International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 15, Issue 1 2023

Review Article

PREVALENCE OF VANCOMYCIN RESISTANT ENTEROCOCCI FROM URINARY TRACT INFECTED PATIENTS

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Received: 30 May 2022, Revised and Accepted: 21 Nov 2022

ABSTRACT

Urinary tract infections (UTIs) are one of the infectious diseases affecting humankind. The microbial agents that infect the tissues of the urinary tract from the renal cortex to the urethral meatus *Enterococci* are opportunistic pathogens that are found in the normal gut flora. *Enterococci* are the second leading cause of UTIs, accounting for 10% of all nosocomial UTIs. This species has become a major pathogen in the United States, Iran, Europe, and other parts of the world, including India. Antibiotic resistance is increasing, which slows the rate of progress in practical therapies, making susceptibility testing necessary. So, *enterococci* were isolated from urine samples of patients with UTI that were subjected to morphological characterization, biochemical assays, etc., The main aim of the study was to help in identifying resistance patterns and the dispersal of *Enterococcus* strains from various samples of urine to antibiotic agents like *Penicillin G, Tetracycline, Teicoplanin, Norfloxacin,* high-level *Gentamycin, Linezolid, Nitrofurantoin,* and with special emphasis on *Vancomycin* antibiotic. The greatest threat posed by Vancomycin-Resistant Enterococci (VRE) is its ability to transfer resistance genes to more dangerous gram-positive bacteria, potentially leading to truly terrifying pathogens in the future. A long stay in the hospital and the use of *Vancomycin* were connected to VRE-UTI and colonisation. Renal dialysis, renal failure, previous aminoglycoside, and third-generation cephalosporin use were all relevant hazard factors for VRE from UTI. The paper also underlines the importance of screening clinical samples for VRE and proposes that control measures be implemented to limit the spread of VRE.

Keywords: Enterococcus, Urinary tract infections, *Vancomycin*, Antibiotic resistance

DOI: https://dx.doi.org/10.22159/ijpps.2023v15i1.45380. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps.

INTRODUCTION

The urinary tract infection (UTI) is invaded by bacteria and infects the ureters, bladder, urethra and etc, and most of the UTI occurs in the urethra bladder. The infection can be seen more in females compared to males because of the shorter urethra and its closeness to the bowel [1]. UTIs are categorised into complicated and uncomplicated risks. The risk factors associated with complicated UTIs are almost always related to pregnancy, immune suppression due to urinary tract carcinoma, neurogenic bladder, renal, ureteral or bladder calculi, renal failure or transplantation, spinal cord injury and catheterization [2, 3]. Uncomplicated UTIs are due to age, a prior UTI, sexual activity, vaginal infection, diabetes, etc. UTIs may lead to some threatening diseases like bacteremia in elderly men. In both community and hospital areas, over 150 million urinary tract-affected individuals per year were observed. In 1984, *Enterococcus,* formerly called Group D *Streptococci*, were endogenous human flora that had also been considered pathogens with low virulence. However, more recently, they have emerged as increasingly important healthcare-nosocomial pathogens. *Enterococci* have been recognised as being potentially pathogenic for humans since the early 1900s, when they were well-established as a cause of endocarditis and UTI [4]. *Enterococci* are prolific colonisers with a high degree of genomic plasticity and a proclivity for surviving in hospital settings, allowing for resistance element transmission and dissemination. Infections are more common in immune-compromised individuals who have previously undergone repeated regimens of antibiotics. During the past few decades, *Enterococci* have emerged as important healthcare-associated pathogens [5]. In the United States, *Enterococcus* has been a leading cause of multidrug-resistant *Enterococcal* infection over the last two decades [6].

Enterococci are widespread in nature. They acquire resistance through mutation or by receiving foreign determinants through plasmids or transposons [7]. This emergence is primarily the cause of multidrug-resistant *Enterococcal* infection in the United States [8]. This emergence is primarily due to their inherent resistance to commonly used antimicrobials and their acquisition of high-level resistance to *Vancomycin*. The emergence of VRE has limited therapeutic options.

