ORIGINAL ARTICLE

Risk factors and clinical outcomes for vancomycin-resistant enterococcus bacteraemia in hospitalised cancer patients in Pakistan: A case-control study

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Abstract

Objective: To compare the risk factors and outcomes of vancomycin-resistant enterococcus with vancomycin-sensitive enterococcus bacteraemia among hospitalised cancer patients.

Methods: The retrospective, case-control study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data of cancer patients whose blood culture grew either vancomycin-sensitive or vancomycin-resistant enterococcus from January 2012 to December 2014. Multivariable logistic regression analyses were used to determine the factors associated with the development of vancomycin-resistant enterococcus bacteraemia and 12-week mortality. Stata 11 was used for data analysis.

Results: Of the 138 cases, 111(80%) were selected, of which 46(41.44%) were of vancomycin-resistant and 65(58.55%) were of vancomycin-sensitive enterococcus. Length of hospital stay prior to bacteraemia (adjusted odds ratio 1.18; 95% confidence interval 1.08-1.28) and use of vancomycin 30 days before the onset of bacteraemia (adjusted odds ratio 9.4; 95% confidence interval 1.70-52.19) were significant risk factors for the development of vancomycin-resistant enterococcus bacteraemia. The overall 12-week mortality rate was 29(63%) for patients with vancomycin-resistant bacteraemia and 28(43.1%) for vancomycin-sensitive enterococcus bacteraemia patients. Risk factors for mortality included the presence of shock at the time of the onset of bacteraemia (adjusted odds ratio 32.91; 95% confidence interval 3.02-358.81).

Conclusion: The length of hospital stay and prior exposure to vancomycin were significant risk factors for the occurrence of vancomycin-resistant enterococcus bacteraemia.

Keywords: Enterococci, Vancomycin-resistant, Vancomycin-sensitive, Bacteraemia. (JPMA 66: 829; 2016)

Introduction

Vancomycin-resistant enterococcus (VRE) infections are a cause of significant morbidity and mortality among patients with underlying malignancy.[1] Enterococci are part of normal human intestinal flora, but prolonged use of broad spectrum antibiotics, which alters the gut dynamics, favours their growth which may be a predictor of subsequent bacteraemia in immunocompromised individuals.

The use of vancomycin has continued to expand because of increased number of patients being infected by methicillin-resistant staphylococcus aureus (MRSA). VRE has been increasingly isolated from wounds, urinary tracts, tracheal aspirates, intra-abdominal infections, skin and soft tissue infections and central lines, but blood stream infections (BSI) are a major cause of morbidity and mortality among cancer patients. The mortality caused by VRE BSI among cancer patients has been documented to be 37%.[2]

Resistance of enterococci to vancomycin was first reported in Europe in 1986.[3] Enterococci have the remarkable ability to survive on the surfaces and in health care environment for at least seven days. Other patients colonised with VRE are also an important source of infection transmission. Multiple risk factors have been described in previous studies linked with development of VRE bacteraemia that include neutropenia, immunosuppression,[4] location in ICU,[5] multiple or prolonged hospitalisations[6] and prolonged use of multiple antibiotics especially vancomycin, third-generation cephalosporin and metronidazole.[7] Other RFs include exposure to multiple devices including central lines and prior history of transplant or gastrointestinal or urinary tract surgery.[8] Limited data is available on the prevalence of VRE isolates from Pakistan. This study was planned to identify the risk factors and outcomes for VRE bacteraemia among cancer patients.

Materials and Methods

The retrospective case-control study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC), Lahore, Pakistan, and comprised

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data of cancer patients whose blood culture grew either vancomycin-sensitive enterococcus (VSE) or VRE from January 2012 to December 2014.

After approval from the institutional review board, cancer patients who received treatment at our centre and whose blood culture grew enterococcus were included. Patients who were lost to follow-up or had incomplete data were excluded. In cases where a patient had more than one episode of enterococcal bacteraemia (EB), only the first one was included.

Patients with VRE bacteraemia were designated as "cases" and those with VSE bacteraemia as "controls."

