Review Article

Targeting Vancomycin-Resistant Enterococci: Mechanisms of Resistance and Future Therapies

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ABSTRACT

Antibiotic resistance is a growing global health concern that is reducing the effectiveness of treatments for bacterial illnesses. Overuse and abuse of antibiotics in healthcare and agriculture has accelerated the development of resistant strains, raising treatment failure rates and mortality rates. Methicillin-resistant Staphylococcus aureus (MRSA), VRE, and multidrug-resistant Escherichia coli are examples of resistant bacteria that pose significant challenges in therapeutic settings. Resistance mechanisms include changes to the target site, efflux pumps, and the enzymatic degradation of antibiotics. The horizontal gene transfer that disperses resistance genes complicates control efforts. A multifaceted approach to addressing antibiotic resistance must include antimicrobial stewardship, the development of novel antibiotics, alternative therapies such as bacteriophages and antimicrobial peptides, and global surveillance initiatives. Vancomycin-resistant enterococci (VRE) are major public health concerns that make hospital infections more difficult to treat. The main species associated with VRE, *Enterococcus faecium* and *Enterococcus faecalis*, develop resistance through van gene clusters, which alter the bacterial cell wall to stop vancomycin binding. VRE persists and spreads because of the extensive use of antibiotics, horizontal gene transfer, and inadequate infection management. Strict infection control measures and public awareness campaigns are also essential to lessen the incidence of this epidemic. Antimicrobial peptides, bacteriophage therapy, and combination antibiotic therapy are examples of novel therapeutic approaches that are necessary due to the high morbidity rate of VRE infections and the lack of effective treatments. In this article, the mechanisms of vancomycin resistance in enterococci, its clinical implications, and strategies to mitigate its impact on global health are discussed.

Keywords: Antibiotic resistance, AMR (Antimicrobial Resistance), Immuno-antibiotics, vancomycin resistance enterococci.

INTRODUCTION

Enterococci are facultative anaerobic, Gram-positive bacteria that commonly infect the genitourinary and gastrointestinal systems of humans. They have developed into important opportunistic pathogens, particularly in immunocompromised and hospitalized individuals, despite often being harmless commensals. Healthcare-associated infections caused by enterococci include surgical wound infections, bacteremia, endocarditis, urinary tract infections, and intra-abdominal infections. Since they are naturally resistant to many common antibiotics and can acquire new resistance determinants through horizontal gene transfer, their therapeutic value has increased dramatically in recent decades. Vancomycin and other glycopeptide antibiotics have long been used as a last resort to treat Gram-positive bacterial infections that are resistant to a variety of medications. However, the emergence of vancomycin-resistant enterococci (VRE) in the late 1980s has presented a major challenge to global public health systems and healthcare providers.

Both *Enterococcus faecalis* and *Enterococcus faecium* are the most clinically significant enterococcal species; E. faecium has extremely high levels of vancomycin resistance. Because VRE can spread quickly in healthcare settings and can transfer resistance genes to other bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA), it raises serious concerns about infection management.

To provide readers with a comprehensive understanding of the virus, this review covers the epidemiology, pathogenesis, resistance mechanisms, diagnostic techniques, treatment challenges, infection control strategies, recent research advancements, and future outlooks for managing this growing threat. In hospital settings, vancomycin-resistant enterococci (VRE) are a major issue that adds to the worldwide worry about antibiotic resistance. Enterococci, particularly the opportunistic pathogens *Enterococcus faecium* and *Enterococcus faecalis*, are responsible for a variety of illnesses, including urinary tract infections, endocarditis, and bloodstream infections. Treatment of Gram-positive bacterial infections is made more challenging when the bacteria that cause them develop resistance to vancomycin, a last-resort antibiotic. When VRE was introduced and spread, it led to higher healthcare costs, longer hospital stays, and higher morbidity.

By altering the bacterial cell wall's structure, these clusters reduce the binding of vancomycin and the production of peptidoglycans. The transmission of these resistance genes from one bacterium to another, known as horizontal gene transfer, can accelerate the spread of resistance. The selection of resistant strains, which is driven by the overuse and misuse of antibiotics in clinical and agricultural settings, has made treatment options more complicated. Because of the increasing prevalence of VRE, infection prevention and treatment strategies have gained importance in hospital settings. Treatment options for VRE infections are currently limited, and they often require combination antibiotic

therapy with linezolid, daptomycin, or more modern medications like tigecycline. However, the growing resistance to these alternatives also underscores the pressing need for new antimicrobial strategies.

WHAT IS ANTIMICROBIAL AND ANTIBIOTIC RESISTANCE?

When bacteria, viruses, fungi, or parasites grow resistant to drugs meant to kill them or stop their growth, they are said to have developed antimicrobial resistance (AMR). These microorganisms—often called "germs"—can respond to drug exposure by undergoing genetic mutations or changes, which allows them to adapt and persist despite treatment. Using antimicrobial medications inappropriately or frequently over time promotes this adaptation, making infections harder to treat. By developing the ability to evade multiple medications, certain resistant bacteria earn the moniker "superbugs." Antibiotic resistance is one type of AMR that is specific to bacteria only. It involves lowering the resistance of bacteria to antibiotics, whether they are bactericidal (they kill germs) or bacteriostatic (they prevent bacteria from growing). Antimicrobial resistance (AMR) is the term used to describe the development of resistance in bacteria, viruses, fungi, or parasites to medications intended to eradicate them or restrict their growth. By undergoing genetic mutations or changes in response to drug exposure, these microorganisms—often referred to as "germs"—can adapt and endure treatment. This adaptation makes infections more difficult to treat when antimicrobial drugs are used improperly or frequently over time. Several resistant bacteria have become known as "superbugs" because they have evolved the capacity to avoid several drugs. One form of AMR unique to bacteria is antibiotic resistance. It entails decreasing the resistance of bacteria to antibiotics, whether they are bacteriostatic (they stop bacteria from growing) or bactericidal (they kill germs).

VANCOMYCIN-RESISTANT Enterococcus (VRE):

Vancomycin

It is an antibiotic that belongs to the class of Glycopeptide antibiotics. It is primarily effective against gram-positive bacteria.

MOA:

- It acts as bactericidal (kills bacteria).
- It inhibits bacterial cell wall synthesis by binding to to the D-Ala-D-Ala terminal of peptidoglycan precursors.
- Prevents cross-linking of peptidoglycan leading to bacterial cell lysis and death. Making vancomycin bactericidal against most gram-positive bacteria.

Adverse Drug Reactions:

- Nephrotoxicity
- Ototoxicity
- Red man syndrome
- Neutropenia (not frequent)
- Thrombocytopenia
- Leukocytosis
- Eosinophilia
- Leukocytoclastic vasculitis
- Phlebitis
- Drug fever is considered infrequent and occasionally appears along with neutropenia
- DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) is rare.
- Stevens-Johnson syndrome (SJS) & Toxic epidermal necrolysis (TEN) are also rare.
- Contraindications:
- Hypersensitivity patients
- Renal impairment patients
- Hearing impairment patients
- History of red man syndrome
- Severe thrombocytopenia patients

Drug Interactions:

- Co-administration with aminoglycosides, NSAIDS, loop diuretics, cyclosporin, ACE inhibitors increases further nephron damage.
- Co-administration with muscle relaxants (succinylcholine, vecuronium) and opioids (morphine, fentanyl) increases risk of Red Man Syndrome.

Uses

- Majorly used to treat Gram positive bacteria. (G +ve pneumonia, penicillin resistant *Streptococcus pneumonia*, methicillin- resistant Staphylococci (MRSA, MRSE))
- In treating skin and soft tissue infections and osteomyelitis.
- Also used in treatment of bacteremia endocarditis, and Meningitis.

