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Prevalence of Vancomycin-resistant Enterococci Colonization, and Susceptibility to linezolid in Pediatric Intensive Care Units of a Referral Pediatric Center in Tehran, Iran

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Background: Vancomycin-resistant Enterococcus (VRE) has been established as a significant health-care associated problem, and caused significant morbidity and mortality.
Objectives: This study was aimed to determine prevalence of VRE colonization in severely ill patients admitted to Pediatric Intensive Care Unit (PICU), and identify potential risk factors for colonization, and in vitro susceptibility of VRE to linezolid.
Patients and Methods: Rectal swabs were taken from 71 children 18 years old or younger who were admitted with serious systemic illness, including malignancy, chronic kidney, lung or liver diseases, treatment with chemotherapeutic agents, immunodeficiency, treatment with high-dose corticosteroids, malnutrition, previous treatment with 2nd or 3rd generation cephalosporin, aminoglycoside, and broad-spectrum β-lactam antibiotics within the past 3 months. Demographics and known risk factors were retrieved and assessed by statistical methods.
Results: A total of 71 patients with a mean age of 29.1 ± 38.5 months were enrolled in this study. The prevalence of VRE rectal colonization was 66.2%. None of the potential risk factors including age, gender, comorbidities, previous admission into ICU, length of stay in ICU, presence of invasive devices were significantly associated with VRE colonization. Linezolid-susceptible isolated strains accounted 97.9%.
Conclusions: The prevalence of VRE was higher compared to previous reports from local and international studies. In order to control the spread of VRE, appropriate use of antibiotics, adherence to infection control measures, and shortening the duration of ICU stay is highly recommended.

Keywords: Pediatric; Vancomycin; Enterococcus; Linezolid

1. Background

Enterococci are facultative anaerobic gram-positive cocci, which are part of the resident flora of the gastrointestinal tract of humans and animals. They may be responsible for a variety of community and hospital-acquired infections, such as bacteremia, endocarditis, meningitis, wound and urinary tract infections; and are sometimes associated with intra-abdominal infections (1). They are now the third most common organism seen in nosocomial infections (2). The most commonly isolated species are *Enterococcus faecalis* (80–90%) and *Enterococcus faecium* (5–10%) (3). Enterococci are intrinsically resistant to many antimicrobial agents, and they have the ability to develop or acquire resistance to other agents (4). Typical risk factors for colonization/infection with enterococci include patients who have received previous antibiotic treatment; have underlying conditions (e.g. organ transplant, renal failure, cancer, diabetes); have been hospitalized in a renal, oncology (including hematology), intensive care or surgical unit; have been hospitalized for prolonged periods; and have undergone invasive procedures (5, 6). Linezolid, a synthetic antimicrobial agent, has activity against all gram-positive cocci, a few gram-negative anaerobes, and some mycobacteria (7). Linezolid is still a promising agent for treatment of multi-resistant gram-positive bacterial infections (8), but clinical resistance has emerged, and has been repeatedly reported mainly in enterococci (9, 10). The increasing prevalence of vancomycin-resistant enterococcus (VRE)

Implication for health policy/practice/research/medical education:
Vancomycin-resistant Enterococcus (VRE) has been established as a significant health-care associated problem, and caused significant morbidity and mortality. There is paucity of data in Iranian Pediatric Intensive Care Unit (PICU) for incidence of VRE colonization and linezolid sensitivity in these cases. This study was aimed to determine prevalence of VRE colonization in severely ill patients admitted to PICU, and identify potential risk factors for colonization, and in vitro susceptibility of VRE to linezolid.

is concerning, because of limited effective antimicrobial agents for VRE infections (11).

2. Objectives

The aim of the present study was to determine the prevalence of VRE in a population of seriously ill patients admitted to PICU, identify the potential risk factors for VRE rectal colonization, and assess the in vitro susceptibility of vancomycin-resistant enterococci to linezolid by Epsilometer test (E-test).

3. Patients and Methods

From January 2012 to June 2013, surveillance of VRE colonization (rectal or stool swab) was performed on all children aged 18 years old or younger admitted to PICU at Ali-Asghar Children's Hospital in Tehran who satisfied the inclusion criteria, which were serious systemic illnesses including: admission to ICU for at least or more than a week , malignancy, chronic kidney, lung or liver diseases, treatment with chemotherapeutic agents, immunodeficiency, treatment with high-dose corticosteroids (more than 1 mg/kg/d) for more than one month, malnutrition (body weight less than 5th percentile), previous treatment with 2nd or 3rd generation cephalosporin, aminoglycoside, and broad-spectrum β-lactam antibiotics within the past 3 months.

