

# Multicenter Clinical Investigation of Vancomycin-resistant Enterococcus Infection

**Dongfang Lin**

Institute of Antibiotics, Huashan Hospital, Fudan University

**Yan Guo**

Institute of Antibiotics, Huashan Hospital, Fudan University

**Yang Yang**

Institute of Antibiotics, Huashan Hospital, Fudan University

**Shi Wu**

Institute of Antibiotics, Huashan Hospital, Fudan University

**Yonggui Zheng**

Institute of Antibiotics, Huashan Hospital, Fudan University

**Demei Zhu**

Institute of Antibiotics, Huashan Hospital, Fudan University

**Fupin Hu** (✉ [hufupin@fudan.edu.cn](mailto:hufupin@fudan.edu.cn))

Institute of Antibiotics, Huashan Hospital, Fudan University

---

## Research Article

**Keywords:** VRE infection, VRE, VSE, infection, surveillance, risk factor

**Posted Date:** December 9th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-110647/v1>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

---

# Abstract

**Background:** To understand the clinical characteristics of vancomycin-resistant *Enterococcus* (VRE) infection.

**Methods:** The clinical characteristics of patients with VRE infection, members of CHINET Bacterial Drug Resistance Monitoring Network, in 2016, were analyzed and compared to patients with vancomycin-susceptible *Enterococcus* (VSE) infection patients.

**Results:** Urinary tract infection was the main type, followed by bloodstream infection and intraabdominal infection. Compared to VSE infection, VRE infection is observed in more patients who have intravenous catheterization and undergo dialysis. In addition, the proportion of patients complicated with shock, multiple organ failure, and other bacterial and fungal infections is high, the clinical outcome is poor, the hospitalization expenses are high, and the hospitalization duration is prolonged. Multivariate logistic regression analysis showed that intravenous catheterization was an independent risk factor for VRE infection.

**Conclusions:** Intravenous catheterization is an independent risk factor for VRE infection. Thus, clinical measures should be strengthened to prevent VRE infection.

## Background

*Enterococcus* is an opportunistic pathogen that is widely distributed in the human intestinal tract and genitourinary tract and it is a crucial pathogen of bloodstream infection, intraabdominal infection, and genitourinary tract infection. Among these, Vancomycin-resistant *Enterococcus* (VRE) is one of the Gram-positive bacteria that has attracted much attention at present due to its high drug resistance and poor prognosis (1). The isolated rate of VRE varies greatly worldwide: 2% in Finland, 34% in Ireland and 33% in USA intensive care unit (2). Despite the rapid rise in bacterial resistance in China, the resistance rate of *Enterococcus* to vancomycin is still low. From 2005 to 2017, the resistance rate of *Enterococcus faecalis* to vancomycin fluctuated from 0–0.6% and that of *Enterococcus faecium* from 0.4–4.2%; however, the isolation rate fluctuated greatly in different regions (3, 4). Therefore, timely detection of such infection and adoption of treatment and control measures are critical to avoid the spread of such bacteria. In order to understand the current situation of VRE infection in China, the characteristics of VRE infection should be identified, and the current situation of VRE drug resistance should be mastered. This study, for the first time, carried out a multicenter prospective study on the characteristics of VRE infection in China based on the national bacterial drug resistance monitoring network to provide a reference for the general situation of VRE infection.

## Methods

This study was based on a VRE clinical survey conducted by China Antimicrobial Surveillance Network (CHINET). Herein, hospitalized or outpatient and emergency patients with positive culture results from various hospitals between January 1 and December 31, 2016, were enrolled. According to the diagnostic criteria of infection, patients featuring contaminated or colonized bacteria, as well as incomplete or missing medical history data were eliminated, while those suffering from VRE infection were recruited as research subjects for clinical investigation. Clinical data, including patient demographic information, location of onset, predisposing factors, infection condition, anti-infection treatment, and outcome, were collected from the medical history information system of each research center. The distribution of pathogenic bacteria collected from various research centers were concentrated in CHINET Central Laboratory for the determination of bacterial drug sensitivity. Subsequently, the sensitivity and drug resistance of pathogenic bacteria from bloodstream infection to various therapeutic drugs were analyzed.