EPIDEMIOLOGY

Global and regional prevalence:

Because there aren't many effective treatment options, vancomycin-resistant enterococci (VRE) are now a major global source of healthcare-associated infections. From 2014 to 2018, the European Antimicrobial Resistance Surveillance Network (EARS-Net) reported that the proportion of vancomycin-resistant *Enterococcus faecalis* invasive isolates increased from 10.4% to 17.3%. In many European countries, managing VRE remains difficult due to the limited number of available treatment options. The prevalence of vancomycin-resistant E. faecium in Germany rose sharply from less than 5% in 2001 to 14.5% in 2013.

Additionally, the German Antimicrobial Resistance Surveillance (ARS) system showed an increase in VRE prevalence from 16.2% in 2008 to 18.5% in hospital settings and from 9.3% to 19.4% in outpatient settings during the same time period, indicating a growing public health concern. Mathur et al. from New Delhi reported the first VRE case in India in 1999. From 1999 to 2021, prevalence rates have varied between 1% and 8.7%. The extensive and frequently inappropriate use of third-generation cephalosporins and vancomycin in hospital settings has been linked to the increased emergence of VRE in India. This pattern is alarming because it illustrates the strain that antibiotic abuse and overuse are placing on clinical practice. VRE is also becoming a more common health issue in Asia. Western Asia has the highest prevalence (11.4%), followed by South Asia (7.7%), East Asia (3.1%), and Southeast Asia (1.8%), according to a regional study which reported a pooled prevalence of 8.1% across the continent (Sreshtha et al., 2021). This is complicated by the fact that VRE carriage in the gastrointestinal tract (GIT) increases the risk of clinical infections and facilitates intra-hospital transmission. To prevent further transmission, effective control requires strict adherence to infection control procedures, monitoring for VRE carriers, and the development of robust antibiotic stewardship guidelines.[1]

Table 1: prevalence of VRE from different studies worldwide[1]

a) Prevalence of VRE from different studies worldwide

Author	Year	Place	Samples	ICU/ward setting	Prevalence of *VRE* (%)
Remschmidt et al.[16]	2018	Germany	Blood, urine	ICU	5.9–16.7
Melese et al.[1]	2020	Ethiopia	Stool, urine, blood and swab specimens	Wards	14.8
Alemayehu et al.[17]	2020	Africa	Animal, human, and environmental sources	_	26.8
Xie et al.[14]	2020	Australia	Blood culture	ICU	99.0
Sreshtha et al.[11]	2021	Asia			8.1
Ashagrie et al.[15]	2021	Ethiopia	Urine, venous blood and wound swab	Wards	34.6
b) Prevalence of VRE across India					
Deshpande et al.[18]	2013	Mumbai	Clinical specimens	Wards	19.6
Tripathi et al.[19]	2016	Lucknow	Pus, urine, blood and other body fluids	Medical units, surgical units and ICU	7.9
Ahmad et al.[20]	2016	Srinagar	Blood, pus and other body fluids, sputum and urine	Wards	6.3
Sivaradjy et al.[21]	2021	Pondicherry	Blood cultures	Wards and ICU	6.0–19.2%

VRE- Vancomycin – Resistant Enterococci; CSF- Cerebrospinal fluid; ICU- intensive care unit.

Risk Factors for VRE Colonization:

Numerous clinical and epidemiological variables have been found to have a strong correlation with vancomycin-resistant enterococci (VRE) population. Prior exposure to one or more antibiotics was associated with a significantly higher risk (OR 3.83, 95% CI 1.79–8.54). Hospitalization for ≥7 days was also independently associated with colonization (OR 4.86, 95% CI 2.30–10.51), and VRE patients stayed in the hospital for significantly longer than controls (P<0.001). The identification of VRE was found to be significantly correlated with prior antibiotic exposure (p<0.001), specifically to ciprofloxacin (p=0.03) and meropenem (p=0.001), as well as diarrhea (p=0.03), with univariate analysis. On the other hand, vancomycin (p=0.33), piperacillin-tazobactam (p=0.07), metronidazole (p=0.16), ticarcillin-clavulanate (p=0.11), and cephalosporin exposure did not correlate with colonization. Remarkably, proximity to other VRE-positive patients in the same ward or nearby rooms did not significantly correlate with any of these outcomes (p>0.05).In multivariate logistic regression, hospital stay ≥7 days (adjusted OR 4.69, 95% CI 2.25–9.73), age ≥65 years (adjusted OR 2.19, 95% CI 1.05–4.58), and exposure to meropenem (adjusted OR 12.24, 95% CI 2.24–66.77) were the three characteristics that continued to be independent predictors of VRE colonization. In addition, colonization was independently associated with exposure to any antibiotic except meropenem after adjusting for these factors (adjusted OR 2.95, 95% CI 1.27–6.88). Interestingly, in the case-control study, 16 patients (9.2%) were admitted to emergency and short-stay units. When these patients were removed from the analysis, sensitivity analysis confirmed the data's robustness and did not change the overall conclusions[2].

Vancomycin and teicoplanin are examples of bactericidal antibiotics that are glycopeptides. They function by binding to the terminal D-alanyl-D-alanine (D-Ala-D-Ala) moiety of the pentapeptide chain in the N-acetylglucosamine (NAG)–N-acetylmuramic acid (NAM) peptidoglycan precursor. This binding weakens the integrity of peptidoglycan by inhibiting the cross-linking, or transpeptidation, of cell wall components, which leads to bacterial cell death. But the primary mediator of glycopeptide resistance in Enterococcus species is the vancomycin resistance (Van) operon, which is present on chromosomes or mobile genetic elements like plasmids. "Van operon" refers to a large genomic cluster consisting of several essential genes. These include the two-component regulatory system vanS-vanR, the D-lactate dehydrogenase gene vanH, the D-Ala-D-Ala dipeptidase gene vanX, and a variety of variable ligase genes. The nine ligase variations that have been identified so far are vanA, vanB, vanC, vanD, vanE, vanG, vanL, vanM, and vanN. The VanS/R response regulator system is crucial for inducible expression because it can identify damage caused by chemicals such as bacitracin and polymyxin B or disruptions in cell membranes caused by glycopeptides. Among the various genes, the ligase variation primarily determines the degree of resistance, which varies from low to high. In terms of clinical significance, vanA, vanB, and vanC are the most crucial genes.

