



Original Article

Evaluation of Using Empiric Glycopeptides in Accordance with the IDSA Guidelines in Hematologic Malignancy Patients with Febrile Neutropenia

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Abstract. Background: This study aimed to evaluate the effects of the appropriate use of empiric glycopeptide therapy in hematologic malignancy patients with febrile neutropenia (FN).

Materials and Methods: Patients with FN who were hospitalized in our clinic and started empiric glycopeptide therapy were retrospectively analyzed. Empiric glycopeptide treatment initial indications were determined according to 7 specific criteria in the IDSA guidelines. In addition, the duration of glycopeptide use according to initial indications, causative pathogens in culture positivity, frequency of VRE infection, and the mortality rate was identified.

Results: 87 patients were included. Of these, 102 episodes of FN were analyzed. Appropriate use of glycopeptides was observed in 98% of patients. The most common initial indication for glycopeptide was skin or soft-tissue infection, with 52% (n = 53). The mean duration of glycopeptide use was 11 (2–22) days. The time of glycopeptide use was longer in patients with catheter-related infections than in those with severe mucositis and hemodynamic instability (p = 0,041/p = 0,016). The duration of glycopeptide use was shorter in patients with consolidation therapy than in those without consolidation therapy. The mortality rate in culture-positive patients was significantly higher than in culture-negative patients (p = 0.041). At 72 h, glycopeptide therapy was discontinued in 8 of 79 FN episodes within culture-negative patients.

Conclusion: This study showed that the mortality rate was higher in culture-positive patients. Additionally, glycopeptides should be discontinued early with no evidence of gram-positive infection.

Keywords: Empiric glycopeptide; Febrile neutropenia; Hematologic malignancy.

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Introduction. Febrile neutropenia (FN) is a severe complication that usually occurs after chemotherapy treatment in about 80% of patients with hematologic malignancies.^{1,2} FN is one of the most important causes of comorbidity and mortality in cancer patients. The FN-related mortality rate varies between 2%–and 20% in studies.³ Therefore, preventing infections and selecting appropriate treatments are vital in these patients.⁴ In the 1980s, Gram-negative bacteria were frequently detected in pathogens isolated in cultures, while gram-positive bacteria have been isolated more recently.⁵

In culture, the most commonly isolated gram-positive pathogens are viridans group streptococci, coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, and *Enterococcus* spp. Therefore, it has become important according to which criteria the use of empirical antibiotics for gram-positive bacteria should be started. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer, 2010 Update by the Infectious Diseases Society of America, identified seven criteria for the empiric start of effective antibiotics against gram-positive bacteria. According to the IDSA guidelines, discontinuation of glycopeptide antibiotics is recommended within 72 h if there is no evidence of gram-positive infection.⁶ The disadvantage of widespread vancomycin use is that it causes the development of vancomycin-resistant organisms and multi-drug resistant organisms.⁷

In the literature, indications for initial glycopeptide were less compatible according to the IDSA guidelines. The most important reason for this is the addition of glycopeptide antibiotics to treatment due to persistent fever in patients.⁸ Therefore, this study aimed to evaluate the compliance of empiric glycopeptide use with IDSA guidelines in hematologic malignancy patients with FN.

Materials and Methods. In this study, patients with FN who were hospitalized in our clinic and started empiric glycopeptide therapy were retrospectively analyzed between January 2020 and January 2021. The hospital where the research was conducted is a tertiary health center with a capacity of 35 adult hematology beds serving approximately 3 million people.

Hematologic malignancy patients with FN who were 18 years of age or older were included in the study. The patients' data were obtained from the hospital information system and the patient file. Patients without hematologic malignancy were not included in the study.

In the FN episode, fever was defined as having a temperature above 38.3°C once in oral or axillary measurement, or at least 1 hour continuously above 38°C. Neutropenia was stated as a situation where the number of neutrophils is expected to be less than 500/uL, or the neutrophil level is between 500–1000/uL and will fall below 500/uL within 48 hours.

Empiric glycopeptide treatment indications were

determined according to 7 specific criteria specified by IDSA guidelines. These main criteria were: hemodynamic instability or other evidence of severe sepsis, skin or soft-tissue infection in any site, positive blood culture for gram-positive bacteria before final identification and susceptibility testing is available, clinically suspected serious catheter-related infection, pneumonia documented radiographically, colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* or penicillin-resistant *Streptococcus pneumoniae*, severe mucositis if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy.

