ORIGINAL RESEARCH PAPER

Volume-8 | Issue-1 | January-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

HOW IMPORTANT ARE ENTEROCOCCI IN CAUSING URINARY TRACT INFECTIONS- WHAT DO WE NEED TO KNOW? A BRIEF REVIEW

Microbiology

Maanasa Bhaskar M Assistant Professor, Department Of Clinical Immunology, Jawaharlal Institute Of Post Graduate Medical Education & Research (JIPMER), Puducherry, India.

Jharna Mandal* Additional Professor, Department of Microbiology, Jawaharlal Institute of Post Graduate Medical Education & Research (JIPMER), Puducherry, India. *Corresponding Author

ABSTRACT

Urinary tract infections are one of the most common infections caused by Enterococci. However, some aspects of Enterococci as a uropathogen remains unclear. Current review article explores the various aspects of Enterococci as uropathogen in view of the increasing importance of Enterococci causing urinary tract infections, their multi drug resistant phenotype and lack of pertinent data regarding the same. In this review, after thorough literature search we have tried to summarize the various virulence factors of Enterococci implicated in causing UTI and other aspects such as reporting and management of Enterococcal UTI in various clinical settings.

KEYWORDS

Enterococci; Urinary tract infection (UTI); Multi drug resistant organism (MDR); Uropathogen; Asymptomatic bacteriuria (ABU)

INTRODUCTION

The genus Enterococcus consist of Gram positive, facultatively anaerobic organisms belonging to the Family *Enterococcaceae* that may appear on Gram stain as Gram positive cocci in pairs and short chains which are often difficult to distinguish from Streptococci by physical characteristics alone. The pathogenicity of these organisms remains controversial as they are often part of the normal human microbial flora. Although they are part of the normal human microbiome of the adult gastrointestinal tract, they are important nosocomial pathogens too. Various nosocomial and community acquired infections caused by Enterococci include urinary tract infections, bacterial endocarditis, bacteraemia, deep seated intra-abdominal infections, meningitis and less frequently respiratory tract infections and skin and soft tissue infections.

Of the various species, the most important ones implicated in infections are *Enterococcus faecalis* and *Enterococccus faecium* although their relative contributions in causing infections vary. Now over the past few decades, these organisms have emerged as important nosocomial pathogens and have gained importance globally due to their multidrug resistant phenotype. The intrinsic resistance coupled with acquisition and dissemination of mobile genetic elements makes the treatment of these infections difficult. Current review article explores the various aspects of *Enterococci* as uropathogen in view of the increasing importance of *Enterococci* causing urinary tract infections, their multi drug resistant phenotype and lack of pertinent data regarding the same.

ENTEROCOCCI AS URINARY PATHOGEN

Urinary tract infection is one of the most common bacterial infection encountered in clinical practice, the distribution of organisms causing UTIs keep changing and the etiological agent for community-acquired and hospital acquired are different. (1). The most important pathogens implicated in urinary tract infections are members of *Enterobacteriaceae* family, other Gram negative bacilli, less frequently *Staphylococcus aureus* and *Staphylococcus saprophyticus* among the Coagulase negative Staphylococci. *Enterococcus* species although less commonly isolated, has been recognized as an important uropathogen.

Inspite of being one of the commonest causes for urinary tract infections and troublesome nature due to the multidrug resistant phenotype exhibited by these organisms little is known about the various bacterial virulence factors and pathogenetic mechanisms responsible for *Enterococcus* species causing urinary tract infections. In this review we have tried to look into the various possible virulence factors and pathogenetic mechanisms after thorough literature search and have summarized here.

VIRULENCE FACTORS – Virulence factors refer to the properties that enable a microorganism to establish itself and replicate on or within a specific host species (2). Enterococci can be an important cause for UTIs in hospital setting where the patient`s defence can be compromised due to the presence of indwelling catheters or immunodeficiencies or both. Although Enterococci are known to cause nosocomial UTI, not much is known regarding the various virulence factors contributing to UTI. The severity of the UTI depends upon a balance between the bacterial virulence factors and the antibacterial host defence mechanism.