MECHANISM OF VANCOMYCIN RESISTANCE

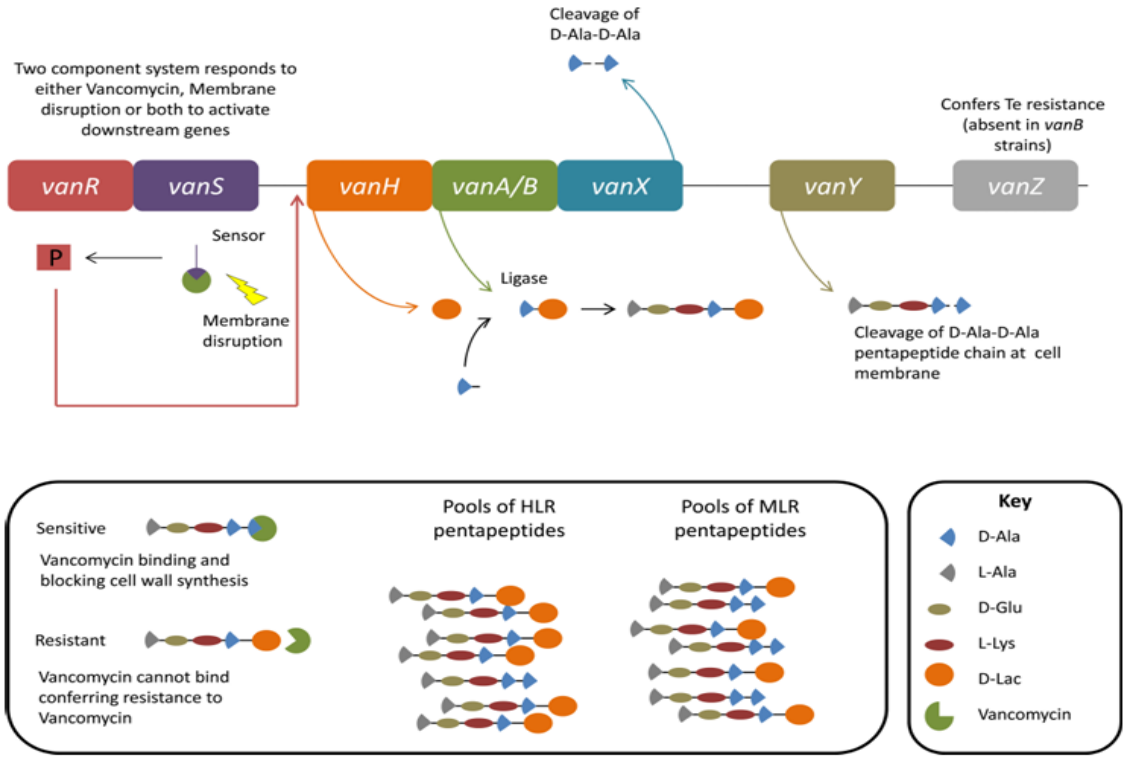

Figure 1: Mechanism of action of vancomycin and development of resistance[4]

Resistance of VanA

Due to its frequent plasmid-borne nature, the vanA operon has the ability to spread widely and promote horizontal gene transfer. The two most clinically significant enterococcal species, *Enterococcus faecium* and *Enterococcus faecalis*, are the main hosts of it. It confers high-level resistance to vancomycin (MIC ≥ 256 µg/ml). By replacing the high-affinity D-Ala-D-Ala target site with D-alanyl-D-lactate (D-Ala-D-Lac), the resistance mechanism is achieved. This change results in a reduction of vancomycin's binding affinity of approximately 1000 times, rendering the drug ineffective. D-Ala-D-Lac-containing NAM subunits cannot be incorporated into the peptidoglycan without the help of additional penicillin-binding proteins (PBPs) in addition to PBP4 and PBP5. When vancomycin is present, these PBPs establish dominance. " Remarkably, these alternative PBPs also exhibit heightened affinity for β-lactams when coupled with glycopeptides, potentially resulting in synergistic antibiotic therapy. Moreover, resistance to the glycopeptide teicoplanin is mediated by the gene vanZ, which is located in the vanA operon, via a mechanism that is still unclear. Due to their dual resistance to teicoplanin and vancomycin, vanA-positive bacteria are therefore more problematic in clinical settings. Around the world, vanA remains the most prevalent mechanism of vancomycin resistance in enterococci.

Resistance of VanB

The vanB operon is present worldwide, albeit less frequently than vanA. However, it is particularly prevalent in Australia, where the majority of E. faecium VRE isolates carry vanB. Resistance develops when D-Ala-D-Ala is swapped out for D-Ala-D-Lac, just like with vanA. Conversely, vanB's phenotypic expression varies, resulting in moderate to high levels of vancomycin resistance (MIC 4–256 µg/ml). It is thought that this variability is caused by a lower percentage of D-Ala-D-Lac substitution in the bacterial cell wall, though the precise cause is unknown. Minimal mechanical alterations, decreased enzymatic activity of VanX or VanB, or decreased expression of the vanB operon could be the cause of this. Since vanZ is absent from the vanB operon, isolates that are vanB-positive usually remain vulnerable to teicoplanin.

Resistance of VanC

The vanC operon is chromosome encoded and intrinsic to species such as E. flavescens, E. casseliflavus, and E. gallinarum. Low-level resistance (MIC 8–32 µg/ml) to vancomycin is the result of D-alanyl-D-serine (D-Ala-D-Ser) replacing D-Ala-D-Ala. Since vanC is not contagious and is associated with less clinically significant enterococcal species, it has a comparatively small overall impact on hospital-acquired infections when compared to vanA and vanB.

Resistance to VanD

The vanD operon is increasingly observed in clinical isolates, although it is less common than vanA or vanB. Whereas vanA is plasmid-borne, vanD is frequently chromosomally encoded, which limits its horizontal transfer but allows for permanent inheritance within bacterial lineages. VanD often offers an intermediate to high level of resistance to vancomycin (MICs often ranging from 64 to 256 µg/ml), but

D-Ala-D-Lac is substituted for D-Ala-D-Ala in a similar mechanism of resistance. Surprisingly, vanD-positive organisms often show fluctuating susceptibility to teicoplanin, in contrast to vanA isolates that are consistently resistant to both glycopeptides. Rather than being strictly inducible, vanD expression is constitutive in some isolates, meaning it is continuously active. This might have an impact on a treatment's effectiveness. The occurrence of vanD in E. faecium and E. faecalis is concerning because it adds another genetic reservoir to the complexity of vancomycin resistance in enterococci, even though it is still uncommon in comparison to vanA and vanB.[4]

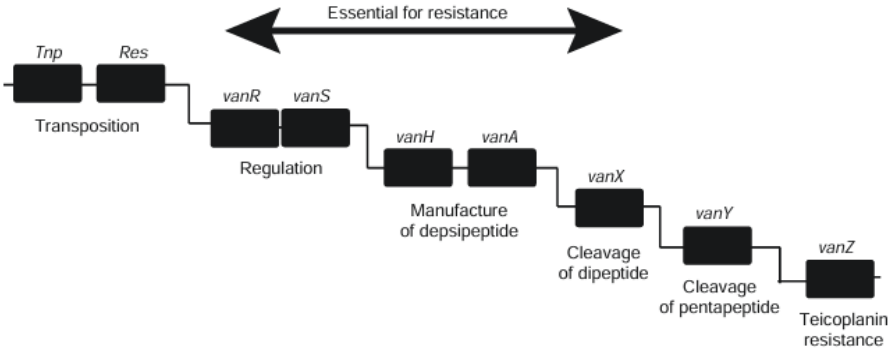

Figure 2: The vanA operon in TN1546 from Patel R. vancomycin-resistant enterococci in solid organ transplantation. Curr Opin Organ Transplant 1999;4;271-280, with permission from Lippincott Williams & wilkins[5]

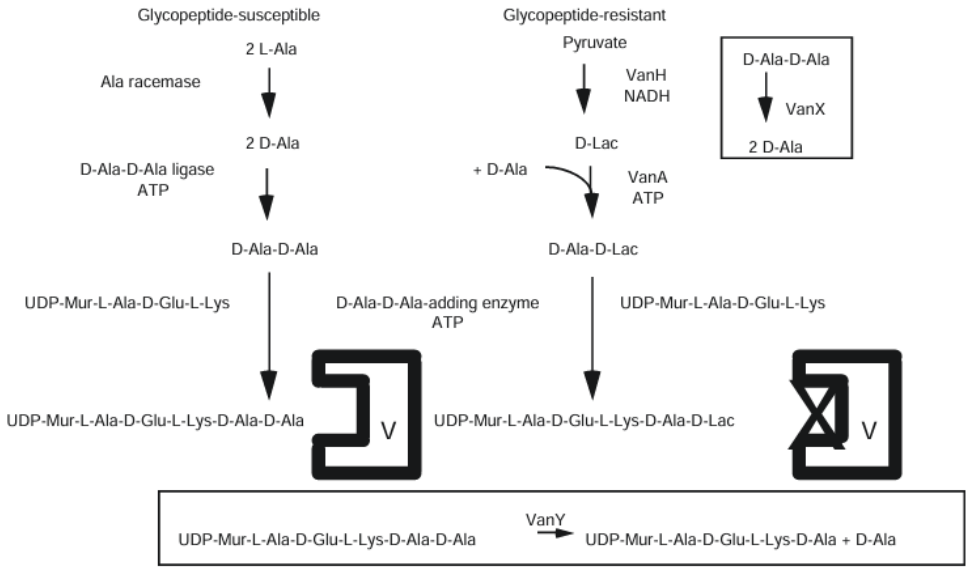

Figure 3: Mechanism of action of vancomycin and mechanisms of vancomycin resistance in enterococci with vanA-associated vancomycin [5]

PATHOGENESIS AND CLINICAL MANIFESTATIONS

VRE is responsible for a large number of clinical infections, particularly in hospitalized and immunocompromised patients. Compared to vancomycin-susceptible strains, VRE are associated with higher morbidity and mortality rates and are often associated with invasive devices, extended hospital stays, or previous antibiotic exposure.