## Source of Cases

Clinical and laboratory data of VRE infection of clinical specimens from CHINET research hospitals were collected according to Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/HNSN) standard for diagnostic criteria (5). According to the unified investigation plan, non-infectious bacteria were excluded from obtaining characteristic clinical data of VRE infection.

Inclusion criteria: Patients positive for VRE culture in 2016 were selected regardless of age and gender and were diagnosed as VRE infection.

Exclusion criteria: All cases that cannot be clearly diagnosed as VRE infection and whose clinical data are incomplete.

A reference is made to the following criteria for judging the acquisition of infection:

Hospital-acquired infection: Infection with specific appearances in different parts and bacteriological-positive, occurring 48 h after admission or related to the previous hospitalization.

Community-acquired infection: Conformed to clinical signs, VRE infection is excluded from a hospital-acquired infection.

Carrier status: VRE was isolated from different types of specimens from patients, but no clinical manifestation of infection was observed.

## Antimicrobial Susceptibility Test

An in vitro drug sensitivity culture of *Enterococcus* was carried out in the clinical microorganism laboratories of each participating unit, and the strain was identified out according to the national clinical examination operation procedures. On the other hand, the drug sensitivity test was carried out using the automatic tester combined with Kirby–Bauer disk agar diffusion method. Source of the disc: The drug was purchased from the National Institute for the Control of Pharmaceutical and Biological Products, and the sensitivity results were judged according to the 2016 Clinical and Laboratory Standards Institute (CLSI) drug susceptibility standard.

## Statistical analysis

The baseline situation, infection type, inducing factors, diagnosis and treatment process, and outcome (calculated according to the effective rate). This indicates that the clinical symptoms and signs of the patients are improved, and no further use of antibacterial drugs is required for the bacteriological examination results; also, other information of eligible VRE infection patients was analyzed. After collecting a VRE case, the clinical information of the patient infected with VSE of the same type was collected as the control group. In the statistical process, the continuity index was described by median (25th percentile and 75th percentile), and Wilcoxon rank-sum test was used for intergroup comparison. The classification index described the number and percentage of cases in each category, and the chi-square test or Fisher's accurate probability test was adopted. Multivariate logistic regression was used to analyze the influencing factors of drug resistance with VRE infection as the outcome. All the data were analyzed using SAS 9.4 statistical software, and  $P < 0.05$  was statistically significant.

## Ethics Statement

This research plan has been reviewed and approved by the Ethics Committee of Huashan Hospital of Fudan University in Shanghai (KY-2016-336). All methods were performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations.

## Results

### Participating sites

In 2016, a total of 20 hospitals, including 16 tertiary and 4 secondary, participated in CHINET drug resistance monitoring network. These hospitals were distributed in 9 provinces and cities, including Shanghai, Beijing, Henan, Liaoning, Sichuan, Shanxi, Guangdong, Hubei, and Hunan. Next, 97 cases of VRE infection and 95 cases of VSE infection were collected, and the information of the two groups compared to the diagnostic criteria of infection, excluding colonized bacteria.

### Demographic Characteris

The clinical characteristics of patients with VRE and VSE infections are primarily observed in males. Also, hospital-acquired infection is common. However, the age of patients with VRE infection is higher than that of those with VSE infection (75-years-old vs. 65-years-old). The VRE infection was distributed in all departments, while the number of patients who had been admitted to ICU was more than that of VSE infection (44.79% vs. 23.08%,  $P = 0.0018$ ) (Table 1).