Role of adherence- Initial interaction with the host cells and colonization of mucosal surfaces are important events in the pathogenesis of many infections(3). Various animal models were used to study the adherence mechanisms. In a typical Uropathogenic *Escherichia coli* (UPEC) infection, bacilli invade the superficial umbrella cells of the bladder, multiply to high levels and forms intracellular bacterial communities (IBC), a process that requires TLR4 mediated response resulting in recruitment of neutrophils to the bladder. In *Enterococcal* UTI, minimal neutrophils were present at the site of infection and was found to be independent of Toll Like Receptor 2 (TLR-2) which is often used by Gram positive organisms. The mechanism by which Enterococci invades the uroepithelium remains unknown. Possible mechanisms are usage of various adhesion proteins, production of various aggregation substances and usage of unique vesicle trafficking system in uroepithelium to be passively engulfed (4,5).

a) Enterococcal surface protein (Esp)- Is a cell wall associated protein coded by chromosomal gene, *Esp*, first described in a highly virulent, gentamicin resistant *E.faecalis* isolate from a bacteraemic patient by Shankar *et al.,*(6). Several investigators have demonstrated contributions of *Esp* in persistence of urinary tract infections in animal models and are thought to play a major role in adhesion, colonization, evasion of immune system and formation of biofilm. The structural gene is unique in that it allows for alternate forms of expression of the *Esp* protein. The *Esp* protein is surface localized and such variation in the cell surface helps in the ability of Enterococci to escape immune mechanisms resulting in persistence of infection. The unique morphology of the *Esp* with multiple repeat motifs helps Enterococci to adhere to the host uroepithelium. Several murine models *Enterococcus faecalis* urinary tract infection has been used to study the role Esp and aggregation substance in the pathogenesis. Most of them are adapted from the models used for studying Gram negative uropathogens and are variations of ascending unobstructed urinary tract infections. Typically, 10^6-10^8 organisms are administered to anesthetized mice via a transurethral catheter, and animals are sacrificed at intervals ranging from one to fourteen days, at which time urine, the bladder, and the kidneys are harvested for quantitative bacterial culture and histopathology(7–9). *E. faecalis* shows tropism for the kidneys causing pyelonephritis in this type of model, and there was significant colonization of kidney tissue in spite of delivering the bacteria only through bladder making it useful for studies focused on factors that contribute to enterococcal pyelonephritis. Bladder remained sterile in all these studies.These and other studies demonstrated that Enterococcus may accelerate the onset and clinical

severity of UTI caused by other pathogens such as *E.coli* and *Pseudomonas aeruginosa* in mixed infections(3,9). Another murine model used to study the pathogenesis was infection of C57BL/6J mice model. Infection of C57BL/6J mice with an *E. faecalis* urinary tract isolate caused an inflammatory response in the kidneys, but not the bladder.The inflammatory response was different than that induced by uropathogenic *E. coli*.

b) Enterococcal aggregation substance (AS) – Aggregation substance (AS) is a plasmid encoded pheromone inducible surface protein which interacts with the Enterococcal binding substance (EBS) constitutively expressed in most of the Enterococci and is used in formation of mating complexes during bacterial conjugation(9).AS is associated with increased virulence and mortality in rabbit models of infective endocarditis. Some studies have found that AS mediates adhesion to cultured renal tubular cells using animal models (10). However,studies by James *et al*., have demonstrated that these aggregation substances and Enterococcal binding substances are not the major contributors to urinary tract colonization in a mouse model of ascending urinary tract infection(9). The possible mechanisms by which it acts as virulence factor are a) it increases the hydrophobicity of the Enterococcal surface which may prevent or delay phagolysosome fusion b) promotes direct opsonin independent binding of *Enterococcus faecalis* to human neutrophils through complement receptor 3 and other receptors on the surface of neutrophils(11). Enterococci expressing AS was found to resist phagocytosis significantly better than isogenic AS negative strain by inhibition of respiratory burst in the macrophages (12).

