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REVIEW ARTICLE

Impact of enterococcal urinary tract infections in immunocompromised – neoplastic patients

Xenofon Giannakopoulos[1]*, Hercules Sakkas[2]*, Vasileios Ragos[3], Evangelos Tsiambas[4]*, Petros Bozidis[2], Angelos M. Evangelou[5], Chrissanthy Papadopoulou[2], Leonidas Petrogiannopoulos[6], Nikolaos Sofikitis[1]

[1]Department of Urology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece; [2]Microbiology Department, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece; [3]Department of Maxillofacial, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece; [4]Department of IHC & Mol Biology, 401 GAH, Athens; [5]Department of Physiology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece; [6]Department of Gastroenterology, 417 VA Hospital

*These authors contributed equally to this work

Summary

Infections in immunocompromised-neoplastic patients represent a severe complication. Among bacteria, Enterococcus species constitute a common causative pathogen of urinary tract infections (UTIs), especially among hospitalized patients with or without urinary tract carcinoma, related commonly to urinary tract abnormalities, urinary catheters or prolonged antibiotic treatment. Although enterococci have been considered more commonly as colonization bacteria in the intestine than virulent agents, they are frequently implicated in UTIs. The high incidence of enterococcal UTIs is associated with several risk factors including age, female gender, previous UTI, diabetes, pregnancy, immunosuppression due to cancer development and progression, renal transplantation and spinal cord injury. Clinical manifestations are usually absent or mild in enterococcal UTIs, which may also become an important source for both bacteremia and endocarditis. Over the last years, the prevalence of multidrug resistant enterococci, particularly vancomycin-resistant E. faecium and E. faecalis has significantly risen worldwide, associated with increased morbidity, limited treatment options and increased health-care costs. In this review, the current knowledge on enterococcal UTIs epidemiology and influence in the corresponding immunocompromised patients is highlighted.

Key words: *bacteria, Enterococcus, urinary, infections, carcinoma*

Introduction

Urinary tract infections (UTIs) are amongst the most common bacterial infections, affecting about 150 million individuals per year, both in the community and hospital settings [1]. Women of all ages are more likely to experience such an infection than men, while half of them may be affected by an uropathogen one time during their lives [2], and 25-30% may develop recurrent UTIs not associated with any functional or anatomical abnormality [3]. Since UTIs can lead to life-threatening infections such as bacteremia, they are considered as a significant cause of morbidity especially in elderly men [1,4]. The infection may be restricted to lower urinary tract or can expand to upper urinary tract resulting to several clinical manifestations from asymptomatic bacteriuria, to urethritis, cystitis, ureteritis, epididymitis, prostatitis and pyelonephritis [5]. Taking into consideration several host

Corresponding author: Evangelos Tsiambas, MD, MSc, PhD. 17 Patriarchou Grigoriou E΄ Street, Ag. Paraskevi, 153 41 Athens, Greece.
Fax: +30 210 6526259, Email: tsiambasecyto@yahoo.gr
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factors that predispose to the infection, UTIs can be classified as uncomplicated or complicated. Risk factors related to uncomplicated UTIs include age, female gender, a prior UTI, sexual activity, vaginal infection, diabetes, while complicated UTIs are commonly related to pregnancy, immunosuppression due to urinary tract carcinoma, neurogenic bladder, renal, ureteral or bladder calculi, renal failure or transplantation, spinal cord injury and catheterization [6,7] (Figure 1).

Escherichia coli is the commonest causative agent in 70-95% and in 50% of all cases of community and hospital acquired UTIs respectively [3]. Other pathogens implicated in UTIs include *Klebsiella* spp and *Pseudomonas aeruginosa* particularly in patients with diabetes and urinary catheters respectively [8], *Proteus* spp, *Enterobacter* spp, *Staphylococcus saprophyticus, Staphylococcus aureus, Streptococcus agalactiae, Enterococcus* spp and *Candida* spp [1,5]. Enterococcus spp is considered an important uropathogen, and the most common type of enterococcal clinical disease occurs in the urinary tract [9]. Although enterococci are not a frequent cause of uncomplicated cystitis and pyelonephritis [8], they have emerged as a significant cause of health-care associated UTIs infections, due to their intrinsic and acquired resistance to various antibiotics, mainly to vancomycin [9,10]. They have been ranked among the top five pathogens for UTIs, while their resistance patterns may vary significantly among patients from different healthcare settings and geographical locations [11].

