Risk Factors for Isolation of Daptomycin Non-Susceptible Enterococci: A Case-Case Control Study

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Abstract

Background: An increase in daptomycin non-susceptible enterococci (DNSE) at our institution was determined to be non-clonal in nature. We sought to define risk factors for DNSE.
Methods: We performed a retrospective case-case control study with case group 1 patients having daptomycin non-susceptible (by broth microdilution) vancomycin-resistant *Enterococcus faecium* (DNS-VRE) from a clinical culture (N=17) matched to case group 2 (daptomycin susceptible VRE, DS-VRE) and non-infected controls in a 1:1:3 ratio by ward location, culture site, and time period (+/- 4 months). Conditional logistic regression models identified individual risk factors for DNS-VRE and DS-VRE respectively compared to controls. For each outcome, a multiple conditional logistic regression model was developed based on risk factors identified on univariate analysis. Models were qualitatively compared to identify DNS-VRE risk factors.
Results: Demographic characteristics and prior antibiotic exposure was not significantly different between case groups. Table displays univariate analysis of DNS-VRE and DS-VRE risk factors. Daptomycin use was rare (2 DNS-VRE, 1 DS-VRE, 0 controls) and not able to be included in the model.

	DNS-VRE		DS-VRE	
	Odds Ratio	p	Odds Ratio	p
Duration Index Hospitalization	1.06	.0498	1.07	.009
Duration Hospitalization Prior to Culture (PTC)	1.35	.0052	1.12	.0408
DOT Antibiotics in 90 days PTC	1.03	.0179	1.02	.0237
Vancomycin PTC	8.92	.0055	3.98	.0499
Linezolid PTC	15	.0134	6.00	.1435
Fluoroquinolone PTC	3.12	.0655	4.48	.0276
Cephalosporin PTC	2.33	.141	4.52	.0278
Charlson Score	1.16	.1778	1.33	.0261

Risk factors for DNS-VRE by multivariate analysis: duration of index hospitalization (OR 1.32, p=.0327) and DOT in 90 days PTC (OR 1.03, p=.0462). Risk factors for DS-VRE: DOT in 90 days PTC (OR 1.03, p=.0417), Charlson score (OR 2.41, p=.0286) and fluoroquinolone PTC (OR 8.07, p=.0306).
Conclusion: Daptomycin exposure was uncommon and not a risk factor for DNS-VRE, but recent exposure to antimicrobials was a risk factor for isolation of both DS- and DNS-VRE. Duration of hospitalization was the only risk factor unique to isolation of DNS-VRE. Additional studies with a greater number of patients with DNSE are needed to further define risk factors for daptomycin non-susceptibility.

Background

- An increase in daptomycin non-susceptible enterococci at our institution was determined to be primarily due to Microscan and Etest overestimating daptomycin minimal inhibitory concentration (MIC) values
- Previous studies of risk factors for DNSE have defined daptomycin non-susceptibility using Etest/Microscan or used a case-control design with risk factors for VRE isolation possibly confounding results[1-2]
- Exposure to daptomycin has been not been consistently associated with isolation of DNSE
- Using a rigorous definition of daptomycin non-susceptibility and a case-case control design we sought to define risk factors for isolation of DNSE

Methods

Design: Case-case control study with 1:1:3 matching
- Case Group 1 = daptomycin non-susceptible, vancomycin resistant *E. faecium* (DNS-VRE) isolated from an inpatient clinical culture
- Case Group 2 = daptomycin susceptible vancomycin-resistant *E. faecium* (DS-VRE) isolated from an inpatient clinical culture
- Control = patient with clinical culture not yielding VRE

Matching: matched on inpatient ward location, site of culture (blood, stool, urine, etc.), and time period (+/- 4 months)
Definitions:
- Daptomycin non-susceptible = broth microdilution MIC>4 µg/mL
- Immunosuppression = active malignancy, organ transplant, neutropenia, systemic steroid use
- Rural vs. Urban = by home zip code using Missouri Census Data Center

Analysis:
- Conditional logistic regression models were used to identify risk factors for DNS-VRE (Case 1 vs. Controls) and for DS-VRE (Case 2 vs. Controls) isolated in clinical culture
- A multiple conditional logistic regression model was developed for each outcome based on risk factors identified on univariate analysis
- Findings were qualitatively compared to determine risk factors associated with isolation of DNS-VRE

Results

- 17 inpatient with cultures positive for DNS-VRE were identified (Blood=5, stool=6, urine=3, wound=1, abdominal infection=2) and matched to 17 DS-VRE and 51 controls
- Isolates were from 2008 to 2012 (2008-2010, 2012=1 each year, 2011=13)
- Demographic characteristics and prior antibiotic exposure was not significantly different between DNS-VRE and DS-VRE
- Daptomycin exposure was rare (DNS-VRE=2, DS-VRE=1, control=0) and not able to be included in the model
- Univariate analysis of risk factors for DNS-VRE and DS-VRE is described in **Table 1**

Results (cont.)

