Factors associated with *vanA*-positive vancomycin-susceptible *Enterococcus faecium* among patients with *E. faecium* bacteremia

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Disclosures

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Background

- *VanA*-positive, vancomycin-susceptible Enterococci have been described from Canada, South Korea, and Norway
- They have been termed **vancomycin-variable Enterococci (VVE)**
- Upon vancomycin exposure, VVE have the ability to revert into a vancomycin-resistant phenotype both *in vitro* and *in vivo*
- Are not detected with conventional VRE screening methods

Coburn et al., J Clin Microbiol. 2014 May;52(5):1766-7.
Thaker et al., Antimicrob Agents Chemother. 2015 Mar;59(3):1405-10.
Choi et al., Diagn Microbiol Infect Dis. 2011 Jan;69(1):105-10
Sivertsen et al., Antimicrob Agents Chemother. 2016 Jun 20;60(7):4119-27

Objectives

- To determine the **prevalence of VVE** among *vanA*-positive *E. faecium* sterile site isolates in South-Central Ontario, Canada
- To compare **clinical characteristics** between patients with VRE, VVE and VSE bacteremia and to identify **risk factors for 30-day mortality**
- To describe patients with **breakthrough *E. faecium* bacteremia**

Methods: TIBDN isolates from sterile sites

Retrospective

Only isolates positive for *vanA* or *vanB*

Prospective

All isolates

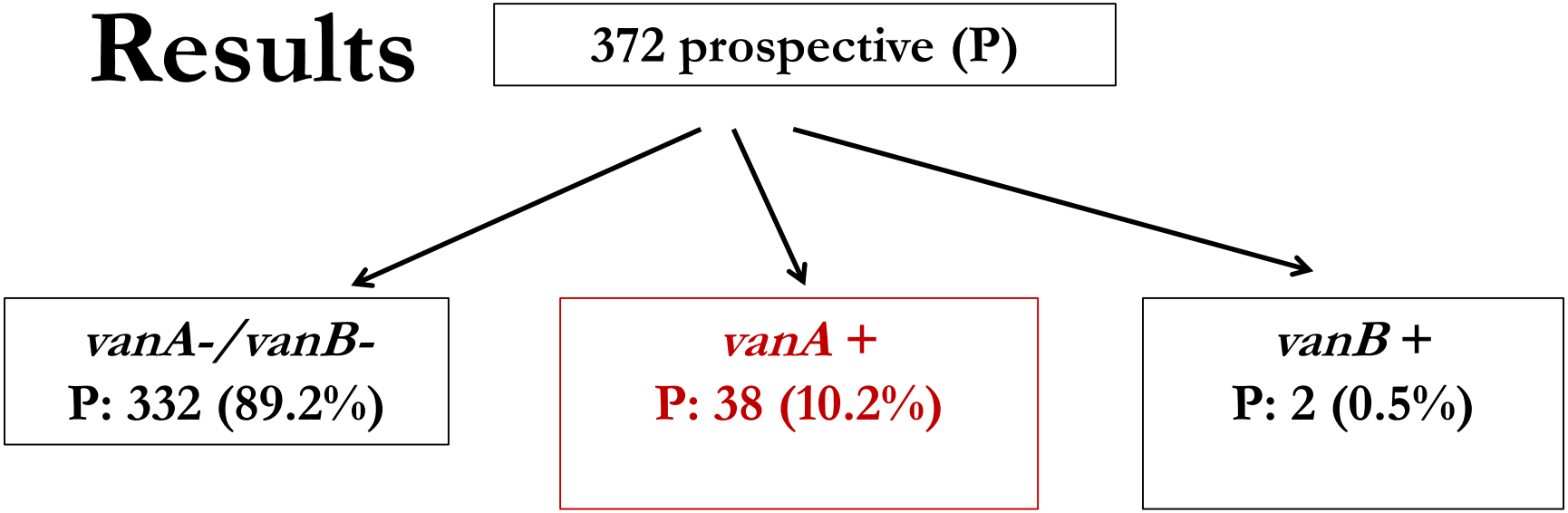
Jan 2012 **Jan 2015** **June 2016**

Chart review on patients with VRE and VVE bacteremia, random sample of patients with VSE

Methods: Analysis

- Univariable comparison of clinical characteristics between VRE, VVE, and VSE patients
- Predictors of 30-day mortality: univariable and multivariable logistic regression analysis
- Description of clinical and microbiological characteristics of patients with breakthrough *E. faecium* bacteremia and comparison of strains by pulsed-field gel electrophoresis (PFGE)