Bacteremia

In patients who are already very sick and on broad-spectrum antibiotics, bacteremia without endocarditis is one of the most typical symptoms of a VRE infection. With an approximate 18% contribution to central line-associated bloodstream infections (CLABSIs) in the US, enterococci are the second most common causative pathogen. GI and GU tracts are the main sources of community-acquired bacteremia, whereas nosocomial infections are often associated with intravascular or urinary catheters, intra-abdominal infections, burn wounds, and biliary origins. Vancomycin-sensitive enterococcal (VRE) bacteremia had a 2.5-fold greater death rate than VSE bacteremia.

Endocarditis Infectious

Infectious endocarditis (IE) is most commonly caused by enterococci, which account for 5–20% of cases. While the tricuspid valve is more frequently affected by VRE E. faecium endocarditis, mitral valve involvement, liver transplantation, and central venous catheterization are typically linked to VRE E. faecalis endocarditis. The gastrointestinal and gastrointestinal tracts remain common entry sites. The clinical presentation is typically subacute and includes weight loss, fever, malaise, and heart

murmurs. Traditional peripheral signs like Roth's patches, petechiae, and Osler's nodes are less common.

Pelvic and Intra-abdominal Infections

When pelvic and intra-abdominal infections (IAIs) arise, enterococci—natural gastrointestinal commensals—are often recovered. Gram-negative and anaerobic organisms are typically present in polymicrobial flora. It is most strongly advised that patients with underlying heart disease, abscesses, peritonitis, or immunocompromised situations have treatment. In addition, enterococci can cause monomicrobial peritonitis, particularly in individuals with cirrhosis or prolonged peritoneal dialysis.

Infections of the Urinary Tract

Healthcare-associated urinary tract infections (UTIs) are now frequently brought on by VRE. Enterococci, which rank second overall in the US, are responsible for 15% of catheter-associated UTIs (CAUTIs). Risk factors include anatomical abnormalities, history of antibiotic usage, extended catheterization, male sex, urologic instrumentation, and recurrent UTIs. Numerous enterococci colonize the urine tract and often result in asymptomatic bacteriuria, which makes it challenging to differentiate colonization from disease.

Infections of the Central Nervous System

Although rare, VRE infections of the central nervous system (CNS) are harmful. Usually, they impact elderly people with severe coexisting diseases, including chronic heart disease, hematologic malignancies, or solid organ cancers. Compared to E. faecalis, E. faecium causes more cases of VRE meningitis. In rare instances, the clinical signs include focal neurologic abnormalities, shock, coma, and acute fever and disturbed mental status. Usually, cerebrospinal fluid results indicate pleocytosis, hypoglycorrhachia, and elevated protein levels.

Infections of the skin and soft tissues

Although they frequently colonize the skin, enterococci can cause skin and skin structure infections (SSSIs), particularly in the presence of other pathogens. Often isolated from diabetic foot infections and decubitus ulcers, they also occasionally have soft tissue abscesses, septic arthritis, and osteomyelitis[4].

DIAGNOSTIC APPROACHES

Guidelines released by the CDC and the SHEA recommend active patient screening for VRE colonization in hospitals and long-term care facilities. However, many hospitals have not followed these recommendations. This is most likely caused by the lack of information on which people should be examined to maximize the cost-benefit ratio and the scant evidence from outcome studies that laboratory screening for VRE offers a significant benefit. There are several different risk markers that can be used to determine who is most at risk and who would benefit from screening, according to an expanding body of research. Risk factors include length of hospital stay, recent or current antibiotic use, immunocompromised patients, patients with previous hospitalizations, and patients who were transferred from long-term care facilities.

Active or passive screening

Guidelines issued by the Centers for Disease Control and Prevention (CDC) and the Society for Healthcare Epidemiology of America (SHEA) recommend active screening for VRE colonization in hospitals and long-term care facilities. However, many hospitals have not implemented these suggestions, mostly due to the lack of evidence of significant advantages and the uncertainty surrounding which patients should be prioritized for screening in order to keep costs down. Risk factors that can be utilized to identify patients most likely to benefit include immunosuppression, recent or current antibiotic use, prolonged hospitalization, prior hospitalizations, and transfers from long-term care facilities. Active and passive screening techniques are the two categories. Identification of VRE in clinical specimens acquired for routine culture without any particular VRE testing is referred to as "passive screening." Patients are only separated following laboratory confirmation or a verified positive history. Because the ratio of VRE-infected to VRE-colonized persons is approximately 1:10, passive screening misses the majority of carriers. According to modeling studies from an intensive care unit at the University of Maryland Medical Center, passive screening would only reduce VRE infection rates by 4.2% compared to no screening at all. In contrast, active screening gathers samples specifically for the aim of identifying VRE, such as rectal swabs or stool cultures. Testing after discharge, continuous screening during hospitalization, and screening of high-risk groups at admission are commonly included. Reflex testing of stool samples collected for C. difficile can also be used to detect VRE colonization early. In high-prevalence hospital settings, especially in intensive care units, active screening has been demonstrated to reduce infection rates by up to 39%. Lowering transmission can also be achieved by assigning specialized healthcare professionals and cohorting patients according to their colonization status, although many institutions lack the financial and human resources necessary to do so[4].

Laboratory considerations for VRE screening

Optimal specimen collection

Choosing the best specimen is essential for a sensitive screening test for vancomycin-resistant enterococci (VRE). The Centers for Disease Control and Prevention (CDC) prefers stool specimens or rectal swabs. Because stool specimens submitted for C difficile testing are noninvasive source specimens that were probably obtained from individuals who already had risk factors for VRE infection, they might be more informative. Positive C. difficile results are 10.4% when compared to stool samples sent for testing, and they were 9.7% positive in rectal swabs from high-risk categories such as surgical intensive care unit patients and transplant recipients. Stool samples may be more sensitive

than rectal swabs, according to a head-to-head study. For example, the sensitivity of rectal swabs compared to stool specimens was only 58% in one investigation using paired samples cultivated on Enterococcosel agar. Low inoculum levels (<4.5 log10 CFU/g) significantly reduce swab sensitivity, raising the possibility that patients with lower bacterial loads will go undetected. Their therapeutic importance is yet unknown because it is not obvious how much of a relative contribution these low-level carriers make to the likelihood of transmission.

Culture-based screening methods

Traditional culture is still commonly used for VRE detection in order to balance cost, sensitivity, and specificity. Chromatogenic agars are the preferred culture medium because of their superior diagnostic efficacy over bile esculin azide agar with vancomycin (BEAV). The chromogenic medium provides sensitivity values of 90 to 99% and specificity of up to 95%, but BEAV may yield sensitivity as low as 85% and specificity between 70 and 75%. These enhanced traits are due to higher vancomycin concentrations (8–10 µg/ml vs. 6 µg/ml in BEAV) and chromogenic markers that facilitate species-level separation, specifically between E. faecium and E. faecalis. Chromatogenic agars also reduce false positives associated with organisms that are inherently resistant but clinically less relevant, such as E. casseliflavus and E. gallinarum. Culture-based methods still require 18 to 24 hours of incubation, though, which causes a delay in the implementation of infection control measures. Although it takes more time and is more complicated, some labs use a pre-enrichment broth phase to boost diagnostic yield. Although culture-based techniques have limitations, they remain cost-effective and provide the advantage of recovering live organisms for epidemiological typing during epidemics.

