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Risk Factors for Vancomycin Resistant *Enterococcus spp.* Infection Development

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Summary

Background. An increased risk of vancomycin resistant *Enterococcus spp.* (VRE) colonization, usually progressing into infection in patients with immunosuppression, hematological malignancies, organ transplantation, increased intensive care unit or hospital stay, infection of an additional body side. The aim of our study was to investigate other risk factors for VRE infection development.

Material and methods. For all study patients the following characteristics were recorded: demographic data, source of infection, the patient ward at the time of infection, days of mechanical ventilation before and after *Enterococcus spp.* infection, days of hospital and intensive care unit (ICU) stay post infection, antimicrobial agents administered during hospitalization before *Enterococcus spp.* infection developed. The cases were assigned as vancomycin resistant *Enterococcus spp.* (VRE) cases if they had VRE infection and as vancomycin sensitive *Enterococcus spp.* (VSE) cases if they had VSE *Enterococcus spp.* infections.

Results. *E. faecium* were more resistant to tested antibiotics in comparison with *E. faecalis* strains. Resistance to vancomycin varied depending on the origin of the source of infection. For patients treated in ICU prior to infection *E. faecium* was found more often in comparison to *E. faecalis*. Univariate analysis revealed that hospitalization in intensive care unit (ICU) prior to infection was a risk factor for VRE infection development. Prior use of antimicrobials was a risk factor for selection of VRE. Only 2 (7.7%) cases of VSE and even 11 (47.8%) cases of VRE were found in carbapenem treatment group ($P=0.002$), 1 (3.8%) of VSE and 6 (26.1%) of VRE cases in quinolones treatment group ($P=0.033$) and 2 (7.7%) of VSE and 11 (47.8%) of VRE in vancomycin treatment group ($P=0.002$).

Conclusions. We found that VRE were isolated from urine more often, especially in patients with abnormal renal function: creatinine and urea concentrations were high. Prior use of vancomycin was a risk factor for VRE infection development: it means that the dose regimen and pharmacokinetics of vancomycin not always was considered, especially for patients with severely impaired renal function.

Keywords: *Enterococcus spp.* infection, risk factors, resistance to vancomycin, *E. faecium*, *E. faecalis*.

INTRODUCTION

Epidemiological data collected over the last two decades have documented the emergence of enterococci as important nosocomial pathogens, exempli-

fied by the expansion of a major hospital-adapted clonal complex (CC) 17 in *E. faecium*, and by CC2 and CC9 in *E. faecalis* (EARSS). *Enterococci* are intrinsically resistant to a broad range of antimicrobial agents including

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cephalosporins, sulphonamides and low concentrations of aminoglycosides. Patient safety in hospitals is challenged by the ability of enterococci to acquire additional resistance through the transfer of plasmids and transposons or mutation. *E. faecalis* and *E. faecium* are opportunistic pathogens that are commonly recovered from patients with significantly compromised host defences and serious co-morbidities, who have received multiple courses of antibiotics and have been hospitalized for prolonged periods [1, 2]. Various studies have shown that infections caused by VRE lead to longer hospital stays, higher mortality, and significantly higher cost than infections caused by vancomycin-susceptible enterococci [3, 4]. VRE species are especially problematic clinically, as these bacteria are resistant to all first-line antibiotics and infection is associated with a marked increase in risk of mortality [5–7]. (*Enterococcus faecalis* (*E. faecalis*) is the major colonizer in gastrointestinal tract, but can also be found to a lesser extent on the skin, in the genitourinary tract, and in the oral cavity [2, 8]. *E. faecalis* is the most common cause of infections, but *E. faecium* is intrinsically more resistant to antibiotics. In Europe VRE is much less prevalent, but on the rise. As Antimicrobial resistance surveillance in Europe (EARSS) data shows, vancomycin resistance in *E. faecalis* remains low in most countries. But *E. faecium* resistance to vancomycin is increasing. The national percentages of resistant isolates ranged from zero (Estonia, Finland, Iceland and Malta) to 45.1% (Ireland) in 2014. VRE has become a major nosocomial pathogen worldwide due to its colonization strategy, persistence in the environment, and genome plasticity [9]. An increased risk of VRE colonization occurs with immunosuppression, hematological malignancies, organ transplantation, increased intensive care unit or hospital stay, infection of an additional body side [10, 11]. The aim of our study was to investigate other the risk factors for VRE infection development.

