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ORIGINAL RESEARCH

Epidemiology and Clinical Impact of Vancomycin-Resistant Enterococcus at King Abdulaziz University Hospital (2015–2022): Prevalence, Risk Factors, and Mortality

Jawahir A Mokhtar[1–3], Dalya Attallah[2], Mohammed W Al-Rabia[1], Mona Abdulrahman Alqarni[1], Khalil K Alkuwaity[3,4], Yousef Almoghrabi[5,6], Hussam Daghistani[5,6], Mazen A Ismail[7], Asim T Sharif[7], Bayan Redwan[7], Alyaa M Ajabnoor[8], Ohood S Alharbi[9], Ibrahim Mohammed Abu[10], Wafaa Alhazmi[4], Mohammed Mufrrih[4,11], Ahmad M Sait[4,6], Abdelbagi Alfadil[1,12], Yassir Daghistani[13], Hattan Jamal Momin[14], Karem Ibrahem[1,2]

[1]Department of Clinical Microbiology and Immunology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia; [2]Department of Clinical Microbiology Laboratory, King Abdulaziz University Hospital, Jeddah, 21589, Saudi Arabia; [3]Vaccines and Immunotherapy Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [4]Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [5]Department of Clinical Biochemistry, Faculty of Medicine, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [6]Regenerative Medicine Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [7]Department of Medical Education, Faculty of Medicine, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [8]Department of pharmacy practice, Faculty of pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia; [9]Department of Microbiology and Parasitology, Faculty of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia; [10]Department of Community Medicine, Faculty of medicine, King Abdulaziz University, Jeddah, 21589, Saudi Arabia; [11]Special Infectious Agents Unit BSL-3, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia; [12]Centre of Research Excellence for Drug Research and Pharmaceutical Industries, King Abdulaziz University, Jeddah, Saudi Arabia; [13]Department of Medicine, Faculty of Medicine, University of Jeddah, Jeddah, Saudi Arabia; [14]Medical Service Center, King Abdulaziz University, Jeddah, 21589, Saudi Arabia

Correspondence: Karem Ibrahem, Department of Clinical Microbiology and Immunology, Faculty of Medicine, King Abdulaziz University, P.O. Box 80205, Jeddah, 21589, Saudi Arabia, Tel +966562525685, Email kaibrahem@kau.edu.sa

Background: *Enterococcus faecalis* and *Enterococcus faecium* are part of the human microbiota but pose significant risks in clinical settings due to increasing antimicrobial resistance. Vancomycin-resistant enterococci (VRE) are a growing concern, linked to high morbidity and mortality in hospitalized patients.

Aim: This study is the first comprehensive investigation of VRE prevalence and associated risk factors at King Abdulaziz University Hospital (KAUH) from 2015 to 2022.

Methods: Clinical samples were collected, and VRE isolates were identified using VRE Card GeneXpert, BioFire PCR, and the VITEK 2 system. Descriptive statistical analysis with Stata version 17 summarized patient characteristics, including demographics, comorbidities, hospital exposure, and laboratory findings. Categorical variables were reported as frequencies/percentages, while continuous variables were expressed as mean ± SD or median [IQR].

Results: Among 254 adult patients with VRE infections, the median age was 61 years. The most common comorbidities were diabetes, hypertension, and kidney disease. VRE infections peaked in 2021, with urine cultures being the most frequent source. Most patients had prior antibiotic exposure, particularly to vancomycin and carbapenems. *Enterococcus faecium* was the predominant species, with the *VanA* phenotype being most common. Alarmingly, 61.8% of VRE-infected patients died during the study period.

Conclusion: These findings underscore the critical need for enhanced infection control measures and antimicrobial stewardship to combat VRE and improve patient outcomes.

Keywords: vancomycin-resistant *enterococci*, AMR, mortality, risk factors, hospital infections

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Introduction

Enterococci are part of the normal microbiota in the intestinal tract and genitourinary tract of humans.[1] The genus *Enterococcus* includes Gram-positive cocci that are catalase-negative, non-spore-forming, and facultatively anaerobic. This genus includes species such as *Enterococcus faecalis, E. faecium, E. durans, E. gallinarum*, and other species.[2,3] *E. faecalis* is the most commonly found species in clinical specimens, while *E. faecium* is known for its drug resistance.[1,4] Interest in enterococci has grown not only due to the serious infections they cause but also because of their increasing resistance to many antimicrobials. Vancomycin, once one of the few effective alternatives, has seen a rise in resistance, which has now spread globally.[1]