Molecular screening methods

For VRE screening, nucleic acid amplification tests (NAATs) have grown in popularity due to their rapid turnaround times. Commercial assays such as the Cepheid Xpert vanA/vanB and the Roche Light Cycler VRE kits directly target vancomycin resistance genes. The stated ranges for sensitivity and specificity are 61.5% to 100% and 14.7% to 99.5%, respectively. These notable differences stem from differences in technical features, research population prevalence, and reference standards. Although NAATs often show strong negative predictive values (NPVs >95%), they sometimes lead to poor PPVs, particularly in low-prevalence circumstances. For example, the Roche Light Cycler kit had a PPV as low as 1.4% for vanB detection when compared to direct culture, although NPVs were around 100%. This low PPV can be explained by the presence of van genes in non-enterococcal organisms such as Streptococcus bovis, Eubacterium lenta, Lactococcus species, and various Clostridium species[4].

THERAPEUTIC CHALLENGES

Resistance to Several Antibiotic Classes in Nature

Vancomycin-resistant enterococci (VRE) are inherently resistant to several common antibiotic families, including β-lactams, aminoglycosides, lincosamides, and trimethoprim-sulfamethoxazole. This intrinsic resistance limits the number of viable treatment options available to clinicians, particularly when treating severe or bloodstream infections. VRE's limited antibacterial armament makes it one of the most difficult multidrug-resistant infections to treat.

Insufficient and Untrustworthy Susceptibility Examination

When it comes to identifying isolates with reduced susceptibility, vancomycin disk diffusion and other common antimicrobial susceptibility testing methods (such as VISA or GISA) usually fail. Despite being essential for precise detection, laboratories rarely perform minimum inhibitory concentration (MIC) testing. Misdiagnosis or underclassification is more likely as a result, which could lead to inefficient treatment and heightened resistance.

Limited Monitoring and Surveillance in the Laboratory

Not all clinical microbiology labs are equipped to routinely measure the minimum inhibitory concentration (MIC) for vancomycin or to spot novel resistance patterns. Inadequate and inconsistent surveillance delays the identification of resistant isolates, makes it more difficult to track resistance trends, and prevents timely infection-control actions.

Glycopeptide-Intermediate Strains: A Growing Threat

The limitations of the current diagnostic techniques and infection-control strategies are highlighted by the rising incidence of vancomycin-intermediate Enterococcus and glycopeptide-intermediate Staphylococcus aureus (GISA) infections. If these strains are not found early and reported immediately, hospitals risk silently propagating them. This novel resistance mechanism makes treatment plans considerably more challenging and poses a serious obstacle to managing VRE.

Lack of Novel Antimicrobial Substances

Another major challenge in the fight against VRE is the lack of newly developed drugs that have been shown to be effective against resistant enterococci. Many of the newer medications are either too expensive or only accessible in areas with limited resources, and there are still few pharmaceutical pipelines for new antimicrobials. The absence of therapeutic alternatives exacerbates the challenge of treating multidrug-resistant VRE infections[7].

ALTERNATIVE TREATMENT OPTIONS

Especially among patients with compromised immune systems and those who have been hospitalized for prolonged periods of time, enterococci are opportunistic bacteria that have emerged as major nosocomial infection causes. The two that are most clinically significant are *Enterococcus faecalis* and *Enterococcus faecium*.

Historically, enterococcal infections have been treated with vancomycin as a last resort. Vancomycin-resistant enterococci, however, has emerged and spread around the world, creating a serious treatment dilemma. The resistance is mediated by transferable genetic components, such as the vanA and vanB gene clusters, which alter the terminal amino acid sequence of the peptidoglycan precursor, thereby reducing vancomycin binding. Both acquired and inherent resistance to certain commonly used antibiotics, such as low-level aminoglycosides and cephalosporins, are present in enterococci. These factors make VRE one of the most difficult infections to treat, often leaving doctors with few options for treatment. For VRE infections, careful antibiotic selection based on host features, infection location, and susceptibility patterns is required. Clinical results vary widely, and resistance may emerge after treatment, even though several drugs exhibit in vitro activity against VRE. This overview lists the many VRE therapeutic modalities, the principles that guide their application, and the limitations that affect how effective they are.

Linezolid

The first medication of the oxazolidinone class, linezolid, significantly changed the way Gram-positive infections, including those caused by VRE, were treated. During protein synthesis, it binds to the 50S ribosomal subunit and prevents the formation of the initiation complex. It is because of this unique mechanism that linezolid continues to work against strains that are resistant to other kinds of medications. Linezolid, however, is bacteriostatic rather than bactericidal. Although this is adequate for many infections, it is a restriction in critical situations such as infective endocarditis, when bactericidal activity is needed. Reports of linezolid resistance due to the cfr gene acquisition or mutations in the 23S rRNA gene have increased, especially in regions where the drug is commonly used. Negative consequences are another problem. Additionally, peripheral and optic neuropathy have been seen in patients receiving therapy for more than four weeks. With serotonergic medications, drug-drug interactions are more risky due to the potential for serotonin syndrome. Despite these limitations, linezolid remains a first-line treatment for VRE, particularly in hospitals where exposure is still significant.

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic that exhibits rapid bactericidal action by attaching itself to the bacterial cell membrane in a calcium-dependent manner, causing depolarization, potassium efflux, and ultimately cell death. Its unique method effectively combats VRE and other Gram-positive bacteria that are resistant to drugs. Daptomycin is useful in treating complex skin and soft tissue infections, bacteremia, and right-sided infective endocarditis conditions. In order to achieve therapeutic effectiveness for VRE infections, higher dosages (8–12 mg/kg/day) are often necessary, especially for bloodstream infections where rapid clearance is necessary. Clinical evidence supports its use as a salvage treatment for chronic VRE bacteremia and in cases when linezolid fails or resistance is common. Daptomycin's major drawback is that resistance may arise during therapy, usually due to gene alterations governing cell membrane charge and phospholipid metabolism. Chronic bacteremia patients are more vulnerable. This issue has been addressed with combination therapy. Daptomycin's bactericidal activity is enhanced by β-lactams such as ampicillin, ceftaroline, or ertapenem, which improve its binding affinity to the bacterial membrane. Refractory VRE bacteremia has been successfully cured in clinical practice using these combinations. Daptomycin side effects include myopathy and rhabdomyolysis, which necessitate weekly creatine phosphokinase (CPK) level checks. Eosinophilic pneumonia is another potential outcome, although it is rare. Despite these risks, daptomycin remains a staple in the management of VRE infections, particularly when paired with other drugs.

Tigecycline

Glycylcycline is an antibiotic. Minocycline is converted to tigecycline, which has a broad spectrum of efficacy against pathogens resistant to several medications, including VRE. By binding to the 30S ribosomal subunit and blocking the entry of aminoacyl-tRNA, it stops bacteria from producing proteins. Beneficial for the treatment of complicated skin infections, complicated intra-abdominal infections, and some cases of hospital-acquired pneumonia. For individuals with limited therapy alternatives, it is a helpful alternative due to its capacity to fight VRE. However, there are serious disadvantages to tigecycline. Endocarditis and bloodstream infections cannot be treated with it due to its low serum concentrations. Additionally, its low urine concentrations limit its use in urinary tract infections. Additionally, tigecycline resistance has been documented, usually due to efflux pump overexpression. It is common to have side effects, particularly gastrointestinal intolerance. Following their treatment plan may be challenging for up to one-third of individuals who experience nausea and vomiting. Concerns about higher mortality rates among patients receiving treatment for severe illnesses have made tigecycline use cautious. Notwithstanding these drawbacks, tigecycline is useful in salvage therapy, particularly for polymicrobial intra-abdominal infections linked to VRE.

