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Case-case-control study on factors associated with *vanB* vancomycin-resistant and vancomycin-susceptible enterococcal bacteraemia

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Abstract

Background: Enterococci are a major cause of healthcare-associated infection. In Australia, *vanB* vancomycin-resistant enterococci (VRE) is the predominant genotype. There are limited data on the factors linked to *vanB* VRE bacteraemia. This study aimed to identify factors associated with *vanB* VRE bacteraemia, and compare them with those for vancomycin-susceptible enterococci (VSE) bacteraemia.

Methods: A case-case-control study was performed in two tertiary public hospitals in Victoria, Australia. VRE and VSE bacteraemia cases were compared with controls without evidence of enterococcal bacteraemia, but may have had infections due to other pathogens.

Results: All VRE isolates had *vanB* genotype. Factors associated with *vanB* VRE bacteraemia were urinary catheter use within the last 30 days (OR 2.86, 95% CI 1.09-7.53), an increase in duration of metronidazole therapy (OR 1.65, 95% CI 1.17-2.33), and a higher Chronic Disease Score specific for VRE (OR 1.70, 95% CI 1.05-2.77). Factors linked to VSE bacteraemia were a history of gastrointestinal disease (OR 2.29, 95% CI 1.05-4.99) and an increase in duration of metronidazole therapy (OR 1.23, 95% CI 1.02-1.48). Admission into the haematology/oncology unit was associated with lower odds of VSE bacteraemia (OR 0.08, 95% CI 0.01-0.74).

Conclusions: This is the largest case-case-control study involving *vanB* VRE bacteraemia. Factors associated with the development of *vanB* VRE bacteraemia were different to those of VSE bacteraemia.

Keywords: Enterococci, Vancomycin-resistant, Vancomycin-susceptible, Bacteraemia

Background

Globally, enterococci are a major cause of nosocomial infection [1-3]. Of concern is vancomycin-resistant enterococci (VRE) bacteraemia, which has been associated with higher mortality and morbidity compared to VRE wound, urinary tract and intra-abdominal infections [4]. In Australia, *vanB* is the major genotype [3,5], in contrast to the United States (US) where *vanA* is predominant [2,6]. Importantly, VRE is increasingly isolated in clinical settings [3], and has emerged in the community viz. aged-care facilities and outpatient clinics [7,8].

Studies which examined the factors associated with VRE colonisation and/or a range of different VRE infections have either had *vanA* genotype as the predominant strain (as reported or through personal communication with the authors) [9-14], or did not report the genotype [4,15-29]. All aforementioned studies were performed in the US, where *vanA* is predominant [2]. Only two studies examining factors linked to the development of VRE bacteraemia involved predominantly the *vanB* genotype [30,31]. The clinical profile of a colonised versus an infected patient is different [32]. Thus, studies [4,23,25-27] that have included both colonised and infected patients as their VRE cases should be interpreted with care. Case-control studies [4,11-14,16,17,19,25] comparing VRE to VSE bacteraemia patients may not accurately account for the impact of vancomycin use; this bias is

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minimised with a case-case-control study that compares VRE bacteraemia patients to controls without enterococcal bacteraemia and VSE bacteraemia patients to controls [33]. Of the two studies involving predominantly *vanB* genotype [30,31], only one [31] was a case-case-control study which used the same control patients for both case groups, thereby enabling meaningful characterisation of the distinct features of bacteraemia specific to the resistant and susceptible enterococci [33]. However, the external validity of the results from this single centre study is limited [31]. Furthermore, that study [31] and another involving *vanA* VRE [12] do not adjust for patient co-morbidities, and duration of hypoalbuminaemia and neutropenia. Other studies [4,9-11,13-30] did not adjust for a combination of factors (co-morbidities and/or duration of antibiotic therapy, hypoalbuminaemia, and/or neutropenia).

Studies have found that neutropenia, use of antibiotics (e.g. cephalosporins, imipenem and metronidazole), urinary catheter and central venous catheter use, older age, gastrointestinal disease, biliary complications, severe mucositis, a higher severity of illness score and low plasma albumin levels were linked to VSE bacteraemia [31,34-40]. Unfortunately, the majority of these studies on factors linked to VSE bacteraemia were descriptive (had small sample size) [34-37], and did not adjust for duration of antibiotic therapy, hypoalbuminaemia and/or neutropenia [31,38,39].