Enterococcus background and clinical manifestations

The genus Enterococcus was described as an intestinal microorganism at the end of the 19th century by Thiercelin, and consists of Gram positive, catalase-negative, non-spore forming, facultative anaerobic bacteria that can occur both as single cocci and in chains [12]. Initially they were classified as group D streptococci. In the 1980's they were distinguished from the genus *Streptococcus* and reclassified as a separate genus, Enterococcus, based on studies involving DNA hybridization and 16S rRNA sequencing [12-14]. Enterococci colonize the gastrointestinal (GI) tract and to a lesser extent the genitourinary (GU) tract, the skin and the oral cavity [10]. At least 12 species, including *E. faecalis, E. faecium, E. avium, E. casseliflavus, E. durans, E. gallinarum, E. hirae, E. malodoratus, E. mundtii, E. pseudoavium, E. raffinosus,* and *E. solitaries* have been considered as causative agents of enterococcal infections, while the first two species *E. faecalis* and *E. faecium*, account from 80-90% and 5-15% of all clinical isolates respectively [14].

Enterococci have emerged as a significant cause of community-acquired and hospital infections [15], being able to survive in hospital environments and colonize patients [16], even though they were recognized more commonly as colonization bacteria in the intestine, than virulent agents [17,18]. More often, they are considered as causative agents of severe systemic infections in immu-

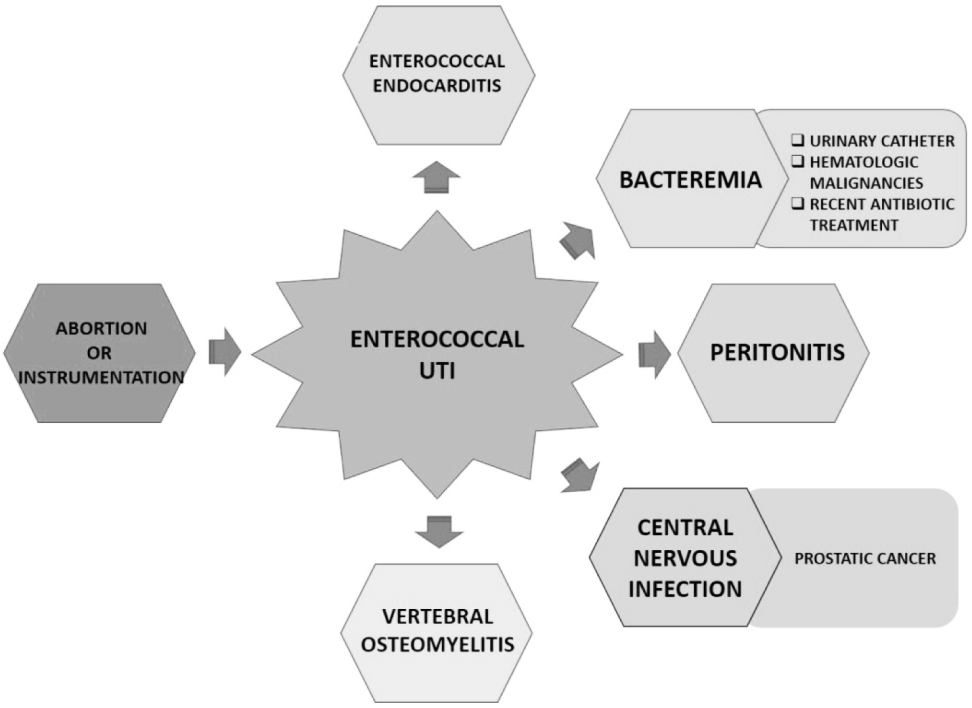

Figure 1. Predisposing factors for uncomplicated and complicated UTIs.