MATERIALS AND METHODS

Patients and bacterial strains

This study was carried out at 2400-bed tertiary-care teaching hospital of Lithuanian University of Health Science. All hospitalized patients with a monobacterial *Enterococcus* spp. infection from any source between 1st January

and 31st May 2015 were included in the study. Only the first *Enterococcus* spp. positive case was included, only one isolate from each patient. All patients were 18 years old. A retrospective data analysis was performed to evaluate patients' risk factors dependent on *Enterococcus* spp. infection. For all study patients the following characteristics were recorded: demographic data, source of infection, the patient ward at the time of infection, days of mechanical ventilation before and after *Enterococcus* spp. infection, days of hospital and intensive care unit (ICU) stay post infection, antimicrobial agents administered during hospitalization before *Enterococcus* spp. infection developed. The clinical cases were assigned as vancomycin resistant *Enterococcus* spp. (VRE) cases if they had VRE infection and as vancomycin sensitive *Enterococcus* spp. (VSE) cases if they had VSE *Enterococcus* spp. infections.

Identification of *Enterococcus* spp. and antimicrobial susceptibility testing

Identification of *Enterococcus* species was performed using mass spectrometry method (Maldi-Tof MS, Bruker, USA). The resistance of *Enterococcus* spp. strains was determined using the disc diffusion method based on the standard guidelines (BBL, USA). All the strains were tested for the following antibiotics: ampicillin, vancomycin, linezolid and teicoplanin. The sizes of inhibition zones were interpreted according to The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. Any resistance in disc-diffusion to vancomycin was confirmed using the MIC test (AB Biodisk, Solna, Sweden) method. *Enterococcus* spp. strains, which had Minimal Inhibitory Concentration (MIC) for vancomycin >4 g/mL, were defined as resistant. Glycopeptides resistance phenotype testing was done at National Public Healthcare Laboratory in Vilnius,

Lithuania according to publication by Arthur M, Courvalin P [12]. The VanA glycopeptides resistance was defined if MIC for vancomycin was found 64 g/mL and for teicoplanin 16 g/mL. The VanB phenotype has MICs of 4–1,000 g/mL for vancomycin and 0.5–1 g/mL for teicoplanin.

Statistical analysis

Comparisons between two groups was carried out using the Student *t* test or Mann-Whitney *U* test (nonparametric values). Proportions were compared using the chi-square or Fisher exact test. Differences were considered significant at $P < 0.05$. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Statistical package SPSS 13.0 for Windows release was used for the data analysis.

RESULTS

In our study we analyzed data of 49 patients with *E. faecium* or *E. faecalis* monobacterial infection, 23 of which were resistant to vancomycin (VRE). Almost half of all isolates were recovered from the intra-abdominal secretions, a quarter from pus or wound and others from sterile body fluid and urine.

Resistance to vancomycin varied depending on the origin of the source of infection. 21 VRE strains had vanA resistance gene, 2 – vanB gene. Vancomycin sensitive *Enterococci* (VSE) more often were isolated from intra-abdominal secretions in comparison to VRE (respectively 69.2%, $n=18$ and 17.4%, $n=4$, $P < 0.001$). VRE more often were isolated from urine, in comparison to VSE (respectively 34.8%, $n=8$ and 16.3, $n=8$, $P=0.001$) (Table 1).

E. faecium were more resistant to tested antibiotics in comparison with *E. faecalis* strains. 71.8% ($n=28$) of *E. faecium* and 10% ($n=1$) of *E. faecalis* strains were resistant to ampicillin ($P < 0.001$), 56.4% ($n=22$) of *E. faecium* and 10% ($n=1$) of *E. faecalis* strains were resistant to vancomycin

Table 1. Sources of *Enterococcus* infection in patients with vancomycin-sensitive versus vancomycin-resistant strains

Source	No of all strains % (n)	No of vancomycin sensitive strains % (n)	No of vancomycin resistant strains % (n)	P value
Sterile body fluid	12.2 (6)	7.7 (2)	17.4 (4)	0.276
Pus, wound	24.5 (12)	23.1 (6)	26.1 (6)	0.534
Intra-abdominal secretion	44.9 (22)	69.2 (18)	17.4 (4)	<0.001
Urine	16.3 (8)	0	34.8 (8)	0.001
Respiratory secretion	2.0 (1)	0	4.3 (1)	0.469

($P < 0.009$), 51.3% ($n=20$) of *E. faecium* and 10% ($n=1$) of *E. faecalis* strains were resistant to teicoplanin ($P < 0.019$) (Table 2).