Table 1: Univariate Risk Factors for Isolation of DNS-VRE and DS-VRE

Risk Factor	DNS-VRE		DS-VRE	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Age	1.014 (0.972-1.058)	0.5202	1.011 (0.973-1.05)	0.5820
LOS Index Hospitalization	**1.061 (1-1.125)**	**0.0498**	**1.066 (1.016-1.118)**	**0.0090**
Duration Hospitalization Prior to Culture	**1.348 (1.093-1.662)**	**0.0052**	**1.121 (1.005-1.25)**	**0.0408**
Rural vs. Urban	2.174 (0.460-10.264)	0.3270	1.380 (0.292-6.518)	0.6841
Immunosuppression	0.403 (0.086-1.889)	0.2488	3.26 (0.541-19.623)	0.1970
Dialysis	0.833 (0.162-4.295)	0.8275	0.795 (0.125-5.077)	0.8087
Diabetes	1.567 (0.4-6.146)	0.5195	1.098 (0.329-3.669)	0.8788
Charlson Score	1.156 (0.936-1.428)	0.1778	**1.326 (1.034-1.7)**	**0.0261**
Nosocomial vs. Community or Healthcare	**5.814 (1.577-21.443)**	**0.0082**	2.108 (0.709-6.262)	0.1800
DOT in 90 days PTC	**1.034 (1.006-1.063)**	**0.0179**	**1.022 (1.003-1.041)**	**0.0237**
Vancomycin	**8.919 (1.904-41.779)**	**0.0055**	**3.983 (1.001-15.847)**	**0.0499**
Linezolid	**15 (1.752-128.391)**	**0.0134**	5.998 (0.544-66.14)	0.1435
Fluoroquinolones	**3.116 (.093-10.44)**	**0.0655**	**4.483 (1.18-17.025)**	**0.0276**
Cephalosporins	2.333 (0.755-72.08)	0.141	**4.523 (1.179-17.351)**	**0.0278**

LOS=length of stay, DOT= days of antimicrobial therapy, PTC=prior to culture
Specific antimicrobials were analyzed dichromatously (exposed vs. unexposed)

Multivariate analysis

- **DNS-VRE Risk Factors**
  - Duration of index hospitalization = OR 1.319 (95% CI 1.023-1.700), *p*=.0327
  - DOT in 90 days PTC = OR 1.026 (95%CI 1.000-1.051), *p*=.0462
  - Age = OR 1.05 (95% CI 0.985-1.116), *p*=.1342
- **DS-VRE Risk Factors**
  - DOT in 90 days PTC = OR 1.032 (95% CI 1.001-1.064), *p*=.0417
  - Charlson score = OR 2.41 (95% CI 1.10-5.28), *p*=.0286
  - Fluoroquinolone receipt PTC = OR 8.07 (95% CI 1.22-53.60), *p*=.0306
  - Age = OR 0.932 (95% CI 0.860-1.009), *p*=.0833

Conclusions

- Isolation of DNS-VRE was not associated with exposure to daptomycin but was associated with exposure to antimicrobials
- As recent exposure to antimicrobials was associated with both DNS- and DS-VRE this exposure is associated primarily with VRE isolation and not specific to the isolation of DNS strains
- Duration of hospitalization was the only risk factor unique to DNS-VRE suggesting a nosocomial origin, but nosocomial isolation was not significant in the multivariate analysis and a PFGE analysis of the isolates demonstrated a lack of relatedness
- Risk factors for isolation of DNS-VRE are poorly defined and larger studies using broth microdilution to define daptomcyin non-susceptibility are needed

References:
1. Kelesidis T, Chow AL, Humphries R, et al. Case-control study comparing de novo and daptomycin-exposed daptomycin-nonsusceptible Enterococcus infections. *Antimicrob Agents Chemother*. 2012;56:2150-2.
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