nocompromised including cancer patients [18], and one of the most frequent causes of health-acquired infections in developed countries [19]. Except UTIs, several infections such as bacteremia, infective endocarditis, intra-abdominal and pelvic infections, skin infections and central nervous system (CNS) infections have been attributed to enterococci [10]. Intra-abdominal, pelvic and post-surgery wound infections have been reported as the second most frequent enterococcal infections [14], whereas enterococci represent the third most common causative agent in both bloodstream infections (BSIs) [20] and infective endocarditis [21], exhibiting significant morbidity and mortality rates [22]. Enterococcal BSIs account for about 10% of all bacteremias [23], while intra-abdominal infections are the commonest risk factor for developing BSIs, followed by UTIs [24]. Extensive studies have shown that enterococci cause about 30% of hospital-associated endocarditis, following *Staphylococcus* spp [25]. *E. faecalis* has been reported the most common cause of both BSIs and UTIs infections, followed by *E. faecium* accounting for 65-70% and 25% of the cases respectively, with limited treatment options because of the spread of multidrug resistant strains [22]. Enterococci have been isolated from skin infections together with other pathogenic bacteria and occasionally they have been reported to cause osteomyelitis, septic arthritis and CNS infections, such as meningitis [10]. Enterococcal infections, in particular those caused by vancomycin-resistant enterococci (VRE), have been associated with high mortality rates, from 25 to 50%, most frequently affecting immunocompromised patients [16].

Urinary tract infections: Risk factors and pathogenicity

UTIs constitute the most common type of clinical disease, caused by enterococci, both within and outside hospital settings [9]. Enterococcus spp was first reported as causative agent of UTIs in 1906 by Andrewes and Horder [26]. They are frequently hospital-acquired, most commonly consisting of complicated UTIs [11], such as pyelonephritis, prostatitis, perinephric abscess [8,26], related to urinary tract malformations, urinary catheters or prolonged antibiotic treatment [27]. The high prevalence of VRE causing urinary tract colonization, asymptomatic bacteriuria or uncomplicated UTIs, is of great concern, associated with increased morbidity, limited treatment options and increased health-care costs [28]. During the last years, many reports have indicated a rising isolation rate of enterococci in outpatients as well [11]. Several studies have shown that urinary tract colonization and infection by Enterococcus species is often polymicrobial, whereas they may also enhance the propagation of several bacteria in the urinary tract [29].

Transmission of enterococci within hospital environments has been well documented, since rapid dissemination from source patient through environmental contamination, health care workers colonization and hands contamination has been reported [30]. Enterococci can survive for long periods on environmental surfaces, including medical equipment, bed rails and doorknobs [14,17]. Furthermore, prolonged hospitalization in long-term facilities, surgical units or intensive-care units, severe comorbidities, urinary catheters, and antibiotic treatment usually in immunocompromised patients, enhance the ability of multidrug-resistant pathogens such as enterococci to cause infection [17].

Enterococcal polysaccharide antigen plays significant role in the pathogenicity of UTIs, including its binding to epithelial cells, biofilm formation and evasion of phagocytosis by neutrophils [16]. Enterococci encode several virulence factors, such as enterococcal surface protein (Esp) and biofilm-associated (Ebp) pili, predisposing to their initial attachment and biofilm formation on urinary catheters, which promote their persistence in the bladder and further dissemination to the kidneys [6,31].

Genitourinary symptoms are mild in enterococcal UTIs, commonly related to catheterization and instrumentation. More often they are asymptomatic [9], considering to be less severe than UTIs caused by other uropathogens [29]. It has been described that *E. faecalis* has been isolated from 16.5% and 5.4% of urine cultures from asymptomatic and symptomatic individuals respectively [29]. Pyuria has been reported as a common manifestation (92%), although it is not specific in asymptomatic UTIs, considering that most of the patients may present several underlying urological and/or neurological disorders leading to obstructive uropathy. Irritative symptoms such as dysuria, urinary frequency, urgency and suprapubic pressure tend to occur infrequently [9]. In addition, fever, leucocytes and nitrites in the urine are usually absent [29] and recurrences are often the result of existing urinary tract abnormalities [27].

Enterococcal UTIs can lead to bacteremia, in about 15-24% of the adult patients in the hospital settings most commonly related to urinary catheter, hematologic malignancies and recent antibiotic treatment with vancomycin or third-generation cephalosporin. Furthermore, enterococcal UTIs commonly associated with genitourinary source are an important source of endocarditis in adults as well [24,26,32]. It has been reported that 50% of

male patients with enterococcal endocarditis had previously UTI or genitourinary instrumentation, whereas 38% of female patients had a preceding genitourinary source such as abortion or instrumentation [26]. More rarely, vertebral osteomyelitis associated with enterococcal hematogeneous spread from a post-operative pyelonephritis [33], and a central nervous infection due to prostatic cancer and enterococcal UTI have been recorded [26], while a case of peritonitis as a complication of enterococcal bacteriuria has been reported as well [29] (Figure 2).