Given that enterococcal bacteraemia is increasing and data on factors linked to *vanB* VRE bacteraemia remain limited, an understanding of the factors associated with *vanB* VRE and VSE bacteraemia would facilitate efforts to prevent and manage these infections. Thus, the primary aim of this study was to identify the potential factors associated with *vanB* VRE bacteraemia and secondarily, to compare them with those for VSE bacteraemia.

Methods

A retrospective case-case-control study was conducted at two tertiary public hospitals, The Alfred (~420 acute-care beds) and Austin Health (~400 acute-care beds) in Victoria, Australia. Both institutions service adult patients, have intensive care units and emergency departments, infectious diseases and infection control units, haematology-oncology services and provide other specialist services. This study was approved by the Human Research Ethics Committees of both hospitals and Monash University. Waiver of patient consent was approved by all ethics committees because no patient recruitment of follow-up occurred, and data utilised in this study included information already collected as part of patient care.

All study participants were admitted to the hospital between January 2002 and March 2010 (inclusive). The sample size was based around all cases of VRE bacteraemia

identified during the study period. The study period was specified a priori, from January 2002 to March 2010, as the infection control interventions against VRE in both hospitals did not change substantially over this time period. Only patients with hospital length of stay (LOS) > 2 days were eligible for inclusion in the study. Pregnant patients and those < 18 years of age were excluded. Selection of all patients was made without knowledge of patient outcomes. Each patient was only included once. Patients from whom one or more blood cultures were positive for VRE were classified as VRE cases. The VRE genotype was determined by polymerase chain reaction [5,41]. Patients who had one or more blood cultures positive for VSE were also identified (VSE cases). Controls without evidence of enterococcal bacteraemia were identified from a list of patients admitted to the hospital and may have had infections (including bacteraemia) due to other pathogens. Matching was performed within the same hospital on a 1:1:1 basis. VSE cases and controls were matched with VRE cases according to date of admission (within 2 years of VRE case admission date), and where possible, unit of admission. Where more than one VSE case or control was eligible for matching on the same admission date, the VSE case or control was randomly chosen.

The present analysis included additional data (e.g. patient co-morbidities, and duration of hypoalbuminaemia and neutropenia) which were not considered in the study discussed above [31] and patients from another hospital. Information on patient demographics and clinical characteristics, antimicrobial use, and outcomes of hospitalisation were collected via a retrospective review of patients' medical records by the same researcher (ALYC). These criteria for the exposure and outcome measures were pre-determined prior to data collection.

Polymicrobial bacteraemia was the isolation of one or more bacterial or fungal pathogens within 24 hours from the same or different blood sample where the initial VRE or VSE was isolated [17]. Chronic Disease Score specific to VRE (CDS-VRE), which has been validated for use in studies on factors linked to disease, was used to measure patient co-morbidities [42]. Gastrointestinal disease included a history of liver disease, peptic ulcers, diverticulitis, graft-versus-host-disease of the gut, inflammatory bowel disease, colon cancer and colorectal cancer. Neutropenia, hypoalbuminaemia, exposure to medical devices, and antibiotic-specific days were defined, respectively, as number of days where neutrophils were < 500/mm³, serum or plasma albumin < 35 g/L, exposure to central lines, mechanical ventilation, urinary catheter and total parenteral nutrition, and total number of days that antibiotic(s) were administered orally or intravenously, within 30 days prior to bacteraemia (for VRE and VSE cases) or death or discharge (controls).

Data analyses were performed with Stata, version 12.0 (Stata Corporation, College Station, Texas, USA).

Categorical variables are expressed as frequencies and percentages. For continuous variables, mean or median are reported for normally or non-normally distributed data, respectively. Conditional logistic regression was used to assess the association between each independent variable and the presence or absence of VRE or VSE bacteraemia. We assessed the assumption of a linear relationship between log odds and each of the continuous exposure factors in the multivariable models for VRE and VSE bacteraemia. The continuous exposure factors were analysed as continuous variables with coefficients expressed as odds ratio because the relationships between log odds and each of the continuous exposure factors were approximately linear. Variables that were significant on univariable analysis, or biologically plausible factors linked to disease, or potential confounders, were inserted into the multivariable models. Link test was used to assess the fit of each of the multivariable models for VRE and VSE bacteraemia [43]. All statistical tests were two-tailed and a $p < 0.05$ was considered significant.

