Vancomycin variable enterococci (VVE) responsible for two cases of severe bloodstream infections in immunocompromised patients colonized with vancomycin resistance *Enterococcus faecium* (VRE)

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Introduction

The emergence of vancomycin variable enterococci (VVE) poses a challenge to vancomycin therapy. VVE are initially susceptible to vancomycin but can switch to a resistant phenotype when exposed to the drug.

Goals

The goal of this study is to describe the clinical, microbiological and genetic pathways of two case where patients with VRE colonization and compromised immune system failed to respond to vancomycin treatment for VVE bloodstream infections.

Materials and Methods

The two *E. feacium* pairs (blood/VVE vs rectal/VRE) from P1 and P2 patients were first analysed for their antibiotic susceptibilities and *vanA* gene, then compared for clonality by PFGE. Furthermore, the genetic element carrying *vanA* cluster was assessed by Long-PCR.

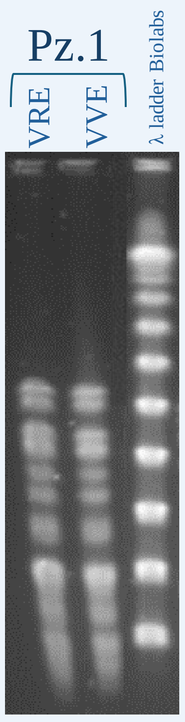
Results

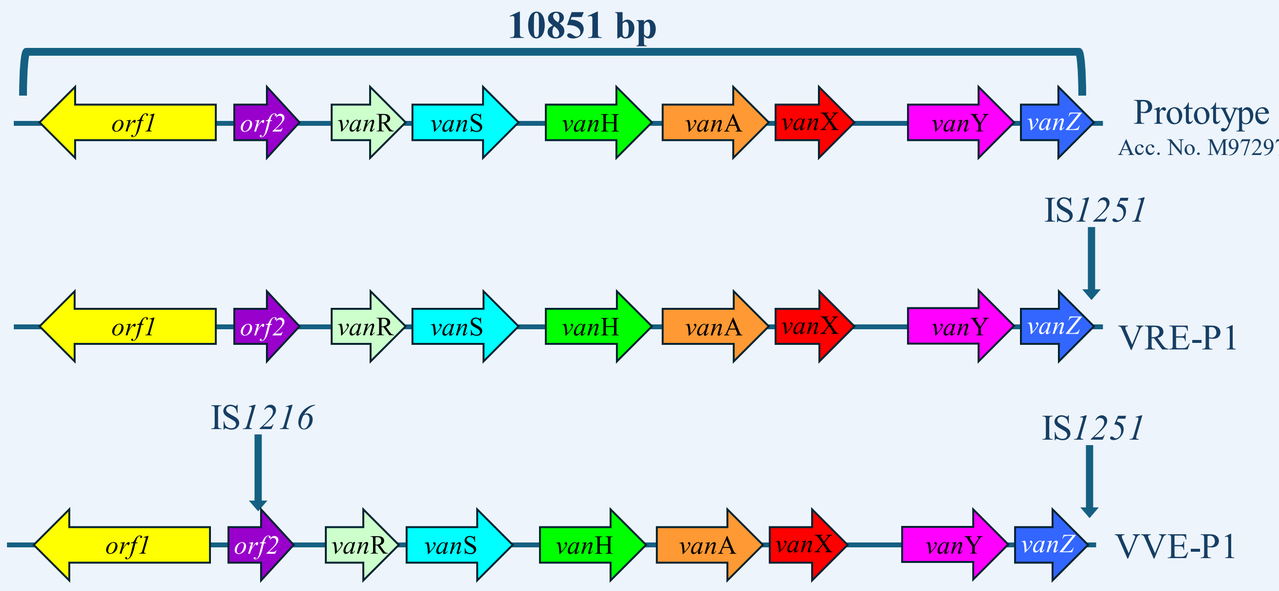
- Due to fever recurrence and glycopeptide treatment-failure, blood cultures of both patients (P1 and P2) were reanalyzed by BIOFIRE® FILMARRAY® and VVE were found (*van*A +).
- Both VVE-P1 and VVE-P2 reverted to a resistant phenotype under vancomycin induction, and carried *vanHAX* cluster.
- **P1**, a metastatic melanoma patient, admitted for *Staphylococcus aureus* bloodstream infection, was empirically treated with vancomycin.

Patient 1	Strain	VA	TEC	P	AML	AMP	CPT	BPR	IMP	LNZ	S	CN	DAP	TGC	DAL	ORI
	VRE	>128	>128	>128	>32	>128	>32	>32	>32	4	>1024	8	2	0.19	0.047	2
	VVE	1	2	>128	>32	>128	>32	>32	>32	4	>1024	4	4	0.19	0.023	0.06

VA: Vancomycin; TEC: Teicoplanin; P: Penicillin; AML; Amoxicillin; AMP: Ampicillin; CPT: Ceftaroline; BPR: Ceftobiprole; IMP: Imipenem; LNZ: Linezolid; S: Streptomycine; CN: Gentamicin; DAP: Daptomycin; TGC: Tigecycline; DAL: Dalbavancyn; ORI: Oritavancyn. Highlighted in red: antibiotics to which the isolates showed resistance. Highlighted in green: antibiotics to which the isolates showed susceptibility.

