Review Article www.pimr.org.in

DOI: 10.47799/pimr.1102.02

Colonizer to Pathogen: A review on Enterococcal urinary tract infections

Rituparna Saha[1]*, Manisha Khandait[2], Moumita Sardar[3], Mukesh Sharma[4]

[1]Assistant Professor, Department of Microbiology, Faculty of Medicine & Health Sciences, SGT University, Gurgaon, Haryana
[2]Professor & Head, Department of Microbiology, Faculty of Medicine & Health Sciences, SGT University, Gurgaon, Haryana
[3]Professor, Department of Microbiology, Faculty of Medicine & Health Sciences, SGT University, Gurgaon, Haryana
[4]Associate Professor, Department of Microbiology, Faculty of Medicine & Health Sciences, SGT University, Gurgaon, Haryana

*Corresponding Author:
Rituparna Saha, Assistant Professor, Department of Microbiology, Faculty of Medicine & Health Sciences, SGT University, Gurgaon, Haryana
E-MAIL: rituparnasaha6@gmail.com

Date of Submission: 24/01/2023 Date of Review: 23/04/2023 Date of Acceptance: 15/05/2023

ABSTRACT

Enterococcus species has been historically known as part of the commensal flora of the normal human alimentary tract. Implicated in a wide array of illnesses encompassing bloodstream infections, urinary tract infections, wound infections as well as intra-abdominal infections, it has been rapidly emerging as a pathogen of interest owing to its propensity to acquire multidrug resistance. Due to the high antibiotic pressure in healthcare settings and salient intrinsic resistance to commonly used classes of antimicrobials, Enterococcus selectively proliferates in nosocomial settings. Their hardy nature and ability to resist a wide array of disinfectants enable them to proliferate on surfaces as well as provide for efficient transmission in hospital settings. Since Urinary tract infection (UTI) is one of the commonest infections caused by Enterococcus species. We attempt to comprehensively overview the paradigm shift of this erstwhile colonizer to one of the common uropathogen in hospital and community settings.

KEYWORDS: Enterococcus, Colonization, Urinary tract infection, Drug Resistance

INTRODUCTION

Enterococci are hardy, facultative anaerobic, gram-positive cocci, predominantly in pairs or sometimes in short chains, that grow and survive in many environments. They are relatively common in the environment and are widely found in soil, water, food, sewage, plants, human skin, the oral cavity, and the large intestine, constituting less than 1% of the total microbiota. [1] Enterococcus is part of the normal flora of the intestine of humans and animals and is traditionally considered to be a low-grade pathogen, but many of them are responsible for serious infections.

The term "Enterococcus" was coined by Thierclein in the late nineteenth century, when he isolated a gram-positive cocci of intestinal origin that caused infections in humans. [2]Subsequently, it was MacCallum and Hastings, who isolated and characterized the gram-positive coccus from a severe case of acute endocarditis. [3] Initially termed Micrococcus zymogenes the cocci thus recovered, once inoculated in pure culture and induced into animal models, it demonstrated lesions of endocarditis in the animals. Thus, fulfilment of the Koch's postulates established the microorganism as a natural human pathogen. Formerly classified as Group D Streptococci, Enterococci were conferred genus status in 1984 based on DNA hybridization and 16S rRNA sequencing. [4]The genus Enterococcus is believed to have diverged from its last common ancestor approximately 425 million years ago. [5]The members of the genus so contrived, grew in the presence of 6.5% NaCl and 40% bile salts over wide-temperature as well ass pH ranges, survived desiccation, host defences and competed in the alimentary canal to persist and disseminate to facilitate the colonization of new hosts.

The paradigm of human infections caused by Enterococcus has much altered since. More than fifty-eight species of Enterococcus have been isolated to date, of whom, particularly two species: Enterococcus faecalis and Enterococcus faecium are particularly pathogenic to man. The other strains of enterococci known to cause human infections include- Enterococcus avium, Enterococcus gallinarum, Enterococcus casseliflavus, Enterococcus raffinosus, Enterococcus mundtii and Enterococcus durans. These non-faecium non-faecalis enterococci are increasingly being reported as the causative agents of the bloodstream and endovascular infections in humans over recent years. [6]

