Published in final edited form as:

Am J Infect Control. 2012 November ; 40(9): 886–887. doi:10.1016/j.ajic.2011.11.005.

Risk Factors Associated with Linezolid Non-susceptible Enterococcal Infections

Jessina C. McGregor, PhD¹, Daniel M. Hartung, PharmD, MPH¹, George P. Allen, PharmD², Randy A. Taplitz, MD³, Robin Traver, PharmD⁴, Tony Tong, PharmD¹, and David T. Bearden, PharmD¹

¹College of Pharmacy, Oregon State University/Oregon Health & Science University, Portland, OR 97239

²University of New England College of Pharmacy, Portland, ME 04103

³Division of Infectious Diseases, Department of Medicine, University of California, San Diego, La Jolla, CA 92093

⁴Care Health Solutions Pharmacy, Vancouver, WA 98662

Abstract

Linezolid is one of few treatment options for vancomycin-resistant enterococci. Our objective was to identify risk factors for linezolid non-susceptible enterococci using a case-control study of 15 cases and 60 control patients. We identified prior hospitalization, admission to a medical service, comorbidity, and linezolid and sulfonamide therapy as risk factors.

Linezolid was approved by the US Food and Drug Administration (FDA) in 2000 and is considered to be first-line treatment for vancomycin-resistant *Enterococcus* (VRE). However, even before approval for clinical use, linezolid non-susceptible *Enterococcus* (LNSE) infections were reported in patients participating in the manufacturer's compassionate use program.¹ Development of linezolid resistance in VRE further limits treatment options. While daptomycin possesses *in vitro* bactericidal activity to VRE, observational data indicate that its effectiveness is equivalent, or even inferior, to linezolid.^{2, 3} Other potential treatment options include ceftaroline, telavancin, and tigecycline; however far less data exist regarding their effectiveness against VRE. Given the rising incidence of VRE infections, determining risk factors for LNSE infection will help guide therapy selection for VRE. Thus, our objective was to identify risk factors for development of LNSE infections at our institution.

METHODS

A case-control study was conducted among patients hospitalized at Oregon Health & Science University (OHSU) hospital between January 1, 2003 and December 31, 2006. OHSU consists of 509 beds, including large transplant and cancer services. At the time of the study, linezolid susceptibility testing was performed at our institution for all enterococcal

© 2011 Association for Professionals in Infection Control and Epidemiology, Inc. Published by Mosby, Inc. All rights reserved.

Corresponding author: Jessina C. McGregor, PhD, OSU/OHSU College of Pharmacy, 3303 SW Bond Ave., CH12C, Portland, OR 97239, Ph: 503-494-4722, Fax: 503-494-8797, mcgregoj@ohsu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

isolates using Vitek-2, and disk diffusion testing was used to confirm all non-susceptible results according to Clinical Laboratory Standards Institute (CLSI) guidelines. Enterococcal isolates with a linezolid MIC $\leq 2 \mu\text{g/mL}$ were considered susceptible, $4 \mu\text{g/mL}$ were classified as intermediate resistance, and $\geq 8 \mu\text{g/mL}$ were classified as resistant.

Case patients were identified as patients with a positive clinical culture for LNSE. For each case, four control patients were randomly selected from patients present in the hospital at the time the case's index culture was collected, but who did not have a positive clinical culture for LNSE. Patient demographic data were collected, as well as admission/discharge dates, admitting service, pharmacy orders, ICD-9 diagnosis codes, and microbiology clinical culture data. All data were collected electronically through the OHSU Center for Information Analysis and Decision Support, which maintains a consolidated data repository of clinical data and links to the electronic medical record data warehouse. Pharmacy order data were used to indicate medication exposures (including antibiotics) and to compile the Chronic Disease Score for VRE (CDS-VRE), an aggregate comorbidity risk index for risk factor studies of VRE.⁴ Medications were categorized by therapeutic class.⁵ Potential risk factors, including antibiotic use, were evaluated during each patient's time at risk for LNSE clinical culture positivity.⁶ Concomitant antibiotic therapies were not separately evaluated. Hospitalizations were categorized by admitting service as either medical or non-medical (e.g. surgical, oncologic, etc.). Univariate analysis was performed using Fisher's Exact and the Wilcoxon rank-sum tests. Predictors with $p < 0.20$ in the univariate analysis were considered for inclusion in the multivariable logistic regression model. Analysis was performed using SAS version 9.2 (SAS Institute; Cary, NC). This study was approved by the OHSU Institutional Review Board.