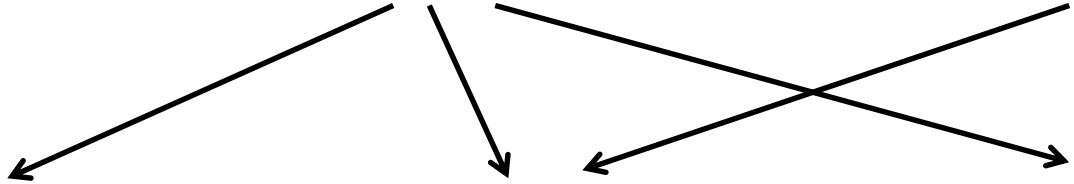
Results



Results

372 prospective (P)

37 retrospective (R)



vanA-/vanB-
P: 332 (89.2%)

vanA +
P: 38 (10.2%)
R: 35

Total 73

vanB +
P: 2 (0.5%)
R: 2

Results

372 prospective (P)

37 retrospective (R)

vanA-/vanB-
P: 332 (89.2%)

vanA
P: 38 (10
R: 35

Total 73

R: 2

3 hospitals accounted for 69% (20/29) of all VVE isolates, while contributing 47% of all *E. faecium* isolates (P=0.02)

44 VRE (60%)

29 VVE (40%)

Results: Patient characteristics

	VRE (n=36)		VVE (n=25)		VSE (n=79)		
	n	%	n	%	n	%	P-value
Hospital-acquired	29	(80.6)	22	(88.0)	59	(74.7)	0.35
On antibiotic treatment	27	(75.0)	19	(76.0)	45	(57.0)	0.08
Source: Central venous catheter (CVC)	20	(55.6)	11	(44.0)	22	(27.8)	**0.01**
Source: Intraabdominal	10	(27.8)	5	(20.0)	40	(50.6)	**0.006**
Hours to appropriate therapy, median (IQR)	53	(32)	30	(18)	26	(26)	**<0.001**
VRE-active treatment	31	(86.1)	17	(68.0)	5	(6.3)	**<0.001**
Days to clearance (IQR), n=98	4	(3)	4	(2)	3	(3)	0.15
30-day mortality	8	(22.2)	11	(44.0)	23	(29.1)	0.18

Results: Predictors of mortality

	Univariable	
	OR (95% CI)	P-value
Male sex	1.8 (0.8-3.8)	0.14
Age, per year	1.01 (0.99-1.03)	0.51
Charlson, per point	1.2 (1.1-1.4)	**0.006**
Pitt bacteremia score	1.3 (1.1-1.5)	**0.003**
Resistance type		0.40
VSE	Reference	-
VVE	1.9 (0.8-4.8)	0.08
VRE	0.7 (0.3-1.8)	0.14
Source of infection		0.33
Other	Reference	-
Primary CLABSI	0.6 (0.2-1.5)	0.15
Intraabdominal	1.1 (0.4-2.7)	0.35
Surgery/procedure for source control	0.2 (0.0-1.4)	0.10
Polymicrobial infection	0.9 (0.4-2.0)	0.88
Hours to appropriate therapy	1.00 (0.99-1.01)	0.83

Results: Predictors of mortality

	Univariable		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Male sex	1.8 (0.8-3.8)	0.14		
Age, per year	1.01 (0.99-1.03)	0.51		
Charlson, per point	1.2 (1.1-1.4)	**0.006**	1.2 (1.1-1.5)	**0.008**
Pitt bacteremia score	1.3 (1.1-1.5)	**0.003**	1.3 (1.1-1.5)	**0.002**
Resistance type		0.40	non-significant	
VSE	Reference	-		
VVE	1.9 (0.8-4.8)	0.08		
VRE	0.7 (0.3-1.8)	0.14		
Source of infection		0.33		
Other	Reference	-		
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Results: Breakthrough bacteremia

Definition

A second positive blood culture with *E. faecium* while on treatment for first episode OR within 30 days after first episode

Results

- 8 patients
- Breakthrough between day 1 and day 34 after first culture
- High in-hospital mortality of 88% (7/8), mostly unrelated

Results: Breakthrough bacteremia

PATIENT	First isolate	Treatment	Second isolate
A	VSE	Vancomycin	VRE
B	VSE	Vancomycin	VRE
C	VSE	Daptomycin	VSE (Dapto-R)

Results: Breakthrough bacteremia

PATIENT	First isolate	Treatment	Second isolate
A	VSE	Vancomycin	VRE
B	VSE	Vancomycin	VRE
C	VSE	Daptomycin	VSE (Dapto-R)
D	VVE	Vancomycin	VRE
E	VVE	Linezolid	VVE (Lin-R)