VRE has increased intensively and is associated with enhanced mortality [9]. Infections with VREs are associated with prolonged hospital stays and excess mortality. Increasing VRE rates pose a serious problem to global health. Limited options are available for *vancomycin-resistant enterococcal* infections [10]. Early guidelines for VRE control focused on the prevention of cross-transmission between patients and medical personnel [11]. The hypothesis is that nosocomial VRE infections can be effectively controlled by screening patients at high risk [12]. Previous contacts with VRE-confirmed patients are often mentioned as a risk factor in VRE acquisition [13].

Clinical microbiologists have become increasingly interested in *Enterococci* in recent years, not only because of their capacity to cause serious infections but also because of their rising resistance to numerous antibiotics [14]. *E. coli* is the most common cause of UTIs, accounting for 50% of all cases. Other bacteria which may cause UTIs are *Klebsiella* species, *Pseudomonas aeruginosa, Streptococcus aureus, Streptococcus agalactiae, Enterococcus spp,* and *Candida Spp* [15, 16]. *Klebsiella spp.* and *P. aeruginosa* are the two pathogens that most commonly cause UTIs in diabetic and urinary catheter patients.

Enterococcus background and clinical manifestations

The genus *Enterococcus* is an opportunistic pathogen and it was described as an intestinal microorganism by Thiercelin in the 19th century. They are gram-positive, non-spore-forming, catalase-negative, facultative anaerobic bacteria. It can appear as single, bilobed cocci or in chains [17]. They can also grow in 40% bile salts, 6.5% sodium chloride, in milk containing 0.1% methylene blue, and at pH 9.6. In the 1980's, the genus *Enterococcus* was reclassified from the genus *Streptococcus* by studying their DNA hybridization and 16s RNA sequencing [17, 18]. Most of the *Enterococci* colonise the gastrointestinal tract and to a lesser extent, the genitourinary tract, the oral cavity, and in skin. The species of *Enterococcus* which act as causative agents of Enterococcal infections are *E. faecalis, E. faecium, E. avium, E. casseliflavus, E. durans, E. gallinarum, E. hirae, E.*

malodoratus, E. mundtii, E. pseudoavium, E. raffinosus, and E. solitarie. Of the first 12 species, the first 2 species, *E. faecium* and *E. faecalis*, account for 80-90% and 5-15% of all clinical isolates, respectively [18].

The *Enterococci* bacteria are identified more commonly as colonising bacteria in the intestine than virulent agents [17, 18]. It is a significant cause of community-acquired and hospital infection [19], and it survives and colonises patients in hospital settings. They are also thought to be the cause of severe systemic infections in immune-compromised people, including cancer patients [20]. Other than UTIs, several infections caused by *Enterococci* are bacteremia, infective endocarditis, intra-abdominal and pelvic infections, skin infections, and central nervous system infections [21]. Whereas, Enterococci are the third most common cause of infection in the bloodstream. A number of studies have shown that *Enterococci* cause about 30% of hospital-acquired endocarditis, followed by *Staphylococcus spp* [20]. The most common cause of bloodstream infections and UTIs is *E. faecalis*. *Enterococci* isolated from skin infections together with other pathogenic agents, have been reported to cause osteomyelitis, septic arthritis, and CNS infections such as meningitis [20]. Nowadays, *Enterococci* infections caused by VRE have been associated with high mortality rates of 25% to 50%, frequently affecting immune-compromised people [22].

Scientific classification

Domain: Bacteria

Phylum: Bacillota

Class: Bacilli

Order: Lactobacillales

Family: Enterococcaceae

Genus: *Enterococcus*

Both *E. faecalis* and *E. faecium* are common in hospital-acquired UTIs and become more common in people with underlying complicating factors such as diabetes, spinal cord injury, and other comorbidities [23]. *Enterococcus* species are the second most frequent uropathogen in complicated UTIs after *E. coli* species [24]. The estimated isolated frequency ratio of *E. faecalis* to *E. faecium* is 5:1, respectively [21]. The isolation rate of *E. faecalis* has increased in recent decades, and it has been reported as a remarkable characteristic [25], owing primarily to urinary catheters and stents associated with biofilm formation [26]. Annually, 110,000 cases of Enterococcal UTIs were estimated in the United States [27].