VRE is a major pathogen among hospitalized patients, leading to significant morbidity, mortality, and increased hospital costs associated with VRE infections.[5] The detection of new VRE cases indicates cross-transmission through the hands of healthcare workers, contaminated equipment, and environmental surfaces.[6] Moreover, *enterococci* can be transferred from the gastrointestinal tract of warm-blooded animals and enter secondary environments like environmental waters, aquatic vegetation, they encounter various challenges.[7]

Significant concern arose when the first reports of VRE emerged in the mid-1980s. Since then, VRE has become a significant cause of hospital-acquired infections in the USA.[8,9] VRE have spread rapidly and are now found in hospitals across most countries.[10] The increasing prevalence of multiple antibiotic-resistant VRE infections among hospitalized patients in Saudi Arabia raises significant concerns about the epidemiology of VRE in the region.[11]

Glycopeptides exert their antibacterial effect by binding to the D-Ala-D-Ala terminus of the pentapeptide involved in bacterial cell wall synthesis, thereby sterically inhibiting transpeptidation.[12] This interaction relies on multiple hydrogen bonds between glycopeptides and the alanine residues, which are critical for the drug's activity. Resistance to glycopeptides primarily arises through modifications of the pentapeptide target, disrupting these essential hydrogen bonds.[13] Two key modifications have been identified: substitution of D-Ala-D-Ala with D-Ala-D-Ser, leading to moderate resistance, and replacement with D-Ala-D-Lac, which significantly increases resistance levels. The D-Ala-D-Lac resistance mechanism is encoded within operons consisting of *core* genes essential for resistance and *accessory* genes that, while present, are not crucial for the resistance phenotype.[12] The core gene cassette is further categorized into regulatory genes and those responsible for synthesizing D-Ala-D-Lac. For instance, in the vanA operon, the regulatory components include vanR and vanS, which control the expression of resistance genes.[12,13]

A study focused on the molecular characterization of VRE in Saudi Arabia revealed an evolving epidemiology. The findings show that VanA/VanB isolates and VanA genotype-VanB phenotype incongruent isolates, which were previously considered colonizers, are now causing clinical infections.[14]

Recent advancements in understanding enterococcal resistance have highlighted the role of specific genetic elements, including *vanA, vanB, vanC, vanD, vanE, vanG, vanL, vanM*, and *vanN*. Among these, the *vanA, vanB*, and *vanC* variants are the most commonly found in clinically significant isolates.[15] The *VanA* variant remains the most prevalent form of resistance among humans worldwide. However, in countries such as Australia and Sweden, most VRE cases predominantly carry the VanB variant.[16]

The emergence and dissemination of VRE in healthcare environments have introduced additional risks and complexities to patient management.[17] VRE is responsible for a range of healthcare-associated infections, notably bacteremia, urinary tract infections, intra-abdominal, pelvic, soft tissue infections, and endocarditis.[17–19] The majority of enterococcal infections are attributed to two species: *E. faecalis* and *E. faecium*.[17] *E. faecium* exhibits a higher level of resistance to antibiotics compared to *E. faecalis*, with over half of its pathogenic isolates showing resistance to vancomycin, ampicillin, and high levels of aminoglycosides. This makes treating infections caused by *E. faecium* particularly challenging, underscoring the significant scale of the problem.[20]

Research has identified key risk factors for VRE carriage upon intensive care unit (ICU) admission including prior hospitalization length, glycopeptide use, chronic heart failure, malignancy, insulin-dependent diabetes, and previous enterococcal infections.[21] Previous VRE colonization and antibiotic use are critical for enterococcal infection during ICU stay, with co-morbidities and patient-to-patient transmission also being significant risk factors.[22,23] A study evaluating the risk factors for VRE found that ICU patients face a high risk of nosocomial infections due to lowered immunity,

indwelling catheters, abdominal surgery, and increased antimicrobial use. This group is particularly vulnerable to penicillin-resistant VRE, with limited treatment options available.[24]

To the best of our knowledge, this study represents the first report from King Abdulaziz University Hospital to assess VRE rates over an eight-year period, from 2015 to 2022. Previously, VRE prevalence and its associated risk factors had not been examined at this institution, particularly considering recent changes in hospital infection control policies and antibiotic usage trends. This study aims to determine the VRE colonization rates among patients admitted to King Abdulaziz University Hospital and to identify key risk factors associated with VRE colonization, providing critical insights into hospital-associated infections and informing targeted strategies for prevention and control.