Data was collected from the hospital's information system on a pre-designed printed proforma regarding patient's age, gender, type of malignancy (solid versus haematological), Acute Physiological and Chronic Health Evaluation (APACHE II) score in the first 24 hours after bacteraemia and co-morbid conditions. Source of bacteraemia was determined by isolation of VRE/VSE from different body specimens (wound, sputum, tracheal aspirates, and urine). Data also included the location of patient (intensive care unit [ICU] vs. non-ICU), length of hospital stay before and after bacteraemia, length of ICU stay before the onset of bacteraemia, length of mechanical ventilation at the onset of bacteraemia, origin of bacteraemia (community acquired vs. healthcare), use of immunosuppressive medications and gastrointestinal / urogenital surgery or transplant 30 days prior to bacteraemia, and exposure to invasive devices like central lines (tunnelled vs. non-tunnelled), endotracheal tubes, haemodialysis catheters, nasogastric tubes, urinary catheters, drains, gastrostomy tubes and nephrostomy tubes.

Vital signs were checked and presence or absence of shock was documented at the onset of bacteraemia. Absolute neutrophil count (ANC) was documented for each case. Other measured variables included documentation of disseminated intravascular coagulation (DIC) score and respiratory dysfunction.

Prior use of antibiotics along with their duration of use was documented, including for vancomycin, teicoplanain, carbapenems, piperacillin, tazobactam, quinolones, third-generation cephalosporins, penicillin, metronidazole, polymixin and colistin. Use of steroids and omeprazole along with their duration of use was also noted. Outcome was measured in terms of survival or death in days after bacteraemia.

For the purpose of the study, neutropenia was defined as ANC of less than 500 cells/µL, and profound neutropenia as ANC of less than 100 cells at the onset of bacteraemia.

Immunosuppression was defined as current use of medications known to depress granulocyte or lymphocyte function.

Immunosuppressive medications were chemotherapeutic agents. Polymicrobial infection was defined by the presence of two or more organisms including fungi from the same blood sample.

Respiratory dysfunction was defined as the receipt of mechanical ventilation at the onset of bacteraemia.

Long-term receipt of mechanical ventilation was defined as requirement of mechanical ventilation for at least 30 days.

Prolonged hospitalisation was defined as a stay of more than seven days.

Prolonged use of antibiotics was defined as use of antibiotics for more than seven days.

Multiple antibiotic use implied use of two or more antibiotics.

BSIs were defined according to the US Centres for Disease Control and Prevention (CDC) criteria for the definition of nosocomial infections.[9]

DIC score was calculated using the International Society of Thrombosis and Haemostasis (ISTH) standards.[10]

APACHE II score in the first 24 hours of bacteraemia was used to classify the severity of disease.[11]

Stata 11 was used for data analysis. Normality of data was checked using Shapiro-Wilk test. Comparisons between characteristics of patients with VRE and VSE bacteraemia were done using parametric tests: t-test for continuous variable and chi-square test for categorical variables.

To assess several risk factors associated with the likelihood of developing VRE, we tested a model using univariable and multivariable logistical regression analyses. The risk factors included in the model were based on the findings from previous studies.[4-8] All statistical tests were two-sided with p=0.05.

Results

Of the 138 episodes observed, 111(80%) were selected. Of them, 46(41.44%) were 'cases' and 65(58.55%) were 'controls'.

The cases and controls were similar with respect to age, gender, co-morbids and total episodes of bacteraemia (Table-1). Enterococcal faecium (E.faecium) bacteraemia

Table-1: Demographic characteristics and source of infection of patients with VRE bacteraemia and patients with VSE bacteraemia.

