulicatella*) are fastidious Gram-positive bacteria that were described for the first time in 1961.[1] They are also called satelliting *streptococci* because they usually form satellite colonies around *Staphylococcus aureus* and other bacteria, including some *Enterobacteriaceae* and other *streptococci*.[2] They are a common component of the oral flora but have been associated with a variety of invasive infections.[3] Colonies of NVS are small (0.2 to 0.5 mm in diameter), and are either non-hemolytic or α-hemolytic on blood agar.[4]

The nutrient requirements of these microbes include cysteine or pyridoxal (active form of vitamin B6) for growth in complex media.[5,6] NVS are divided in two genera (*Abiotrophia and Granulicatella*) comprising four species that have been identified from human specimens: *Abiotrophia defectiva, Granulicatella adiacens, Granulicatella elegans, and Granulicatella para-adiacens.*[2]

Materials and Methods. We retrospectively reviewed all cases of NVS bacteremia occurring from June 1999 to April 2014 at H. Lee Moffitt Cancer Center and Research Institute. The computerized epidemiology report provided by the microbiology laboratory identified thirteen cancer patients with NVS bacteremia. We collected data regarding baseline demographics and clinical characteristics, such as age, sex, underlying malignancy, neutropenic status, duration of neutropenia, treatment, and outcome. Data was recorded from the Infectious Disease consultation reports and discharge summaries. Resolution of the infection was defined as repeated negative blood cultures. When reporting data, all percentages were rounded to the tenth decimal point.

Results. Thirteen patients were identified with positive NVS blood stream infection. Ten patients (77%) had hematologic malignancies, including chronic lymphocytic leukemia (CLL)(1), multiple myeloma (MM)(1), acute myelogenous leukemia (AML)(4), and non Hodgkin's lymphoma (NHL)(4)(**Table 1, Figures 1 and 2**).

The non-hematologic malignancies included esophageal cancer(2) and bladder cancer(1). Seven patients (54%) were neutropenic (defined as Absolute Neutrophil Count < 1500 cells/uL) with an average duration of 14 days. The median age was 60 years. There was no gender predilection. Seven patients had mucositis at the time of diagnosis either due to chemotherapy or graft versus host disease. One patient had gingivitis with a dental abscess. None of the patients developed infective endocarditis. Most patients were on empiric antimicrobial therapy with ciprofloxacin, levofloxacin or piperacillin/tazobactam at the time of breakthrough bacteremia. Almost all patients received vancomycin as definitive treatment. All the patients had transient bacteremia with an average duration of positive blood cultures of 1 day. The 30-day mortality rate was 16.67%. Mortality was not attributable to NVS bacteremia

Discussion. During this study, we collected the data spanning fourteen years period (1999-2014) at Moffitt Cancer Center. We found that NVS blood stream infections are commonly found in hematological malignancies. Our study was compared to Senn et al, and found that NVS blood stream infections were common in neutropenic patients with hematological

Table 1. Nutritionally Variant Streptococci Bacteremia in Cancer Patients

No.	Age (years)	Gender	Malignancy	Duration of Bacteremia (Days)	Duration of Neutropenia (Days)	Treatment	Outcome
1	60	M	CML	1	-	Vancomycin, Levofloxacin	Survived
2	58	M	MM	1	-	Vancomycin, Cefepime	Deceased due to complications
3	76	M	AML	1	22	Vancomycin	Deceased due to complications
4	27	F	AML	1	34	Vancomycin, Tobramycin	Deceased at hospice
5	50	F	NHL	1	-	Bactrim	Deceased due to complications
6	64	F	NHL	1	7	Vancomycin, Cefepime	Survived
7	86	M	Bladder cancer	1	-	Ampicillin/sulbactam, Levofloxacin	Survived
8	39	F	NHL	1	4	Piperacillin/tazobactam	Deceased at hospice
9	59	M	Esophageal cancer	1	-	Piperacillin/tazobactam, Linezolid	Deceased due to complications
10	49	M	NHL	1	19	Cefepime, Vancomycin	Survived
11	66	M	Esophageal cancer	1	-	Aztreonam, Linezolid	Survived
12	66	M	AML	1	10	Piperacillin/tazobactam, Vancomycin	Survived
13	80	M	AML	1	2	Vancomycin	Survived

CML indicates Chronic myelogenous leukemia; MM, Multiple myeloma; AML, Acute myeloid leukemia; NHL, Non-Hodgkin lymphoma