Methods

Sample Collection and Collection Technique

Clinical specimens testing positive for VRE were collected over an eight-year period (2015 to 2022) for bacterial isolation. This information were collected from previous medical records. This study analyzed risk factors, as well as the clinical and epidemiological characteristics of patients across different age groups who tested positive for VRE. Patients were included if they had a confirmed positive VRE culture and exhibited signs and symptoms of infection. Exclusion criteria included patients with VRE colonization without clinical signs of infection and those with incomplete medical records. Comprehensive data on underlying illnesses and co-existing conditions were collected for each patient.

The Research Ethics Committee at KAUH granted approval for the study under approval number HA-02-J-008. The protocol was rigorously reviewed, ensuring full adherence to ethical standards, and the committee permitted the study to proceed without requiring individual patient consent. This study dedicated to maintaining the highest ethical standards, strictly adhering to the Declaration of Helsinki and prioritizing patient confidentiality. All data used in this study was handled with great care to ensure privacy and full compliance with ethical guidelines. Patient isolates, routinely handled for infection diagnosis, were managed following strict ethical guidelines as per hospital standards.

Microbial Identification of Bacterial Isolates & VRE Screening for Confirmation Test

The detection of *vanA* and *vanB* genes in *Enterococcus* species is critical for managing vancomycin-resistant infections. This study evaluates VRE Card GeneXpert (Cepheid, Sunnyvale, CA, USA) demonstrated rapid and accurate detection of vancomycin resistance genes directly from clinical samples within two hours, BioFire FilmArray a real-time PCR platform identified *vanA*/*vanB* as part of Blood Culture Identification 2 (BCID2) panel which used for Blood Culture specimens, providing a pathogen profile within one hour and VITEK 2 systems (BioMérieux, Marcy-l'Étoile, Lyon, France) for the organism identification, albeit with a longer turnaround time of 12–24 hours. Together, the molecular and traditional method technologies offer a synergistic approach to accurately identify and characterize vanA/vanB isolates, facilitating timely interventions in clinical settings.[25,26]

The GeneXpert vanA/vanB assay is a qualitative test designed to rapidly detect the presence of vanA and vanB genes associated with vancomycin resistance in *enterococci* directly from clinical specimens. As a qualitative assay, it does not provide quantitative measurements; therefore, specific values for the limit of quantification are not applicable. Regarding the limit of detection, studies have demonstrated that the GeneXpert vanA assay can detect as few as 100 colony-forming units (CFU) per milliliter. This sensitivity enables the identification of vanA-positive VRE directly from rectal swabs, facilitating prompt infection control measures.[27]

Antimicrobial Susceptibility Testing (AST)

Antimicrobial susceptibility testing (AST) was performed using the VITEK 2 system (BioMérieux, Marcy-l'Étoile, Lyon, France), employing AST-GP susceptibility cards (P580 panel) specifically designed for Gram-positive bacteria, in accordance with the manufacturer's protocol. The AST-GP panel for *Enterococcus* species in the VITEK 2 system typically includes a range of antibiotics designed to assess susceptibility to commonly used antimicrobial agents such as Vancomycin, Teicoplanin, Linezolid, Daptomycin, Quinupristin-Dalfopristin, Ampicillin, Penicillin, Gentamicin (High-Level), and Streptomycin (High-Level). The VITEK 2 system autonomously processed the cards, generating

susceptibility results within 10 to 18 hours. Data were cross-referenced with the Gram-positive bacterial database for accuracy and interpreted following the Clinical and Laboratory Standards Institute (CLSI) M100 guidelines, which classify bacterial isolates as susceptible, intermediate, or resistant. This standardized approach ensured the reliability and clinical relevance of the results, which were delivered within the specified timeframe.

Statistical Analysis

Descriptive statistical analysis was performed using Stata version 17 to summarize the characteristics of patients with vancomycin-resistant *Enterococcus* (VRE) infection. Categorical variables, including sex, year of VRE infection, comorbidities, hospital ward, indwelling devices, recent antibiotic use, VRE screening results, culture sources, isolated *Enterococcus* species, and VRE phenotypes, were expressed as frequencies and percentages. Continuous variables, such as age and time from admission to culture, were presented as mean [standard deviation (SD)] for normally distributed variables, and as median [Interquartile range (IQR)] for non-normally distributed variables. This analysis provided an overview of the demographic and clinical characteristics of the study population, the distribution of comorbidities, hospital exposure factors, antimicrobial use, and laboratory findings related to VRE infections.