RESULTS

Fifteen case patients and 60 control patients were included in the study. Table 1 describes patient characteristics and the frequency of healthcare exposures for cases and controls. The median age of cases was 58 and was 56 for controls ($p=0.54$). Cases had a greater median CDS-VRE score than controls (4.4 versus 1.0, respectively; $p < 0.01$). The median total duration of hospitalization was 39 days for cases and 12 days for controls.

Among the case patients, 5 (33.3%) patients had enterococcal isolates resistant to linezolid, while the remaining 10 (66.7%) patients had isolates with intermediate resistance to linezolid. All isolates were vancomycin resistant (MIC $\geq 64 \mu\text{g/mL}$). The majority of isolates were collected from blood (53.3%) and urine (26.7%) cultures.

Due to the small number of cases identified, multivariable regression produced unstable estimates with large standard errors (data not shown). Thus Table 2 presents unadjusted odds ratios for significant predictors of LNSE clinical culture positivity.

DISCUSSION

LNSE represents a newly emergent pathogen, with poorly defined risk factors. Epidemiologic data of LNSE infections is currently limited, and existing studies have not consistently identified prior linezolid use as a risk factor for LNSE infection. Case-control studies conducted by Pai et al. and Kainer et al. both identified linezolid therapy as an independent risk factor for LNSE infection. However, both studies used control groups consisting of patients with linezolid-susceptible enterococcal isolates; use of such a control group has been demonstrated to overestimate the magnitude of the association with the resistance-defining antibiotic.⁷⁻⁹ A recent case-case-control study by Pogue et al. did not identify linezolid use as a significant risk factor, but did identify peripheral vascular disease,

receipt of a solid organ transplant, total parenteral nutrition, piperacillin-tazobactam therapy, and cefepime therapy as independent, significant risk factors for linezolid-resistant VRE but not for linezolid-susceptible VRE.¹⁰

Our study includes the first emergent cases of LNSE in our institution. The small sample size did not permit multivariate regression analysis; however, prior linezolid therapy, sulfonamide therapy, CDS-VRE, prior hospitalization, and admission to a medical service were all identified as significant risk factors in the unadjusted analysis. While the route of acquisition cannot be definitively determined in this retrospective study, patients with a history of hospitalization may have been more likely to have been colonized with VRE and subsequent treatment with linezolid may have contributed to the emergence of an endogenously sourced infection. The lack of consistency across previous studies may indicate that person-to-person transmission is not the major route of acquisition in all settings.

Prior sulfonamide therapy was identified as a significant predictor; all patients receiving sulfonamide therapy received trimethoprim-sulfamethoxazole (TMP/SMX). Of those patients, all cases had urine cultures performed, suggesting that TMP/SMX may have been initiated for suspected urinary tract infections. Sulfonamides have not been previously identified as a risk factor for LNSE; the differing antibiotics identified as risk factors to date may be due to differences in practice patterns or may be spurious.

Our study provides insight into the epidemiology of LNSE in a setting in which the organism is newly emergent. The epidemiology of LNSE likely varies across regions, thus making ongoing local or institutional surveillance critical to inform both therapeutic decision-making and infection control policies.