Search strategy

Published studies and reports of UTIs were searched using PubMed, Free text and index terms (Medical topic headings) related to UTI, India, and prevalence were used, and to maximise the retrieval of relevant articles, a broad search approach was used. The elements like the following search terms were identified: UTI, *Enterococcus,* uropathogen, *Vancomycin* resistant Enterococci etc. range of years used as filter were past 2011-22. The bibliographies of other reviews and original studies were carefully searched for other relevant papers to maximise search results.

Epidemiology

From 20 y of study, in urology patient's isolation rates of UTI`s *E. faecalis* and *E. faecium* were 13.3%-21% and 7.6-10%, respectively, while the rates among urology outpatients were 11.7-18.6% and 1-2.3% respectively [1]. Except these two species there is another species i.e. *Enterococcus hirae* causes symptomatic UTI`s in a diabetic patient with benign prostatic hyperplasia [28]. *Enterococcal* UTI`s occurs at the ages before 10 and after 60 years, when genitourinary malformations and obstructive uropathy are more common [29]. In tertiary care areas 8.5% of UTI`s was isolated from 40% of patients belonging to the age group 30-59years [30]. Compared to community-acquired cases, nosocomial infections are more frequent and accounting for 12-15% and 2-8% respectively, mainly associated with anatomical abnormalities of urinary tract such as vesicoureteral reflux, urethral instrumentation or antibiotic prophylaxis. These patients have more commonly such anatomical abnormalities and worse prognosis in term of recurrence scaring, need of surgery than children with UTI`s caused by gram-negative bacteria [18, 30]. The most frequently isolated *Enterococcal* bacteria from children with UTI`s are *Enterococcus faecalis*[4]. The estimated rate of bacteria in the majority of healthcare-acquired UTI`s have been recorded in ICUs, namely 8-21% *E. coli, P. aeruginosa* and *Enterococci* are the predominant pathogens. About 95% of infections have been associated with indwelling urinary catheters [31]. According to recent research, the most commonly observed pathogen in kidney transplant recipients was *Enterococcus* spp. (35%), followed by *E. coli* (32%), and *Klebsiella* species (13%). According to recent studies, the incidence of UTIs was caused by *E. coli* (54%), followed by *Enterococci* (25%), and the predominant *E. faecalis,* responsible for 19% of the total cases [32].

In the year 2014 January to December study of a private tertiary care hospital at Shivamogga district in Karnataka, results showed that out of 66 enterococcal isolates, 32 isolates were from urine samples which majority of the *Enterococcal* isolates were from females [33]. In Mysuru region, Mysore Medical College and Research Institute study results show that among 100 different samples, 50 isolates were pathogenic *Enterococcal* isolates. The comparison of the resistant patterns of commensal *Enterococcal* isolates with pathogenic isolates shows that there is more resistance to antibiotics in pathogenic *Enterococci* and also shows multidrug resistance to antibiotics [34].

Pathogenicity and risk factors

In 1906, scientists Andrewes and Horder reported that *Enterococcus* spp. are the causative organisms of UTIs. These are the most common clinical disease caused by *Enterococcus* spp. in both hospital and outpatient settings. It consists of complicated UTIs such as pyelonephritis, prostatitis, perinephric abscess [22, 35] and related to urinary tract malformations, urinary catheters, or long-time antibiotic treatment [30]. The high prevalence of VRE causing urinary tract colonization, asymptomatic bacteriuria, or uncomplicated UTI's, is of great concern and is associated with increased morbidity, limited treatment options, and increased healthcare costs [36].

Studies have shown that UTIs by *Enterococcus* species are often polymicrobial, whereas they may also enhance the growth of several bacteria in the urinary tract [37]. Some of the reasons for the transmission of *Enterococci* in the hospital environment have been clearly documented, such as rapid dissemination from patient sources through environmental contamination, healthcare worker colonization, and hand contamination [37]. The ability of Enterococci to survive for long periods of time in environmental areas such as medical equipment, bed rails, and doorknobs [19, 38].

