1080

Changing Epidemiology and Long-term Outcome of Bloodstream Infection Due to Enterococcus for Patients with Acute leukemia: Impact and Limitations on Strategy of Restricting Antibiotics

Raeseok Lee[1], Sung-Yeon Cho[1], Dong-Gun Lee[1], Tae-hoon No[1], Su-Mi Choi[1], Si-Hyun Kim[1], Jae-Ki Choi[1], Sun Hee Park[1], Jung-Hyun Choi[1], Jin-Hong Yoo[1]

[1] Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea,

• **Corresponding author: Dong-Gun Lee, MD. PhD**

Division of Infectious Diseases,
Department of Internal Medicine,
The Catholic Blood and Marrow Transplantation Center, Vaccine Bio Research Institute, College of Medicine,
The Catholic University of Korea, Seoul, Korea

Seoul St. Mary's Hospital,
222, Banpo-daero, Seocho-gu, Seoul, 137-701, Korea

• Tel : 82-2-2258-6003 (office) / Fax : 82-2-535-2494
• E-mail: symonlee@catholic.ac.kr

Background and Aim

- *Enterococcus* has emerged as the third most common pathogen of bloodstream infection (BSI) in patients with hematologic malignancies.
- Epidemiological trends of Enterococcal BSI in acute leukemia has not been fully clarified and its relations with the antibiotic consumption and prophylactic use of fluoroquinolones has not been established either.

- **The aim** of this study was to determine the epidemiological trends of Enterococcal BSI of patients with acute leukemia. This results was assessed with standardized antibiotics consumption.
- We also examined the long-term outcome and risk factors of Enterococcal BSI.

Methods

- **Study design** Retrospective cohort study
- **Study period** January 2014 – December 2018
- **Study hospital** Seoul St. Mary's Hospital
- **Study population**
  - Adult patients (aged ≥ 18) with acute leukemia diagnosed with Enterococcal BSI regardless of undergoing treatment
- **Prophylactic antibiotics strategy of study hospital**
  - Before October 2016, oral ciprofloxacin (500mg twice a day) was used as routine prophylaxis during chemotherapy or hematopoietic stem cell transplantation (HSCT).
  - After October 2016, routine antibacterial prophylaxis was discontinued and selectively administered to the high-risk group such as induction chemotherapy of acute leukemia or cord blood transplantation.
- **Outcome measures**
  - Time trends of incidence of Enterococcal BSI was assessed with standardized antibiotics consumption.
  - Antibiotics consumption data presented in defined daily doses (DDDs) per 1,000 bed days.
  - .Overall survival were assessed at the time of discharge, 1, 2 and 3 year following after the first episode of Enterococcal BSI.

Results

1. Characteristics of study population

- No difference in the baseline characteristics between vancomycin susceptible *Enterococcus* (VSE) and vancomycin-resistant *Enterococcus* (VRE)

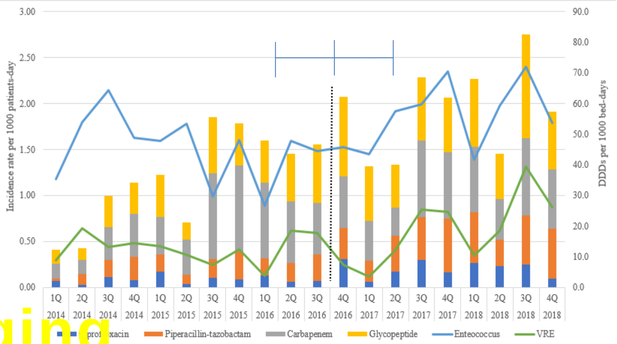
❖ **Table 1. Baseline characteristics of Enterococcal bloodstream infection**

	Total (N=511)	VSE BSI (N=339)	VRE BSI (N=172)	
Variables	N (%)	N (%)	N (%)	P-value
Age group, ≥60 years	184 (36.0%)	119 (35.1%)	65 (37.8%)	0.617
Sex, female	243 (47.6%)	156 (46.0%)	87 (50.6%)	0.378
Diagnosis				0.598
AML	372 (72.8%)	242 (71.4%)	130 (75.6%)	
ALL	136 (26.6%)	95 (28.0%)	41 (23.8%)	
MPAL	3 (0.6%)	2 (0.6%)	1 (0.6%)	
Disease stage at BSI				0.158
Naïve	135 (26.5%)	96 (28.4%)	39 (22.8%)	
CR	182 (35.8%)	124 (36.7%)	58 (33.9%)	
Advanced[a]	192 (37.7%)	118 (34.9%)	74 (43.3%)	
Treatment at BSI				0.230
Chemotherapy	418 (82.9%)	271 (80.9%)	147 (87.0%)	
HSCT	47 (9.3%)	35 (10.4%)	12 (7.1%)	
Post-HSCT	39 (7.7%)	29 (8.7%)	10 (5.9%)	
Time of BSI after treatment, median, IQR	15.0 [12.0;19.0]	15.0 [11.0;18.0]	16.0 [13.0;20.0]	0.025
Pitt bacteremia score, median, IQR	0.0 [0.0; 1.0]	0.0 [0.0; 1.0]	0.0 [0.0; 1.0]	0.055
Prior use of glycopeptide	122 (23.9%)	49 (14.5%)	73 (42.4%)	**<0.001**
Time of appropriate antibiotics therapy after BSI, median, IQR	1.0 [1.0; 2.0]	1.0 [0.0; 1.0]	3.0 [2.0; 3.0]	<0.001
Mortality				
In-hospital mortality	135 (26.4%)	83 (24.5%)	52 (30.2%)	0.198
100-Day mortality	178 (34.8%)	109 (32.2%)	69 (40.1%)	0.092
365-Day mortality	307 (60.1%)	200 (59.0%)	107 (62.2%)	0.545