For patients treated in ICU prior to infection *E. faecium* was found more often in comparison to *E. faecalis* (respectively 35.9%, $n=14$ and 0, $P=0.002$), but prior use of antibiotics didn't have influence on different strains selection (Table 3).

Univariate analysis revealed that hospitalization in intensive care unit (ICU) prior to infection was a risk factor for VRE infection development: 43.5% ($n=10$) VRE in comparison to 15.4% ($n=4$) VSE infection cases. *E. faecium* was found more often in comparison to *E. faecalis* (respectively 35.9%, $n=14$ and 0, $P=0.002$) in patients treated in ICU prior to *Enterococcus* isolation. 88.5% ($n=23$) of patients with VSE infection and 60.9% ($n=14$) with VRE infection have undergone surgery prior to *Enterococcus* isolation ($P=0.027$). VRE infection was found more often in patients with abnormal renal function. Creatinine and urea concentrations 102.4 ± 89.6 mol/L and 7.7 ± 7.1 mmol/L were found in VSE cases in comparison to 132.6 ± 92.6 mol/L and 10.1 ± 7.2 mmol/L in VRE cases ($P=0.03$) (Table 4).

Prior use of antimicrobials was a risk factor for selection of VRE. Only 2 (7.7%) cases of VSE and even 11 (47.8%) cases of VRE were found in carbapenem treatment group ($P=0.002$), 1 (3.8%) of VSE and 6 (26.1%) of VRE cases in quinolone treatment group ($P=0.033$) and 2 (7.7%) of VSE and 11 (47.8%) of VRE in vancomycin treatment group ($P=0.002$) (Table 5).

DISCUSSION

The differences of resistance of *Enterococcus* species are well established. Of all enterococcal species, *E. faecium* is more resistant to antibiotics and is the most difficult to treat. In our study more than 50% of all isolated *E. faecium* strains were resistant to vancomycin and to teicoplanin in comparison to only 10% of *E. faecalis* [13]. Study demonstrated that most VRE isolates were *E. faecium*, whereas the VSE isolates were predominantly *E. faecalis*. *Enterococcus spp.* carrying *vanA* are highly resistant to glycopeptides and are the dominant VRE variants of *E. faecium* and *E. faecalis* globally [9]. Use of urinary catheters within the previous 30 days were associated with increased odds of vanB

Table 2. *Enterococcus spp.* resistance to tested antibiotics

Antibiotic	<i>E. faecalis</i> N=10	<i>E. faecium</i> N=39	P value
Ampicillin resistant strains, % (n)	10.0 (1)	71.8 (28)	0.001
Vancomycin resistant strains, % (n)	10.0 (1)	56.4 (22)	0.009
Teicoplanin resistant strains, % (n)	10.0 (1)	51.3 (20)	0.019

Table 3. Risk factors for *Enterococcus spp.* infection

	<i>E. faecalis</i> N=10	<i>E. faecium</i> N=39	P value
ICU stay before infection, % (n)	0	35.9 (14)	0.022
Patients treatment department			
Surgery	100 (10)	73.7 (28)	0.058
Internal medicine	0	23.1 (9)	0.103
Prior antibiotic use, % (n):			
Cefuroxime, ceftazidime, cefotaxime	90.0 (9)	87.2 (34)	0.645
Carbapenem	10.0 (1)	30.8 (18)	0.180
Ciprofloxacin, ofloxacin	10.0 (1)	15.4 (6)	0.559
Gentamycin, amikacin	20.0 (2)	5.1 (2)	0.180
Piperacilin/tazobactam	10.0 (1)	15.4 (6)	0.559
Vancomycin	20.0 (2)	28.2 (11)	0.469
Ampicillin/sulbactam	0	10.3 (4)	0.388

Table 4. Univariate analysis of risk factors for vancomycin resistant *Enterococcus* infections