Prolonged hospitalisation in long-term care facilities, surgical units, severe co-morbidities, urinary catheters, and antibiotic treatment, which is most common in immune compromised patients, increases the ability of multidrug resistant pathogens to cause infections [35]. The polysaccharide antigen of *Enterococcus* plays an important role in the pathogenicity of UTIs, including its binding to epithelial cells, biofilm formation, and evasion of phagocytosis by neutrophils [4]. *Enterococci* encode several virulence factors, such as *Enterococcal* surface protein (ESP) and biofilm-associated pili (Ebp), predisposing to their initial attachment and biofilm formation on urinary catheters, which promote their persistence in the bladder and further dissemination to the kidneys [2, 23]. Genitourinary symptoms are mild in Enterococcal UTIs, commonly related to catheterization and instrumentation. They are often asymptomatic [39], considered to be less severe than UTIs caused by other uropathogens [37]. UTIs caused by Enterococci can cause bacteremia in 15-24% of adult patients in hospital settings and are commonly associated with urinary catheter hematologic malignancies and recent antibiotic treatment with Vancomycin and others [39, 40]. It has been noted that 50% of male patients having Enterococcal endocarditis had previously had UTIs, whereas 38% of female patients had genitourinary sources such as abortion or instrumentation [40] (fig. 1).

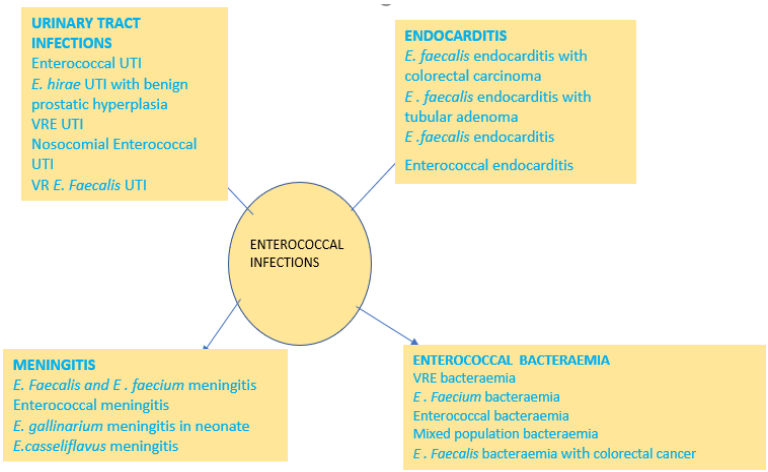

Fig. 1: Infections caused by genus *Enterococcus* [67]

Virulence of *Enterococci*

Enterococci are one of the major causes of endocarditis, UTIs, and bacteremia. The majority of the findings reveal that *Enterococci* is the top cause of nosocomial infections in the United States, accounting for 20–30% of all nosocomial infections, and is the world's second biggest cause of nosocomial infections [10]. According to the Chinese report, *E. faecium* represented about 74% of the causative pathogens, followed by *E. faecalis* that accounted for 20% of the blood stream infections with a mortality rate [41]. The infections caused by these pathogens are tough, persistent, and may be troublesome (fig. 2).

The virulence of enterococcus includes but is not limited to cytolysin (CyILLLSM), *enterococcal* surface protein (Esp.), aggregation substance (AS), gelatinase (GelE), E. *faecium* cell wall adhesion factors and sex pheromones Cob and Ccf. Cytolycin plays a major role in the progression of *enterococcal* infection through its hemolytic activity and bactericidal activity against gram-positive bacteria. As helps in conjugation and mating at the site of infection, there is an accumulation of bacteria at the site of infection. GelE hydrolyses haemoglobin and other peptides, resulting in inflammation, and the sex pheromones transfer plasmids carrying one or more antibiotic-resistant genes [42]. *Enterococci* is a common pathogen that causes nosocomial infections and can develop antibiotic resistance through chromosomes, plasmids, or transposons.

Vancomycin resistance *Enterococci* (VRE`s)

The first *vancomycin* resistance *Isolates of Enterococci* isolates were identified by investigators in the United Kingdom and France [43, 44]. Related strains of VRE were detected in hospitals in the eastern half of the United States [45]. Based on the level of resistance to glycopeptides, VREs can be classified into different classes in that two strains of the Van A type possess inducible, high-level resistance to *Vancomycin* [46]. The genes vanA, vanR, vanS, vanH, vanX, vanY, and vanZ are present on a transposon Tn1546, which resides on a plasmid [47] (fig. 3).