Literature Cited

1. Zurenko GE, Gibson JK, Shinabarger DL, Aristoff PA, Ford CW, Tarpley WG. Oxazolidinones: a new class of antibacterials. *Curr Opin Pharmacol*. Oct; 2001 1(5):470–476. [PubMed: 11764772]
2. Crank CW, Scheetz MH, Brielmaier B, Rose WE, Patel GP, Ritchie DJ, et al. Comparison of outcomes from daptomycin or linezolid treatment for vancomycin-resistant enterococcal bloodstream infection: A retrospective, multicenter, cohort study. *Clin Ther*. Sep; 2010 32(10): 1713–1719. [PubMed: 21194593]
3. McKinnell JA, Patel M, Shirley RM, Kunz DF, Moser SA, Baddley JW. Observational study of the epidemiology and outcomes of vancomycin-resistant *Enterococcus* bacteraemia treated with newer antimicrobial agents. *Epidemiol Infect*. Nov 15.2010 :1–9.
4. McGregor JC, Perencevich EN, Furuno JP, Langenberg P, Flannery K, Zhu J, et al. Comorbidity risk-adjustment measures were developed and validated for studies of antibiotic-resistant infections. *J Clin Epidemiol*. Dec; 2006 59(12):1266–1273. [PubMed: 17098569]
5. American Society of Health-System Pharmacists. AHFS drug handbook. 2. Bethesda, Md.; Philadelphia, PA: American Society of Health-System Pharmacists; Lippincott Williams & Wilkins; 2003.
6. Harris AD, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. *Clin Infect Dis*. Apr 1; 2001 32(7):1055–1061. [PubMed: 11264034]
7. Pai MP, Rodvold KA, Schreckenberger PC, Gonzales RD, Petrolatti JM, Quinn JP. Risk factors associated with the development of infection with linezolid- and vancomycin-resistant *Enterococcus faecium*. *Clin Infect Dis*. Nov 15; 2002 35(10):1269–1272. [PubMed: 12410489]
8. Kainer MA, Devasia RA, Jones TF, Simmons BP, Melton K, Chow S, et al. Response to emerging infection leading to outbreak of linezolid-resistant enterococci. *Emerg Infect Dis*. Jul; 2007 13(7): 1024–1030. [PubMed: 18214174]

9. Harris AD, Samore MH, Lipsitch M, Kaye KS, Perencevich E, Carmeli Y. Control-group selection importance in studies of antimicrobial resistance: examples applied to *Pseudomonas aeruginosa*, *Enterococci*, and *Escherichia coli*. *Clin Infect Dis*. Jun 15; 2002 34(12):1558–1563. [PubMed: 12032889]
10. Pogue JM, Paterson DL, Pasculle AW, Potoski BA. Determination of risk factors associated with isolation of linezolid-resistant strains of vancomycin-resistant *Enterococcus*. *Infect Control Hosp Epidemiol*. Dec; 2007 28(12):1382–1388. [PubMed: 17994519]

TABLE 1

Characteristics and Healthcare Exposures of Cases and Controls

Variable	No. (%) of patients		Fisher's Exact
	Case group (N=15)	Control group (N=60)	p-value
Male sex	10 (67)	37 (62)	0.77
White race	11 (73)	48 (83)	0.47
Comorbidities			
Cancer	4 (27)	7 (12)	0.21
Diabetes	11 (73)	23 (38)	0.02
Peptic ulcer disease	7 (47)	21 (35)	0.55
End-stage renal disease	8 (53)	5 (8)	<0.01
Transplant	5 (33)	4 (7)	0.01
Admission to a medical service	12 (80)	14 (23)	<0.01
Hospitalization in prior 30 days	9 (75)	3 (25)	<0.01
Corticosteroid therapy ^a	5 (33)	25 (42)	0.77
Antibiotic therapy ^a			
Aminoglycosides	1 (7)	7 (12)	>0.99
Cephalosporins	5 (33)	37 (62)	0.08
Miscellaneous β -lactams	5 (33)	10 (17)	0.16
Macrolides	0 (0)	1 (2)	>0.99
Penicillins	6 (40)	17 (28)	0.53
Quinolones	0 (0)	1 (2)	>0.99
Sulfonamides	4 (27)	2 (3)	0.01
Tetracyclines	0 (0)	1 (2)	>0.99
Miscellaneous ^b	9 (60)	16 (27)	0.03
Linezolid therapy ^a	4 (27)	1 (2)	<0.01
Vancomycin therapy ^a	7 (47)	14 (23)	0.11

VRE, vancomycin-resistant *Enterococcus*^aExposure during time at risk^bIncludes clindamycin, daptomycin, linezolid, quinupristin/dalfopristin, rifaximin, and vancomycin

TABLE 2

Unadjusted Associations for Potential Risk Factors for Linezolid Non-Susceptible *Enterococcus* Clinical Culture Positivity

Variable	OR (95% CI)	p-value
Prior Linezolid therapy	21.5 (2.2, 210.6)	0.009
Prior Sulfonamide therapy	10.5 (1.7, 64.8)	0.011
CDS-VRE	1.8 (1.3, 2.4)	0.001
Previous hospitalization	28.5 (6.0, 134.8)	<0.001
Medical admit service	13.1 (3.2, 53.3)	<0.001