Risk factors	<i>Enterococcus spp.</i>		p value
	Vancomycin sensitive strains, N=26	Vancomycin resistant strains, N=23	
Age, year	68.92 $\pm$ 14.07	66.35 $\pm$ 15.05	0.348
<65, % (n)	34.6 (9)	43.5 (10)	0.366
65, % (n)	65.4 (17)	56.5 (13)	
Sex: male, % (n)	50.0 (13)	43.5 (10)	0.433
female, % (n)	50.0 (13)	56.5 (13)	
ICU stay before infection, % (n)	15.4 (4)	43.5 (10)	0.031
Endotracheal tube, % (n)	7.7 (2)	21.7 (5)	0.161
Central venous catheter, % (n)	38.5 (10)	47.8 (11)	0.355
Peripheral venous catheter, % (n)	65.4 (17)	73.9 (17)	0.370
Urinary catheter, % (n)	65.4 (17)	73.9 (17)	0.370
Surgery, % (n)	88.5 (23)	60.9 (14)	0.027
Creatinine, mol/L	102.4 $\pm$ 89.6	132.6 $\pm$ 92.6	0.028
Urea, mmol/L	7.7 $\pm$ 7.1	10.1 $\pm$ 7.2	0.03
Antibiotic use before infection, % (n)	92.3 (24)	100 (23)	0.276

Table 5. Prior use of antimicrobials as a risk factor for selection of vancomycin resistant *Enterococcus spp.*

Risk factors	<i>Enterococcus spp.</i>		p value
	Vancomycin sensitive strains, N=26	Vancomycin resistant strains, N=23	
Antibiotic use before infection, % (n)	92.3 (24)	100 (23)	0.276
Prior antibiotic use, % (n):			
Cefuroxime, ceftazidime, cefotaxime	84.6 (22)	91.3 (21)	0.395
Carbapenem	7.7 (2)	47.8 (11)	0.002
Ciprofloxacin, ofloxacin	3.8 (1)	26.1 (6)	0.033
Gentamycin, amikacin	11.5 (3)	4.3 (1)	0.353
Piperacilin/tazobactam	7.7 (2)	21.7 (5)	0.161
Vancomycin	7.7 (2)	47.8 (11)	0.002
Ampicillin/sulbactam	3.8 (1)	13.0 (3)	0.259

VRE bacteraemia [14]. The distribution of enterococci showed a predominance of *E. faecium* in the VRE group with equivalent proportions of

E. faecium and *E. faecalis* in the VSE group [13]. In VRE bacteraemia, *E. faecium* was the most common isolate in contrast to VSE bacteraemia,

whereas three-quarters of the isolates were *E. faecalis* in Peel study as well [15]. We found that prior use of antimicrobials was a risk factor for selection of VRE, particularly the use of carbapenems, ciprofloxacin and vancomycin, but gentamycin, piperacilin/tazobactam and ampicillin/sulbactam had no action on resistance selection. Elimination of normal gut flora by commonly used broad spectrum antibiotics (vancomycin, cephalosporins and metronidazole) encourages the selective proliferation of VRE [16, 17]. Other studies have also reported that antibiotic exposure prior to infection were significant risk factors for VRE infection. Significantly more patients in the VRE group had prior exposure to vancomycin, metronidazole aminoglycosides, third-generation cephalosporins, fluoroquinolones, imipenem and ureidopenicillins [18]. Exposure to anti-anaerobic antibiotics has been linked to VRE gastrointestinal tract colonization [19] and rate of vancomycin use has been independently associated with VRE prevalence [20].

Murray in description of enterococcal infections wrote that antibiotic alone will not select for VRE if resistant bacteria are not already present or if a patient does not come into contact with them [1], but we found that VRE more often were isolated from urine, especially in patients with abnormal renal function: creatinine and urea concentrations were high.

It was found that prior use of vancomycin was a risk factor for VRE infection development: it means that the dose regimen and pharmacokinetics of vancomycin not always considered, especially for patients with severely impaired renal function. It was observed that vancomycin pharmacokinetics was not always paid attention to, especially for patients with severely impaired renal function. The dose regimen of vancomycin was not considered. In cases where serum vancomycin concentration was being tested, it varied highly – from subtherapeutic to toxic. It is necessary to calculate the creatinine clearance and consider it when vancomycin dose is injected intravenously. The dose can be reduced or time of administration can be prolonged. As it was shown in an earlier study, the majority (53.3%) of vancomycin concentration measured timely was above and 15.9% below therapeutic values [21].

Our study shows that VSE was isolated more often from intra-abdominal secretions and patients who have undergone surgery prior to *Enterococcus* isolation in comparison to VRE.

Other studies show that renal failure, prior hospitalization, longer length of stay prior to infection, and presence of malignancy were significant risk factors for VRE infection [13, 22]. The risk of nosocomial acquisition of VRE increased by prolonged hospitalization as well as by proximity to a patient colonized by VRE, care by a nurse who also cares for patients positive for VRE, longer stay in an intensive care unit, and hospitalization in an institution with a high proportion of other patients with colonization with VRE [9]. Asymptomatic colonization is typically transient but can persist from months to years; decolonization is not recommended, since it can contribute to the accelerated development of resistance [15]. Colonized patients are a potential risk to health care facilities, serving as a source for transmission via shedding of VRE into the surrounding environment and onto health care workers [9, 23].