Results

Of the 724 patients with enterococcal bacteraemia identified during the study period, 121 (17%) and 603 (83%) were VRE and VSE cases, respectively. A final number of 116 VRE cases (and corresponding matched VSE cases and controls) were reviewed given four VRE patients had missing medical records and one VRE patient was pregnant. The ratio of enterococcal isolates that were vancomycin-resistant to -susceptible was 6% in 2002, and increased to 39% in 2009 and 22% in the first quarter of 2010. All VRE isolates were *vanB* genotype.

Demographics of the VRE and VSE cases, and controls are shown in Table 1. For the studied admission, the reason for admission and co-morbidities were similar between cases and controls. Most VRE isolates were *Enterococcus faecium*, whereas the VSE isolates were predominantly *E. faecalis*. To account for this difference, factors associated with VSE bacteraemia due to *E. faecium* (haematological malignancy and duration of neutropenia) and *E. faecalis* (urinary catheter use) [44], were included in the multivariable analysis. We also accounted for time at risk for enterococcal bacteraemia by adjusting in the multivariable analyses for the following factors occurring in the 30 days prior to bacteraemia (for VRE and VSE cases) and death or discharge (for controls): number of days of antibiotic administration, neutropenia and hypoalbuminaemia, and use of medical devices (e.g. catheters). Adjustment for age was performed on multivariable analysis when age was found to be significant on univariable analysis.

In patients with *vanB* VRE bacteraemia, 54 (47%), 22 (19%) and 14 (12%) were treated with teicoplanin monotherapy, linezolid monotherapy and no antibiotics,

respectively. For 26 (22%) *vanB* VRE bacteraemia patients, a combination (concurrent or in sequence) of teicoplanin, linezolid, quinupristin-dalfopristin or benzylpenicillin was administered as definitive therapy. In VSE patients, 46 (40%), 21 (18%), 1 (1%), 9 (8%), 6 (5%), and 2 (2%) patients were administered definitive therapy using intravenous glycopeptides (teicoplanin or vancomycin), penicillins (ampicillin, benzylpenicillin, ticarcillin-clavulanic acid, piperacillin-tazobactam), meropenem, no antibiotics, combination of intravenous gentamicin and ampicillin, and oral linezolid, respectively. In 30 (26%) VSE patients, a combination (concurrent or in sequence) of vancomycin, teicoplanin, linezolid, ampicillin, benzylpenicillin or meropenem was administered.

Tables 2 and 3 summarise the analyses of factors linked to VRE and VSE bacteraemia, respectively. In the multivariable analysis, a higher CDS-VRE score, an increase in duration of metronidazole therapy, and use of urinary catheters within the previous 30 days were associated with increased odds of *vanB* VRE bacteraemia (Table 2). When patients with VSE bacteraemia were compared to controls (Table 3), after adjustment for confounders, admission to the haematology/oncology unit (compared to non-haematology/oncology units) was associated with lower odds of VSE bacteraemia whilst, gastrointestinal disease and duration of metronidazole use were associated with higher odds of VSE bacteraemia.

Discussion and conclusions

Unlike earlier studies [4,23,25-27], the current study only included data from patients who had *vanB* VRE bacteraemia and did not assess colonised patients. It is not a single-centre study [4,9-12,15-27,30,31] and, to our knowledge, is the largest case-case-control study involving *vanB* VRE bacteraemia. The present report is the only case-case-control study to identify the factors associated with *vanB* VRE and VSE bacteraemia, while adjusting for patient co-morbidities and duration of antibiotic therapy, hypoalbuminaemia, and neutropenia.