c) Sortases & Endocarditis and biofilm associated pili (Ebp)- Sortases are extracellular transpeptidases that are found in the plasma membrane that sort and anchor the proteins that are designed to be on the cell surface. They can be divided into 4 classes A,B,C and D based on their structure. Class A is the major group found in Gram positive bacteria and are found to anchor a number of proteins. Sortase C class of enzymes are predicted to anchor a much smaller set of substrates and the genes coding for these are also associated with pilus biosynthesis in addition to surface anchoring. *Enterococcus* species are found to harbour class A and Class C sortases. These enzymes act as microbial surface components recognizing adhesive matrix molecules resulting in attachment of *Enterococcus* species to extracellular matrix and play an important role in virulence(13). Studies have found that Ebp locus is important for colonisation of kidneys in a murine model of UTI.

d) Bacterial persistence and Biofilm formation- Ability to form aggregates of microorganisms on abiotic surfaces is an important virulence property of Enterococci. Biofilms are bacterial communities encased within an extracellular matrix composed of proteins, carbohydrates and nucleic acids. They provide a favourable milieu for the microorganism survival within the host. The exact virulence mechanisms and genes involved in biofilm formation in *Enterococci* causing urinary tract infections is not clear(14). Several studies have postulated the role of Esp and gelatinase in the formation of biofilms but the results are conflicting. In addition to Esp, additional determinants may contribute to formation of biofilms in Enterococci (15,16). The enhanced antibiotic tolerance coupled with intrinsic resistance to many of the clinically used antibiotics of the organism and the propensity to disseminate the antimicrobial resistance genes suggests that biofilm formation of *Enterococci*in a hospital settingcan be really problematic (17).

UTI related bacteraemia due to *Enterococcus* sp- Urinary tract infections with *Enterococcus* species are often associated with bacteraemia also. Enterococcal UTI tend to be common among the hospitalized patients or long-term care settings. Several studies have been done to identify the predictors associated with bacteraemia due to *Enterococcus* species. Male sex, presence of indwelling urinary catheters, obstructive urological diseases, immunosuppressive therapy, cigarette smoking, diabetes mellitus for patients more than 70 years of age and prior antibiotic treatmentare the various risk factors.

Several studies have evaluated different gender distributions and have found that male sex accounts for about 53-68% of cases of Enterococcal bacteraemia associated with UTI (18–21). Association of presence of urinary catheters and bacteraemia may be due to the disruption of the uroepithelium and exposing the blood stream to the bacteria resulting in bacteraemia. Jerkeman and Braconier, 1992, found that urinarycatheters were more common in a bacteraemic patient group compared to a non-bacteraemic group(18). Similar to urinary catheters, urological procedures may also disrupt the uroepithelium resulting in bacteraemia. Appropriate antibiotic treatment following urine culture for specific patient subgroups may be given to enhance patient safety and reduce the risk of development of bacteraemia due to *Enterococcus* sp (22).

Laboratory Diagnosis Of Enterococcal Urinary Tract Infections

Assuming normal urine to be sterile, laboratory guidelines for diagnosis of urinary tract infections was put forward by Kass way back in 1950s(23). While this is commonly followed in most of the clinical microbiology laboratories, the interpretation of urine culture has become really difficult with the recent concept that normal urine is not sterile(24,25). Urine samples may also become contaminated with normal microbiome present in the urethra during the collection process making things difficult to interpret. According to Kass concept, term significant bacteriuria provides a means for differentiating true urinary tract infection in a freshly voided clean catch mid-stream urine sample from contamination. Significant bacteriuria refers to bacterial count of $\geq 10^5$ CFU/ml of urine using a standardized loop. However, some pathogens like *Enterococcus* species can cause urinary tract infections at a significantly low numbers (10^2CFU/ml) and some contaminants may be present at a significantly high numbers(26).

Reporting of *Enterococci* from urine samples – Are we doing the right thing?

Appropriate diagnosis and treatment of UTI is a challenge both for the clinicians as well as the clinical microbiologist. In most of the cases, clinical microbiologists do not want to be responsible for missing UTIs with low number of organisms in culture, but at the same time, over reporting can also lead to unnecessary antibiotic prescription for the patient resulting in development of antimicrobial resistance and adverse drug effects. So, we need to balance these two aspects while reporting any case of UTIs with significantly low numbers of organisms.