COLONIZATION

Enterococci depict a wide host range, from invertebrates and insects to mammals. The diverse array of host species underscores the hardy nature and its ability to thrive in varied gut environments by evasion of host defences. According to several studies, Enterococci are one of the earliest colonizers of the infant human gut and constitute the core members of the human gut microbiome. [7, 8] Likewise, they are abundantly found as part of the commensal flora of both domestic and wild animals; which may subsequently lead to infection in animals as well. However, despite being an integral constituent of the host microbiome, enterococci comprise <1% of the total gut microbiota in healthy human beings. With the use of antimicrobials, these microorganisms proliferate within the gut environment due to intrinsic and acquired drug resistance. The proficiency of Enterococci to colonize the healthy human gut in addition to patients on antibiotic therapy positions them to effectively exploit the iatrogenic dysbiosis arising from various therapeutic interventions and subsequently promotes the establishment of a pathogenic micro-environment. [9, 10] Several studies conducted in three mice models comprising of mice-pretreated with antibiotics to deplete the gut flora, germ-free mice and antibiotic-naïve mice; have postulated and converged on insights of the mechanism of intestinal colonization of Enterococcus spp. [11–13]

The theory of nutritional adaptation of enterococci relies on the fact that the genome of Enterococcus spp. does not code for the prerequisites for the biosynthesis of amino acids and vitamins. [14] Consequently, these microorganisms rely on the intestinal microenvironment and compete with the gut microbiota for nutrients. Studies have revealed the presence of a four-gene cluster, encoding a putative mannose/fructose/sorbose family phosphotransferase system (PTS) in clinical isolates of Enterococcus faecium, responsible for specialized, carbohydrate uptake. Deletion of the ptsD gene subsequently resulted in impaired colonization in antibiotic-perturbed mice. [15] Analysis of enterococcal transcriptome by RNA-seq revealed that the majority of induced genes of Enterococcus faecalis are involved in nutrient transport or metabolism in germ-free mice. Studies have shown the downregulation of virulence genes like SprE (a serine protease) and GelE metalloprotease in germ-free mice which further emphasizes the increased reliance of Enterococcus on the import of environmental nutrients for establishing colonization. [16]

Vancomycin-resistant Enterococcus faecalis strains harbouring a chromosomally integrated bacteriophage V583 have been found to demonstrate enhanced colonization in the antibiotic-treated alimentary canal of experimental mice models in comparison to Enterococcus faecalis strains devoid of the bacteriophage. [17] Enterococcus faecalis resistant to phage infection failed to portray the competitive advantage; thus highlighting the role of bacteriophages in the colonization of Enterococcus in the gastrointestinal tract. [18] Additionally, the genomic plasticity of Enterococcus spp is influenced by naturally occurring plasmids, which in turn aid in the evolution of multi-drug resistant strains, especially in nosocomial settings. It has been established that a plasmid bearing the hyaluronidase gene in Enterococcus faecium, enhanced its gut colonization in an antibiotic-treated mouse model. [19]

Production of certain conjugative plasmid-mediated antimicrobial substances among the gut flora is inhibitory to the growth of competing microorganisms in the alimentary ecosystem. [20] Concordantly, the bacteriocin-encoding plasmid pPD1 has been found to facilitate gut colonization of Enterococcus faecalis as well as enhance its propensity to displace pre-existing gut flora, in experimental mice models. [12] Inhibition of VRE by commensal enterococci has been demonstrated ex vivo, which may be attributed to induced signal transduction between commensal enterococci with VRE via mobile genetic elements. These findings not only establish the pivotal role of mobile genetic elements in establishing colonization in the host gut but also features the incompatibility of commensal enterococci with multi-drug resistant enterococci.

In E. faecalis, IreK, a transmembrane Serine/Threonine kinase is crucial in maintaining the cell envelope integrity and resistance against cell wall active antimicrobial. The deletion of ireK in E. faecalis resulted in a marked deficit in gut colonization in an experimental antibiotic-naive mouse model. [21] Concurrently, the conserved locus encoding for enterococcal polysaccharide antigen (Epa) locus, a rhamnose-containing cell-wall polysaccharide which is known to play a role in the maintenance of cell shape, resistance to phage-induced lysis, biofilm formation and virulence in mice; has been shown to portray variance in organization and gene content among strains. An enriched accessory epa gene epaX has been detected in hospital-associated Enterococcus faecalis infections, which in turn alter the composition of Epa polysaccharide, consequently increasing its susceptibility to bile acid cholate, which leads to impaired GIT colonization in antibiotic-treated mice. [22] This not only implicates the accessory genes in colonization but also underscores the strain-specific biochemical properties of Enterococcus to alter gut colonization.