Characteristics	VRE bacteraemia		VSE bacteraemia		p
	N=46	95% CI	N=65	95% CI	
Age group; N (%)					
Paediatric	28 (60.9)		32 (49.2)		0.25
Adult	18 (39.1)		33 (50.8)		
Age in years; Mean (SD)	20.2 (19.9)	14.3 - 26.1	25.8 (23.6)	20.0 - 31.7	0.19
Sex; N (%)					
Female	15 (32.6)		16 (24.6)		0.39
Male	31 (67.4)		49 (75.4)		
Comorbid conditions; N (%)					
None	35 (76.1)		49 (75.4)		0.82
Any	11 (23.9)		16 (24.6)		
Type of primary malignancy; N (%)					
Solid organ	12 (26.1)		33 (50.8)		0.01
Haematological	34 (73.9)		32 (49.2)		
Subtype; N (%)					
E. faecalis	2 (4.3)		1 (1.5)		<0.01
E. faecium	16 (34.8)		3 (4.6)		
E. gallinarum	1 (2.2)		0 (0)		
Enterococcus specie not specified	27 (58.7)		61 (93.8)		
Polymicrobial infection; N (%)					
No	38 (82.6)		36 (55.4)		<0.01
Yes	8 (17.4)		29 (44.6)		
Total episodes of bacteraemia; N (%)					
1	38 (82.6)		57 (87.7)		0.58
2 or more	8 (17.4)		8 (12.3)		
APACHE-II score in 24 hours after bacteraemia; Mean (SD)	22.7 (8.5)	20.2 - 25.2	17.8 (5.4)	16.5 - 19.2	<0.01
Absolute neutrophil count					
More than 500	14 (30.43)		33(50.77)		0.05
Zero count	32 (69.57)		32(49.23)		
Community/health care associated; N (%)					
Community acquired	0 (0)		9 (13.8)		0.01
Health care associated	46 (100)		56 (86.2)		
Source of infection; N (%)					
Unknown	21 (45.65)		40 (61.54)		<0.01
IV catheter	20 (43.48)		9 (13.85)		
UTI	1 (2.17)		7 (10.77)		
Intra-abdominal infection including cholangitis	0 (0.00)		5 (7.69)		
More than one focus of infection	4 (8.70)		4 6.15)		

Values are mean (±standard deviation)
SD: Standard deviation
VRE: Vancomycin-resistant enterococcus
VSE: Vancomycin-sensitive enterococcus
CI: Confidence interval
E. faecalis: Enterococcus faecalis
E. faecium: Enterococcus faecium
E. gallinarum: Enterococcus gallinarum
APACHE: Acute Physiological and Chronic Health Evaluation
IV: Intravenous
UTI: Urinary tract infections.

was more common in the VRE group with 16(34.8%) incidences. Patients with haematological malignancies were found more prone to developing VRE bacteraemia compared to those with solid organ malignancies (p=0.01). Polymicrobial infections were more common among controls (p=<0.01). Patients with VRE bacteraemia were found to have higher APACHE II score compared to those with VSE BSIs (p=<0.01). There was no significant difference

Table-2: Risk factors for VRE bacteraemia among hospitalised cancer patients.

Characteristics	VRE bacteraemia		VSE bacteraemia		p
	N=46	95% CI	N=65	95% CI	
Location of patient at onset of bacteraemia; N (%)					
Intensive care unit	23 (50.0)		9 (13.8)		
Inpatient floor	23 (50.0)		41 (63.1)		<0.01
Others (ER /OPD)	0 (0)		15 (23.1)		
Length of hospital stay at onset of bacteraemia; Mean (SD)	17.1 (8.9)	14.5 - 19.8	5.4 (7.3)	3.6 - 7.2	<0.01
Length of ICU stay at onset of bacteraemia; Mean (SD)	4.7 (6.2)	2.9 - 6.5	1.4 (3.5)	0.5 - 2.2	<0.01
Length of mechanical ventilation at onset of bacteraemia; Mean (SD)	3.3 (5.8)	1.6 - 5.0	1.1 (3.7)	0.2 - 2.0	0.02
Number of hospital admissions since registration (prior to index hospitalisation); Mean (SD)	3.0 (3.3)	2.0 - 4.0	3.7 (4.4)	2.6 - 4.8	0.4
Central venous catheter; N (%)					
Non tunnelled	24 (52.2)		12 (18.6)		<0.01
Tunnelled	11 (23.91)		21 (32.31)		
None	11 (23.91)		32 (49.23)		
Prolonged use of multiple antibiotics for 7 days; N (%)					
No	5 (10.87)		54 (83.08)		<0.01
Yes	41 (89.13)		11 (16.92)		
Use of immunosuppressive drugs in last 30 days; N (%)					
No	10 (21.7)		21 (32.3)		0.28
Ye	36 (78.3)		42 (67.7)		
Gastrointestinal/genitourinary surgery or transplantation within 30 days prior to bacteraemia; N (%)					
No	38 (82.6)		60 (92.3)		0.14
Yes	8 (17.40)		5 (7.70)		
Exposure to devices; N (%)					
No exposure	7 (15.2)		18 (27.7)		<0.01
Exposure to at least 2 devices	19 (41.3)		43 (66.1)		
Exposure to multiple devices	20 (43.5)		4 (6.2)		