Figure 1. Type of Malignancy Associated with NVS Bacteremia

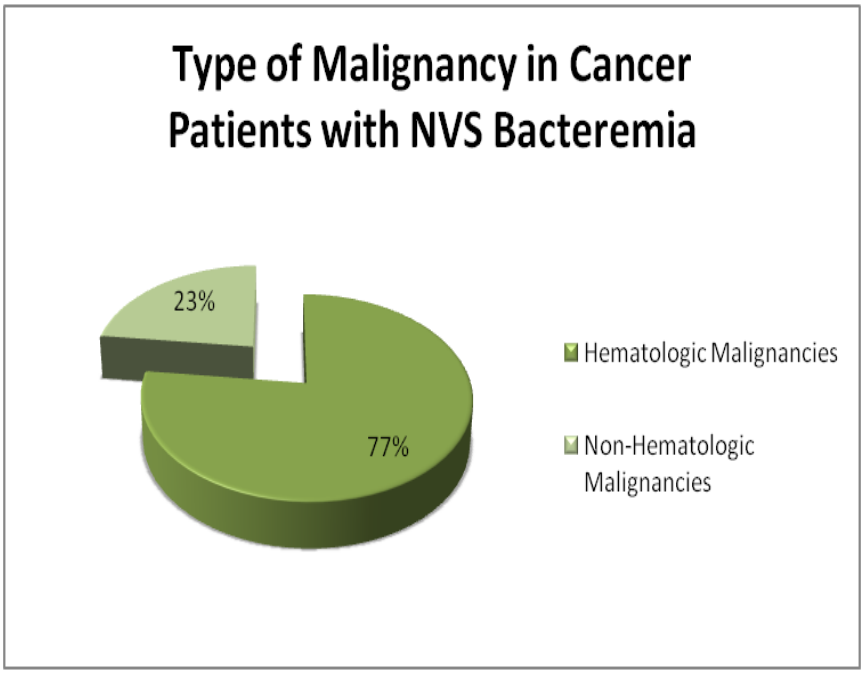
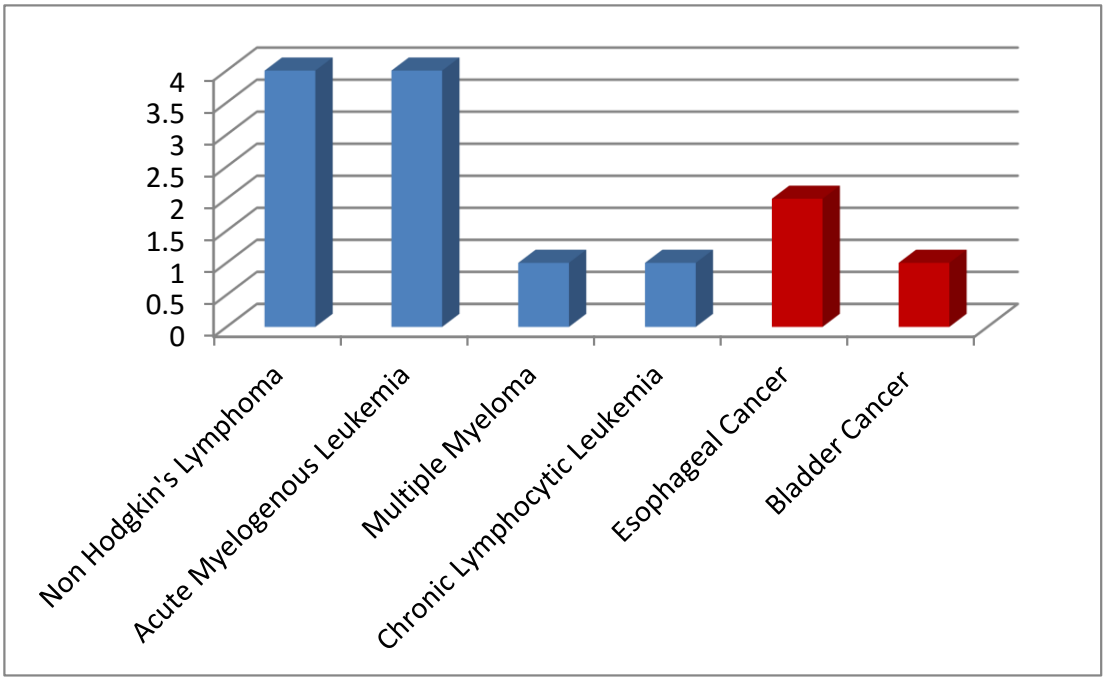


Figure 2. Hematologic vs Non Hematologic Malignancies



malignancies.[1]