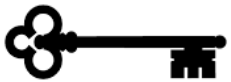
Results: Breakthrough bacteremia

PATIENT	First isolate	Treatment	Second isolate
A	VSE	Vancomycin	VRE
B	VSE	Vancomycin	VRE
C	VSE	Daptomycin	VSE (Dapto-R)
D	VVE	Vancomycin	VRE
E	VVE	Linezolid	VVE (Lin-R)
F	VRE	Linezolid	VSE
G	VRE	Linezolid	VVE
H	VRE	Daptomycin	VSE

Results: Breakthrough bacteremia

PATIENT	First isolate	Treatment	Second isolate	PFGE
A	VSE	Vancomycin	VRE	-
B	VSE	Vancomycin	VRE	Different strain
C	VSE	Daptomycin	VSE (Dapto-R)	**Same strain**
D	VVE	Vancomycin	VRE	-
E	VVE	Linezolid	VVE (Lin-R)	**Same strain**
F	VRE	Linezolid	VSE	-
G	VRE	Linezolid	VVE	**Same strain**
H	VRE	Daptomycin	VSE	**Same strain**

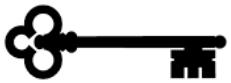
Key point 1



High VVE prevalence of 40%, VVE are mostly nosocomial pathogens

VRE screening by PCR for *vanA*/*vanB* instead of selective cultures

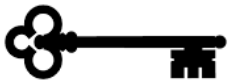
Key point 2



Clinical characteristics of patients with VVE similar to those with VRE (e.g. associated with CVC, less IAI)

Probably because both VVE and VRE are mostly nosocomial pathogens

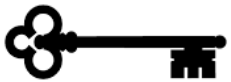
Key point 3



30-day mortality was mainly determined by underlying comorbidities and severity of disease, but not by type of vancomycin resistance

Limitation of our study: sample size

Key point 4



VVE patients not overrepresented among patients with breakthrough bacteremia. Breakthrough seems to occur irrespective of initial resistance pattern and treatment.

Only descriptive analysis, most VVE patients treated with VRE-active substances

Thank you

FNSNF
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Background

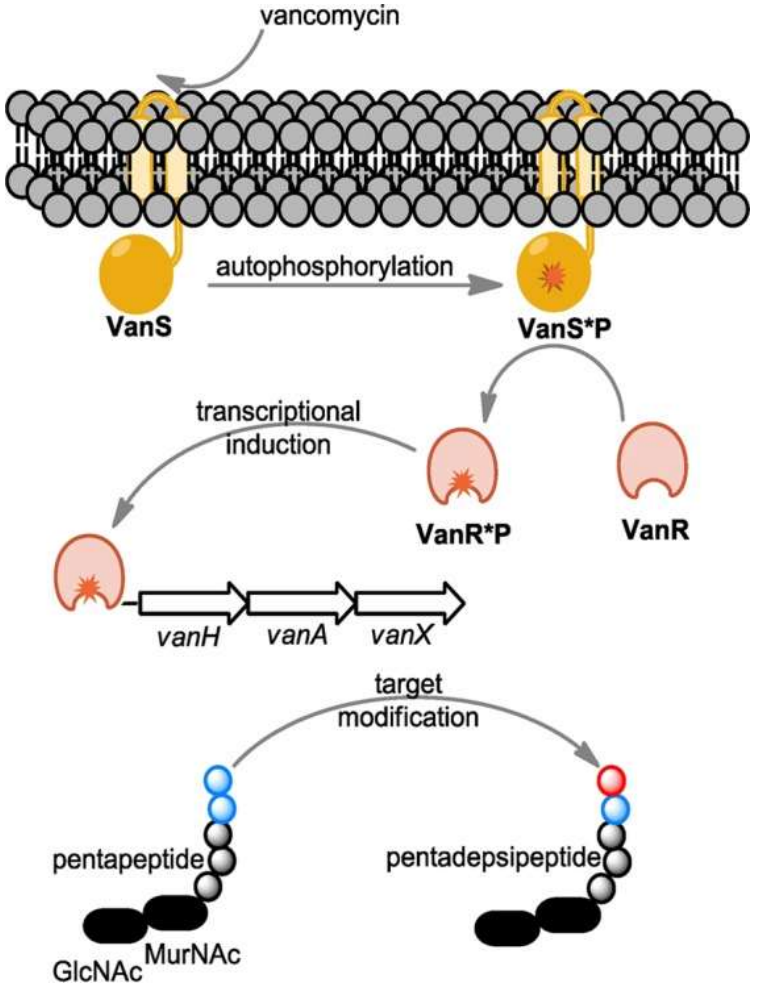
VanS: sensory kinase

VanR: regulatory protein

VanHAX: resistance cassette

VVE

- lack of *vanS/vanR*
- Activation of vanHAX resistance cassette through mutations in the promotor region



Thaker et al., Antimicrob Agents Chemother. 2015 Mar;59(3):1405-10.