The association between patient co-morbidities, as measured by the CDS-VRE score, and development of *vanB* VRE bacteraemia was investigated. The CDS-VRE score was calculated based on medications ordered within 24 hours of hospital admission for medical conditions such as diabetes, peptic ulcers, kidney disease, history of transplantation and cancer [42]. A weight is assigned for each medical condition and the final CDS-VRE score is a weighted sum of the medical conditions for each patient. The presence of a higher number of co-morbidities included in the score is associated with a higher CDS-VRE score. Co-morbidities related to immune-suppression such as transplantation and cancer were given a higher weighting, compared to diabetes and peptic ulcer. As such,

Table 1 Patient demographics

Characteristics	VRE cases (n = 116)	VSE cases (n = 116)	Controls (n = 116)
Age, median (IQR), years	60 (47–68)	63.5 (51–76)	58 (44–68)
Sex			
Male	69 (59)	72 (62)	63 (54)
Female	47 (41)	44 (38)	53 (46)
Unit of admission			
Haematology/oncology	61 (53)	43 (37)	67 (58)
Non-haematology/oncology	55 (47)	73 (63)	49 (42)
Reason for admission			
Medical	89 (77)	87 (75)	89 (77)
Surgical	27 (23)	29 (25)	27 (23)
Charlson score, median (IQR)	4 (2–5)	3 (1–5)	4 (1–4)
Chronic disease score-VRE (CDS-VRE), median (IQR)	1 (0–1.9)	0 (0–1)	0 (0–1.6)
Lung disease	17 (15)	17 (15)	17 (15)
Ischaemic heart disease	25 (22)	23 (20)	11 (9)
Myocardial infarction	10 (9)	10 (9)	3 (3)
Congestive heart failure	13 (11)	14 (12)	2 (2)
Cerebrovascular disease	7 (6)	13 (11)	5 (4)
Gastrointestinal disease	54 (47)	64 (55)	38 (33)
Renal disease	21 (18)	18 (16)	15 (13)
Diabetes mellitus	25 (22)	30 (26)	20 (17)
Cancer	74 (64)	64 (55)	74 (64)
Solid organ transplant recipient	14 (12)	7 (6)	5 (4)
Enterococcus species			
<i>E. faecalis</i>	9 (8)	71 (61)	-
<i>E. faecium</i>	107 (92)	39 (34)	-
<i>E. casseliflavus</i> , <i>E. gallinarum</i> , or <i>E. durans</i>	-	4 (3)	-
Both <i>E. faecalis</i> and <i>E. faecium</i>	-	1 (1)	-
Unknown	-	1 (1)	-
Polymicrobial bacteraemia	33 (28)	50 (43)	-
Infection (other than due to Enterococci) prior to bacteraemia (VRE and VSE cases) and prior to discharge (controls)	61 (53)	43 (37)	34 (29)
Days from admission until bacteraemia, median (IQR), days	16 (7–24)	7.5 (1–18.5)	-
Total length of stay, median (IQR), days	35 (22.5–50.5)	25 (16–45.5)	9 (5–20)
In-hospital mortality	42 (36)	30 (26)	5 (4)

Note:

Data are number (%) of patients unless indicated otherwise. Percentages were rounded to the nearest whole number.

patients with co-morbidities associated with immune-suppression tend to have high CDS-VRE scores. Our results show that patients with a higher CDS-VRE score have higher odds for *vanB* VRE bacteraemia. This was consistent with studies that reported association between haematological malignancy and *vanA* VRE bacteraemia [11]. Diabetes [20], acute renal failure [19], and severity of gut

mucositis [18] may predispose patients to the development of VRE bacteraemia; VRE genotype was not determined in these studies.

Antibiotic use has been linked to VRE colonisation in the gastrointestinal tract and/or infection, including bacteraemia [19,26,45]. In the present study, duration of therapy with specific antibiotics was considered, unlike