NVS are typically associated with endocarditis in immunocompetent patients and bacteremia in immunocompromised patients[1,7] and interestingly none of our patients had developed endocarditis. Chemotherapy-induced mucositis and neutropenia have previously been identified as risk factors in cancer patients.[1]

NVS infections have been reported in patients with infectious crystalline keratopathy,[8] vertebral osteomyelitis,[9] endophthalmitis,[10] meningitis[11] and in cancer patients.[12-15]

Once a suspected NVS is cultured, its identity should be confirmed by establishing its requirement for pyridoxal.[2] This test should be carried out on a medium that is incapable of supporting the organism's growth without pyridoxal supplementation.[2] A positive pyrrolidonyl arylamidase test along with typical morphology should further serve to identify an isolate as an NVS.[2] The 16S rRNA gene PCR and restriction fragment length polymorphism analysis are different modalities to identify different species of NVS.[1,3,16-18]

Endocarditis caused by NVS has a higher rate of complications and treatment failure.[19] NVS blood stream infections should be treated in the same way as viridans streptococci and enterococcus.[3] It is recommended that a combination therapy of benzyl penicillin and amoxicillin plus a gentamicin for a

course of 4 to 6 weeks is used to treat these microorganisms.[19,20] Vancomycin is an alternative therapy when a penicillin-aminoglycoside combination is ineffective or contraindicated.[21]

In our study, most patients were on empiric antimicrobial therapy with ciprofloxacin, levofloxacin or piperacillin/tazobactam at the time of breakthrough bacteremia. Almost all patients received vancomycin as definitive treatment. All the patients had transient bacteremia with an average duration of positive blood cultures of 1 day.

Unlike streptococcus viridans, NVS does not typically cause adult respiratory distress syndrome and septic shock and is more benign.[22,23] Although patients who develop fungemia, gram-negative bacteremia, or sepsis syndrome are best treated by catheter removal in addition to antimicrobial therapy, an increasing body of evidence suggests that many gram-positive bacterial catheter infections can be treated by use of antimicrobial agents without catheter removal.[24,25]

Conclusion. NVS should be considered as a possible agent of Gram-positive bacteremia in cancer patients with neutropenia and a breach in oral or gastrointestinal mucosa, especially chemotherapy-induced mucositis or gingivitis. We recommend against routine removal of the central venous catheters given the benign course of NVS bacteremia, rapid clearance from blood, and likely oral or GI tract source of the pathogen. NVS bacteremia did not contribute to the mortality of patients in our study.

References:

1. Senn L, Entenza JM, Greub G, et al. Bloodstream and endovascular infections due to Abiotrophia defectiva and Granulicatella species. BMC Infect Dis. 2006. 20;6:9.
2. Ruoff KL. Nutritionally variant streptococci. Clin Microbiol Rev. 1991;4(2):184-90. PMid:2070344 PMCid:PMC358190
3. Cargill JS, Scott KS, Gascoyne-Binzi D, et al. Granulicatella infection: diagnosis and management. J Med Microbiol. 2012;61(Pt 6):755-61. http://dx.doi.org/10.1099/jmm.0.039693-0 PMid:22442291
4. Perkins A, Osorio S, Serrano M, et al. A case of endocarditis due to Granulicatella adiacens. Clin Microbiol Infect. 2003;9(6):576-7. http://dx.doi.org/10.1046/j.1469-0691.2003.00646.x PMid:12848740
5. Koh YR, Yi J, Kim HH, et al. Discrepant satellitism for identification of Granulicatella adiacens isolates. Ann Lab Med. 2014;34(2):174-6. http://dx.doi.org/10.3343/alm.2014.34.2.174 PMid:24624359 PMCid:PMC3948836
6. Bouvet A, van de Rijn I, McCarty M. Nutritionally variant streptococci from patients with endocarditis: growth parameters in a semisynthetic medium and demonstration of a chromophore. J Bacteriol. 1981;146(3):1075-82. PMid:7240084 PMCid:PMC216963
7. Giuliano S, Caccese R, Carfagna P, et al. Endocarditis caused by nutritionally variant streptococci: a case report and literature review. Infez Med. 2012;20(2):67-74. PMid:22767303
8. Ormerod LD, Ruoff KL, Meisler DM, et al. Infectious crystalline keratopathy. Role of nutritionally variant streptococci and other bacterial factors. Ophthalmology. 1991 Feb;98(2):159-69. http://dx.doi.org/10.1016/S0161-6420(91)32321-2
9. Fukuda R, Oki M, Ueda A, et al. Vertebral osteomyelitis associated with Granulicatella adiacens. Tokai J Exp Clin Med. 2010;35(4):126-9. PMid:21319041
10. Namdari H, Kintner K, Jackson BA, et al. Abiotrophia species as a cause of endophthalmitis following cataract extraction. J Clin Microbiol. 1999;37(5):1564-6. PMid:10203522 PMCid:PMC84829
11. Shivappa SG, Kulkarni M, Oral B. Granulicatella elegans bacteremia & meningitis in a child without neurosurgical interventions. IOSR Journal of Dental and Medical Sciences . 2014;13(9):PP 01-04
12. Wang Y, Xue J, Zhou X, et al. oral microbiota distinguishes acute lymphoblastic leukemia pediatric hosts from healthy populations. PLoS ONE. 2014. 9(7): e102116
13. Liao CH, Teng LJ, Hsueh PR, et al. Nutritionally variant streptococcal infections at a University Hospital in Taiwan: disease emergence and high prevalence of beta-lactam and macrolide resistance. Clin Infect Dis. 2004;38(3):452-5. http://dx.doi.org/10.1086/381098 PMid:14727223
14. Murray CK, Walter EA, Crawford S, et al. Abiotrophia bacteremia in a patient with neutropenic fever and antimicrobial susceptibility testing of Abiotrophia isolates. Clin Infect Dis. 2001;32(10):E140-2. http://dx.doi.org/10.1086/320150 PMid:11317266
15. Lopardo H, Mastroianni A, Casimir L. Bacteremia due to Abiotrophia defectiva in a febrile neutropenic pediatric patient. Rev Argent Microbiol. 2007;39(2):93-4. PMid:17702254
16. Ohara-Nemoto Y, Tajika S, Sasaki M, et al. Identification of Abiotrophia adiacens and Abiotrophia defectiva by 16S rRNA gene PCR. J Clin Microbiol. 1997;35(10):2458-63. PMid:9316889 PMCid:PMC229992
17. Roggenkamp A, Leitritz L, Baus K, et al. PCR for detection and identification of Abiotrophia spp. J Clin Microbiol. 1998;36(10):2844-6. PMid:9738030 PMCid:PMC105074
18. Biermann C, Fries G, Jehnichen P, et al. Isolation of Abiotrophia adiacens from a brain abscess which developed in a patient after neurosurgery. J Clin Microbiol. 1999;37(3):769-71. PMid:9986849 PMCid:PMC84549
19. Gould FK, Denning DW, Elliott TSJ, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. J. Antimicrob. Chemother. 2012;67(2): 269-289. http://dx.doi.org/10.1093/jac/dkr450 PMid:22086858
20. Lin CH, Hsu RB. Infective endocarditis caused by nutritionally variant streptococci. Am J Med Sci. 2007;334(4):235-9. http://dx.doi.org/10.1097/MAJ.0b013e3180a6eeab PMid:18030177
21. Bouvet A, Cremieux AC, Contrepois A, et al. Comparison of penicillin and vancomycin, individually and in combination with gentamicin and amikacin, in the treatment of experimental endocarditis induced by nutritionally variant streptococci. Antimicrob. Agents Chemother. 1985;28(5):607-611 http://dx.doi.org/10.1128/AAC.28.5.607
22. Shelburne SA 3rd, Lasky RE, Sahasrabhojane P, et al. Development and validation of a clinical model to predict the presence of ß-lactam resistance in viridans group streptococci causing bacteremia in neutropenic cancer patients. Clin Infect Dis. 2014;59(2):223-230. http://dx.doi.org/10.1093/cid/ciu260 PMid:24755857
23. Yacoub AT, Mojica L, Jones L, et al. The Role of Corticosteroids in Adult Respiratory Distress Syndrome caused by Viridans Group Streptococci Bacteremia in Neutropenic Patients. Mediterr J Hematol Infect Dis. 2014;6(1):e2014055. http://dx.doi.org/10.4084/mjhid.2014.055 PMid:25237468 PMCid:PMC4165499
24. Bullard KM, Dunn DL. Bloodstream and intravascular catheter infections. In: Holzheimer RG, Mannick JA, editors. Surgical Treatment: Evidence-Based and Problem-Oriented. Munich: Zuckschwerdt; 2001. Available from: http://www.ncbi.nlm.nih.gov/books/NBK7008/
25. O'Grady NP, Alexander M, Burns LA, et al. Summary of recommendations: Guidelines for the Prevention of Intravascular Catheter-related Infections. Clin Infect Dis. 2011;52(9):1087-1099 http://dx.doi.org/10.1093/cid/cir138 PMid:21467014 PMCid:PMC3106267