Rectal swabs were sent to the Pediatric Infection Research Center (PIRC) at Mofid Children's Hospital in thioglycollate broth. Included patients were selected on daily basis by researchers and the samples were sent immediately to PIRC on sampling days (2 days per week). The samples were inoculated onto enterococcosel agar after 24 hours of incubation at 37°C. Isolates were confirmed to be enterococci by Gram stain, pyrrolidonyl arylamidase test (PYR), motility, and catalase, and were then sub-cultured onto three culture media: (1) Mueller–Hinton agar to determine their growth at 15°C and 45°C, (2) NaCl 6.5%, and (3) bile esculin agar containing 6 mg/mL vancomycin and 64 mg/mL ceftazidime for screening for resistance. All media were kept at 37°C for 24 h. Susceptibility testing for enterococci was carried out by E-test method for linezolid (30 mcg, BBL, Becton Dickinson co) and interpreted according to CLSI 2012 (12) breakpoints. Mueller-Hinton agar (Oxoid, England) plates for enterococci were inoculated by swabbing the surface with a suspension of organisms adjusted to equal the turbidity of a 0.5 McFarland opacity standard. After incubation for 22-24 hours at 37°C in room temperature, the inhibition zone diameters were interpreted according to CLSI criteria (CLSI AST Standards, January 2012). Susceptibility to other antibiotics was determined using disk diffusion method. The study was approved by ethics committee of Tehran University of Medical Sciences.

3.1. Statistical Analysis

Univariate analysis was used to identify potential risk factors. Chi-square test or Fisher's exact test was used for categorical variables, and Student's t-test was used for continuous variables. All tests were two-tailed, and $P < 0.05$ was considered significant. All statistical analyses were performed with STATA 12 (www.stata.com, College Station, TX).

4. Results

A total of 71 patients who met the inclusion criteria over a period of 18 months were enrolled in this study. Of the patients, 38 (53.5%) were male, and 33 (46.5%) were female, with a mean age of 29.1 ± 38.5 months (range from 2 days to 147.5 months). Sixty-four patients (90.1%) were colonized with enterococcus. Of 64 strains, 47 (73.4%) were resistant to vancomycin. The remaining isolates were either sensitive (11 strains, 17.2%), or intermediate-resistant (6 strains, 9.4%). The correlation between clinical characteristics compared between vancomycin-resistant strains and vancomycin-sensitive strains are demonstrated in Table 1. None of these characteristics showed significant difference between VRE and vancomycin-sensitive enterococci (VSE) colonized patients. The resistance of VRE and VSE strains to the eight antimicrobials tested is shown in Table 2. Table 3 shows susceptibility to linezolid between VRE strains evaluated by disk-diffusion method and e-test, which are comparable.

5. Discussion

In this study the prevalence of VRE colonization was 66.2% among patients admitted to ICU, which is higher compared to previous studies from other countries (13-16). Lower rates of VRE colonization have been reported in intensive care unit setting in Turkey (14.6%) (17), United States (3.6%) (18), and Brazil (49.4%, during an outbreak) (19). However, the comparison of data is very difficult and should be done by caution; since the populations studied differ in age group, methodology, and different antibiotic practice in different centers. In this study, we investigated the prevalence of VRE among seriously ill patients admitted to PICU, and used broth enrichment technique for detection of VRE; both of these factors might have contributed to this alarming result (20). In a previous report in 2008, we identified VRE in 25% of 130 children with ALL in our hospital (21). Even comparing to our previous report, we can conclude that the prevalence of rectal colonization with VRE has extremely risen. Concerning intermediate resistance to vancomycin, there is no consensus about clinical interpretation but for immunodeficient cases, these isolates have been considered as resistant, so vancomycin should not be used for treatment in these cases as well (22).

Table 1. The Relationship Between Clinical Characteristics of Patients With Vancomycin-Resistant Enterococci (VRE) Compared With VSE, by Disk Diffusion Method [a,b]

Demographic Data and Underlying Diseases	VRE (n = 47)	VSE (n = 17)	P Value
Age, mo	26.5 ± 35.8	35.4 ± 46.9	0.42
Gender			0.41
Male	25 (69.4)	11 (30.6)	
Female	22 (78.6)	6 (21.4)	
Diabetes mellitus	1 (50)	1 (50)	0.46
Solid tumor	3 (100)	0	0.55
Blood Dyscrasia	8 (100)	0	*0.09*
Immunodeficiency	4 (100)	0	0.56
Chronic renal disease	3 (75)	1 (25)	1.00
ICU admission over 7 days	34 (77.3)	10 (22.7)	0.30
Chronic lung disease	3 (75)	1 (25)	1.00
Presence of invasive device	27 (67.5)	13 (32.55)	0.16
Previous ICU admission in the past 3 months	9 (81.8)	2 (18.2)	0.71
Treatment with chemotherapeutic agents	8 (100)	0	0.09
Treatment with Corticosteroids	2 (100)	0	1.00
ICU admission over 7 days	34 (77.3)	10 (22.7)	0.36

[a] Abbreviations: ICU, intensive care unit; VRE, vancomycin-resistant enterococcus; VSE, vancomycin-sensitive enterococci.
[b] Data are presented as mean ± SD or No. (%).