Results

Characteristics of VRE Infected Patients

During the observation window of this study (from 2015 to 2022), 254 adult patients were isolated with VRE. Table 1 describes the baseline characteristics of VRE infected patients. Median age of patients was 61 year, IQR 47 to 72 years. VRE infection was more prevalent on the year 2021, and least prevalent on the year 2022. The most common baseline comorbidity among VRE infected patients was diabetes mellitus (63.4%), hypertension (62.2%), kidney disease (52.4%), respiratory disease (43.7%), malignancy and receiving chemotherapy (26.4%), heart failure (21.7%), ischaemic heart disease (13%), and liver disease (12%). Of all VRE patients, 91 patients were admitted in ICU (26% in medical ICU and 9.8% in surgical ICU), 30.7% of patients were in medical ward, 15.4% were in surgical ward, 11% were in emergency

Table 1 Summary of Clinical Characteristics, Comorbidities, Hospital Settings, Antibiotic Usage, and Infection Profiles for Patients with VRE Infection (n = 254). Demographic Data, Comorbid Conditions, Hospital Ward Distribution, Recent Antibiotic Usage Within 7 days, Presence of Indwelling Devices, Isolated Enterococcus Species, and the Median Time From Admission to Culture (Days) are Presented

Characteristics	**Patients Infected with VRE (n=254)**
Male, n (%) Female, n (%) Median age (IQR)	130 (51.2) 124 (48.8) 61 (47–72)
Year of VRE infection, n (%)	
2015 2016 2017 2018 2019 2020 2021 2022	22 (8.7) 17 (6.7) 28 (11) 30 (11.8) 27 (10.6) 46 (18.1) 70 (27.6) 14 (5.5)

(*Continued*)

Table 1 (Continued).

Characteristics	Patients Infected with VRE (n=254)
Comorbidities, n (%)	
Hypertension	158 (62.2%)
Diabetes mellitus	161 (63.4)
Heart failure	55 (21.7)
Ischemic heart disease	33 (13)
Kidney disease	133 (52.4)
On haemodialysis	36 (14.2)
Liver disease	31 (12)
Respiratory disease	111 (43.7)
Malignancy (receiving chemotherapy)	67 (26.4)
Hospital ward, n (%)	
Medical ICU	66 (26)
Surgical ICU	25 (9.8)
Medicine	78 (30.7)
Surgery	39 (15.4)
Emergency	28 (11)
Others	18 (7.1)
Indwelling devices, n (%)	
Urinary catheter	96 (37.8)
Central line	33 (12.9)
Endotracheal tube	16 (6.3)
Recent antibiotic use (within 7 days) (%)	
Vancomycin	137 (53.9)
Carbapenems	128 (50.4)
Aminoglycosides	4 (1.6)
Fluoroquinolones	26 (10.2)
Trimethoprim-Sulfamethoxazole	7 (2.8)
Colistin	37 (14.6)
Teicoplanin	9 (3.5)
Tigecycline	4 (1.6)
Cefepime	5 (2)
Piperacillin-Tazobactam	33 (13)
Ceftazidime-Avibactam	9 (3.5)
VRE screening, n (%)	
Positive	11 (4.3)
Negative	12 (4.7)
Not done	231 (90.9)
Median time from admission to culture (days)	21 (10–44)
Isolated *Enterococcus Spp*, n (%)	
Enterococcus faecium	240 (94.5)
Enterococcus casseliflavus	12 (4.7)
Enterococcus faecalis	2 (0.8)

Abbreviations: N, number; %, percent; Spp, specious; IQR, Interquartile Range.

department, and 7.1% in other hospital settings. Ninety-six patients had indwelling urinary catheter (37.8%), 33 patients had central line catheter (13.7%) and 16 patient had endotracheal intubation (6.3%). More than 50% of patients (n= 137), have received vancomycin within seven days before the VRE positive culture. Moreover, recent exposure to antibiotics included; carbapenems in 50.4% of patients, followed by colistin (14.6%), Piperacillin-Tazobactam (13%), **F**luoroquinolones (10.2), Teicoplanin (3.5%) and Ceftazidime-Avibactam (3.5%).