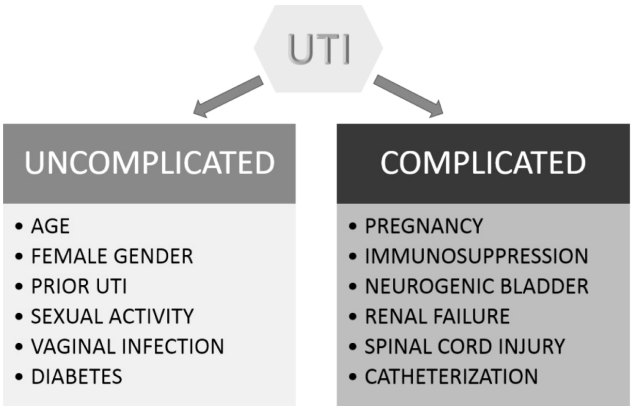

Figure 2. Infections associated with enterococcal UTIs.

Epidemiology

The prevalence of both *E. faecalis* and *E. faecium* in community-acquired UTIs is infrequent and becomes higher among patients with underlying complicating factors including diabetes, spinal cord injury and other comorbidities [31,34]. On the contrary both species are the third commonest cause of hospital-acquired UTIs, accounting for 15-30% of catheter related infections [31], and the second most frequent uropathogen in complicated UTIs, after *E. coli* [6]. The isolation frequency of *E. faecalis* is higher than *E. faecium*, with an estimated ratio 5:1 [31]. The increasing isolation rate of *E. faecalis* during the last decades has been reported as a remarkable characteristic [11,29], mainly due to urinary catheters and stents, associated with biofilm formation [29]. It is estimated that enterococcal UTIs account for 110,000 cases in USA annually [33]. During a 20-year period study, the isolation rates of UTIs *E. faecalis* and *E. faecium* among urology inpatients, 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 [11]. Apart from both species, there is a recent report of symptomatic UTI in a diabetic man with benign prostatic hyperplasia, caused by *E. hirae* [35].

Enterococcal UTIs typically occur at the ages before 10 and after 60 years, when genitourinary malformations and obstructive uropathy are more common [9]. However, there is a report on Enterococcus spp, accounting for 8.5% of UTIs from an Indian tertiary care setting, which was isolated from 40% of patients belonging to age group 30-59 years [1]. Also, enterococci are frequently isolated from male patients with chronic bacterial prostatitis [29].

The nosocomial enterococcal UTIs reported in children are more frequent than the community-acquired cases accounting for 12-15% and 2-8%, respectively, associated mainly with anatomical abnormalities of the urinary tract such as vesicoureteral reflux, urethral instrumentation, or antibiotic prophylaxis. Actually, these patients have more commonly such anatomical abnormalities and worse prognosis in terms of recurrence, scarring and need of surgery than other children with UTIs caused by Gram negative bacteria [8,27,30]. The most frequent Enterococcus species isolated from childrens' urine with congenital urinary tract disorders is *E. faecalis* [16].

UTIs have been documented the most common type of infection among elderly patients living in nursing homes and the second cause of community-acquired infections, associated with immunosuppression due to carcinoma development, underlying comorbidities, urinary catheter, prolonged hospitalization and treatment [36]. Enterococci have been reported as the most commonly identified uropathogens among elderly male inpatients and outpatients, isolated in 22.5% of their urine cultures, while 40% of them were catheterized [37]. In another study the percentage of *E. faecalis* in catheter-related specimens of old male and female patients was 14.5% and 9.3% respectively, whereas *E. faecium* was isolated from 2% and 2.6% correspondingly [36]. Enterococcus spp was also found to be the second most common pathogen after *E. coli*, isolated from 22% of catheter-associated UTIs among elderly trauma patients [38]. Additionally, Enterococcus spp was accounting for 9.89% of identifications of the urine samples in a study that included patients over 65 years old and excluded those with urinary catheter [39]. Furthermore, the prevalence of enterococci in elderly outpatients diagnosed with benign prostatic hyperplasia and recurrent UTIs was 15.3%, while the most commonly isolated uropathogen was *E. coli* (60%) [40].