Table 2 Factors associated with *vanB* VRE bacteraemia

Factors associated with <i>vanB</i> VRE bacteraemia	VRE cases (n = 116)	Controls (n = 116)	Univariable			Multivariable		
			OR	95% CI	p-value	OR	95% CI	p-value
Age, median (IQR), years	60 (47–68)	58 (44–68)	1.01	0.99-1.02	0.481			
Female	47 (41)	53 (46)	0.81	0.48-1.36	0.432			
Transfer from another hospital	28 (24)	14 (12)	2.56	1.18-5.52	0.017			
Unit of admission								
Non-haematology/oncology to read Non-haematology/oncology	55 (47)	49 (42)	Reference					
Haematology/oncology	61 (53)	67 (58)	0	-	-			
ICU admission in prior 30 days	39 (34)	13 (11)	6.57	2.97-14.55	<0.001			
CDS-VRE score, median (IQR)	1 (0–1.9)	0 (0–1.6)	1.36	1.02-1.80	0.036	1.70	1.05-2.77	0.032
<i>Clostridium difficile</i> toxin positive	5 (4)	1 (1)	5.00	0.58-42.80	0.142			
Infection(s) due to pathogens other than Enterococci	61 (53)	34 (29)	2.93	1.60-5.37	0.001	0.97	0.39-2.46	0.953
Gastrointestinal disease	54 (47)	38 (33)	2.00	1.10-3.64	0.024			
Liver disease	16 (14)	15 (13)	1.14	0.41-3.15	0.796			
Haematological malignancy	66 (57)	63 (54)	1.6	0.52-4.89	0.410	0.41	0.06-2.61	0.342
Bone marrow transplantation type								
Nil	97 (84)	100 (86)	Reference			Reference		
Autologous	3 (3)	7 (6)	0.33	0.07-1.65	0.178	0.27	0.03-2.22	0.221
Allogeneic	16 (14)	9 (8)	2.40	0.85-6.81	0.100	2.79	0.57-13.66	0.206
Ceftriaxone days, median (IQR), days	0 (0)	0 (0)	1.09	0.98-1.22	0.130	1.16	0.91-1.48	0.234
Third generation cephalosporin days, median (IQR), days ^a	0 (0–1)	0 (0–0.49)	1.04	0.95-1.13	0.439			
Fluoroquinolone days, median (IQR), days ^b	1 (0–7.63)	0 (0–2.42)	1.07	1.01-1.12	0.016			
Metronidazole days, median (IQR), days	0 (0–1.78)	0 (0)	1.54	1.16-2.04	0.003	1.65	1.17-2.33	0.004
Ticarcillin-clavulanic acid days, median (IQR), days	0 (0)	0 (0)	1.02	0.92-1.13	0.674			
Piperacillin-tazobactam days, median (IQR), days	0 (0–2.18)	0 (0)	1.04	0.96-1.14	0.352			
Meropenem days, median (IQR), days	0 (0–5.94)	0 (0)	1.15	1.06-1.25	0.001			
Vancomycin days, median (IQR), days	2.58 (0–8)	0 (0–2.18)	1.10	1.04-1.17	0.002	1.04	0.95-1.15	0.401
Neutropenia days, median (IQR), days	1 (0–10)	0 (0–1)	1.08	1.03-1.14	0.003	1.04	0.96-1.11	0.341
Hypoalbuminaemia days, median (IQR), days	13 (7.5–20)	5.5 (2–14.5)	1.08	1.04-1.12	<0.001	0.97	0.91-1.04	0.435
Central line use	94 (81)	55 (47)	5.22	2.56-10.66	<0.001	3.06	0.94-9.99	0.063
Mechanical ventilation	29 (25)	7 (6)	5.40	2.08-14.02	0.001			
Urinary catheter	57 (49)	27 (23)	3.50	1.84-6.65	<0.001	2.86	1.09-7.53	0.033
Parenteral nutrition	28 (24)	8 (7)	3.86	1.68-8.86	0.001			

Note:

Data are number (%) of patients unless indicated otherwise.

^aThird generation cephalosporins include cefotaxime, ceftriaxone, and ceftazidime.