The production of biofilms by commensal Enterococcus faecalis in intestinal sections of germ-free mice models, suggests biofilm production as an important factor in establishing colonization. The Enterococcus faecalis microcolonies are thought to be adherent to the inner mucus layer of intestinal epithelium facilitated by the formation of biofilms. In vitro, gene-encoded biofilm production has been demonstrated by Enterococcus faecalis which facilitates its colonization in the intestinal tract. The deletion of ebrB which encodes a transcriptional regulator necessary for biofilm formation, was seen to decrease enterococcal colonization. [23] Additionally, the EbrB is also presumed to be vital for the expression of virulence gene Esp, which in turn is essential for biofilm formation. Similarly, alterations in bop (biofilm on plastic) locus, has been implicated in delayed gut colonization by Enterococcus faecalis, whereas strains devoid of

the gene exhibited copious biofilm production in the presence of glucose but not maltose. These findings point to the role of biofilms along with the nature of available nutrients in biofilm-mediated colonization of enterococci within the intestine. [18, 24] Similarly Sortase A (SrtA), a membrane-associated enzyme that mediates the anchoring of surface proteins to the enterococcal cell wall also promotes biofilm formation. The genome of Enterococcus faecalis is known to encode for several sortase-dependent cell wall-anchored proteins, including cell-surface adhesins such as Ace and Ebp pilus, which facilitate binding to the extracellular matrix and help produce biofilm respectively. It has also been seen that Enterococcus faecalis devoid of the SrtA was deficiently adherent to mucin in vitro, which was specifically in association with loss of combination of the virulence genes Ace and Ebp. [18]

Antimicrobial therapy induces the proliferation of colonized enterococci in the alimentary canal owing to the elimination of regulatory components within the microenvironment either directly or in synchronous action with the host mucosal immune system. Studies have revealed colonization with certain bacteria like Barnesiella spp., Clostridium bolteae and Blautia producta to confer resistance to colonization and increased elimination of multidrug-resistant Enterococcus from the gastrointestinal tract. [25, 26] The studies about the effects of alteration of gut microbiota on the colonization of Enterococcus, though are a handful and may not be generalizable, nevertheless reaffirm the potential role of gut microbiota alteration in directly modulating multidrug-resistant Enterococcus spp carriage.

Owing to their high resilience, Enterococci can survive in the presence of commonly used antiseptics and disinfectants, encouraging its persistent growth on inanimate surfaces, especially in hospital settings. [4, 27] Furthermore, the isolation of Enterococcus from the hands of healthcare workers, condones its widespread nosocomial transmission.

INFECTIONS

The spectrum of infections caused by Enterococci ranges from bloodstream infections, urinary tract infections, endocarditis, pyogenic infections, intra-abdominal infections and pelvic infections. However, over the past decade, they have been consistently emerging as an important cause of nosocomial infections due to an increasing trend of acquiring antimicrobial resistance. Urinary tract infections are the most common enterococcal infection in hospital settings. This is followed by intraabdominal and intrapelvic abscesses or post-surgery wound infections, as the second most frequent enterococcal infections, where Enterococci form a part of mixed flora of the gut. Bloodstream infections constitute the third largest bulk of enterococcal infections. Other less frequent infections include- infections of the central nervous system and neonatal infection; while respiratory tract infections, osteomyelitis, or cellulitis are relatively rare. [28] The highest detected rate of enterococcal UTI was in Canada (16.8%), followed by the US (12.5%) and Europe (11.7%), while they account for more than 9% of bloodstream infections in the USA and Canada. [29] Likewise, the Indian scenario resonates with these emerging trends and Enterococci have been isolated as a nosocomial pathogen from diverse clinical conditions like urinary tract infections and bacteremias. Recently Enterococci have been gaining immense clinical importance due to their propensity for multidrug resistance. The development of drug resistance of Enterococci, in turn, is largely attributed to its ability to colonize the gastrointestinal tract of hospitalized patients for a long duration. The CDC in a survey indicated that a high percentage of hospital-acquired infections are caused by Enterococcus, next only to MRSA and ESBL producers. [30]