Enterococci are considerably uncommon as a cause of any type of UTI in pregnancy [5], although UTIs are the commonest infections during pregnancy and pyelonephritis one of the most frequent bacterial complications affecting 1-2% of pregnant

women [2]. Moreover, enterococci have been isolated in <5% of total cases in young healthy women with no undergone instrumentation, structural abnormalities or recurrent infections [26].

In general, patients with diabetes have a significantly increased incidence of bacteriuria compared to non-diabetic patients [2], while UTIs are one of the top ten concurrent or complicating illnesses with diabetes [8], usually complicated to severe manifestations such as emphysematous cystitis or pyelonephritis [2]. The most common pathogens are *E. coli*, followed by other Gram-negative rods such as *Klebsiella* spp, Pseudomonas spp and *Proteus* mirabilis, as well as *Candida* species, *Streptococcus* group B, and enterococci [41]. The latter species has been considered as important uropathogen among patients with diabetes, leading to 13% of asymptomatic bacteriuria in diabetics compared to 4.9% in non-diabetics [31]. Furthermore, enterococci have been isolated from 10% of diabetic patients with prostatitis [31] Also, enterococci have been also considered as the predominant uropathogen in patients with HIV infection [2].

The majority of healthcare-acquired UTIs have been recorded in intensive care units (ICUs), with an estimated rate of 8-21%, with *E. coli, P. aeruginosa* and enterococci being the predominant pathogens. The majority of these infections (>95%) have been associated with indwelling urinary catheters [42]. In USA enterococci have accounted for 14.9% of catheter-associated UTIs in ICU patients [43]. Enterococci are common pathogens along with *E. coli, Pseudomonas* spp and *Proteus* mirabilis, in UTIs among patients with spinal cord injuries, which are related with high rates of morbidity and mortality. It is estimated that UTI usually occur in one out of three patients, with spinal cord injuries whereas the mortality rate accounts for up to 40% due to renal-related complications [2]. UTI is the most common infection encountered in the renal transplant patients, accounting for 45-72/% of all infections, whereas the total incident of complicated infections within the first year ranges from 60 to 70% [44]. Enterococcal UTIs often occur in patients early after kidney transplantation [45], usually in the first 6 months [44], accounting up to 47% of the isolated bacteria from kidney transplantation recipients with recurrent UTIs [45]. In a recent study of UTIs in kidney transplant recipients, *Enterococcus* spp was the most frequent pathogen identified (35%), followed by *E. coli* (32%) and *Klebsiella* spp (13%) [44]. UTIs often occur in patients after urodynamic study, whereas the reported rates range from 1.1 to 28.3%. In a recent study the incidence of UTIs after such an invasive procedure in male patients was 9.83%, caused by *E. coli* (54.7%) and followed by enterococci (25%), while the predominant *Enterococcus* species was *E. faecalis* responsible for 19% of the total cases [46].

Antimicrobial resistance and management in immunocompromised patients

Enterococci exhibit intrinsic and acquired resistance to various antibiotics, such as β-lactams, aminoglycosides, macrolides, lincosamides, cotrimoxazole, glycopeptides, associated with mobile genetic elements or chromosomal exchange and mutations [19]. The most significant issues in enterococcal antibiotic resistance concerns the glycopeptide resistance including vancomycin, high-level resistance to aminoglycosides, and resistance to β-lactams especially to ampicillin [14]. *E. faecalis* UTIs are associated with intrinsic resistance to first-line antimicrobial agents, and with acquired resistance, specifically to gentamycin and vancomycin [4], while *E. faecium* expresses both resistance and virulence at higher rates to multiple antibiotics [19,24]. By far, the most important enterococcal antibiotic resistance concerns vancomycin [19]. Vancomycin resistance was first reported in 1988 in a clinical isolate in Europe and since then VRE were isolated from livestock and food as well [15,43].