Values are mean (±standard deviation)
SD: Standard deviation
VRE: Vancomycin-resistant enterococcus
VSE: Vancomycin-sensitive enterococcus
CI: Confidence interval
ER: Emergency room
OPD: Outpatient department
ICU: Intensive care unit.

in ANC between cases and controls (p=0.05). All VRE 46(100%) and most of the VSE 56(86.2%) bacteraemia were health-care associated (p=0.01); intravenous (IV) catheter was the main source of infection for both (p=<0.01).

There was no difference in the length of mechanical ventilation before bacteraemia, number of hospitalisations before the index case of bacteraemia, use of immunosuppressive medications and gastrointestinal / genitourinary surgery or transplantation within 30 days prior to bacteraemia between the cases and the controls (Table-2). However, 23(50%) of the cases were in ICU at the onset of bacteraemia compared to 9(13.8%) of controls (p<0.01).

Mean length of hospital stay for cases before the onset of bacteraemia [17.1±8.9 days; 95% confidence interval (CI): 14.5-19.8] was significantly higher compared to controls [5.4±7.3 days; 95% CI: 3.6-7.2] (p=<0.01).

We looked at the use of drugs, especially antibiotics, 30 days prior to the onset of bacteraemia. Empiric use of antibiotics including vancomycin, teicoplanin, carbapenams, piperacillin/tazobactam, metronidazole, colistin and other drugs, including steroids and omeprazole, was significantly higher among the cases compared to the controls (p=<0.01).

Multivariable logistic regression analyses showed that length of hospital stay before the onset of bacteraemia and prior exposure to vancomycin were major risk factors for VRE bacteraemia.

Patients with VRE bacteraemia were significantly less

Table-3: Outcomes in patients with VRE bacteraemia and those with VSE bacteraemia.

Characteristic	VRE bacteraemia N=46	VSE bacteraemia N=65	p
Survival at 12 weeks after onset of bacteraemia; N (%)			
Yes	17 (37.0)	37 (56.9)	0.05
No	29 (63.0)	28 (43.1)	
Survival in days after onset of bacteraemia			
(for patients who did not survive to 12 weeks); Mean (95% CI)	14.5 (8.0-20.9)	19.7 (12.7 - 26.6)	0.26
Length of hospital stay after bacteraemia; Mean (SD)	11.4 (9.1)	7.8 (8.8)	0.04
Total duration of ICU stay; Mean (SD)	6.6 (8.3)	1.7 (4.1)	<0.01
Glasgow coma scale			
15	29 (63.04)	55 (84.62)	<0.01
10-14	5 (10.86)	6 (9.23)	
<10	12 (26.08)	4 (6.15)	
Shock			
No	28 (60.87)	58 (89.23)	<0.01
Yes	18 (39.13)	7 (10.77)	
Respiratory dysfunction requiring ventilation			
No	22 (47.83)	54 (83.08)	<0.01
Yes	24 (52.17)	11 (16.92)	
DIC score); Mean (95% CI)	3.0 (2.2 - 3.7)	1.3 (0.9 - 1.6)	<0.01

Values are mean (±standard deviation)
SD: Standard deviation
VRE: Vancomycin-resistant enterococcus
VSE: Vancomycin-sensitive enterococcus
CI: Confidence interval
DIC: Disseminated intravascular coagulation.

Table-4: Univariable and multivariable logistic regression analyses to assess the risk factors for mortality.