Characteristics of VRE Isolates

The most common type of VRE culture was from urine in 118 patients (46.5%), followed by blood culture in 48 patients (18.9%), wound swab culture in 24 patients (9.5%), peritoneal fluid culture in 19 patients (7.4%), respiratory culture in 17 patients (6.7%), and the remaining were isolated from other fluid sources (Figure 1). The majority of patients (90.9%) did not receive screening for VRE. Among those who were screened for VRE (n= 23), 11 patients were positive for VRE and 12 were negative. The most commonly isolated *Enterococcus* species *Enterococcus faecium* in 94.5% off patients, followed by *Enterococcus casseliflavus* (4.7%), and *Enterococcus faecalis* (0.8%). VRE genotypic identification was only done in 107 patients and the most prevalent VRE phenotype was *VanA* in 40.9% of patients, and *VanB* in 1.2% of patients (Figure 2).

VRE Attributable Mortality

Among the 254 VRE infected patients, 157 patients (61.8%) have died during the study observation period.

Discussion

Understanding the risk factors and prevalence rate of infection is essential to effectively reduce the incidence of infections.[28] It is vital to monitor co-existing conditions and implement appropriate preventative measures.[29] This study is the first to present a comprehensive analysis of the prevalence and risk factors associated with VRE colonization

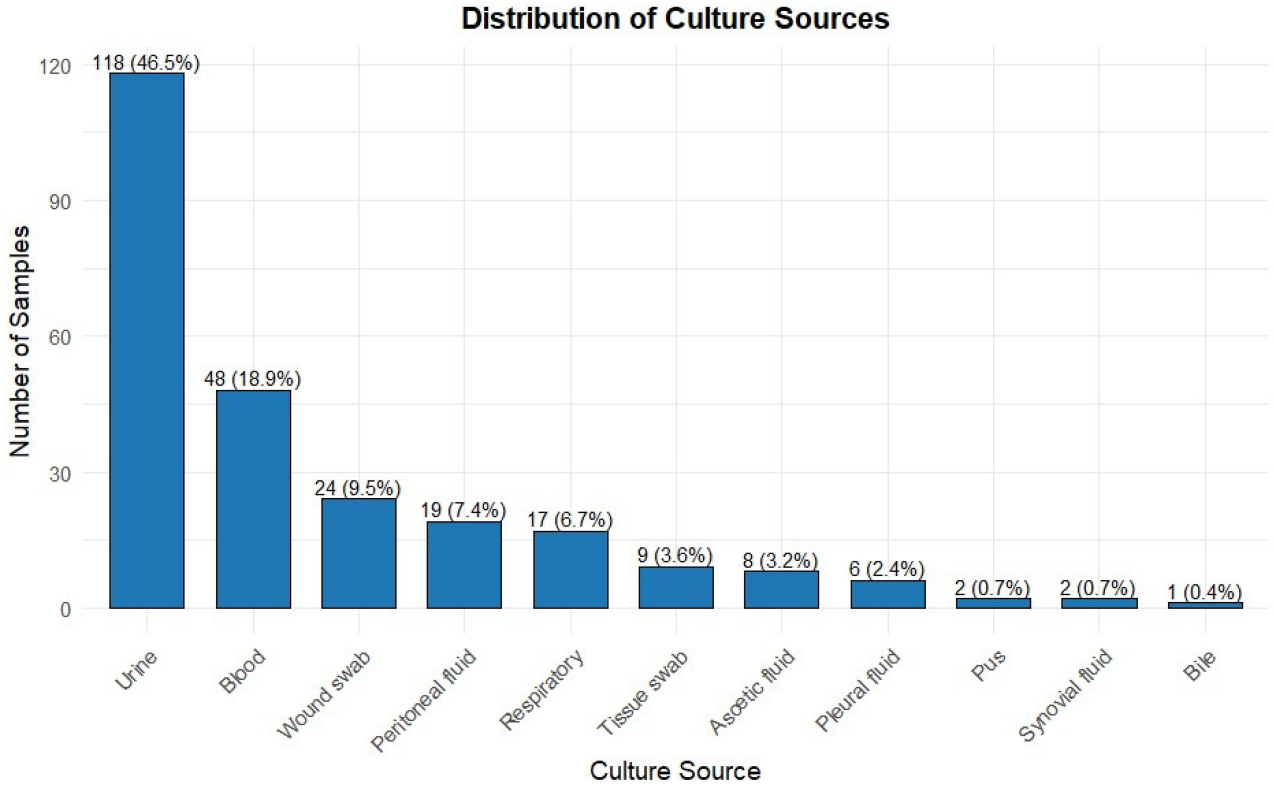

Figure 1 Distribution of Isolates according to the source of isolation.