Quinupristin–Dalfopristin

Quinupristin and dalfopristin are streptogramins that bind to different parts of the 50S ribosomal subunit and decrease protein synthesis. It has a powerful effect on *Enterococcus faecium*, in contrast to *Enterococcus faecalis*. Previously, it was believed that this antibiotic was necessary to treat VRE infections, particularly bacteremia. Its use has, however, declined due to its adverse effects and poor tolerance. Myalgia, arthralgia, and responses associated with infusion are prevalent in patients. It is often necessary to administer medication centrally for common phlebitis. Quinupristin–dalfopristin is also a strong cytochrome P450 3A4 inhibitor, which may cause major drug interactions that complicate treatment for patients on multiple medications. Quinupristin–dalfopristin may nevertheless be helpful in

some cases of refractory E. faecium infections when no other treatment options are available, despite these disadvantages. Its decreasing use in clinical practice, however, is a result of the development of more tolerable substitutes like daptomycin and linezolid.

Fosfomycin

Fosfomycin, an earlier antibiotic, inhibits the bacterial cell wall's early synthesis by binding permanently to enolpyruvyl transferase. Its capacity to fight off illnesses that are resistant to several drugs, like VRE, has reignited interest in it. The most often given drug in clinical practice for uncomplicated UTIs is fosfomycin. Fosfomycin, however, has been found to cooperate with other antibiotics, including aminoglycosides, linezolid, and daptomycin. Some combinations have shown promise in endocarditis and bacteremia experimental models. Among fosfomycin's disadvantages are low serum concentrations and the ability to rapidly develop resistance when taken as a monotherapy. Systemic infections are therefore rarely treated with it alone. But when combined with other medications, fosfomycin may increase bactericidal effectiveness and prevent the development of resistance.

Newer lipoglycopeptides

The semisynthetic vancomycin derivatives oritavancin, dalbavancin, and telavancin show anti-resistant Gram-positive bacterial activity due to structural changes. The prolonged half-lives of these medications facilitate outpatient therapy by permitting sporadic dosing schedules. Specifically, oritavancin has been shown to have an in vitro effect against strains of VRE that include vanA and vanB resistance genes. Still, there is a dearth of clinical data supporting its use in VRE infections. As further study is conducted, these drugs may prove to be effective alternatives to the current standard treatments for VRE.

Principles of combination therapy

Since monotherapy has limitations, combination regimens are increasingly being used to treat VRE infections. Combination therapy is supported by its capacity to improve clinical outcomes in situations of severe infections, prevent the development of resistance, and generate a synergistic bactericidal effect. Combining a β-lactam antibiotic with high-dose daptomycin is one of the most studied combinations. β-lactams, such as ampicillin, ceftaroline, or ertapenem, modify the cell wall surface, improving daptomycin binding and action. With this approach, refractory VRE bacteremia has been effectively eradicated. Linezolid and fosfomycin, which increase bactericidal effect, and tigecycline with aminoglycosides for intra-abdominal infections are other combinations. Although these regimens are supported by limited experimental data and clinical series, there are no strong randomized controlled trials.

Thus, combination therapy should be considered in critically ill patients, infections involving prosthetic material, or when monotherapy has failed.

Limitations of current treatment options

Although there are several medications available, VRE is still not adequately managed. Despite being bacteriostatic rather than bactericidal, most antibiotics that work against VRE, such as tigecycline and linezolid, are less effective against potentially lethal diseases like endocarditis. During therapy, even with bactericidal medications like daptomycin, resistance can emerge rapidly. Pharmacokinetic restrictions also place limitations on therapy. Because of its low serum concentrations, tigecycline is not suitable for bacteremia. Because fosfomycin has insufficient systemic levels, its usage outside of the urinary tract is restricted. Intolerance and toxicity are quinupristin-dalfopristin's drawbacks.

Toxicities can make lengthy treatment regimens more difficult. Linezolid causes neuropathy and bone marrow suppression. Daptomycin may cause myopathy; thus, it's important to monitor CPK. Musculoskeletal pain is caused by quinupristin –dalfopristin, while tigecycline's gastrointestinal side effects reduce compliance. Newer drugs like oritavancin and dalbavancin are not commonly accessible because of their high price and lack of VRE certification.

The need for individualized care, susceptibility testing, and careful antibiotic management is highlighted by these limitations. Medical professionals must balance medication availability, toxicity, and effectiveness when treating VRE infections[8].

Conventional Antimicrobial Agents in the Management of VRE

Traditional antimicrobial medications, including β-lactams, aminoglycosides, fluoroquinolones, and some earlier compounds, have been used to treat Enterococcus infections in the past. However, because of the emergence and global spread of vancomycin-resistant enterococci (VRE), the efficacy of these medications has suffered greatly. Despite these disadvantages, conventional drugs can nevertheless be helpful in certain therapeutic settings, either as a preventative measure when susceptibility is preserved or in combination regimens to achieve synergistic bactericidal activity.

β-lactam antibiotics

Ampicillin and other β-lactam antibiotics have long been the cornerstone of treatment for *Enterococcus faecalis*. When used alone to treat uncomplicated infections or in combination with other treatments, such as ceftriaxone, to treat infective endocarditis, the drug is still considered effective against strains that are still susceptible to ampicillin. However, E. faecium, which has nearly universal ampicillin resistance, is responsible for most VRE infections. Other β-lactams, particularly cephalosporins, have little intrinsic activity against enterococci, despite the fact that ceftaroline has been shown to increase the efficacy of daptomycin in combination therapy, indicating a potential adjuvant role beyond direct clinical value. Because

carbapenems like imipenem have a poor action rate, they are considered unreliable therapy options for VRE.

Aminoglycosides

Cell wall-active medications, particularly streptomycin and gentamicin, were previously utilized in conjunction with aminoglycosides to produce synergistic bactericidal effects against enterococcal endocarditis. However, the widespread development of high-level aminoglycoside resistance (HLAR) has threatened this strategy. The aminoglycosides are only used on rare, particularly vulnerable strains of VRE because they no longer have a meaningful therapeutic benefit in the majority of isolates.

TMP-SMX

Findings on the effectiveness of trimethoprim-sulfamethoxazole (TMP-SMX) against enterococci have been conflicting. Resistance is common, and the outcomes of treatment are not always consistent. TMP-SMX is often avoided in systemic VRE infections; however it may be used sometimes for mild UTIs caused by susceptible isolates.

fluoroquinolones

Among the fluoroquinolones, ciprofloxacin, levofloxacin, and moxifloxacin have only limited intrinsic action against enterococci. DNA gyrase and topoisomerase IV mutations are the cause of resistance, which is extremely prevalent, particularly among E. faecium strains. Their significance in VRE infections is therefore quite limited, but if in-vitro susceptibility has been demonstrated, they may occasionally be employed to treat urinary tract infections.

chloramphenicol

hloramphenicol, a pioneering broad-spectrum antibiotic, has demonstrated in vitro efficacy against enterococci, including several VRE strains.The potential for potentially lethal hematological harm, such as aplastic anemia and bone marrow suppression, has, however, reduced its clinical use. Chloramphenicol is only utilized as a salvage treatment in settings with limited resources or in the absence of any other accessible therapeutic options in contemporary practice.

Lincosamides

Finally, clindamycin and other lincosamides have little to no clinical value in enterococcal infections. Because they are inherently ineffectual, they are excluded from treatment plans for susceptible and resistant strains. In the era of vancomycin resistance, the conventional antibiotics that were formerly the mainstay of enterococcal infection treatment now have a more limited and targeted function. When susceptibility is established, ampicillin continues to be effective against E. faecalis, aminoglycosides may be used occasionally in synergy, and chloramphenicol or TMP-SMX may be used as last resorts in specific circumstances. However, the majority of VRE infections, particularly those caused by E. fecium, do not consistently respond to these conventional drugs, necessitating the use of more modern and potent treatment medicines[11].