^bFluoroquinolones include moxifloxacin, norfloxacin and ciprofloxacin.

many earlier studies [12,13,16,17,19–22,24,27,28,30]. Exposure to anti-anaerobic antibiotics has been linked to VRE gastrointestinal tract colonisation [45] and bacteraemia [10,46]; however, the VRE genotype was either *vanA* VRE [10,46] or not determined [45]. In our study, an increase in duration of therapy with metronidazole (an anti-anaerobic antibiotic) was linked to VRE bacteraemia. Whilst exposure to metronidazole may be a marker for bacteraemia with suspected intra-abdominal source, this was not explored as it was beyond the scope

of the current work. A recent study reported an association between increased ceftriaxone usage and VRE bacteraemia (genotype not reported) [29]. An association with ceftriaxone therapy, however, was not observed in our study which adjusted for patient co-morbidities. Although VRE overgrowth and subsequent VRE colonisation and/or infection may occur with vancomycin exposure [11,13], multivariable analysis suggests that the use of vancomycin was not associated with increased odds of VRE bacteraemia in this study. This is probably

Table 3 Factors associated with VSE bacteraemia

Factors associated with VSE bacteraemia	VSE cases (n = 116)	Controls (n = 116)	Univariable			Multivariable		
			OR	95% CI	p-value	OR	95% CI	p-value
Age, median (IQR), years	63.5 (51–76)	58 (44–68)	1.02	1.00-1.04	0.019	1.01	0.99-1.03	0.305
Female	44 (38)	53 (46)	0.74	0.44-1.23	0.243			
Transfer from another hospital	21 (18)	14 (12)	1.64	0.77-3.46	0.198			
Unit of admission								
Non-haematology/oncology to read Non-haematology/oncology	73 (63)	49 (42)	Reference			Reference		
Haematology/oncology	43 (37)	67 (58)	0.04	0.01-0.30	0.002	0.08	0.01-0.74	0.026
ICU admission in prior 30 days	29 (25)	13 (11)	2.60	1.25-5.39	0.010	1.71	0.52-5.58	0.373
CDS-VRE score, median (IQR)	0 (0–1)	0 (0–1.6)	0.89	0.66-1.20	0.446			
<i>Clostridium difficile</i> toxin positive	2 (2)	1 (1)	2.00	0.18-22.06	0.571			
Infection(s) due to pathogens other than Enterococci	43 (37)	34 (29)	1.45	0.82-2.56	0.201			
Gastrointestinal disease	64 (55)	38 (33)	3.00	1.60-5.62	0.001	2.29	1.05-4.99	0.037
Liver disease	13 (11)	15 (13)	0.71	0.23-2.25	0.566			
Haematological malignancy	35 (30)	63 (54)	0.15	0.06-0.39	<0.001	0.40	0.12-1.33	0.134
Bone marrow transplantation type								
Nil	105 (91)	100 (86)	Reference			Reference		
Autologous	2 (2)	7 (6)	0.29	0.06-1.38	0.118			
Allogeneic	9 (8)	9 (8)	1.00	0.38-2.66	1.000			
Ceftriaxone days, median (IQR), days	0 (0–0.5)	0 (0)	1.10	0.99-1.24	0.088			
Third generation cephalosporin days, median (IQR), days ^a	0 (0–1)	0 (0–0.49)	1.03	0.94-1.13	0.523			
Fluoroquinolone days, median (IQR), days ^b	0 (0–1.04)	0 (0–2.42)	0.96	0.91-1.02	0.190			
Metronidazole days, median (IQR), days	0 (0)	0 (0)	1.23	1.06-1.43	0.007	1.23	1.02-1.48	0.032
Ticarcillin-clavulanic acid days, median (IQR), days	0 (0)	0 (0)	1.02	0.93-1.11	0.711			
Piperacillin-tazobactam days, median (IQR), days	0 (0)	0 (0)	0.89	0.79-1.00	0.054			
Meropenem days, median (IQR), days	0 (0)	0 (0)	1.00	0.92-1.08	0.934			
Vancomycin days, median (IQR), days	0 (0–1.25)	0 (0–2.18)	0.97	0.92-1.03	0.343			
Neutropenia days, median (IQR), days	0	0 (0–1)	0.98	0.94-1.02	0.344	1.00	0.94-1.06	0.911
Hypoalbuminaemia days, median (IQR), days	7 (1–16)	5 (1–13.5)	1.01	0.98-1.05	0.479	1.00	0.95-1.05	0.888
Central line use	59 (51)	55 (47)	1.17	0.67-2.05	0.572			
Mechanical ventilation	17 (15)	7 (6)	2.67	1.04-6.81	0.040			
Urinary catheter	46 (40)	27 (23)	2.12	1.19-3.77	0.011	1.16	0.47-2.88	0.741
Parenteral nutrition	16 (14)	8 (7)	2.00	0.86-4.67	0.109			

Note:

Data are number (%) of patients unless indicated otherwise.