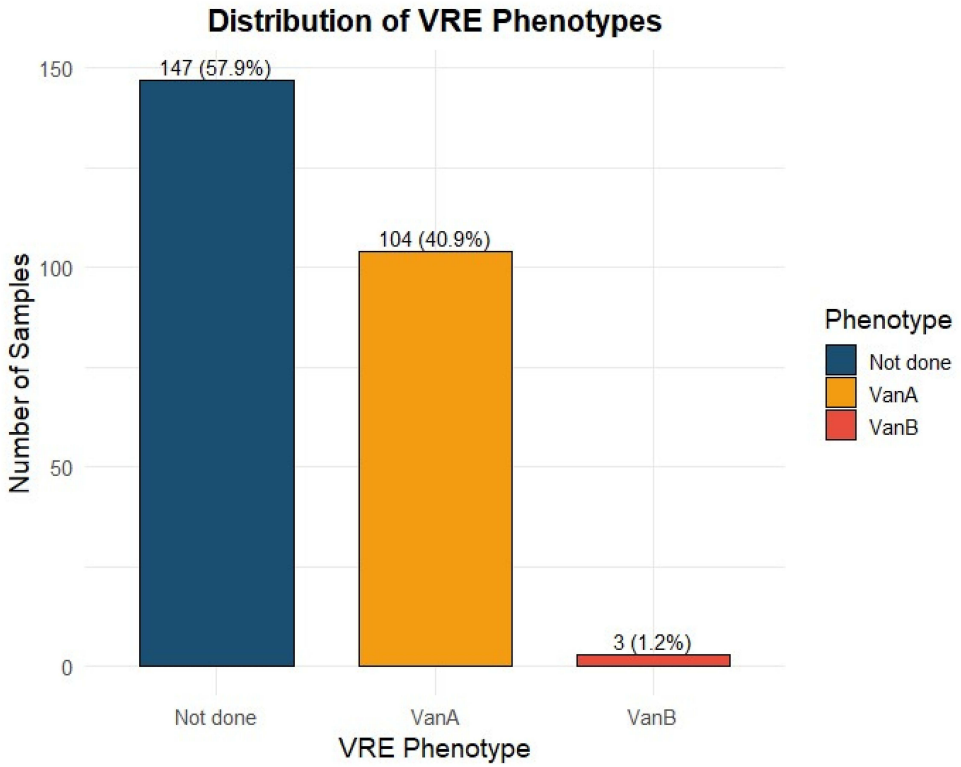

Figure 2 Distribution of VRE phenotype.

at King Abdulaziz University Hospital over an eight-year period, from 2015 to 2022. Our findings offer significant insights into the epidemiological trends, clinical implications, and challenges posed by this pathogen.

The higher prevalence of VRE infections during 2020–2021 could be attributed to a temporary lapse in strict infection control measures, as healthcare systems were overwhelmed by the COVID-19 pandemic. Moreover, the observed decrease in VRE cases in 2022 can likely be attributed to the impact of strict isolation measures and lockdown protocols implemented during the COVID-19 pandemic. These infection control measures played a crucial role in limiting patient movement, visitor access, and healthcare personnel interactions, which may have directly contributed to a reduction in VRE transmission.[30] It has been shown that while self-isolation effectively protected residents and caregivers from SARS-CoV-2 exposure, it also led to a significant decrease in mobility. This reduced movement has been associated with an increase in certain bedridden conditions, such as pressure ulcers and pressure sores, which are commonly observed in immobilized patients. However, the simultaneous isolation of both residents and caregivers within the same setting likely minimized external sources of infection, reducing the overall incidence of hospital-acquired pathogens, including VRE.[31] These findings highlight the unintended but beneficial impact of pandemic-related infection control measures on the transmission dynamics of multidrug-resistant organisms in healthcare settings.

The importance of conducting this first study lies in its ability to provide a unique and comprehensive analysis of the prevalence and risk factors associated with VRE isolated at King Abdulaziz University Hospital over an extensive eight-year period. As the first study of its kind at this institution, it fills a critical gap in understanding the local epidemiology of VRE, offering invaluable insights into its trends, clinical implications, and the challenges posed by this pathogen. By identifying key risk factors and prevalence patterns, this research lays the foundation for developing targeted infection control strategies, optimizing antimicrobial stewardship, and improving patient outcomes in the hospital setting. Furthermore, it serves as a reference point for future studies, enhancing the global understanding of VRE and its evolving resistance profiles.