The cultures were taken (blood, urine, sputum, wound, and stool) during the FN episode and then checked for gram-positive bacteria. In addition to that, VRE surveillance was conducted by rectal swab.

The primary endpoint was to determine the ratio of empiric glycopeptide use in accordance with IDSA guidelines. In addition, FN-related mortality and the frequency of VRE were determined. FN-related mortality was defined as patient death in the presence of persistent or recurrent fever or a documented infection at any time of the FN episode.

Statistical analysis. Statistical analysis was conducted using SPSS version 23. Continuous variables were described as mean and confidence interval (CI) or median and range, while categorical variables were expressed as n (%). The difference between independent variables was analyzed with a One-Way ANOVA with a *post hoc* Tukey Test. A p-value < 0.05 was considered statistically significant.

Ethical statement. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of our hospital.

Results. One hundred two febrile neutropenic episodes were evaluated in 87 patients included in this study. The median age of the patients was 51 (19–76), and 57% were female. There were 59 patients with acute leukemia, 15 lymphomas, ten multiple myelomas, two myelodysplastic syndromes, and one chronic myeloid leukemia. The mean duration of glycopeptide use was 11 (2–22) days. Seventy-eight (90%) patients were admitted for chemotherapy, 6 (7%) for radiotherapy, and 3 (3%) for supportive treatment (**Table 1**). Initial glycopeptide therapy was vancomycin in 75 (73%) FN episodes and teicoplanin in 27 (26%) FN episodes. Intravenous vancomycin dosage regime was 1 gr every 12 hours, and intravenous teicoplanin dosage regime was an initial dose of 6 mg/kg every 12 hours for two doses, followed by 6 mg/kg every once daily. Unfortunately, we were not able to measure vancomycin levels in our hospital. The reason for starting teicoplanin as the initial treatment was

Table 1. Demographic properties of patients.

Properties	n=87	%
Gender		
Male	37	43
Female	50	57
Median age	51 (19-76)	
Average treatment duration (median day)	11(2-22)	
Diagnosis		
Acute myeloid leukemia	41	47
Acute lymphoblastic leukemia	18	20
Lymphoma	15	17
Multiple myelom	10	11
Myelodysplastic syndrome	2	2
Chronic myeloid leukemia	1	1
Treatment		
Chemotherapy	78	90
Radiotherapy	6	7
Supportive treatment	3	3

Table 2. Indications of glycopeptide use in febrile neutropenia episodes

Treatment Indications	# of episodes (102)	%
Skin or soft-tissue infections at any site	53	52
Severe mucositis if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy	17	17
Hemodynamic instability or other evidence of severe sepsis	15	15
Positive blood culture for gram-positive bacteria before final identification and susceptibility testing is available	8	8
Pneumonia documented radiographically	4	4
Clinically suspected serious catheter-related infection (E.g.: chills or rigors observed by infusion with cellulite and catheter around the catheter inlet/outlet area)	3	3
Colonization with methicillin-resistant <i>Staphylococcus aureus</i> , vancomycin-resistant <i>Enterococcus</i> or penicillin-resistant <i>Streptococcus pneumoniae</i>	0	0
Prolonged fever	2	2

a history of allergic reactions to vancomycin, an allergic reaction had developed, or renal failure.

When all FN episodes in this study were examined, the most common indication for starting empiric glycopeptide was skin or soft-tissue infection in 52% (n = 53). While severe mucositis, 17% (n = 17), was observed with the second frequency, other treatment indications were given in **Table 2**. Empiric glycopeptide was not started according to the appropriate criteria in the two cases, and it was noted that the leading cause of the start was prolonged fever.

There was no significant difference in the duration of glycopeptide use between the two groups when comparing culture-positive and culture-negative patients. The duration of glycopeptide use was longer in patients with catheter-related infections (median 16 days; range 16-22) than in those with severe mucositis (median 9 days; range 4-18) and hemodynamic instability (median 6 days; range 2-22) (p = 0,041, p = 0,016 respectively). However, when patients receiving consolidation therapy (median six days; range 5-14) for acute leukemia were compared with patients receiving induction therapy (median 11 days; range 2-22), the duration of antibiotic use was significantly shorter in the group receiving

consolidation therapy (p = 0.017) (**Table 3**).

Gram-positive pathogen isolated in cultures taken in 23 patients with FN episodes. VRE that was positive in culture was observed only in 3 (3%) episodes of FN. The most common pathogens in culture were *Enterococcus* spp. and *Staphylococcus* spp. (**Table 4**). FN-related mortality rate was 18.3% (n = 16) in all patients. Seven of the patients with mortality were culture-positive patients. The mortality rate in patients with culture-positive was significantly higher than in patients with culture-negative (p = 0,041). The median overall survival of all patients was 23.5 months (27.8–55.6, CI %95) (**Figure 1**). There was no significant difference in overall survival between patients with culture-positive and culture-negative (p > 0.05) (**Figure 2**).