Urinary Tract Infection

E. faecalis, has been implicated as a causative agent of CAUTI and HAI. The E. faecalis strains do not contain flagella or pili but adherence to the host cell is primarily mediated by surface proteins line as Esp (Enterococcal Surface Proteins) and Ebp (Endocarditis and biofilm-associated pilus). The Esp is a surface protein with repetitive domains which provides bacterial resistance in response to antibiotics. [31] Proteins encoded by esp facilitate E. faecalis adherence to fibrinogen and collagen ligands in the urinary bladder cells in a mice model as well as facilitate the biofilm formation. [32]

The Ebp protein of Enterococcus spp essentially comprises EbpA, B, and C, that exhibit affinity to the host cells and lead to early biofilm production. Ebp is presumed to be assembled on cell membranes with the help of anchoring proteins like SortaseA, and C (SrtA and SrtC), it is thought to play a pivotal role in biofilm production and establishment of infection in the urinary tract. [33] Studies have illustrated the initial regulatory steps of in-vitro biofilm production during the pathogenesis of UTI to be modulated by SrtA and SrtC-Ebp. Additionally, SrtA and Ebp have also been known to regulate biofilm formation during the establishment of CAUTI. [34]

Various pilus components assist the Ebp in adhering and early biofilm formation is initiated via Agg (aggregation substances), and Ace (adhesin to collagen). Ace proteins are mainly involved in the formation of biofilm and colonization of murine UTI models. [35] Gelatinase (gelE), is a secreted protease which is involved in the dissemination of bacterium by the degradation of polymerized fibrin, whereas, Agg binds to the renal epithelium. [36, 37]

Thus, Ebp plays a major role in biofilm formation on the biotic and abiotic surfaces during the pathogenesis of UTI. The biofilm formation in turn is regulated by intracellular transduction or quorum sensing which regulates and coordinates the collective expression of biofilm within the micro colonies of Enterococcus. [38] Cross-contamination, through persistent colonization of the gastrointestinal tract, is considered a major source of urinary tract infection by E. faecalis in patients with CA-UTI. Hence, it is the synchronous ability of Enterococcus to colonize by adherence, produce biofilms on biotic and abiotic surfaces as well as inherent

resistance to many classes of antimicrobials that facilitate them to evade host immune response and establish infection in the urinary tract.

ANTIMICROBIAL RESISTANCE

A combination of penicillin and gentamicin had been the mainstay of treatment of enterococcal infections until the recent past. Still, with the emergence of high-level aminoglycoside resistance (HLAR), vancomycin remained the only alternative available. Furthermore, the widespread use of glycopeptides in hospitals has lately led to the emergence of Vancomycin-Resistant Enterococcus (VRE), which is a major concern for healthcare professionals. Infection with VRE is associated with increased mortality, length of hospital stay, admission to the ICU, surgical procedures & cost. The resistance of Enterococci to many antibiotics confers a great challenge to the treatment of these infections.

VRE was initially isolated from clinical isolates in England and France (1986), which was closely followed by the isolation of Vancomycin-resistant Enterococcus faecalis in the United States, the following year. The threat of colonization and subsequent infections with VRE increased in 2002; when the first patient case of VRE transmitting vanA resistance genes to methicillin-resistant Staphylococcus aureus (MRSA) to form a vancomycin-resistant Staphylococcus aureus (VRSA) isolate was reported. [39] E. faecium comprises the majority of VRE infections and exhibits more resistance to glycopeptides, although E. faecalis is more pathogenic in comparison. Enterococci inherently harbours efficient mechanisms for attaining antimicrobial resistance. They exhibit a spectrum of acquired and intrinsic mechanisms of resistance. Portraying remarkable plasticity in their genome, they are known to exploit several transferable genetic elements like plasmids, transposons, and insertion sequences for acquisition and conferring antimicrobial resistance. This facilitates the intra and inter-species dissemination of resistance genes. Currently, eight phenotypic variants of acquired glycopeptide resistance and one phenotypic intrinsic resistance in enterococci are documented. VanA, VanB, VanD, VanE, VanG, VanL, VanM, and VanN are the acquired glycopeptide resistance phenotypes in Enterococcus whereas the intrinsic resistance (VanC) is found exclusively in E. gallinarum and E. casseliflavus.