Characteristics	Univariable analysis		Multivariable analysis	
	Odds ratio	95% CI	Adjusted odds ratio	95% CI
Paediatric (Compared to adults)	0.768	0.36-1.63	1.01	0.35- 2.84
Male (Compared to females)	1.17	0.51-2.71	1.43	0.46-4.39
Haematological malignancies (Compared to solid ones)	1.01	0.47-2.17	0.68	0.24-1.94
Location in hospital at onset of bacteraemia (Compared to patients in ICU)				
Inpatient	0.14	0.05-0.41	1.66	0.36-7.60
Others (OPD / ER)	0.15	0.03-0.60	3.89	0.45-33.15
APACHE-II score at onset of bacteraemia	1.14	1.05-1.22	1.05	0.95-1.15
Length of hospital stay in days before onset of bacteraemia	1.06	1.01-1.11	1.009	0.94-1.07
Shock(Compared to patients not in shock at onset of bacteraemia)	38.54	4.93-301.31	28.34	2.57-312.44
DIC score	1.43	1.16-1.76	1.11	0.78-1.57
Received vancomycin within 4 weeks prior to bacteraemia	3.42	1.56-7.51	3.14	0.98-10.00

CI: Confidence interval
ICU: Intensive care unit
DIC: Disseminated intravascular coagulation
ER: Emergency room
OPD: Outpatient department
APACHE: Acute Physiological and Chronic Health Evaluation.

likely (p=0.05) to survive for 12 weeks compared to patients with VSE bacteraemia (Table-3). Among those who did not survive for 12 weeks, the mean survival time was 14.5±8 days for the cases and 19.7±12.7 days for the controls. Among the cases, 18(39.1%) had shock at the time of bacteraemia, compared to 7(10.7%) controls (p=<0.01). There were 24(52.2%) cases requiring mechanical ventilation at the time of bacteraemia compared to 11(16.92%) controls (p=<0.01). Similarly, mean DIC score was higher among cases (p=<0.01).

Risk factors for mortality were also worked out (Table-4). Patients who were in shock at the onset of bacteraemia were 28.3 times (95% CI: 2.57-312.44) more likely to die within 12 weeks compared to those who were not. Moreover, patients who received carbapenems or omeprazole within four weeks prior to bacteraemia were 3.98 times (95% CI: 1.09-14.51] and 3.15 times (95% CI: 1.12-8.78) more likely to die within 12 weeks compared to those who did not receive these drugs.

Discussion

Enterococcal infections have emerged as one of the leading causes of nosocomial infections.[12] Vancomycin resistance among enterococci has become an increasingly important concern for hospitals in recent years.[7] Previous studies have documented that patients with cancer are at high risk of acquiring VRE and developing VRE BSI.[13]

Little is known about the prevalence of VRE bacteraemia in Pakistan, especially among cancer patients. One study carried out in Rawalpindi showed that the proportion of VRE among all isolates other than blood was 11.6%.[14] Another study involving child patients in ICU settings showed a high prevalence of nasal and rectal carriage of VRE strains.[15] Similar findings have been reported from elsewhere in Pakistan.[16]

Since our study site is a cancer specialised centre, the patients hospitalised on the floors or ICU are generally very sick owing to their underlying malignancy and the side effects associated with the use of chemotherapeutic agents. While in the hospital they were exposed to multiple invasive devices that increased the risk of infection with resistant organisms. Other risk factors included gastrointestinal or genitourinary surgery, bone marrow (BM) transplant, and empiric use of antibiotics among patients presenting with febrile neutropenia. We found that patients with haematological malignancies were more likely to have VRE bacteraemia and had high APACHE-II score and their likelihood of being in the ICU at the onset of bacteraemia was quite high. After adjusting for covariates, patients with VRE bacteraemia had also significantly longer hospital stay prior to bacteraemia and were less likely to survive for 12 weeks after the onset of bacteraemia compared to patients with VSE bacteraemia. The former were also significantly more likely to have received empirical therapy of several antibiotics in the 30 days prior to the onset of bacteraemia.