INFECTION CONTROL AND PREVENTION

Monitoring in the Lab and MIC Testing

Correctly identifying vancomycin resistance is the cornerstone of prophylaxis. Regular minimum inhibitory concentration (MIC) testing for vancomycin in Staphylococcus aureus and enterococci isolates is advised for clinical microbiology labs. This allows clinicians to adapt treatment before resistance extends further by quickly identifying vancomycin-intermediate and resistant strains. Disk diffusion of vancomycin is insufficient on its own since it may not detect isolates with reduced glycopeptide susceptibilit.

Practices for Hospital Infection Control

It is essential to strictly follow infection-control protocols in order to limit the spread of VRE in healthcare environments. According to the Centers for Disease Control and Prevention, specific measures include active surveillance cultures in high-risk units, contact precautions, and early notification of infection-control personnel about resistant illnesse.

Source and Environmental Control

Environmental factors can lead to the spread of multidrug-resistant organisms outside of the therapeutic context. Proper wound care, timely surgical debridement, and the removal of contaminated catheters are still necessary for controlling localized infections. On a larger scale, efficient sewage disposal systems are required to reduce the likelihood of resistant bacteria from infected patients spreading across the community.

Measures for Public and Community Health

Hospital settings are not the only places to implement preventive measures. It is necessary to promote personal hygiene, reduce the use of unnecessary antibiotics, and support antimicrobial stewardship programs in order to control the emergence of resistance. Through local surveillance of bacterial populations, early action can allow public health responses and quickly identify resistance tendencies. Also, especially in dialysis centers and long-term care facilities, rigorous cross-infection control protocols are necessary to protect high-risk patient groups. Information about the recommended safety precautions for treating patients who tested positive for vancomycin-resistant enterococci, the rules for isolating these patients, and the degree to which the 1997 policies and procedures were adhered to were mostly anecdotal. Of the long-term care facilities that responded to our survey, most stated that they either isolated or grouped patients who tested positive for vancomycin-resistant enterococci together (21 of 23 in 1998 [91 percent]; 22 of 25 in 1999 [88 percent]). In 1998 and 1999, all four acute care facilities reported following CDC guidelines12. In 1999, it was required that employees and patients who tested positive for vancomycin-resistant enterococci stay segregated in their rooms at all times in two of the twenty-two long-term care institutions with

policies (9 percent). Proper adherence to contact precautions is required of participants.

By allowing these patients to engage in individual or group activities outside of their rooms if they were able to wash their hands and were either incontinent or had their bodily fluids contained, providing ways to clean wheelchairs and other equipment these patients used outside of their rooms, or encouraging the use of waterless hand sanitizers for both patients and staff in place of strict isolation, twenty long-term care facilities (91 percent) deviated from the CDC's recommendations[10].

Infection Control and Antimicrobial Stewardship Using Whole Genome Sequencing

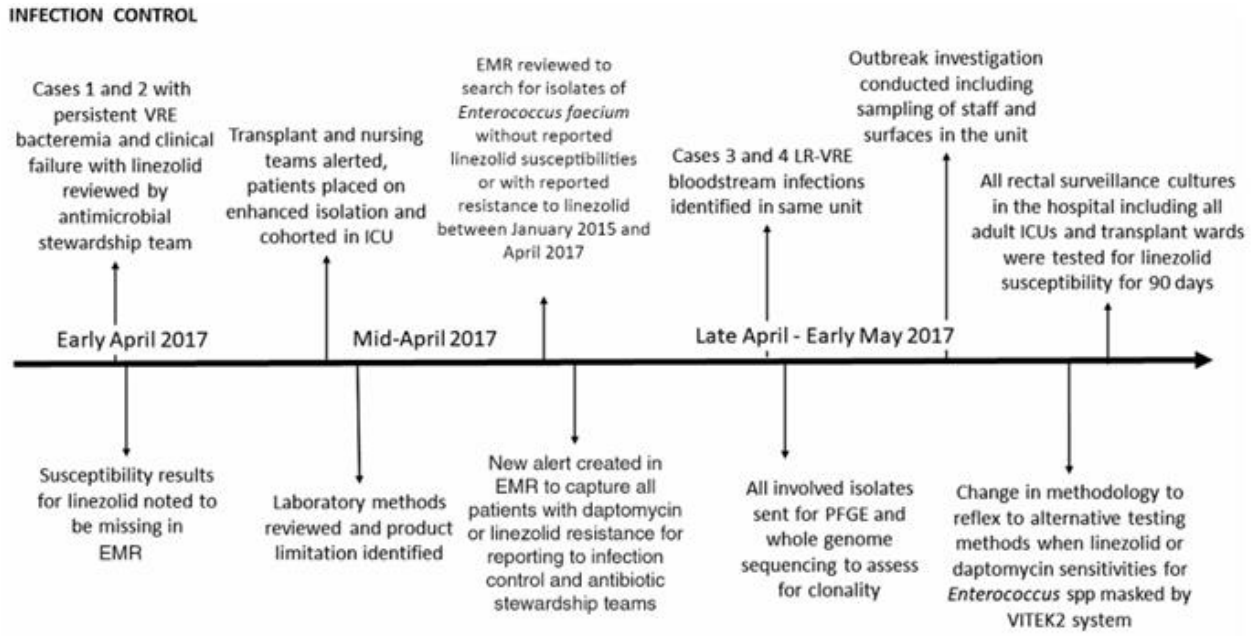

Figure 4: Cluster investigation timeline. Abbreviations. EMR, electro medical report; ICU, intensive care unit, LR-VRE linezolid and vancomycin-resistant *Enterococcus faecium*, PFGE, pulsed-field gel electrophoresis; VRE, vancomycin-resistant enterococci [11]

The efficient treatment and prevention of infections caused by linezolid- and daptomycin-resistant vancomycin-resistant Enterococcus (LR-VRE) require a multimodal approach that includes laboratory vigilance, active surveillance, strict hygiene practices, and antibiotic stewardship. Accurate laboratory diagnosis is crucial since automated techniques might not be able to identify drug resistance to some medications, like daptomycin and linezolid. Alternative methods such as broth microdilution or the E-test are recommended for accurate susceptibility determination, early resistance pattern discovery, and avoiding false therapeutic efficacy assumptions. Active surveillance, such as rectal swab screening of high-risk patients upon admission to intensive care units or other sensitive settings, is necessary to identify colonized people prior to a clinical illness developing. By facilitating the quick implementation of isolation measures, this tactic reduces horizontal transmission inside healthcare settings. Continued monitoring and reinforcement of hand hygiene compliance among patients, visitors, and healthcare staff further reduces the risk of disease transmission. Reduced cross-contamination necessitates strict attention to contact precautions, such as wearing gloves and gowns. Cleaning and disinfecting patient rooms and high-touch surfaces as well as potential VRE reservoirs offers an additional layer of security. The prevention of the emergence and spread of drug-resistant bacterial strains depends on antimicrobial stewardship programs. Working together, microbiology labs and physicians can better choose and administer antibiotic medicines, particularly combination regimens like daptomycin and ampicillin that have shown clinical success in treating resistant infections. Routine susceptibility testing is performed on all VRE isolates, and continuous monitoring for emerging resistance ensures that infection control strategies keep up with evolving threats. Effective LR-VRE infection prevention generally relies on a mix of active surveillance, thorough laboratory testing, strict hygiene, environmental cleaning, and the wise use of antibiotics. These actions improve patient outcomes in hospital settings, reduce horizontal transmission, and control epidemics[11].