Glycopeptide antibiotics inhibit the cell wall by binding to d-Ala-d-Ala terminals of the pentapeptide precursors of bacterial cell wall peptidoglycans owing to their strong affinities. Resistance to glycopeptide arises when low-affinity d-Ala-d-Lac or d-Ala-d-Ser pentapeptide precursors are formed replacing the d-Ala-d-Ala pentapeptide precursors. A change in the precursor to d-Ala-d-Lac as observed in genotypic resistance VanA, VanB, VanD and VanM, causes a 1,000-fold decreased affinity for vancomycin. On the other hand, the change of cell wall to d-Ala-d-Ser as seen in VanC, VanE, VanG, VanL, and VanN genotypes results in a 7-fold decrease in affinity for vancomycin. [40] VanA is responsible for the majority of human cases of VRE worldwide and is mostly harboured by E. faecium. The most widespread clinical course of Vancomycin-Resistant Enterococci (VRE) is longstanding asymptomatic intestinal colonization serving as a reservoir for transmission to other patients. Urinary tract infections (UTI) are the commonest healthcare-associated infection caused by Enterococci. Selective pressure arising from commonplace suboptimal indicated use of antimicrobials like third-generation cephalosporins and antibiotics against anaerobes have been established to predispose to colonization and subsequent infection with VRE. Case-control studies found the use of parenteral metronidazole as well as of third-generation cephalosporins to be highly significant and independent risk factors for the isolation of VRE. [41]

With the emergence of VRE, Linezolid, the first oxazolidinone antibiotic, quickly became an antimicrobial of choice for treating infections due to VRE. However, with widespread utilization of linezolid, linezolid-resistant VRE strains were insidiously isolated from the US in 2001 and in the UK in 2002. [42, 43] Sequencing of linezolid-resistant VRE strains revealed a G2576U mutation in the 23S ribosomal RNA subunit. [44] Linezolid-resistant VRE later isolated from Thailand was found to carry the cfr methyl transferase on a plasmid, causing methylation at position A2503 in the 23S rRNA and thus conferring high-level resistance. [45]

CONCLUSION

Enterococcus has eerged as a pathogen of interest in hospital as well as community settings alike. Their propensity to acquire resistance to high-end antimicrobial agents including vancomycin, teicoplanin and linezolid, impose immense therapeutic challenges by shrinking the available spectrum of therapeutics immensely. The prevalence of enterococcal urinary tract infection in patients with pre-existing comorbidities like diabetes, renal failure, and immunosuppression as well as patients on cancer chemotherapy, merely add to the complexity of treatment and simultaneously add to the accruing cost of treatment, morbidity and mortality inherently associated with these conditions. The increasing use of high-end antibiotics in community settings, especially in the animal industry has been implicated in the rise of resistance to higher antibiotics like glycopeptides. Colonization with multidrug-resistant stains and the possibility of horizontal transmission of resistance among colonizers further increase the risk of infection in colonized individuals. To counteract the alarming rise in this pathogen, the elucidation of factors facilitating the transmission of enterococcal antimicrobial resistance within the hospital environment for appropriate clinical management as well as prevention of the dissemination of high-end antimicrobial resistance, through elaborate evidence-based research, is imperative.

REFERENCES

1. Raza T, Ullah SR, Mehmood K, Andleeb S. Vancomycin-resistant Enterococci: A brief review. J Pak Med Assoc. 2018;68(5):768–72.

2. Thiercelin ME. Morphologie et modes de reproduction de l'enterocoque. Comptes Rendus des Seances de la Societe de Biologie et des ses Filiales. 1899;11(11):551–553.

3. Maccallum WG, Hastings TW. A case of acute endocarditis caused by Micrococcus zymogenes (nov. spec.), with a description of the microorganism. J Exp Med. 1899;4(5-6):521–555.

4. Fiore E, Tyne DV, Gilmore M. Pathogenicity of enterococci Microbiol Spectr. 2019;7:3–0053.

5. Lebreton F, Manson AL, Saavedra JT, Straub TJ, Earl AM, Gilmore MS. Tracing the enterococci from Paleozoic origins to the hospital. Cell. 2017;169(5):849–61.

6. Saha R, Singh N. Non-faecalis and non-faecium enterococci as uropathogens: An update from a tertiary care centre. Intr J Sci Res. 2022;p. 11–11.

7. Eggesbø M, Moen B, Peddada S, Baird D, Rugtveit J, Midtvedt T. Development of gut microbiota in infants not exposed to medical interventions. Apmis. 2011;119(1):17–35.