Table 2. Antibiotic Activity Against VRE and VSE From Rectal Swabs [a,b]

Antibiotic	Sensitive	Intermediate	Resistance
VSE strains (n = 17)			
teicoplanin	100.00	0.00	0.00
chloramphenicol	64.71	29.41	5.88
ampicillin	70.59	0.00	29.41
ciprofloxacin	35.29	23.53	41.18
quinupristin	58.82	17.65	23.53
rifampin	29.41	17.65	52.94
penicillin	52.94	0.00	47.06
linezolid	88.24	11.76	0.00
VRE Strains (n = 47)			
teicoplanin	19.15	2.13	78.72
chloramphenicol	25.53	27.66	46.81
ampicillin	14.89	0.00	85.11
ciprofloxacin	4.26	14.89	80.85
quinupristin	68.09	8.51	23.40
rifampin	8.51	4.26	87.23
penicillin	17.02	0.00	82.98
linezolid	76.60	21.28	2.13

[a] Abbreviations: VRE, vancomycin-resistant enterococcus; VSE, vancomycin-sensitive enterococci.
[b] Data are presented as %.

Table 3. Susceptibility to Linezolid Between VRE Strains Evaluated by Disk-Diffusion Method and E-test [a]

	Sensitive	Intermediate	Resistance
Disk-diffusion	76.60	21.28	2.13
E-test	97.87	0.00	2.13

[a] Data are presented as %.

Numerous studies have demonstrated the changes in antibiotic susceptibility to antimicrobials among enterococci, and there is evidence that most of the isolates are now multi-drug resistant (4). A higher degree of resistance to other antimicrobials tested was observed among VRE strains in the present study. Linezolid still shows promise as an alternative to vancomycin in the treatment of serious infections due to resistant gram-positive organisms. We found only one VRE strain to be resistant to linezolid. A high susceptibility rate to linezolid has been reported previously. In a recent report from Pakistan, all strains isolated from PICU of three tertiary care hospitals were sensitive to linezolid (23). Similarly, a report from India indicated one hundred percent sensitivity to linezolid among VRE (24). In this study quinupristin was the next most active drug against VRE with 23.4% resistance among isolated strains. We found that over 80% of isolates were resistant to rifampin, penicillin, ampicillin, and ciprofloxacin, were and resistance to teicoplanin was also observed in 78.7% of isolates. High rate of resistance to teicoplanin might be due to existence of Van A genotype in most of our isolates as we had found in our previous study in this center (21).

Several studies have investigated the risk factors for VRE colonization. However, again, because of the lack of homogeneity in study population, drawing a reliable conclusion is very difficult. Gender and mean age of patients did not show any difference between patients colonized with VSE, compared to those with VRE. This finding was consistent with results of previous studies (14, 25-28). Length of hospital or ICU stay (29, 30), duration of hospitalization in the preceding 6 months (31), previous antibiotic exposure (14), duration of antibiotic administration (31), immunodeficiency (6), underlying hematological malignancy (6), renal insufficiency (32), and chronic dialysis (16), have all been reported to be associated with

colonization with VRE. The presence of invasive devices has been shown previously to be correlated with VRE colonization and infection in some studies (33, 34). Altoparlak et al. in a study on 128 patients, hospitalized in burn unit, did not find any significant association between acquisition of VRE and the presence of invasive devices (27). In the present study we could not find a significant association between presence of comorbidities, previous admission into ICU, length of stay in ICU, presence of invasive devices and increased risk of rectal colonization with VRE.

Control of transmission of VRE from colonized or infected patients to other patients demands a multipronged approach. Ergaz et al. reported successful elimination of VRE from a neonatal ICU in Israel. They achieved control of the outbreak by enhanced contact isolation precautions, cohorting of patients and staff, improved environmental decontamination and closure of the unit to new admissions, along with weekly fecal screening for VRE colonization (35). In another report from Korea, Yoon et al. implemented aggressive interventions to control the outbreak of VRE in intensive care units, including establishing a VRE cohort ward, frequent rectal cultures, daily cleaning of surfaces, antibiotic restriction, and training of hospital staff. They successfully decreased the rectal acquisition rates of VRE from 6.9/100 in September 2006 to none in January 2007 (11). Although, we tried to increase the number of patients enrolled in our study by elongating the period of sampling, the interpretation of our results is mainly limited by the small number of sample size.

In conclusion, our study reports a high prevalence of VRE colonization of fecal samples in patients admitted to PICU. This prevalence is higher than that reported by local and international studies. Partial explanations are the use of an enrichment broth step, as it could increase the number of VRE, and the presence of serious underlying disease in the study population. Linezolid is still a promising antibiotic, since 97.9% of the isolated strains were susceptible to this agent. Based on the results, we strongly recommend appropriate use of antibiotics, adherence to infection control measures, and shortening the duration of ICU stay, to decrease spread of VRE in ICU setting.

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Authors' Contribution

Dr Alireza Nateghian: proposed and wrote the study design and supervised the study, Dr Ghasemi: performed the test and helped in data manuscript. Dr Mehrazma: supervised the pathological information and data gathering. Dr. Lahouti Harahdashti: data analysis and interpretation, preparing the draft of the manuscript. Masoumeh Navidnia: supervised performing the laboratory tests. All authors had read and approved all content of the study.

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The authors do not have any conflict of interest.

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