Reporting in an asymptomatic patient- A clinical scenario much difficult to understand is presence of Asymptomatic bacteriuria (ABU). Enterococci are part of the human microbiome of the lower gastrointestinal tract in humans and their presence in urine is often asymptomatic. Asymptomatic bacteriuria is defined as the presence of bacteria in the urine of the individual without signs and symptoms of UTI. Its thought to be present in around 3-5 % of young healthy sexually active women and more common in elderly patients and diabetics (27). According to current Infectious disease society of America (IDSA) guidelines, asymptomatic bacteriuria (ABU) should not be treated except in pregnant women, before performing transurethral resection of prostate, in patients undergoing urological procedures for which mucosal bleeding is anticipated and in neonates, young children and school going girls where it indicates underlying vesicoureteric reflex. Recent guidelines also clearly states that pyuria accompanying ABU should not be an indication for antimicrobial treatment (28). In patients with indwelling catheters, presence of pyuria is an indication of inflammation and should not be used to distinguish UTI and ASB.

Increasing incidence of Enterococcal urinary tract infections and their association with presence of indwelling catheters often makes the clinicians to treat Asymptomatic bacteriuria with Enterococci. In these situations, presence of Enterococci is normal in the urinary tract and should not be treated even in the presence of positive urine culture. Despite published evidence-based guidelines, nearly one-third of cases of ABU are treated inappropriately with antibiotics globally(29). Treatment of ABU does not provide any benefit in many groups including elderly age group, diabetics, sexually active young women and those with spinal cord injuries(30).

a) Role of ABU treatment prior to surgery

There are two main conditions in everyday clinical practice that require special attention- the role of ABU in pre-operative cases and in women with recurrent urinary tract infections. In most of the instances, the usage of prophylactic antibiotics as a pre-operative strategy has substantially reduced the incidence of post-operative infections and its complications, irrational usage of these antibiotics and their extended usage in the post-operative period has contributed in the development of multidrug resistant organisms, increased treatment costs and unwanted side effects. According to European association of Urology guidelines (EAU), a urine sample should be sent for culture before

surgical intervention which requires entering of urinary tract and breaching the mucosa and antibiotic should be given if suggestive of ABU. These recommendations highlight the need for sending urine culture before any urological surgical procedure and limitation of antibiotics usage. However, treatment of ABU has not shown any benefit in patients undergoing orthopaedic prosthetic surgery, in case of open heart surgeries and in short and long term follow ups of patients with kidney transplantation. Even though ABUs are common among the kidney transplant patients during the first year of post-transplant, recent evidence suggests that antibiotic treatment for ABU offers no benefit (31–33).

b) Role of ABU treatment in women with recurrent urinary tract infections

Three important conclusions put forward by Cai et al., after conducting a randomized clinical trial on sexually active females with ABU are 1) treatment of ABU is associated with a higher probability to develop symptomatic recurrence rate, 2) It is also associated with modification of the isolated bacterial strain, 3) In patients without any risk factors, presence of ABU is associated with protective role in development of symptomatic bacteriuria especially with *Enterococcus faecalis.* The findings from the above study will help us in optimizing the antibiotic usage and thus preventing development of MDR organisms. In essence, it is hypothesized that being a part of the normal human microbiome, *Enterococcus faecalis* is an important defence mechanism which will prevent the development of symptomatic UTI with other organisms especially *E.coli*(27).

Reporting in a symptomatic patient

UTI can be subdivided into infection localized to the bladder and urethra (cystitis and urethritis) and upper tract infection of the collecting system and renal parenchyma (pyelonephritis). These occur in any age group. Vast majority of symptomatic infections involve young women. In the absence of prostatitis, bacteriuria and symptomatic UTI are rare in men. Diagnosis of simple cystitis to pyelonephritis could be done with certainty only with urine culture and further reporting by applying significant bacteriuria concept.(1,34). Enterococcal UTI is not uncommon and is usually associated with obstructive uropathy associated with urological/neurological disorder. Diagnosis of Enterococcal UTI often indicates presence of undiagnosed urological abnormalities. A high degree of suspicion is necessary as the signs and symptoms associated with UTI is often mild and hence mild and nonspecific abnormalities detected in urine analysis should be taken into account. (35)

TREATMENT

In the past few years *Enterococcus* has received special attention. This pathogen is of particular interest in the hospital situation where multidrug resistant strains often prevail. The rapid acquisition of transferrable multidrug resistance, biofilm formation and ability to thrive and persist in the urinary tract makes the diagnosis and treatment of these organisms difficult (4).