Abbreviations: VSE, vancomycin-susceptible Enterococcus; VRE, vancomycin-resistant Enterococcus; AML, acute myelogenous leukemia; ALL, acute lymphocytic leukemia; MPAL, mixed phenotype acute leukemia; CR, complete remission; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range
[a]Advanced stage includes refractory and relapsed leukemic state

2. Trends of Incidence

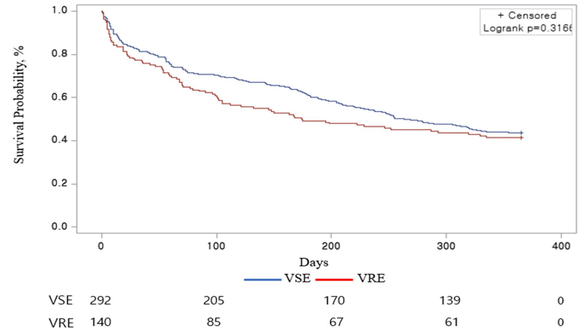
- The incidence of Enterococcal BSI and VRE BSI were 1.67 and 0.51/1,000 patient-days respectively.
- The incidence rate of VRE BSI decreased for 6 months after the strategy change (39.2% vs 12.2%, Odds ratio [OR]=0.312, 95% confidence interval [CI], 0.116-0.843, p=0.018).
- The incidence rate showed increasing trend with the increased use of total antibiotics consumption.



❖ **Figure 1. Incidence rate of Enterococcal BSI with changes of aggregated antibiotics utilization in acute leukemia cohort. Vertical black dash line is the time of new institutional strategy of restricting fluoroquinolone prophylaxis and use of carbapenem**
Abbreviations: DDDs, defined daily doses; Q, quarter

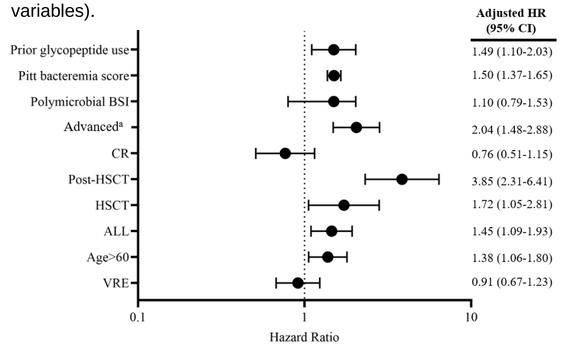
3. Overall mortality

- VRE BSI was associated with higher 100-day mortality (adjusted hazard ratio [HR]=1.477; 95% CI, 1.027-2.125, p=0.035).



❖ **Figure 2. Kaplan-Meier curves estimate of overall survival by 1-year**
Abbreviations: VSE, vancomycin-susceptible Enterococcus; VRE, vancomycin-resistant Enterococcus

- No difference in long-term outcome over 1-year between VRE BSI *vs* VSE BSI
- High-risk groups such as prior exposure of glycopeptides, clinically severe infection, advanced stage of disease, 60 years or older and BSI complications in hematopoietic cell transplantation recipient were strongly associated with worse overall mortality at 1-year (p<0.05 for all variables).



❖ **Figure 3. Multivariable analysis of risk factors for overall survival at 1-year**
Abbreviations: HR, hazard ratio; CI, confidence interval; BSI, bloodstream infection; CR, complete remission; HSCT, hematopoietic stem cell transplantation; ALL, acute lymphocytic leukemia; VRE, vancomycin-resistant Enterococcus
[a]Advanced stage includes refractory and relapsed leukemic state

Conclusion

- Restricting prophylactic fluoroquinolone could reduce the resistance rate of *Enterococcus.* However, restricting the use of prophylactic fluoroquinolone alone is not sufficient to reduce total antibiotics consumption but also Enterococcal BSI.
- The overall incidence of Enterococcal BSI is closely related to the total antibiotic consumption.
- The rate of vancomycin resistance remains relatively stable.
- Recent exposure of glycopeptides is a major risk factors of resistance and prognosis.
- VRE BSI is associated the poor prognosis until 100 days.
- The disease status and severity of infection have a more significant effect to long-term survival.