CLINICAL IMPACT AND OUTCOMES

The Mayo Clinic reported seven clinical isolates of vancomycin-resistant, linezolid-resistant Enterococcus fecium (LR-VRE) between 2001 and 2002. According to E. coli numbering, all isolates had a G→T mutation at position 2576 of 23S rRNA, and PFGE analysis showed indistinguishable patterns that suggested a clonal outbreak. An intra-abdominal infection caused by vancomycin-resistant, linezolid-susceptible E. fecium and hepatic artery thrombosis led to the development of the linezolid-resistant strain in a liver transplant recipient. It's likely that the linezolid treatment for this disease selected for resistance.

Although strict infection control measures, including private rooms, isolation of the index patient, and universal gloving of healthcare professionals, prevented six further patients from being nosocomially exposed to the resistant strain." The diarrhea in the index patient, which was associated with tube feeding, may have facilitated environmental contamination and transmission. LR-VRE development is a significant clinical concern. 2.2% of VRE infections treated with linezolid are estimated to develop resistance. In addition to the risk to patients, many institutions may not be aware of the possibility of nosocomial infection. Not everyone is routinely screened for VRE colonization, and even then, linezolid susceptibility tests may not be included. LR-VRE may not be detectable using normal culture media used for stool or rectal swabs when sensitive strains predominate in mixed populations.These results emphasize the significance of infection control strategies, antibiotic stewardship, and attentive surveillance in preventing the emergence and spread of highly resistant VRE strains in healthcare environments[12].

Morbidity and mortality associated with VRE

Table 2: Comparison of the characteristics between survivors and non-survivors within 30 days of ampicillin-susceptible enterococci bloodstream infections [14]

Characteristic	Death (n = 46)	Survival (n = 114)	p Value	OR	95% CI
Mal	25 (54.3)	71 (62.3)	0.354	0.72	0.36–1.44
Age (years)	77 (65–85)	74 (61–80)	0.052 *		
ACCI; median (IQR)	6.5 (5–8)	5 (4–7)	<0.001 *		
ACCI 0–2 (n = 21)	0	21			
ACCI 3–5 (n = 58)	15 (32.9)	43 (37.7)			
ACCI 6–13 (n = 81)	31 (67.4)	50 (43.9)			
Immunocompromised	9 (19.6)	14 (12.3)	0.235	1.74	0.69–4.35
Time from admission to bacteremia (days); median (IQR)	10 (2.5–31.5)	0 (0–12)	0.001 *		
HA-bacteremia	35 (76.1)	56 (49.1)	0.002	3.3	1.52–7.12
Intensive care unit	18 (39.1)	17 (14.9)	0.001	3.67	1.67–8.04
Mechanical ventilation	26 (56.5)	32 (28.1)	0.001	3.33	1.64–6.79
Septic shock	20 (43.5)	17 (14.9)	<0.001	4.39	2.02–9.56
PBS; median (IQR)	3.5 (2–5)	1 (0–3)	<0.001 *		
PBS 0–3 (n = 113)	22 (47.8)	91 (79.8)			
PBS 4–7 (n = 41)	20 (43.5)	21 (18.4)			
PBS 8–11 (n= 6)	4 (8.7)	2 (1.8)			
Site of infection					
Primary bacteremia	17 (37)	30 (26.3)	0.181	1.64	0.79–3.4
Intraabdominal infection	13 (28.3)	22 (19.3)	0.215	1.65	0.75–3.64
Intravascular catheter infection	6 (13)	20 (17.5)	0.485	0.71	0.26–1.89

Table 3: Thirty-day mortality rate between antibiotic regimens to treat patients with ampicillin-susceptible enterococci bloodstream infections[14]

Regimens between Group 1 and Group 2 [1]	p Value	OR	95%CI
Vancomycin vs. Anti-enterococcal beta-lactams	0.02	4.55	1.39–14.92
Vancomycin vs. Anti-enterococcal beta-lactams combination	0.039	4.8	1.13–20.46
Anti-enterococcal beta-lactams vs. Anti-enterococcal beta-lactams combination	0.917	1.06	0.38–2.89

[1] Group 2 as reference. Abbreviations: CI, confidence interval; OR, odd ratio.

RECENT ADVANCES AND FUTURE DIRECTIONS

Enterococcal infections, particularly vancomycin-resistant enterococci (VRE), have become more common in recent years, largely due to antibiotic misuse and the resistance that results. A long-term strategy could be developing a vaccine to vaccinate high-risk individuals. Enhancing healthcare practices and developing new, powerful antibiotics are additional tactics. Using pharmacogenomics to create compounds that target key microbial activities is a promising strategy that may lead to the creation of resistant-less drugs. Although drug resistance develops dynamically due to high mutation rates and selection pressure, rational drug design driven by comparative analysis of drug-target polymorphisms can provide next-generation therapies that work in a range of patient groups. The development of resistance may be rare in some circumstances due to changes in genes that are vital to bacterial survival. It is still necessary to optimize existing medications such as linezolid, Synercid, and fluoroketolides in order to control VRE and MRSA. In Phase 2 development, solithromycin, a novel fluoroketolide, has shown consistent activity comparable to that of telithromycin and clindamycin. Among the pharmaceutical companies creating new antimicrobials in the pipeline are Vicuron, P113 (Phase 2; Demegen), WCK 771 (Wockhardt), ranbezolid, and iseganan. The purpose of these medications is to fight the resistance of VRE and other harmful disorders. The severity of VRE infections makes it imperative to carry out additional research, develop new drugs, and enhance existing therapies to combat this growing risk in healthcare settings.[15]

CONCLUSION

Because of their multidrug resistance and capacity to produce major nosocomial infections, vancomycin-resistant enterococci (VRE) have become one of the most difficult organisms to treat in contemporary healthcare. The overuse and abuse of antibiotics, which provide selective pressure that leads to the creation of resistant strains, is mostly to blame for the sharp rise in VRE infections in recent years. Because of its high mutation rates and capacity to acquire and spread resistance genes, VRE can quickly adapt to antimicrobial therapy, which makes management very challenging. The complex interaction between bacterial genetics and therapeutic pressure is highlighted by the molecular mechanisms underlying vancomycin resistance, which include target site modification, acquisition of van gene clusters, and alterations in cell wall production. It is essential to comprehend these mechanisms in order to create tactics that effectively counteract VRE. There are still few therapeutic options available for VRE infections; the mainstay of current care consists of linezolid, daptomycin, and more recent medications like tigecycline. However, the need for new antimicrobial development is highlighted by the emergence of resistance to last-resort medicines, such as linezolid-resistant VRE. New approaches to discovering crucial microbial targets have been made possible by pharmacogenomics and logical drug design, which has allowed for the creation of next-generation drugs that are less likely to acquire resistance. Fluoroketolides, ranbezolid, WCK 771, P113, BM-415, and dalbavancin are promising compounds in the pipeline that have demonstrated efficacy

against resistant enterococcal pathogens in preclinical and early clinical investigations. In order to lower the danger of collateral resistance, these innovative medicines seek to both overcome resistance and lessen the selective pressure on commensal bacteria.

Preventive measures are becoming more and more important in addition to pharmaceutical treatments. While strict infection control procedures, like as surveillance, isolation, and environmental decontamination, are essential in preventing nosocomial transmission, vaccine development for high-risk populations may provide long-term protection and lessen colonization. Pharmacokinetics and pharmacodynamics-guided optimization of current antibiotic medication can increase efficacy and prevent the emergence of resistance. Overall, because of its quick growth, versatility, and potential for hospital outbreaks, VRE poses a serious clinical and public health threat. A multimodal strategy that incorporates molecular discoveries, creative drug development, preventive measures, and prudent antibiotic stewardship is needed to combat this danger. Future studies that concentrate on mechanistic comprehension. To create efficient methods that lessen the burden of VRE infections worldwide, targeted therapies and translational application will be crucial. To remain ahead of this changing pathogen and guarantee the best possible outcomes for patients, a concerted effort including physicians, microbiologists, and pharmaceutical developers is essential.

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