The treatment of UTI focuses on the site of infection, the pathogen involved and the patient profile. Unless symptoms are present, no attempt should be made to eradicate bacteriuria until catheters, stones or obstructions are removed.

Uncomplicated cystitis can almost always be treated using orally administered antimicrobial agents. Ampicillin is the drug of choice for the treatment of Enterococcal UTIs. Ampicillin with sulbactam can be used for the treatment of infections with those strains resistant to ampicillin due to the production of beta lactamase enzyme. In patients allergic to penicillin, Nitrofurantoin or vancomycin can be given. The main problem clinicians are facing in the treatment of enterococcal infections is the inherently resistant nature of the organism to many antibiotics as well as their ability to acquire resistance to almost all the antimicrobial agents available. Resistance to multiple antibiotics especially vancomycin has become common especially in infections involving Enterococcus faecium. For a long time, the treatment for betalactam resistant Enterococcal UTI was vancomycin. With the Increasein incidence of UTIs caused by Vancomycin resistant enterococci (VRE), management of infections caused by these Multidrug resistant pathogens (MDR) has become challenging. Routine treatment of asymptomatic UTI with these MDR pathogens is not recommended. Appropriate antibiotic usage should be based on the urine culture and susceptibility results. Potential orally active antimicrobial agents against MDREnterococci for treatment of uncomplicated UTI are nitrofurantoin, fosfomycin and fluoroquinolones. Potential parenteral agents for the treatment of complicated UTI and pyelonephritis are linezolid, tigecycline, telavancin, tedizolid, daptomycin and quinipristin- dalfopristin. However, these newer agents should be reserved for the treatment of life threatening and serious infections due to these MDR pathogens and none of these agents are free of developing resistance (11,29,36–39).

SUMMARY

Current review article recommends few changes in the guidelines practiced with respect to reporting and management of Enterococcal urinary tract infections. Needed action items are highlighted below.

- Enterococci are part of the normal human microbiome of the lower gastrointestinal tract and urinary tract infections is one of the most common infections caused by Enterococci. Enterococcal UTI is not uncommon although it is not clinically readily apparent. Clinical microbiologists need to develop clear practice guidelines while reporting UTI due to Enterococci.
- Accurate diagnosis of UTI is important both to target appropriate antibiotic therapy and to minimise inappropriate antibiotic usage.
- ABU should not be treated except in pregnant women, before performing transurethral resection of prostate, in patients undergoing urological procedures for which mucosal bleeding is anticipated and in neonates, young children and school going girls where it indicates underlying vesicoureteric reflex.
- Definite diagnosis of Symptomatic UTI should be based on the urine culture and sensitivity report. Diagnosis of Enterococcal UTI may indicate abnormality of the urinary tract that has yet to be diagnosed. A high degree of suspicion is necessary since the supporting clinical and laboratory findings are often mild or minimal.
- Team work by clinical microbiologists, Urologists, Infectious disease physician and women and child health specialist is important for defining reporting and treatment guidelines for appropriate management in patients with UTI.