8. Lawley TD, Walker AW. Intestinal colonization resistance Immunol. 2013;138(1):1–1.

9. Gilmore MS, Lebreton F, Van Schaik, W. Genomic transition of enterococci from gut commensals to leading causes of multidrug-resistant hospital infection in the antibiotic era. Curr Opin Microbiol. 2013;16(1):10–16.

10. Arias CA, Murray BE. The rise of the Enterococcus: beyond vancomycin resistance. Nat Rev Microbiol. 2012;10(4):266–78.

11. Orrhage K, Nord CE. Factors controlling the bacterial colonization of the intestine in breastfed infants. Acta Paediatrica. 1999;88:47–57.

12. Kommineni S, Bretl DJ, Lam V, Chakraborty R, Hayward M, Simpson P. Bacteriocin production augments niche competition by enterococci in the mammalian gastrointestinal tract. Nature. 2015;526(7575):719–741.

13. Fanaro S, Chierici R, Guerrini P, Vigi V. Intestinal microflora in early infancy: composition and development. Acta paediatrica. 2003;92:48–55.

14. Gilmore MS, Clewell DB, Ike Y, Shankar N. Enterococci: From Commensals to Leading Causes of Drug Resistant Infection [Internet]. 2014;.

15. Kaval KG, Singh KV, Cruz MR, Debroy S, Winkler WC, Murray BE. Loss of ethanolamine utilization in Enterococcus faecalis increases gastrointestinal tract colonization. MBio. 2018;9(3):790–808.

16. Lindenstrauß AG, Ehrmann MA, Behr J, Landstorfer R, Haller D, Sartor RB. Transcriptome analysis of Enterococcus faecalis toward its adaption to surviving in the mouse intestinal tract. Arch Microbiol. 2014;196(6):423–456.

17. Duerkop BA, Clements CV, Rollins D, Rodrigues JL, Hooper LV. A composite bacteriophage alters colonization by an intestinal commensal bacterium. Proceedings of the National Academy of Sciences. 2012;109:17621–17627.

18. Banla LI, Salzman NH, Kristich CJ. Colonization of the mammalian intestinal tract by enterococci. Cur Opin Microbiol. 2019;47:26–31.

19. Rice LB, Laktičova V, Carias LL, Rudin S, Hutton R, Marshall SH. Transferable capacity for gastrointestinal colonization in Enterococcus faecium in a mouse model. J Infect Dis. 2009;199(3):342–351.

20. Hibbing ME, Fuqua C, Parsek MR, Peterson SB. Bacterial competition: surviving and thriving in the microbial jungle. NAt Rev Microbiol. 2010;8(1):15–25.

21. Banla IL, Kommineni S, Hayward M, Rodrigues M, Palmer KL, Salzman NH. Modulators of Enterococcus faecalis cell envelope integrity and antimicrobial resistance influence stable colonization of the mammalian gastrointestinal tract. Infect Immun. 2018;86(1):381–398.

22. Rigottier-Gois L, Madec C, Navickas A, Matos RC, Akary-Lepage E, Mistou MY. The surface rhamnopolysaccharide epa of Enterococcus faecalis is a key determinant of intestinal colonization. J Infect Dis. 2015;211(1):62–71.

23. Top J, Paganelli FL, Zhang X, van Schaik W, Leavis HL, van Luit-Asbroek M et al. The Enterococcus faecium enterococcal biofilm regulator, EbrB, regulates the esp operon and is implicated in biofilm formation and intestinal colonization. PloS one. 2013;8(5):e65224.

24. Creti R, Koch S, Fabretti F, Baldassarri L, Huebner J. Enterococcal colonization of the gastro-intestinal tract: role of biofilm and environmental oligosaccharides. BMC Microbiol. 2006;6(1):1–8.

25. Caballero S, Kim S, Carter RA, Leiner IM, Sušac B, Miller L. Cooperating commensals restore colonization resistance to vancomycin-resistant Enterococcus faecium. Cell Host Microbe. 2017;21(5):592–602.

26. Ubeda C, Vanni Bucci, Caballero S, Djukovic A, Toussaint NC, Equinda M et al. Intestinal microbiota containing Barnesiella species cures vancomycin-resistant Enterococcus faecium colonization. Infection and immunity. 2013;81(3):965–973.

27. Miller WR, Murray BE, Rice LB, Arias CA. Vancomycin-resistant enterococci: therapeutic challenges in the 21st century. Infect Dis Clin. 2016;30(2):415–454.