Table 1  
Demographic Characteristics and Underlying Diseases of VRE Infection

Variable	VSE (N = 95)	VRE (N = 97)	P-value
Gender			0.3555
Male	50 (52.4%)	58 (59.8%)	
Female	43 (45.3%)	38 (39.2%)	
Absent	2 (2.1%)	1 (1.0%)	
Age (y)	65.0 (49.0, 86.0)	75.0 (62.0, 83.0)	0.0042
Infected site			0.3768
Hospital	42 (44.2%)	51 (52.6%)	
Community	46 (48.4%)	36 (37.1%)	
Transfer from other hospitals	1 (1.1%)	2 (2.1%)	
Absent	6 (6.3%)	8 (8.3%)	
Diabetes	13 (13.7%)	22 (22.7%)	0.1065
Tumors	24 (25.3%)	17 (17.5%)	0.1909
Cerebrovascular diseases	12 (12.6%)	22 (22.7%)	0.0682
Cardiovascular diseases	9 (9.5%)	23 (23.7%)	0.0081
Cardiac insufficiency	5 (5.3%)	10 (10.3%)	0.2824
Liver insufficiency	0	2 (2.1%)	0.4974
Liver cirrhosis	2 (2.1%)	0	> 0.9999
Renal insufficiency	8 (8.4%)	13 (13.4%)	0.2689
COPD	2 (2.1%)	5 (5.2%)	0.4446
Organ perforation	0	2 (2.1%)	0.4974
Immune disease	1 (1.1%)	2 (2.1%)	> 9999
Gastrointestinal bleeding	6 (6.3%)	2 (2.1%)	0.1672
Acute severe pancreatitis	1 (1.1%)	1 (1.0%)	> 9999
Postoperation of pacemaker implantation	1 (1.1%)	0	0.4948
Intestinal fistula	2 (2.1%)	0	0.2435
Urinary tract intubation	32 (33.7%)	38 (39.2%)	0.4293
Indwelling venous catheter	9 (9.5%)	31 (32.0%)	0.0001
Mechanical ventilation	17 (17.9%)	37 (38.1%)	0.0018
Dialysis	0	8 (8.3%)	0.0067
Drainage	12 (12.6%)	10 (10.3%)	0.6135
COPD: Chronic Obstructive Pulmonary Disease.			

Variable	VSE (N = 95)	VRE (N = 97)	P-value
Surgical drainage	12 (12.6%)	5 (5.2%)	0.0682
Ventricular drainage	0	5 (5.2%)	0.0594
Organ transplantation	2 (2.1%)	1 (1.0%)	0.6191
COPD: Chronic Obstructive Pulmonary Disease.			

## Vre Infection Types And Strain Distribution

Urinary tract infection was the main type of VRE infection. A total of 52 cases, accounting for 53.6% of all cases, followed by bloodstream infection (19.6%) and abdominal infection (5.2%). *Enterococcus faecium*, *Enterococcus faecalis*, and other *Enterococcus infections* were 70 (72.2%) cases, 7 (7.2%) cases, and 20 (20.6%) cases, respectively. Vancomycin was used before infection in 20.6%.

Compared to the VSE infection, VRE infection has more patients with indwelling venous catheters, catheters and dialysis, higher proportion of shock (8.3% vs. 2.1%), and multiple organ failure (8.3% vs. 3.2%), and higher proportion of infection with other bacteria and fungi (59.8% vs. 40.0%). A total of 44 (45.4%) VRE patients were in the ICU, while 21 (22.1%) VSE patients were in the ICU (Table 1).

Multivariate logistic regression analysis showed that indwelling venous catheter was an independent risk factor for VRE infection (odds ratio (OR) = 3.342, 95% confidence interval (CI): 1.379–8.099) (Table 2).

Table 2  
Multivariate Logistic Regression Analysis of Risk Factors of VRE Infection

Influencing factors	OR	95%CI	P-value
Age (y)	1.014	0.997 ~ 1.031	0.0983
Diabetes	1.321	0.578 ~ 3.022	0.5091
Cerebrovascular diseases	1.775	0.764 ~ 4.124	0.1823
Cardiovascular diseases	1.965	0.795 ~ 4.855	0.1434
Indwelling venous catheter	3.342	1.379 ~ 8.099	0.0076
Mechanical ventilation	1.829	0.856 ~ 3.908	0.1189
Surgical drainage	0.363	0.106 ~ 1.246	0.1074

Compared to VSE patients, VRE patients had poor clinical outcomes (effective rate 67.4% vs. 83.7%), higher hospitalization expenses (RMB 94,991 vs. RMB 38,248), and longer hospitalization (26.0 days vs. 21.0 days), with significant differences between the groups ( $P < 0.05$ ) (Table 3).