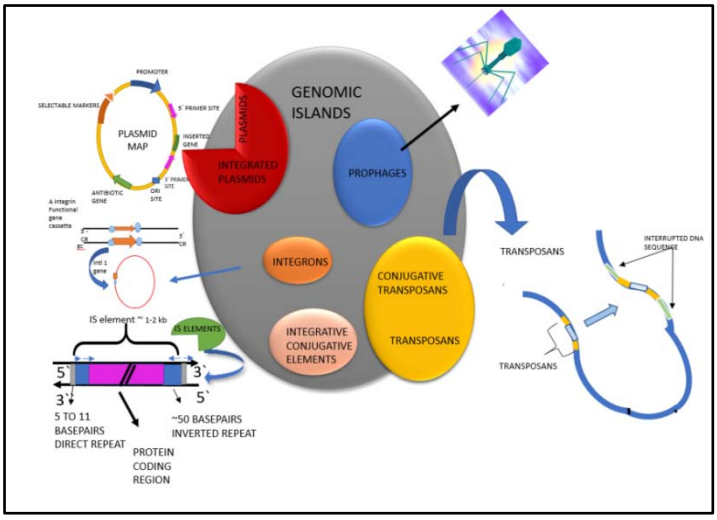

Fig. 2: Mobile genetic elements of bacteria [67]

Historical yearly usage of *Vancomycin*

The graph above depicts detailed data on Vancomycin drug usage over the last 20 y. The data was collected by the Lilly database between 1975 and 1983, when Lilly supplied Vancomycin drug on its own. From 1984 to 1996, the data was obtained from IMS international. Vancomycin drug usage increased in the 1980s, and it was eventually sold out in the form of oral formulations in the mid 1980s. Later, commercial oral formulations were identified because the injectable formulation was administered orally [9, 48], but orally absorbed Vancomycin is not absorbed and is only used to treat intestinal infections. The use of *vancomycin continued* rapidly throughout the world in the 1980s and early 1990s. Following 1994, a slight decrease in Vancomycin use reflects the beginning of efforts

to restrict Vancomycin use in response to concerns about the spread of vancomycin-resistant bacteria.

The major reason for the *Enterococci* that shows resistant to *Vancomycin*

The presence of Tn1546 on conjugative plasmids or, in some instances, on sex pheromone-responsive plasmids, explains *why vancomycin* resistance has spread rapidly among different strains of *Enterococci* [49, 50]. Teicoplanin is usually susceptible to vancomycin. Vancomycin inhibitory concentrations in vanB genes range from 8 to more than 1,000 microg/ml [51, 52]. Most of the Van A and van B strains are either *E. faecalis* or *E. faecium*. Also, van C strains can be identified, but most of the *Enterococcal* infections are caused by van A and van B strains [53] (fig. 4).

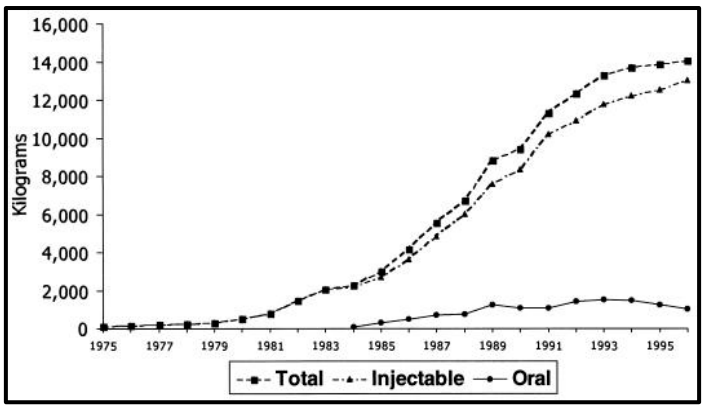

Fig. 3: fig. shows the respective of historical yearly usage of *Vancomycin* [68]