Discussion. In most studies, gram-positive bacteria have increased morbidity and mortality in febrile neutropenic patients.⁹⁻¹¹ In our study, the mortality rate in patients with culture-positive was significantly higher than in those with culture-negative, which supports the studies conducted.

The use of empiric glycopeptide treatment in FN has shown low starting rates with an appropriate indication

Table 3. Comparison of glycopeptide durations in empiric glycopeptide indications and treatment regimens.

Treatment regimens	Median day (min-max)	Pairwise Comparison
Induction therapy*	11 (2-22)	Consolidation therapy - Induction therapy $p = 0.017$
Consolidation therapy**	8 (5-9)	
Radiotherapy	6.5 (2-16)	
Supportive treatment	6 (4-14)	
Glycopeptid indications		
Catheter-related infection	16 (16-22)	Catheter-related infection - Severe mucositis $p = 0.041$
Skin or soft-tissue infections	11 (2-19)	
Severe mucositis	9 (4-18)	Catheter-related - Hemodynamic instability $p = 0.016$
Hemodynamic instability	6 (2-22)	
Positive blood culture signal	12 (5-18)	
Pneumonia documented radiographically	9 (5-15)	

*7+3 (cytarabine+idarubicin) regimen for acute myeloid leukemia; Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen for acute lymphoblastic leukemia.

**HiDAC (high dose cytarabine) regimen for acute myeloid leukemia; Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen for acute lymphoblastic leukemia.

Table 4. Bacteria isolated from culture.

Determinant	n=23	%
Enterococci		
<i>Enterococcus faecium</i>	7	30
<i>Enterococcus spp</i>	2	9
<i>Enterococcus faecalis</i>	1	4
Staphylococci		
<i>Staphylococcus aureus</i>	4	17
<i>Staphylococcus hominis</i>	3	13
<i>Staphylococcus epidermidis</i>	3	13
<i>Staphylococcus haemolyticus</i>	1	4
Coagulase negative <i>Staphylococcus spp</i>	1	4
Other		
<i>Lactobacillus rhamnosus</i>	1	4

Spp: species.

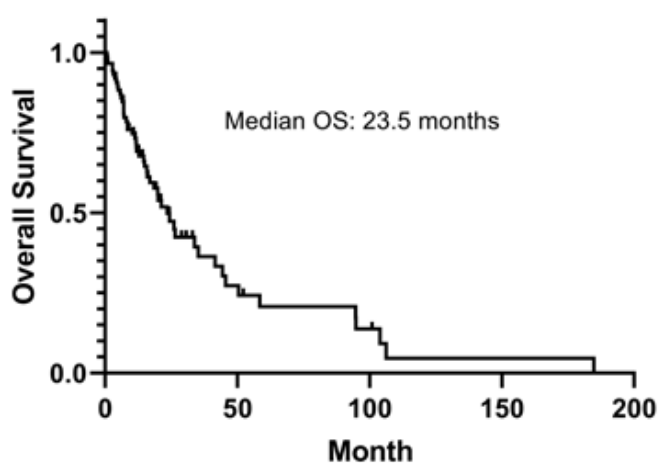


Figure 1. Overall survival all of patients (Kaplan-Meier curve).

in many centers. Libuit et al. found compliance with the

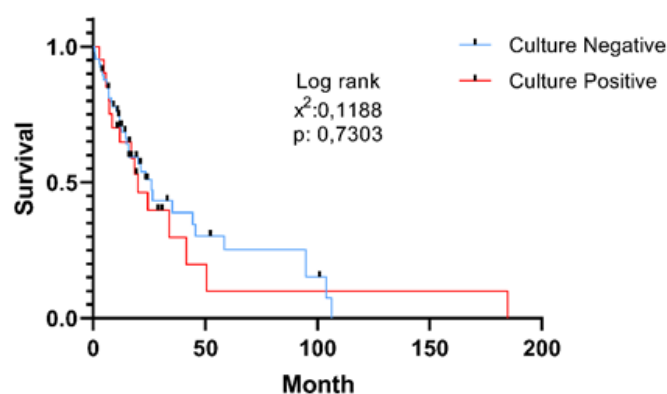


Figure 2. Comparison of overall survival of culture-negative patients and culture-positive patients (Kaplan-Meier curve).