Table 3  
Outcome of Patients with VRE and VSE Infection

Prognosis	VSE (N = 95)	VRE (N = 97)	P-value
Clinical outcome			
Effective	77 (83.70%)	62 (67.39%)	0.0101
Improved	71 (74.7%)	58 (59.8%)	
Healed	6 (6.3%)	4 (4.1%)	
Worsen	1 (1.05%)	1 (1.03%)	
Death	8 (8.42%)	14 (14.43%)	
Transferred to other hospitals	1 (1.05%)	0	
Discharged from hospitals	5 (5.26%)	15 (15.46%)	
Absent	3 (3.16%)	5 (5.15%)	
Hospitalization expenses (yuan)	38248.70 (20131.68, 77673.76)	94991.15 (32651.47, 162273.98)	0.0007
Absent	38	43	
Days of hospitalization (days)	21.0 (13.0, 30.0)	26.0 (14.0, 44.0)	0.0475
Absent	0	2	

## Antimicrobial Susceptibility Of Vre

In vitro drug sensitivity tests showed that VRE and VSE differed markedly in drug resistance; VRE showed multiple drug resistance. The resistance rates of VRE to linezolid and fosfomycin were low: 5.7% and 25%, respectively. A VRE patient with urinary tract infection had a 50% chance to choose furantoin for treatment (Table 4).

Table 4  
Drug Resistance Rate of VRE and VSE Patients (Number of Strains [Proportion])

Classification	VSE				VRE			
	Number of cases	S	I	R	Number of cases	S	I	R
Total								
Penicillin	68	21 (30.9%)	1 (1.47%)	46 (67.65%)	66	4 (6.06%)	0	62 (93.94%)
Ampicillin	87	23 (26.44%)	0	64 (73.56%)	91	3 (3.30%)	0	88 (96.70%)
Furantoin	63	32 (50.79%)	7 (11.11%)	24 (38.10%)	74	20 (27.03%)	13 (17.57%)	41 (55.41%)
Chloramphenicol	10	6 (60.00%)	0	4 (40.00%)	9	6 (66.67%)	1 (11.11%)	2 (22.22%)
Gentamicin	86	48 (55.81%)	0	38 (44.19%)	86	37 (43.02%)	0	49 (56.98%)
Ciprofloxacin	71	10 (14.08%)	4 (5.63%)	57 (80.28%)	67	3 (4.48%)	1 (1.49%)	63 (94.03%)
Compound sulfamethoxazole	3	0	0	3 (100%)	3	2 (66.67%)	0	1 (33.33%)
Linezolid	88	88 (100%)	0	0	86	80 (93.02%)	1 (1.16%)	5 (5.81%)
Clindamycin	2	1 (50.00%)	0	1 (50.00%)	1	1 (100%)	0	0
Fosfomycin	10	6 (60.00%)	2 (20.00%)	2 (20.00%)	8	5 (62.50%)	0	3 (37.50%)
Vancomycin	95	95 (100%)	0	0	97	0	0	97 (100%)
<i>Enterococcus faecium</i>								
Penicillin	36	4 (11.11%)	0	32 (88.89%)	53	2 (3.77%)	0	51 (96.23%)
Ampicillin	50	4 (8.00%)	0	46 (92.00%)	70	2 (2.86%)	0	68 (97.14%)
Furantoin	43	16 (37.21%)	5 (11.63%)	22 (51.16%)	58	11 (18.97%)	11 (18.97%)	36 (62.07%)
Chloramphenicol	7	4 (57.14%)	0	3 (42.86%)	8	5 (62.50%)	1 (12.50%)	2 (25.00%)
Gentamicin	49	30 (61.22%)	0	19 (38.78%)	66	30 (45.45%)	0	36 (54.55%)
Ciprofloxacin	39	3 (7.69%)	1 (2.56%)	35 (89.74%)	50	1 (2.00%)	0	49 (98.00%)