E. faecium made up 34.8% of VRE isolates which is consistent with the results from other studies.[17] Besides, 34(73.9%) of our patients with VRE bacteraemia had underlying haematological malignancy. This is similar to results of previously published studies[18] and also indicates that patients with haematological malignancies receive more aggressive chemotherapeutic regimens, which results in more immunocompromised state, making them prone to resistant infections. Polymicrobial infections were common among patients presenting with VSE bacteraemia compared to VRE bacteraemia in our study although other studies show different results.[19]

In this study, cases had higher APACHE II score compared to controls. This was not a surprise as patients with VRE bacteraemia tend to be sicker than those with VSE bacteraemia.[6,20]

All VRE and most of the VSE bacteraemia instances were healthcare associated which needs special attention in terms of infection control. Furthermore, we do not know the status of colonisation of our cancer patients with VRE which is a drawback of this study. It is a point to be addressed in subsequent studies because patients with VRE colonisation are more likely to become bacteraemic as focused in other studies.[4]

We found that major source of infection was IV catheters in both study groups: 20(43.5%) among cases and 9(13.85%) among controls. Other studies have shown variable sources of infections among cancer patients. In one study analysing BSI among patients with solid organ tumours, the major source of infection was found to be cholangitis (21%) followed by intra-abdominal (19.5%) and urinary tract infections (UTIs) (17%).[21]

Antibiotic use has been linked to the VRE colonisation in the gastrointestinal tract and/or infection, including bacteraemia.[7] In our study we individually analysed all possible drugs used at our hospital along with their duration of use. We found that vancomycin use was very high among VRE cases (84.78%) compared to controls (23.08%). Similarly the duration of vancomycin use among cases was also quite high (mean 10.5; CI 8.38-12.70) compared to controls (mean 1.6; CI 0.69-2.50).

Among other drugs, use as well as duration of treatment with teicoplanin, carbapenams, piperacillin/tazobactam, quinolones, metronizazole, colistin, steroids and omeprazole was significantly high among cases than controls.

VRE bacteraemia was associated with poor outcomes at 12 weeks, a finding consistent with other studies.[22] We found that length of hospital stay and prior uses of vancomycin were important RFs for bacteraemia although they were not significant predictors of mortality. A previous meta-analysis of 13 studies of patients with

VRE versus VSE bacteraemia suggested a higher risk of death related to infection by VRE and attributable mortality rate was estimated to be 17%. That study found hospital stay to be 2.9 to 27 days longer in patients with infections caused by VRE.[23]

In our study we also tried to look for association of EB with endocarditis but in majority of cases either echocardiography was not done or was normal. There was only one proven case of aortic valve endocarditis with vegetation on aortic valve secondary to VSE infection. Similarly, there was limited data available to document an association with clostridium difficile infection and enterococcal bacteraemia as stool testing for C. difficile toxin was not available in the early part of the study period.

This study has several shortcomings. First, this was a retrospective analysis of data from cancer patients who received treatment at a single centre. Second, while we controlled for several risk factors in our analyses, it is likely that patients with VRE and VSE bacteraemia in our sample differed from each other in several other respects that have remained unmeasured. Third, because of the retrospective nature of the data we could not check the colonisation status of the cases. Finally, our study had a relatively small sample size. Consequently, our analyses to assess the importance of several clinically important risk factors in mortality associated with VRE bacteraemia compared to VSE bacteraemia may have resulted in multiple comparisons problem. In a future study we plan to collect data prospectively and to undertake a more detailed analysis of the risk factors with a larger sample size.

Shock, prior use of carbapenems and omeprazole were found to be independent risk factors for mortality. Shock is a known predictor for high mortality but association with use of carbapenems and omeprazole seems indirectly related to mortality which may be adding up to the patient's underlying condition by altering the stomach pH and gut flora, favouring the growth of resistant bacteria.[24]

Conclusion

We suggest rational use of broad-spectrum antibiotics, especially carbapenems and vancomycin, to prevent the emergence of drug-resistant organisms, including VRE infections. Besides, rising VRE infections also indicate compromised infection control practices, an issue which needs more attention. Active surveillance by early detection, isolation of the patients and better compliance with hand hygiene can help reduce the spread of such infections among already compromised neutropenic cancer patients.

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