REFERENCES

1. Wilson ML, Gaido L. Laboratory Diagnosis of Urinary Tract Infections in Adult Patients. Clin Infect Dis. 2004 Apr 15;38(8):1150–8.
2. Köves B, Wullt B. The Roles of the Host and the Pathogens in Urinary Tract Infections. Eur Urol Suppl. 2016 Jul 1;15(4):88–94.
3. Guzmàn CA, Pruzzo C, Li Pira G, Calegari L. Role of adherence in pathogenesis of Enterococcus faecalis urinary tract infection and endocarditis. Infect Immun. 1989 Jun;57(6):1834–8.
4. Horsley H, Malone-Lee J, Holland D, Tuz M, Hibbert A, Kelsey M, et al. Enterococcus faecalis Subverts and Invades the Host Urothelium in Patients with Chronic Urinary Tract Infection. PLOS ONE. 2013 Dec 10;8(12):e83637.
5. Johnson JR, Clabots C, Hirt H, Waters C, Dunny G. Enterococcal Aggregation Substance and Binding Substance Are Not Major Contributors to Urinary Tract Colonization by Enterococcus faecalis in a Mouse Model of Ascending Unobstructed Urinary Tract Infection. Infect Immun. 2004 Apr;72(4):2445–8.
6. 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 Jan;67(1):193–200.
7. Shankar N, Lockatell CV, Baghdayan AS, Drachenberg C, Gilmore MS, Johnson DE. Role of Enterococcus faecalis Surface Protein Esp in the Pathogenesis of Ascending Urinary Tract Infection. Infect Immun. 2001 Jul;69(7):4366–72.
8. Singh KV, Lewis RJ, Murray BE. Importance of the epa locus of Enterococcus faecalis OG1RF in a mouse model of ascending urinary tract infection. J Infect Dis. 2009 Aug 1;200(3):417–20.
9. Johnson JR, Clabots C, Hirt H, Waters C, Dunny G. Enterococcal aggregation substance and binding substance are not major contributors to urinary tract colonization by Enterococcus faecalis in a mouse model of ascending unobstructed urinary tract infection. Infect Immun. 2004 Apr;72(4):2445–8.
10. Kreft B, Marre R, Schramm U, Wirth R. Aggregation substance of Enterococcus faecalis mediates adhesion to cultured renal tubular cells. Infect Immun. 1992 Jan;60(1):25–30.
11. Mundy LM, Sahm DF, Gilmore M. Relationships between Enterococcal Virulence and Antimicrobial Resistance. Clin Microbiol Rev. 2000 Oct;13(4):513–22.
12. Upadhyaya PG, Ravikumar KL, Umapathy BL. Review of virulence factors of Enterococcus : An emerging nosocomial pathogen. Indian J Med Microbiol. 2009 Oct 1;27(4):301.
13. Kemp KD, Singh KV, Nallapareddy SR, Murray BE. Relative Contributions of Enterococcus faecalis OG1RF Sortase-Encoding Genes, srtA and bps (srtC), to Biofilm Formation and a Murine Model of Urinary Tract Infection. Infect Immun. 2007 Nov;75(11):5399–404.
14. Kafil HS, Mobarez AM. Assessment of biofilm formation by enterococci isolates from urinary tract infections with different virulence profiles. J King Saud Univ - Sci. 2015 Oct 1;27(4):312–7.
15. Upadhyaya GP, Lingadevaru UB, Lingegowda RK. Comparative study among clinical and commensal isolates of Enterococcus faecalis for presence of esp gene and biofilm production. J Infect Dev Ctries. 2011;5(05):365–9.
16. Moniri R, Ghasemi A, Moosavi SGA, Dastehgoli K, Rezaei M. Virulence Gene's Relationship With Biofilm Formation and Detection of aac (6')/aph (2") in Enterococcus faecalis Isolated From Patients With Urinary Tract Infection. Jundishapur J Microbiol. 2013 Jul;6(5).
17. Kristich CJ, Li Y-H, Cvitkovitch DG, Dunny GM. Esp-Independent Biofilm Formation by Enterococcus faecalis. J Bacteriol. 2004 Jan 1;186(1):154–63.
18. Jerkeman M, Braconier JH. Bacteremic and non-bacteremic febrile urinary tract infection--a review of 168 hospital-treated patients. Infection. 1992 Jun;20(3):143–5.
19. Chang R, Greene MT, Chenoweth CE, Kuhn L, Shuman E, Rogers MAM, et al. Epidemiology of hospital-acquired urinary tract-related bloodstream infection at a university hospital. Infect Control Hosp Epidemiol. 2011 Nov;32(11):1127–9.