P1 blood/VVE and rectal/VRE genotyping confirmed clonality





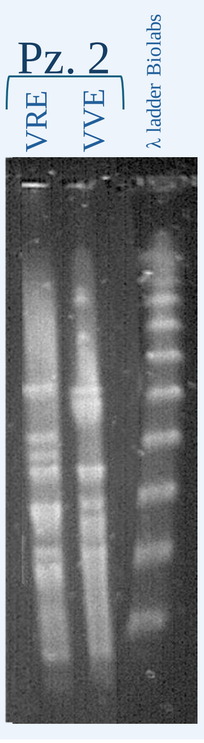
Schematic representation of *van*A cluster reconstruction of VRE-P1 and VVE-P1 isolates in comparison with prototype (Acc. No. M97297).

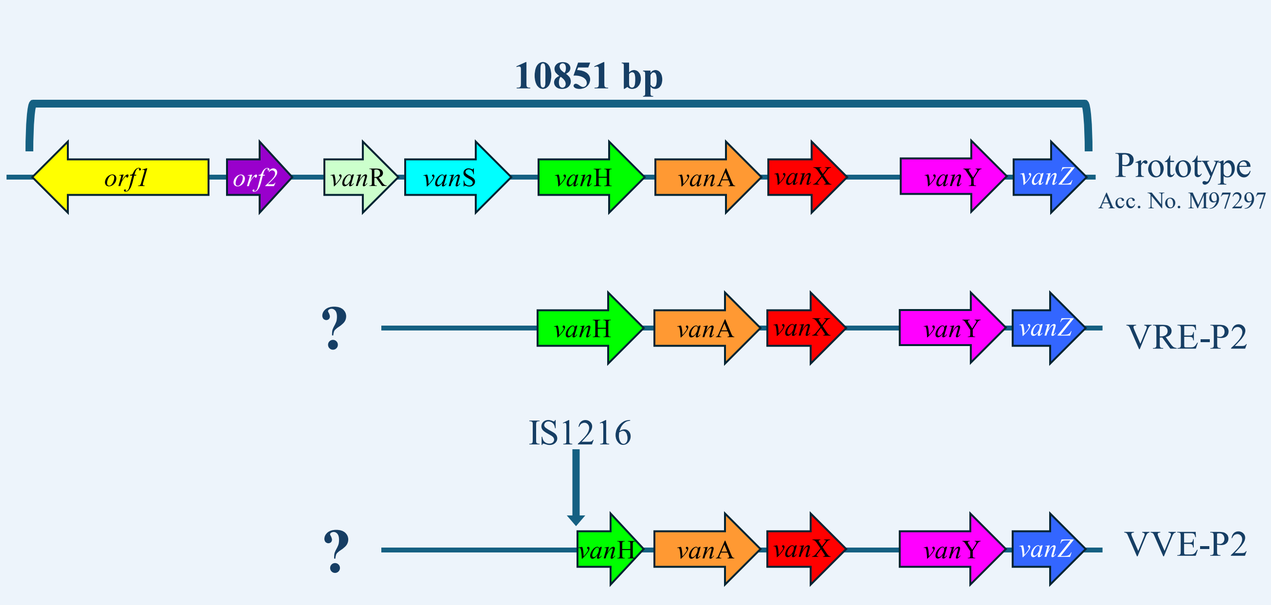
VVE-P1 carried IS*1216* between the resolvase (*orf*2) and the *vanS* genes, probably responsible for the attenuation of *vanHAX* expression. Both VVE-P1 and VRE-P1 carried IS*1251* downstream

- **P2**, an OLT patient with previous VSE bacteremia, was admitted for fever recurrence under teicoplanin therapy.

Patient 2	Strain	VA	TEC	P	AML	AMP	CPT	BPR	IMP	LNZ	S	CN	DAP	TGC	DAL	ORI
	VRE	128	>128	>128	>32	>256	>32	>32	>32	4	32	6	2	0.5	0.0125	2
	VVE	0.5	2	>128	>32	>128	>32	>32	>32	2	>1024	>1024	4	4	0.047	0.06

P2 blood/VVE and rectal/VRE genotyping **not** confirmed clonality





Schematic representation of *van*A cluster reconstruction of VRE-P2 and VVE-P2 isolates in comparison with prototype (Acc. No. M97297).

Both VVE-P2 and VRE do not amplified *van*RS regulator *locus*, but VVE carried the IS*1251* upstream the *van*A gene, hypothetically responsible for the variable *vanHAX* expression conferring resistance

Acknowledgment

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Discussion and conclusions

In immunocompromised patients colonized with VRE, attention should be paid to contemporaneous or subsequent clinical vancomycin-susceptible strains as these may horizontally acquire silent *vanA* that can be activated through genomic rearrangements upon exposure to vancomycin. In this study, both patients were colonized by VRE during hospitalization, affected by VVE bacteremia and successfully treated with linezolid. Since the routine susceptibility testing could not reliably identify VVE, without a molecular confirmation, vancomycin should be avoided as empiric or definitive treatment for VRE colonized patients.