This study provides a comprehensive analysis of the clinical characteristics, prevalence, and mortality predictors among patients infected with VRE in King Abdulaziz University Hospital. The findings underscore the substantial

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burden posed by VRE infections, reflected by the high mortality rate which aligns with previous reports highlighting the significant morbidity and mortality associated with multidrug-resistant enterococcal infections in hospitalized patients. It has been displayed that invasive VRE infection mortality was 64.6%, with antibiotics increasing risk.[32]

The increasing prevalence of VRE, particularly in 2021, suggests that this pathogen continues to be a growing public health concern. The predominance of VRE among patients with serious comorbidities, including diabetes mellitus, hypertension, kidney disease, and respiratory conditions, reflects the susceptibility of these high-risk groups.[33] Patients with chronic health issues often undergo repeated hospitalizations, antibiotic treatments, and invasive procedures, making them particularly vulnerable to VRE colonization and subsequent infection.[34] The high rates of ICU admissions (26% in medical ICU, 9.8% in surgical ICU) further emphasize the critical vulnerability of patients in intensive care environments, where prolonged hospital stays and exposure to invasive devices like central lines and ventilators increase the likelihood of acquiring VRE infections. Study indicates that up to 10.6% of patients admitted to the ICU are already colonized with VRE upon arrival, and an additional similar percentage will acquire VRE during their stay. Notably, initial colonization at admission significantly influences the spread of VRE within the ICU, as the likelihood of VRE-related infections closely correlates with colonization status.[21]

The study's findings indicate that urine (46.5%) and blood (18.9%) were the most common sources of VRE cultures. The high prevalence of urine samples as a primary source of VRE isolates highlights the significance of urinary tract infections as a major concern in VRE infections. Our results showed that *Enterococcus faecium* was the most prevalent VRE species, accounting for the majority of isolates, followed by *Enterococcus casseliflavus* and *Enterococcus faecalis*. This contrasts with findings from other studies, where *Enterococcus faecalis* was reported as the dominant species among VRE isolates.[35] However, our study aligns with the study indicating that *E. faecium* has become the predominant species in hospital settings, particularly among multidrug-resistant strains.[36] These findings reinforce the need for targeted infection control measures to limit the spread of *E. faecium*, which poses a greater challenge due to its intrinsic resistance to multiple antibiotics. The high incidence of urinary infections may be linked to the frequent use of urinary catheters, while bloodstream infections are particularly concerning due to their association with increased mortality and complex clinical management.[37] The predominance of *Enterococcus faecium* in 94.5% of isolates also aligns with previous studies, highlighting its increasing role as a causative agent in hospital-acquired infections due to its inherent resistance to several antimicrobials.

In Saudi Arabia, it has been demonstrated that VRE isolates were obtained from clinical specimens, with blood as the predominant source followed by urine.[38] Among the VRE isolates, *Enterococcus faecium* was the most common species. Notably, 62% of *E. faecium* isolates displayed a *vanA /vanB* genotype associated with the VanB phenotype, making it the most frequent type. Interestingly, one *vanA E. faecium* isolate also exhibited a VanB phenotype, highlighting a genotype-phenotype incongruence. These findings suggest an evolving epidemiological profile of VRE infections. The presence of *vanA/vanB* and *vanA* genotype-*VanB* phenotype incongruence strains, traditionally considered colonizers, is now being observed in clinical infections. This shift raises concerns about the potential for increased transmission and infection rates of these resistant strains, posing challenges to infection control and treatment strategies.[14] Ongoing surveillance and further investigation into the mechanisms behind these genotype-phenotype discrepancies are essential to better understand and manage the changing landscape of VRE infections in healthcare settings.