20. Pinholt M, Ostergaard C, Arpi M, Bruun NE, Schønheyder HC, Gradel KO, et al. Incidence, clinical characteristics and 30-day mortality of enterococcal bacteraemia in Denmark 2006-2009: a population-based cohort study. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2014 Feb;20(2):145–51.
21. Malone DA, Wagner RA, Myers JP, Watanakunakorn C. Enterococcal bacteremia in two large community teaching hospitals. Am J Med. 1986 Oct;81(4):601–6.
22. Kg H, Fb H, Sc R, N F-M. UTI-Related Bacteremia Due to Enterococcus faecalis: A Retrospective Case Control Study of Potential Risk Factors. Epidemiol Open Access. 2015 Jun 12;5(2):1–4.
23. Kass EH. Bacteriuria and the Diagnosis of Infections of the Urinary Tract: With Observations on the Use of Methionine as a Urinary Antiseptic. AMA Arch Intern Med. 1957 Nov 1;100(5):709–14.
24. Wolfe AJ, Toh E, Shibata N, Rong R, Kenton K, FitzGerald M, et al. Evidence of Uncultivated Bacteria in the Adult Female Bladder. J Clin Microbiol. 2012 Apr 1;50(4):1376–83.
25. Hilt EE, McKinley K, Pearce MM, Rosenfeld AB, Zilliox MJ, Mueller ER, et al. Urine Is Not Sterile: Use of Enhanced Urine Culture Techniques To Detect Resident Bacterial Flora in the Adult Female Bladder. J Clin Microbiol. 2014 Mar 1;52(3):871–6.
26. Brecher SM. Commentary: Complicated Urinary Tract Infections: What's a Lab To Do? J Clin Microbiol. 2016 May 1;54(5):1189–90.
27. Cai T, Mazzoli S, Mondaini N, Meacci F, Nesi G, D'Elia C, et al. The Role of Asymptomatic Bacteriuria in Young Women With Recurrent Urinary Tract Infections: To Treat or Not to Treat? Clin Infect Dis. 2012 Sep 15;55(6):771–7.
28. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults. Clin Infect Dis. 2005 Mar 1;40(5):643–54.
29. Lin E, Bhusal Y, Horwitz D, Shelburne SA, Trautner BW. Overtreatment of Enterococcal Bacteriuria. Arch Intern Med. 2012 Jan 9;172(1):33–8.
30. Abigail Zuger MD. As Always, Asymptomatic Bacteriuria Is Best Ignored. NEJM J Watch. 2012 Oct 11 [cited 2018 Jun 19];2012.
31. Green H, Rahamimov R, Goldberg E, Leibovici L, Gafter U, Bishara J, et al. Consequences of treated versus untreated asymptomatic bacteriuria in the first year following kidney transplantation: retrospective observational study. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol. 2013 Jan;32(1):127–31.
32. Sousa R, Muñoz-Mahamud E, Quayle J, Dias da Costa L, Casals C, Scott P, et al. Is asymptomatic bacteriuria a risk factor for prosthetic joint infection? Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 Jul 1;59(1):41–7.
33. Soltanzadeh M, Ebadi A. Is presence of bacteria in preoperative microscopic urinalysis of the patients scheduled for cardiac surgery a reason for cancellation of elective operation? Anesthesiol Pain Med. 2013;2(4):174–7.
34. Najar MS, Saldanha CL, Banday KA. Approach to urinary tract infections. Indian J Nephrol. 2009 Oct;19(4):129–39.
35. Barros M, Martinelli R, Rocha H. Enterococcal urinary tract infections in a university hospital: clinical studies. Braz J Infect Dis. 2009 Aug;13(4):294–6.
36. Taneja N, Rani P, Emmanuel R, Sharma M. Significance of vancomycin resistant enterococci from urinary specimens at a tertiary care centre in northern India. Indian J Med Res. 2004 Feb;119(2):72–4.
37. Shrestha NK, Amuh D, Goldman MP, Riebel WJ, Tomford WJ. Treatment of a Complicated Vancomycin-Resistant Enterococcal Urinary Tract Infection with Fosfomycin. Infect Dis Clin Pract. 2000 Dec;9(9):368.
38. Swaminathan S, Alangaden GJ. Treatment of resistant enterococcal urinary tract infections. Curr Infect Dis Rep. 2010 Nov;12(6):455–64.
39. Khair HN, VanTassell P, Henderson JP, Warren DK, Marschall J, CDC Prevention Epicenters Program. Vancomycin resistance has no influence on outcomes of enterococcal bacteriuria. J Hosp Infect. 2013 Nov;85(3):183–8.