28. Schaberg DR, Culver DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. Am J Med. 1991;91(3):72–77.

29. Low DE, Keller N, Barth A, Jones RN. Clinical prevalence, antimicrobial susceptibility, and geographic resistance patterns of enterococci: results from the SENTRY Antimicrobial Surveillance Program, 1997-1999. Clin Infect Dis. 2001;32:133–178.

30. Patel R. Clinical impact of vancomycin-resistant enterococci. J Antimicrob Chemother. 2003;51(3):13–21.

31. Shankar V, Baghdayan AS, Huycke MM, Lindahl G, Gilmore MS. Infection-derived Enterococcus faecalis strains are enriched in esp, a gene encoding a novel surface protein. Infect Immun. 1999;67(1):193–200.

32. Tendolkar PM, Baghdayan AS, Gilmore MS, Shankar N. Enterococcal surface protein, Esp, enhances biofilm formation by Enterococcus faecalis. Infection and immunity. 2004;72(10):6032–6039.

33. Nielsen HV, Flores-Mireles AL, Kau AL, Kline KA, Pinkner JS, Neiers F. Pilin and sortase residues critical for endocarditis-and biofilm-associated pilus biogenesis in Enterococcus faecalis. J Bacteriol. 2013;195:4484–95.

34. Nielsen HV, Guiton PS, Kline KA, Port GC, Pinkner JS, Neiers F. The metal ion-dependent adhesion site motif of the Enterococcus faecalis EbpA pilin mediates pilus function in catheter-associated urinary tract infection. MBio. 2012;3(4):177–189.

35. Roh JH, Singh KV, Rosa L, Cohen SL, Murray AL, E B. The two-component system GrvRS (EtaRS) regulates ace expression in Enterococcus faecalis OG1RF. Infect Immun. 2015;83(1):389–95.

36. Waters CM, Antiporta MH, Murray BE, Dunny GM. Role of the Enterococcus faecalis GelE protease in determination of cellular chain length, supernatant pheromone levels, and degradation of fibrin and misfolded surface proteins. J Bacteriol. 2003;15(12):3613–3636.

37. Rozdzinski E, Marre R, Susa M, Wirth R, Muscholl-Silberhorn A. Aggregation substance-mediated adherence of Enterococcus faecalis to immobilized extracellular matrix proteins. Microbial pathogenesis. 2001;30(4):211–220.

38. Cook LC, Federle MJ. Peptide pheromone signaling in Streptococcus and Enterococcus. FEMS Microbiol Rev. 2014;38(3):473–92.

39. Giacometti A, Cirioni O, Schimizzi AM, Prete MSD, Barchiesi F, Mm D. Epidemiology and microbiology of surgical wound infections. J Clin Microbiol. 2000;38(2):918–940.

40. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A. Antimicrobial-resistant pathogens associated with healthcare-associated infections summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention. Infect Control Hosp Epidemiol. 2009;34(1):1–4.

41. Procop GW, Church DL, Hall GS, Janda WM. Koneman's color atlas and textbook of diagnostic microbiology. Jones & Bartlett Learning; 2020.

42. Gonzales RD, Schreckenberger PC, Graham MB, Kelkar S, Denbesten K, Quinn JP. Infections due to vancomycin-resistant Enterococcus faecium resistant to linezolid. Lancet. 2001;357(9263):1179–1179.

43. Auckland C, Teare L, Cooke F, Kaufmann ME, Warner M, Jones G. Linezolid-resistant enterococci: report of the first isolates in the United Kingdom. J Antimicrob Chemothr. 2002;50(5):743–749.

44. Marshall SH, Donskey CJ, Hutton-Thomas R, Salata RA, Rice LB. Gene dosage and linezolid resistance in Enterococcus faecium and Enterococcus faecalis. Antimicrob Agents Chemother. 2002;46(10):3334–3340.

45. Diaz L, Kiratisin P, Mendes RE, Panesso D, Singh KV, Arias CA. Transferable plasmid-mediated resistance to linezolid due to cfr in a human clinical isolate of Enterococcus faecalis. Antimicrob Agents Chemother. 2012;56(7):3917–3939.

How to cite this article: Saha R, Khandait M, Sardar M, Sharma M. **Colonizer to Pathogen: A review on Enterococcal urinary tract infections**. Perspectives in Medical Research. 2023;11(2):3-8
DOI: 10.47799/pimr.1102.02