An increased risk of VRE colonization occurs with immunosuppression, hematological malignancies, organ transplantation, increased intensive care unit or hospital stay, residence in a long-term care facility, infection of an additional body site, proximity to another colonized or infected patient, and hospitalization in a unit with a high prevalence of VRE, serious

co-morbid conditions such as diabetes, renal failure [11, 18].

CONCLUSION

It is necessary to limit the use of Watch and Reserve group of antibiotics (as defined by WHO model list of Essential medicines), as well as be wary about possible enterococcal infections in patients being treated with metronidazole. Study results show that prior use of vancomycin, carbapenems and quinolones was a risk factor for VRE infection development. Most importantly – the dose regimen and pharmacokinetics of vancomycin was possibly not always considered, especially for patients with severely impaired renal function. Serum vancomycin concentrations were not measured in all cases, while in cases where it was measured, concentrations varied from subtherapeutic to toxic.

We found that VRE more often were isolated from urine, especially in patients with abnormal renal function: creatinine and urea concentrations were high. Surgery and stay in ICU prior to infection were also associated with higher risk of VRE infection. ♦

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Santrauka

VANKOMICINUI ATSPARIOS *ENTEROCOCCUS* SPP. INFEKCIJOS IŠSIVYSTIMO RIZIKOS VEIKSNIAI

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Darbo tikslas. Vankomicinui atsparių *Enterococcus* spp. (VAE) kolonizacijos ir paskesnės infekcijos rizika padidėja pacientams, ilgai gydomiems stacionare, ypač intensyviosios terapijos skyriuje (ITS), taip pat pacientams, sergantiems onkologinėmis kraujo ligomis ar po organų transplantacijos. Mūsų tyrimo tikslas buvo ištirti ir kitus VAE infekcijos išsivystymo rizikos veiksnius.

Metodai. Atlikta retrospektyvioji tiriamų pacientų demografinių duomenų analizė, įvertinta mechaninės plaučių ventilacijos trukmė iki ir po *Enterococcus* spp. infekcijos išsivystymo, gydymo stacionare ir ITS praleistų dienų skaičius, vartoti antimikrobiniai preparatai. Pacientai buvo suskirstyti į dvi grupes: infekuotų vankomicinui atsparia arba vankomicinui jautria *Enterococcus* spp. paderme (VJE).

Rezultatai. Pacientams, gydytiems ITS iki prasidedant infekcijai, *E. faecium*

buvo išskirtas dažniau nei *E. faecalis*. Nustatyta, kad atsparumas vankomicinui priklauso nuo infekcijos šaltinio – iš šlapimo VAE padermės išskirtos dažniau esant inkstų pažeidimui, t. y. laboratoriniais tyrimais nustatius didelę kreatinino ir šlapalo koncentraciją. Rezultatų analizė parodė, kad hospitalizacija ITS prieš prasidedant infekcijai ir anksti pradėtas antimikrobinų medžiagų vartojimas buvo rizikos veiksniai išsivystyti VAE. Pacientams, kurių gydymui buvo skirtas chinolonų klasės antibiotikas, VAE padermės rastos dažniau nei VJE padermės (26,1 %, n = 6 ir atitinkamai 3,8 %, n = 1; p = 0,033). Patikimai dažniau VAE padermės buvo nustatytos ir karbapenemais arba vankomicinu gydytų pacientų grupėje, palyginti su šiais antibiotikais negydytų pacientų grupe (47,8 %, n = 11 ir atitinkamai 7,7 %, n = 2; p = 0,002).

Išvados. Hospitalizacija ITS prieš prasidedant infekcijai ir anksti pradėtas antimikrobinų medžiagų vartojimas buvo rizikos veiksniai išsivystyti VAE infekcijai. VAE dažniau išskiriami iš šlapimo tų pacientų, kurių inkstų funkcija yra sutrikusi, t. y. nustatytos didelės kreatinino ir šlapalo koncentracijos, ir kuriems skiriamas gydymas vankomicinu netiriant šio vaisto koncentracijos.

Reikšminiai žodžiai: *Enterococcus* spp. infekcija, rizikos veiksniai, atsparumas vankomicinui, *E. faecium*, *E. faecalis*.

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