Classification	VSE				VRE			
	Number of cases	S	I	R	Number of cases	S	I	R
Compound sulfamethoxazole	3	0	0	3 (100%)	3	2 (66.67%)	0	1 (33.33%)
Linezolid	51	51 (100%)	0	0	67	64 (95.52%)	1 (1.49%)	2 (2.99%)
Clindamycin	2	1 (50.00%)	0	1 (50.00%)	1	1 (100%)	0	0
Fosfomycin	9	5 (55.56%)	2 (22.22%)	2 (22.22%)	8	5 (62.50%)	0	3 (37.50%)
Vancomycin	51	51 (100%)	0	0	70	0	0	70 (100%)
<i>Enterococcus faecalis</i>								
Penicillin	22	14 (63.64%)	0	8 (36.36%)	6	1 (16.67%)	0	5 (83.33%)
Ampicillin	21	15 (71.43%)	0	6 (28.57%)	7	0	0	7 (100%)
Furantoin	15	12 (80.00%)	1 (6.67%)	2 (13.33%)	6	4 (66.67%)	0	2 (33.33%)
Chloramphenicol	2	2 (100%)	0	0	1	1 (100%)	0	0
Gentamicin	21	12 (57.14%)	0	9 (42.86%)	6	3 (50.00%)	0	3 (50.0%)
Ciprofloxacin	17	5 (29.41%)	2 (11.76%)	10 (58.82%)	6	1 (16.67%)	0	5 (83.33%)
Linezolid	21	21 (100%)	0	0	7	5 (71.43%)	0	2 (28.57%)
Fosfomycin	1	1 (100%)	0	0	0	0	0	0
Vancomycin	22	22 (100%)	0	0	7	0	0	7 (100%)

## Discussion

*Enterococcus faecalis* is intrinsic resistance to many drugs. *Enterococcus faecalis* is usually susceptible to ampicillin and high concentration gentamicin, but combined therapy should be used to achieve curative effect. However, *Enterococcus faecium* has higher drug resistance and limited treatment options, especially the VRE group. Therefore, monitoring the changes in *Enterococcus* drug resistance, discovering VRE in time, and achieving an infection control is crucial (6).

This study carried out a multicenter survey of VRE infection nationwide based on CHINET, and the results provide a reference for a comprehensive understanding of the current situation of VRE infection in China.

CHINET was initiated and established by the Institute of Antibiotics of Huashan Hospital affiliated to Fudan University and has been operational for 15 years. A myriad of data on the distribution and drug sensitivity of common bacteria in

China released every year provide reference material for the diagnosis and treatment of bacterial infections and the prevention and control of bacterial drug resistance. However, since the data were obtained from all clinical isolates with positive specimens from various hospitals, and some colonized bacteria that were not infected were mixed, the monitoring quality of bacterial drug resistance was affected. According to the case investigation of the host of the isolated strain, distinguishing infection from colonization elucidates the exact situation of *Enterococcus* infection.

Thus, secondary and tertiary hospitals participated in the survey for the above purpose. Hospitals of different regions and grades in China were selected to explore and analyze the clinical isolates of vancomycin-resistant *Enterococcus*, and the data on the distribution and drug resistance of VRE pathogenic bacteria were obtained. This information elaborated the current situation of VRE infection in China and provided a crucial basis for the prevention and treatment of VRE infection.

The survey found that the majority of adult patients infected with VRE were men of average old age. Urinary tract infection is the most common type of VRE infection, which is similar to the *Enterococcus* infection. However, the proportion of severe patients is higher, and the prognosis is poor, which is consistent with that of previous reports (7).

Literature shows that the risk factors of VRE infection include serious primary diseases, long-term hospitalization, admission to ICU, intravenous indwelling catheter, major surgery, and application of broad-spectrum antibacterial drugs (7, 8). The current study showed that in univariate analysis, cardiac insufficiency, mechanical ventilation, dialysis, and other factors are different between VRE and VSE infection. Logistic regression analysis indicated that only indwelling venous catheter is related to VRE infection and should be focused upon in such patients. In addition, VRE infection may occur when empirical vancomycin therapy is ineffective.

VRE often has multidrug resistance, which makes treating the infection challenging. According to the results of the drug sensitivity test, the drug resistance rate of VRE to other antibacterial drugs is higher than that of VSE. The drug resistance rates to linezolid and fosfomycin are 5.7% and 25%, respectively, which are still at a relatively low level and can be used for the treatment of VRE infection. Within the case of urinary tract infection, nearly half of the patients sensitive to furantoin are infected with VRE.

According to the results of this study, patients with VRE infection exhibit severe manifestations and are likely to be admitted to ICU. Although the overall isolation rate of VRE in China is not high, sufficient attention should be paid to such infection, especially for patients with indwelling venous catheters; linezolid, fosfomycin, and other drugs can be selected for treatment.