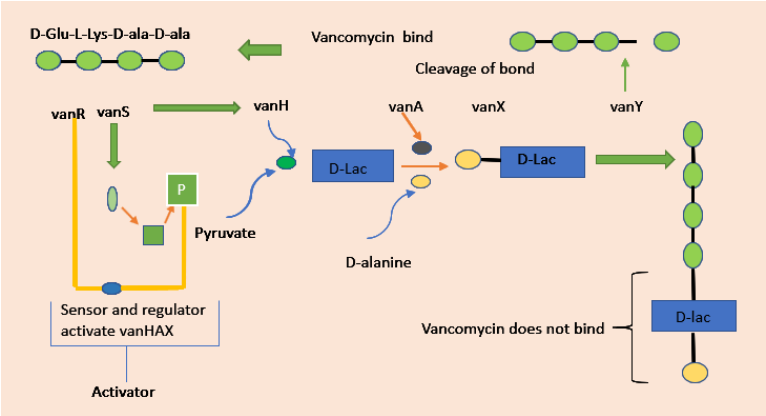

Fig. 4: The development of Vancomycin-resistant pattern in *Enterococci* [67]

Types of *Vancomycin* resistance

Vancomycin has been used in therapeutic settings for over 30 y without eliciting significant resistance in recent years. There are two types of *Vancomycin* resistance present namely; Intrinsic resistance, which shows low level of resistance to *Vancomycin,* Acquired Resistance, *Enterococci* resistant to *Vancomycin* by the acquisition of genetic information from another organism.

Intrinsic resistance can be seen in isolates of *Enterococcus* are *E. gallinarum* and *E. casseliflavus* or *E. flavescens*. Isolates of *Enterococcus,* which shows acquired resistance commonly, are *E. faecium* and *E. faecalis and also recognised* in *E. raffinosus*, *E. avium*, *E. durans*, and several other *Enterococcal species.*

Geographic distribution of *Vancomycin*-resistant *Enterococcus*

After the initial recovery of *Enterococcal* infections in patients in the United Kingdom, Italy, Malaysia, the Netherlands, Spain, and the United States, almost all isolates from all geographical areas contain the same vanA gene or Tn1546-like sequences, suggesting that similar resistance determinants have spread worldwide. The molecular typing of VRE isolates depends on the number of investigators who have provided evidence that transmission of VRE may occur between states and hospitals in the same city [45]. From 1989 to 1993, the percentage of nosocomial infections by *Enterococci* reported to the Centres for Disease Control and Prevention's National nosocomial infection surveillance system that were due to VRE increased from 0.3%-7.9%. The reason for the increase was mainly due to the 34-fold rise (from 0.4 to 13.6%) of VRE infections in intensive care unit (ICU) patients and also a trend towards increased VRE infections also noted in non-ICU patients [54].

Risk factors

The emergence of VRE in the United States reported that most of the VRE were in intensive care unit patients in the early studies and other risk factors that have been associated with infection include previous antimicrobial therapy, exposure to contaminated medical things such as electronic thermometers, and previously known VRE cases [54-56]. The main risk factors associated with VRE infections are bacteremia, malignancy, increased acute physiology and chronic health evolution score, neutropenia, long-term hospitalization, and antibiotic therapy [57-60].

However, prior therapy with the antimicrobial agent Vancomycin is most frequently implicated as a major risk factor [45, 56, 61-63]. Some studies show primarily intravenous *Vancomycin*, others show that oral *Vancomycin* may be more important, and at the present time, it is not clear which one of the therapies is the most likely to promote colonization [61, 64] with VREs.

In the last 10-15 y, the use of *vancomycin* in the United States has increased and its selective pressure is exerted. The amount of *vancomycin* used at one university hospital increased 20-fold from 993 g in 1981 to 19,957 g in 1991 [65]. On a national level, *vancomycin* (parenteral plus oral) sales in the United States increased from approximately 5 million g in 1987 to 12.8 million g in 1995. By way of comparison, a total of 22,000 g of *Vancomycin* were used to treat human infections in Denmark in 1993. On a per capita basis, the amount of *vancomycin* sold in the United States in 1993 (482 g/100,000 people) was more than ten-fold higher than the amount used in Denmark (424 g/100,000 people).