Moreover, it has been shown that a total of 228 Enterococci clinical samples were collected from various hospitals in Saudi Arabia. Following subculturing, strain isolation, and antimicrobial susceptibility testing, it was found that 82% of isolates were susceptible to vancomycin, 7% of isolates were resistant, and 11% were intermediate. Most VRE isolates were from Jeddah hospitals. The most common infections caused by *Enterococci* were urinary tract infections followed by blood and wound infections.[11]

The analysis revealed several significant predictors of mortality, including ICU admission, mechanical ventilation, and recent exposure to broad-spectrum antibiotics.[39,40] These findings emphasize the critical role of ICU care and the impact of invasive procedures on patient outcomes.[41] Mechanical ventilation, often necessary in severe cases, poses additional risks of ventilator-associated pneumonia (VAP), which complicates treatment and increases mortality risk.[42] The association between recent antibiotic exposure and mortality further underscores the need for caution in antibiotic administration, as excessive use can worsen patient outcomes by promoting resistant infections.[43]

A notable finding in this study is the strong association between prior antibiotic exposure and VRE infections. Over half of the VRE-infected patients had received vancomycin within a week prior to the positive VRE culture, while significant proportions were also exposed to carbapenems, colistin, and piperacillin-tazobactam. These antibiotics are often reserved for severe infections, and their use, particularly in high doses or over extended periods, likely contributes to the selection pressure favouring VRE colonization and infection. This pattern aligns with existing literature suggesting that broad-spectrum antibiotic use is a major driver of vancomycin resistance. Study has shown that VRE colonization in patients treated with broad-spectrum beta-lactam antibiotics, such as carbapenems and cephalosporins, can lead to the development of bacteremia.[44] By optimizing antibiotic prescribing practices, limiting unnecessary use of broad-spectrum antibiotics, and implementing targeted infection control measures, healthcare facilities can reduce selective pressure that drives VRE emergence and transmission.

The identification of *VanA* as the most prevalent phenotype in genotyped samples (40.9%) highlights the ongoing challenge of high-level vancomycin resistance in VRE infections, particularly in severely ill patients with limited treatment options. Additionally, the emergence of *vanA+/vanB+* isolates, once considered mere colonizers, underscores the evolving nature of VRE epidemiology and their increasing clinical significance. These findings emphasize the urgent need for alternative therapeutic strategies and stricter infection control measures to curb the spread of resistant strains and mitigate their impact in healthcare settings.

By conducting a detailed retrospective analysis, we have identified key risk factors that contribute to VRE colonization and infection among hospitalized patients. These factors include lowered immunity, indwelling catheter use, and increased antimicrobial usage, particularly in ICU settings. Our study highlights the critical importance of continuous monitoring and targeted interventions to address these risk factors and reduce VRE transmission.

Overall, our eight-year retrospective study provides valuable data that can inform future research and guide healthcare policies aimed at controlling VRE infections. The comprehensive understanding of prevalence, risk factors, and epidemiological trends gleaned from our findings will play a crucial role in developing effective strategies to combat this formidable pathogen and improve patient outcomes in hospital environments.

Looking forward, there is a need for more robust interventions, including enhanced VRE screening, especially in high-risk areas such as ICUs, and the development of targeted therapies to overcome resistance mechanisms. Research into novel antimicrobial agents and alternative treatments, such as bacteriophage therapy and antimicrobial peptides, could provide new avenues for managing VRE infections. Additionally, a more detailed understanding of the genomic factors contributing to VRE resistance would be beneficial for identifying potential therapeutic targets.

While this study offers valuable insights, several limitations should be considered. First, the assessment of prior antibiotic exposure was based on a retrospective review of medical records rather than a controlled prospective design. Antibiotic administration was documented from patient records, but we did not collect specimens at the time of hospital admission and then re-evaluate after a few days to assess changes in VRE colonization over time. This limits our ability to determine the exact timing and progression of VRE acquisition. Additionally, while we confirmed VRE status using the VITEK 2 system, we did not perform molecular testing for some specimens to correlate MIC values with the presence of VanA or VanB genes. Furthermore, our study was conducted at a single hospital, which may limit the generalizability of our findings to other healthcare settings. Despite these limitations, our study provides valuable insights into the clinical and epidemiological characteristics of VRE infections and highlights the potential impact of infection control measures on antimicrobial resistance trends. The retrospective design may introduce biases related to missing or incomplete data, especially for certain clinical variables, Minimum inhibitory concentration and genotypic characterizations, which were not uniformly available across all patients. Thus, future studies could benefit from multicentre designs to capture a broader population and more diverse clinical settings.

Conclusion

In summary, this study highlights the substantial mortality and clinical burden associated with VRE infections in hospitalized patients. Key risk factors, including ICU admission, mechanical ventilation, and prior antibiotic exposure, were identified as significant predictors of mortality. The findings emphasize the critical need for effective antimicrobial

stewardship, improved infection control practices, and ongoing research into alternative therapeutic options to address the challenges posed by VRE in healthcare settings.

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