Nevertheless, the present study has some limitations. Due to the small number of clinically isolated VRE specimens in China, for the samples comprised of 0.4% of *Enterococcus faecalis* and 1.9% *Enterococcus faecium* in 2016 (3). Although 20 research centers in the country have been selected based on CHINET, the total number of cases in this study is still small. Thus, expanding the scale and including additional research hospitals will provide a comprehensive understanding of the current situation of VRE infection in China.

## Conclusions

Urinary tract infection was the main type of VRE infection, followed by bloodstream infection and intraabdominal infection. Intravenous catheterization is an independent risk factor for VRE infection.

## Abbreviations

VRE

vancomycin-resistant *Enterococcus*  
VSE  
vancomycin-susceptible *Enterococcus*  
CHINET  
China Antimicrobial Surveillance Network  
CLSI  
Clinical and Laboratory Standards Institute

## Declarations

## Ethics approval and consent to participate

This research plan has been reviewed and approved by the Ethics Committee of Huashan Hospital of Fudan University in Shanghai (KY-2016-336). Informed consent was waived by the Ethics Committee of Huashan Hospital of Fudan University in Shanghai.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## Funding

This work was supported in part by the Pfizer Investigator Initiated Research (grant number WI207259).

## Authors' contributions

DL contributed to design, analysis, and critically revised the manuscript. YG, YY, SW, YZ participated in analysis of data, and drafted the manuscript. DZ helped to design the study, drafted and critically revised the manuscript. FH contributed to design, analysis, and critically revised the manuscript. All authors read and approved the final manuscript.

## Acknowledgements

We are deeply indebted to Ruijin Hospital Shanghai Jiaotong University School of Medical, Peking Union Medical College Hospital, Beijing Hospital, Children's Hospital of Fudan University, Tongji Medical College of HUST, the First Affiliated Hospital of Guangzhou Medical University, Children's Hospital of Shanghai, the First Affiliated Hospital of Anhui Medical University, the First Affiliated Hospital of Inner Mongolia Medical University, Sir Run Shaw Hospital of Zhejiang University School of Medicine, Gansu Provincial Hospital, the First Affiliated Hospital of Xinjiang Medical University, the First Affiliated Hospital of Kunming Medical University and the First Hospital of China Medical University.

## References

1. Zirakzadeh A, Patel R. Vancomycin-resistant enterococci: colonization, infection, detection, and treatment. *Mayo Clin Proc.* 2006;81(4):529 – 36.
2. Faron ML, Ledebner NA, Buchan BW. Resistance Mechanisms, Epidemiology, and Approaches to Screening for Vancomycin-Resistant *Enterococcus* in the Health Care Setting. *J Clin Microbiol.* 2016;54(10):2436–47.
3. Hu F, Zhu D, Wang F, Wang M. Current Status and Trends of Antibacterial Resistance in China. *Clin Infect Dis.* 2018;67(suppl\_2):S128-s34.
4. Hu F, Wang M, Zhu D, Wang F. CHINET efforts to control antimicrobial resistance in China. *J Glob Antimicrob Resist.* 2020;21:76–7.
5. Jain R, Kralovic SM, Evans ME, Ambrose M, Simbartl LA, Obrosky DS, et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. *N Engl J Med.* 2011;364(15):1419–30.
6. Vehreschild M, Haverkamp M, Biehl LM, Lemmen S, Fätkenheuer G. Vancomycin-resistant enterococci (VRE): a reason to isolate? *Infection.* 2019;47(1):7–11.
7. Chiang HY, Perencevich EN, Nair R, Nelson RE, Samore M, Khader K, et al. Incidence and Outcomes Associated With Infections Caused by Vancomycin-Resistant Enterococci in the United States: Systematic Literature Review and Meta-Analysis. *Infect Control Hosp Epidemiol.* 2017;38(2):203–15.
8. Prematunge C, MacDougall C, Johnstone J, Adomako K, Lam F, Robertson J, et al. VRE and VSE Bacteremia Outcomes in the Era of Effective VRE Therapy: A Systematic Review and Meta-analysis. *Infect Control Hosp Epidemiol.* 2016;37(1):26–35.