^aThird generation cephalosporins include cefotaxime, ceftriaxone, and ceftazidime.

^bFluoroquinolones include moxifloxacin, norfloxacin and ciprofloxacin.

due to a reduction in bias [33,47] as the present study did not use VSE as controls, in contrast to studies that had included VSE patients as controls [11,13]. In this study, the controls without enterococcal bacteraemia have had exposure to vancomycin. Thus, a comparison of VRE to VSE bacteraemia patients could be made to identify factors linked to VRE bacteraemia; however, we chose to compare VRE bacteraemia patients to controls without enterococcal bacteraemia in a case-case–control study as it will minimise the selection bias that affects

the identification, and the magnitude, of the effect due to vancomycin [33,47]. To further minimise selection bias related to choice of controls in the current study, VSE patients and controls were randomly chosen and matched to VRE cases for time of admission and wherever possible, unit of admission.

Similar to studies that demonstrated VRE bacteraemia was associated with exposure of patients to VRE contaminated ‘exogenous’ sources [16,31], urinary catheter use was independently associated with the development

of VRE bacteraemia. The need for a urinary catheter may also be an indicator of severe underlying illness [16]. Compared to an earlier study that only considered hypoalbuminaemia and neutropenia in a binary manner (i.e. presence or absence) [31], in the present study the durations of these conditions were found to be linked to VRE bacteraemia. The use of a continuous variable (i.e. duration) provides a more robust measure of exposure to these potential factors linked to disease.

The duration of metronidazole therapy was linked to VSE bacteraemia, similar to our finding for *vanB* VRE bacteraemia. However, other factors linked to disease differed between these two types of bacteraemia. We found that a history of gastrointestinal disease was associated with VSE bacteraemia. Changes in the gastrointestinal tract may predispose to the migration of gut microorganisms such as enterococci, increasing the link to VSE bacteraemia [48]. Due to the difficulty in matching VSE cases to VRE cases from the haematology/oncology unit, we adjusted for unit of admission in the multivariable analysis for VSE bacteraemia. Interestingly, admission to the haematology/oncology unit compared to other units was associated with reduced odds of VSE bacteraemia. This finding may be due to an unmeasured confounder such as exposure in this group of patients to antibiotics that are active against VSE, thereby reducing the odds of VSE bacteraemia. Unlike earlier studies that did not adjust for duration of hypoalbuminaemia and neutropenia [31,38], the present study found no association between the duration of low albumin and neutrophil levels, and odds of VSE bacteraemia.

Through this case-case-control study we were able to differentiate the factors associated with VRE and VSE bacteraemia. It is recognised that data collected retrospectively may be subject to variability in reporting from different clinicians and missing data. Whilst the effect of individual enterococcal species on the results of this study was not specifically studied given the sample size, the potential effects of enterococcal species on study findings were accounted for in the analysis. Failure to adjust for confounding may result in falsely elevated or reduced odds ratio [49]. Accordingly, multivariable analyses were also performed in the current study to minimise bias associated with confounding.

This study, the largest published case-case-control study involving only *vanB* VRE bacteraemia has identified and differentiated the factors associated with *vanB* VRE and VSE bacteraemia. VSE bacteraemia was linked to a history of gastrointestinal disease. In contrast, a higher burden of patient co-morbidities and urinary catheter use were associated with *vanB* VRE bacteraemia.

Competing interest

DCMK has sat on advisory board for Merck, Sharp & Dohme, and Pfizer. He receives financial support (not related to the current work) from Pfizer,

Novartis, Merck and Gilead Sciences. All other authors: No relevant disclosures.

Authors' contributions

ALYC was involved in the design of the study, carried out the data collection, performed the statistical analyses, drafted the manuscript. TP, BN, DS, MLG was involved in the design of the study and critical review of the manuscript, and advised on data collection. RN and DK participated in the design of the study, advised on data collection, and helped to draft the manuscript. All authors read and approved the final manuscript.

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