IDSa guidelines for empirical vancomycin use in 66 adult cancer patients with FN was 27.3%.¹² In a similar study by Wright et al., it was shown that empirical vancomycin was used in accordance with the guideline in 67% of patients with FN.¹³ In our study, empiric glycopeptide antibiotic initiation criteria were 98% compliant with IDSa guidelines. In addition, it was noted that vancomycin was added to the treatment due to prolonged fever in only two FN episodes. Therefore, our empiric glycopeptide treatment was highly compliant with the IDSa guideline compared to other studies in the literature.^{11,12}

At 72 h, glycopeptide therapy was discontinued in 8 of 79 FN episodes in which there was no microbiological evidence of gram-positive infection. We thought that the main reason for the prolonged use of glycopeptide in patients with culture-negative were concerns about the deterioration in the clinical condition of patients and prolonged fever.

Cytotoxic chemotherapy, the disease used to treat hematologic cancers, leads to myelosuppression and

immunosuppression.¹⁴ Bradley et al. reported reducing the frequency of hospitalization for FN in AML patients under consolidation chemotherapy use of G-CSF prophylaxis.¹⁵ This study demonstrated a shorter duration of glycopeptide use in acute leukemia patients undergoing consolidation therapy than induction therapy. It may be associated with G-CSF prophylaxis in all patients undergoing consolidation therapy.

Enterococcal infections are the leading cause (20%–30%) of hospital-acquired infections in the United States in neutropenic patients. Prolonged use of vancomycin and prolonged hospitalization increase the risk of developing VRE.⁹ In recent years, guidelines limiting the use of empiric vancomycin in febrile neutropenic patients have been associated with a reduced incidence of VRE.¹⁵ Kirkizlar et al. found a VRE infection rate of 10.5% in febrile neutropenic patients with hematologic malignancy.¹⁰ Heisel et al. found a VRE infection rate of 14% VRE bloodstream infections rate of 11.7% among all newly diagnosed VRE colonized acute myeloid leukemia and myelodysplastic syndrome patients.¹⁷ In our findings, the frequency of VRE infection was 3%. However, the frequency of VRE was found to be lower since it was evaluated only in patients with FN who started empiric glycopeptide.

Neutropenic patients are at high risk for catheter-related bloodstream infections (CRBSI). Especially those with a neutrophil count of less than 100/uL are at increased risk. CRBSI was higher in hematologic malignancies than in solid tumors.^{18,19} Ghanem et al. found the mean duration of antibiotic therapy in CRBSI was 20.2 days with hematologic and solid tumors.²⁰ The mean duration of antibiotic treatment in CRBSI in this study was 18 days and was longer as studies in the literature.^{18,20}

FN-related mortality rates range from 2% to 20% in most studies.^{21,22,23} In a multicenter randomized study of

611 febrile neutropenic patients, the mortality rate was 7.6% in the group where empiric vancomycin was started. In contrast, the mortality rate was 5.6% in patients who started linezolid.²⁴ In a study of 41,779 patients with febrile neutropenia in the United States, the in-hospital mortality rate was 9.5%. Mortality rates were 8% in solid tumors, 8.9% in lymphoma patients, and 14.3% in leukemia patients.²³ According to our results, the FN-related mortality rate was 18.3% higher than in most studies because 68% (n = 59) of the patients were diagnosed with acute leukemia. Mortality rates were 12.6% for acute leukemia, 3.4% for lymphoma, and 2.2% for multiple myeloma patients.

Mert et al. found that the most frequently isolated gram-positive bacteria were coagulase-negative *Staphylococcus* (CNS) in patients with hematologic malignancies.²⁵ Özdemir et al. reported that the most commonly isolated gram-positive bacteria were CNS and *Enterococcus faecium* in febrile neutropenic patients.²⁶ In our study, the most frequently isolated gram-positive bacteria were CNS and *Enterococcus faecium*, similar to other studies.

Limitations of our study include its small sample size, its retrospective nature, and not being evaluated by other guidelines.

Conclusions. This study is being conducted to evaluate the use of empiric glycopeptides in hematologic malignancy patients with FN. Our empiric glycopeptide treatment was highly compliant with the IDSA guideline. However, the adherence to discontinuation at 72 h of treatment was not high. In addition, our study showed mortality rate was higher in culture-positive patients. Therefore, glycopeptides with no microbiological evidence of gram-positive infection should be discontinued early according to the IDSA guideline.

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