Many Gram-positive organisms are highly effective against vancomycin. The increased use of the antibiotic Vancomycin has been linked to a significant increase in VREs. It spreads to other virulent organisms like *Staphylococcus aureus*. Despite the use of linezolid and tigecycline, the rise in antibiotic resistance is difficult to treat [66].

Modes of transmission

The most common mode of nosocomial transmission of VRES is by healthcare workers whose hands become transiently contaminated with the organism while caring for affected patients. It facilitates the recovery of VREs and other resistant Enterococci from cultures provided by healthcare workers' hands [37, 67, 68]. The chances of transmission of VRE may also occur by way of contaminated medical equipment, but this is probably much less of a factor than transmission by the hands of personnel. Beds, stethoscopes, blood pressure cuffs, commodes, and other items have been found to be contaminated with VRE, but further studies are needed to determine the extent to which these items contribute to the transmission of VRE.

Disposable cover gowns worn by personnel who care for VRE patients have also been shown to be contaminated with the patient's organism. Presumably, the clothing of personnel who do not wear cover gowns may also become contaminated with VRE. At the present time, however, there is no conclusive proof that VRE is spread by contaminated clothing. There is no proof that *Enterococci*, including VRE, are spread by the airborne route [51].

Controlling measures or management aspects of VRE`s

The control of VREs from the enteric gut of affected patients has been reducing the reservoir of resistant *Enterococcus* pathogens. The prescribed medicines to cure VREs include oral bacitracin, novobiocin, doxycycline, or rifampin [59, 68]. Some patients appear to respond to these medicines, but no medicines have been uniformly effective in eradicating VREs.

The dramatic increases in *vancomycin* resistance in *Enterococci,* the Subcommittee on Prevention and Control of Antimicrobial-Resistant Microorganisms in Hospitals of the CDC Hospital Infection Control Practices Advisory Committee (HICPAC), had several meetings in the years 1993-94. To control the nosocomial transmission of VREs, HICPAC published recommendations in February 1995 (CDC, 2009).

The recommendations are mainly based on: Prudent use of *Vancomycin,* Education of hospital staff effective use of the microbiology laboratory and implementation of infection control measures (including use of gloves and gowns, isolations). Educating hospital staff includes attending and consulting physicians, students, pharmacy personnel, medical residents, laboratory personnel, and other direct patients' caregivers must includes information about the epidemiology of VRE and potential impact of the pathogen on the prices and outcome of patient care. It helps to high performance standards for hospital personnel, special awareness and educational sessions may be indicated.

Early detection of patients infected with VRE is an essential subject of any hospital program to designed to prevent nosocomial transmission of VRE, because once prevalence of VRE increase in high level in a hospital region may leads difficulty in prevention. Once VRE have been detected in hospital, Enterococci recovered from the all body site should be tested for Vancomycin.

The current important aspects to isolate VRE`s are recommended by HICPAC are: Isolate VRE`s infected person in a single room, Wearing of clean, sterile gloves and gowns when enter into VRE`s patients' room and remove immediately when leave the room, Wash the hands thoroughly with antiseptic soap or waterless antiseptic agents, so that contaminated hand from VRE`s through gloves leaks or gloves removal can be controlled. Once gloves and gowns are removed avoid touching of VRE`s contaminated site in the patient room [5].

CONCLUSION

The spread of antibiotic resistance in *Enterococcus* species may leads to serious challenge to society. The emergence of increasing prevalence of *Enterococcal* species in immune compromised patients, including neoplastic ones constitute major health problems and leading to high rates of morbidity, mortality, economic costs and also limited treatment options. To encounter these problems, there is an urgent need of evidence-based research focusing on the identification of the factors which are facilitating the transmission of *Enterococcal* antimicrobial resistance within the hospital areas and also for suitable clinical management and therapeutic approaches. Additionally, further investigation is in need to consider the use of antibiotics that has major role in increased transmission rate of resistance.

ACKNOWLEDGMENT

We extend our gratitude to JSS Academy of Higher Education and Research, S S Nagar, Mysuru for supporting the work.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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