The incidence of vancomycin resistant *Enterococcus* species at global level is variable. European countries such as Germany, Greece, England, Ireland and Portugal have demonstrated high VRE rates accounting for >10% [43]. More specifically, >30% of VRE have been isolated from clinical samples in Greece, Ireland, United Kingdom and <1% in Scandinavia [17,47]. In Germany, it has been demonstrated that >99% of VRE strains belong to *E. faecium*, whereas vancomycin resistant *E. faecalis* account for <1% [18]. According to other studies, the prevalence of VRE in Europe varies from 1% to 30%, while 30% of hospital-acquired enterococcal infections in USA are identified as VRE [48]. In addition, in USA, the vancomycin resistant *E. faecium* isolates have been risen from 0% in 1980s to >80% by 2007 [17], considering that USA demonstrates much higher rates of glycopeptide-resistance than Europe [47].

The majority of VRE strains are reported sensitive to ampicillin, however during the last two decades, in the majority of European countries, an increase in ampicillin-resistant enterococci [32,43], in particular ampicillin-resistant *E. faecium* is observed. The emergence of such resistant pathogens, has been well documented in the relative published literature [19,34]. In a recent study ampicillin – resistant *E. faecium* was isolated from renal allograft recipients with recurrent UTIs [45].

Although VRE demonstrate global distribution, their epidemiological trait is characterized by geographic differences associated mainly with their reservoirs, and potentially with factors related to overuse of antimicrobials in human and veterinary practice. In many EU countries, healthy individuals are considered to be the main carriers, due to use of avopracin, a glycopeptide antibiotic, as growth promoter in productive animals breeding; this practice is implicated in the initiation of emergence and transmission of drug-resistant strains to humans through the animal-food-environment chain, since avopracin confers cross-resistance to vancomycin and teicoplanin. In USA where avopracin is not licensed for use as a food additive in farm animals, the predominant VRE reservoirs appear to be the hospitalized patients, medical equipment and environmental surfaces within the clinical settings [13,14]. Taking also into consideration that an epidemiological link between *E. faecalis* originating from food-producing animals, acting also as a causative agent for human UTIs has been reported, there is a urgent need for interrupting such transmission links. Restriction of the transmission modes, concerted efforts to eradicate gastrointestinal colonization, active surveillance programs, prudent use of antimicrobials, hygiene management, prompt removal of indwelling catheters, and management of VRE in long-term care facilities, should be used as effective control and prevention measures [4,13,18,34,49].

The implications of UTIs caused by multidrug-resistant enterococci are of outmost health and socioeconomic importance, including high hospitalization costs, overuse of antimicrobials, significant mortality and morbidity rates [50]. The systematic use of several antibiotics for treatment or prophylaxis is regarded as a major causative agent of enterococcal colonization, hence enterococcal UTIs are considered a result of this therapeutic practice [27]. In addition, since in most clinical cases the treatment in colonized patients is unnecessary, the use of antibiotics for such a reason is of big concern in clinical settings [28]. However, the rate of multi-resistant enterococcal UTIs has significantly risen worldwide during the last years, and the treatment is a matter of great concern [19]. Therefore, asymptomatic bacteriuria should be treated only in specific patient groups such as pregnant women and patients undergoing urologic procedures [51]. Aminopenicillins, specifically ampicillin have been reported as the optimal treatment strategy for ampicillin-susceptible enterococci, including VRE, since they are safe and cost-effective [28,50]. Nitrofurantoin and fosfomycin should be used in patients with uncomplicated UTIs, whereas daptomycin and linezolid have been considered as the most effective agents for the treatment of pyelonephritis and complicated UTIs caused by multidrug-resistant enterococci [32].

Conclusions

In the recent years, enterococcal UTIs have emerged within and outside hospital settings, with significant increase in colonization and antimicrobial resistance. The emergence of the increased prevalence especially among immunocompromised patients - including neoplastic ones- constitute a major health issue, leading to high rates of morbidity and mortality, economic costs and limited treatment options. To encounter this alarmingly increasing health problem, there is urgent need for evidence-based research focusing on the identification of the factors facilitating the transmission of enterococcal antimicrobial resistance within the hospital environment, and also for appropriate clinical management and therapeutic approach. Especially referring to patients with urothelial carcinoma of the bladder, significant studies have shown that application of prophylactic antibiotics following radical cystectomy leads to a significant decrease in urinary tract infections and readmission from post-surgery sepsis [52].

Conflict of interests

The authors declare no conflict of interests.

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