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Nursing & Health Sciences Research Journal

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Optimizing Empiric Vancomycin Use in Febrile Neutropenia Patients

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ABSTRACT

Introduction: National guidelines do not support routine empiric vancomycin use in the initial management of febrile neutropenia (FN) and only recommend it in patients with specific clinical indications. This bi-phasic quality improvement project aimed to evaluate current vancomycin use in FN and improve compliance with a guideline-driven algorithm (GDA) to ensure appropriate prescribing and therapy duration in a community hospital.

Methods: Phase I was a retrospective review of charts of adults receiving empiric vancomycin therapy for FN at a community hospital. Phase II was a prospective review of charts of patients with FN, who received pharmacist-led interventions, to improve de-escalation of vancomycin as warranted.

Results: A total of 48 and 32 patients were included in phase I and phase II, respectively. While initiation of vancomycin therapy according to guideline-recommended clinical indications was comparable among phases, appropriate de-escalation of vancomycin increased from 23% in phase I to 78% in phase II. Overall compliance with the GDA increased from 15% in phase I to 38% in phase II. Average duration of therapy in phase I was 4.77 days versus 2.69 days in phase II and there were less patients who continued vancomycin beyond 48 hours in phase II. The pharmacy intervention rate was 56% (18 of 32) and the health-care practitioner acceptance rate was 100%.

Discussion: Pharmacist interventions had an impact in increasing compliance with national guideline recommendations and decreasing the duration of empiric vancomycin therapy in patients with FN.

Keywords: Vancomycin, febrile neutropenia

INTRODUCTION

Febrile neutropenia (FN) is the cause of an astounding annual number of cancer-related hospitalizations – approximately 60,000 per year (Tai et al., 2017). Febrile neutropenia is a complication of chemotherapy resulting in a temperature of 100.4°F or greater accompanied by an absolute neutrophil count (ANC) below 500 cells/mm³ or an ANC below 1000 cells/mm³ and expected to decrease below 500 cells/mm³ within 48 hours (Patel & West, 2017). Febrile neutropenia occurs in approximately 50% of solid tumors and over 80% of hematologic malignancies. It can occur any time during the course of illness, from as early as the time of diagnosis to end-stage disease. Patients with FN are not only at a higher

risk of infection, but are more likely to experience more severe infection (Patel & West, 2017). Therefore, timely administration of empiric antibiotics in this subset of patients is crucial for reducing morbidity and mortality. However, prolonged empiric antimicrobial treatment can lead to antimicrobial resistance (e.g. dissemination of vancomycin-resistant organisms) and organ toxicity (e.g. acute kidney injury) (Freifeld et al., 2011; Paul et al., 2005). Previous studies have failed to show a true clinical advantage with the addition of vancomycin to empiric therapy (Paul et al., 2005). The European Organization for Research and Treatment of Cancer (EORTC, 1991) conducted a randomized clinical trial consisting of 747 patients (“Vancomycin added to empirical combination antibiotic therapy for fever

in granulocytopenic cancer patients”). The patients were randomized to receive ceftazidime and amikacin with or without vancomycin. The results showed no significant difference in duration of fever or improvement in survival. However, antibiotic-associated nephrotoxicity was more frequent in the vancomycin arm. According to the National Comprehensive Cancer Network (NCCN, 2021) and Infectious Diseases Society of America (IDSA) guidelines (Freifeld et al., 2011), routine addition of vancomycin to empiric antimicrobial regimens to treat FN is not recommended. Vancomycin is only recommended in patients with specific clinical indications such as suspected catheter-related infection, hemodynamic instability, skin or soft-tissue infection, colonization with penicillin (PCN)/cephalosporin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus* (MRSA), preliminary gram positive blood cultures, pneumonia, and severe and refractory mucositis (summarized in Table 1). The guidelines also acknowledge the use of vancomycin in the setting of a severe beta lactam allergy (Freifeld et al., 2011; NCCN, 2021). The purpose of this project was to evaluate current use of vancomycin for FN and improve compliance with a guideline-driven algorithm (GDA) to ensure appropriate prescribing and therapy duration within a local South Florida community hospital.

METHODS

This was a biphasic, IRB-reviewed quality improvement project evaluating adult patients receiving empiric vancomycin therapy for FN. This single-center project was conducted at a not-for-profit community hospital with over 900 beds that serves a significant amount of oncology patients as it is associated with a large neighboring cancer center. The community hospital has 84 inpatient oncology beds between two dedicated floors. Phase I of this project was a retrospective evaluation of therapy based on National Oncology guidelines from January 2019 to December 2019, while phase II was a prospective evaluation of therapy based on guidelines from January 2021 to March 2021. An algorithm based on national guidelines was created to guide pharmacists’ de-escalation interventions in phase II. The algorithm also provided a systematic method to assess adherence to national guideline recommendations and incorporated recommendations for appropriate initiation and de-escalation of vanco-

mycin empiric therapy. The GDA is summarized in Figure 1.

Patients were identified using vancomycin dispense reports generated through the electronic medical record reporting software. Patients were included if they were 18 years and older with a vancomycin order for the selected indication of “neutropenic fever,” “sepsis of unknown origin,” or “other.” Patients with one-time orders of vancomycin and patients who lacked a documented diagnosis or did not meet the clinical definition of FN were excluded. Oncology pharmacists were provided with an educational presentation to help identify patients meeting inclusion criteria in phase II for timely intervention. Data collection variables included patient demographics, indication, pertinent labs and cultures, therapy duration and compliance with the GDA. In phase II, pharmacists implemented an algorithm to recommend de-escalation or discontinuation of vancomycin as warranted. Data were collected, stored, and analyzed using Microsoft Excel. Descriptive statistics were used to report results.

RESULTS

Forty-eight patients were included in phase I, and 32 patients were included in phase II. Subject characteristics (summarized in Table 2) were similar across phases with the exception of age, bone marrow transplant (BMT) status, positive cultures, and acute kidney injury. Phase II had a higher average patient age and higher percentage of BMT patients, while phase I had a higher percentage of patients with positive blood cultures and acute kidney injury. The percentage of patients initiated on vancomycin empiric therapy in the presence of guideline-recommended clinical indications was 42% in phase I versus 41% in phase II. The rate of appropriate de-escalation increased from 23% in phase I to 78% in phase II. The overall compliance with the GDA, which is defined as both appropriate initiation and de-escalation of empiric vancomycin, increased from 15% in phase I to 38% in phase II (See Table 3). The average duration of therapy decreased from 4.77 days (range: 1 to 16 days) in phase I, to 2.69 days (range: 1 to 9 days) in phase II. The number of patients who continued on empiric vancomycin beyond 48 hours decreased from phase I to phase II (See Figure 2). In the prospective interventional phase, 18 pharmacy-initiated interventions were made at an intervention rate of 56%. All interventions were accepted

by the physician or advanced practitioner for an acceptance rate of 100%. The pharmacy-initiated interventions included discontinuation of vancomycin (94.4%) and vancomycin dose optimization (5.6%).

DISCUSSION

The results of this project show that pharmacist intervention resulted in a higher percent compliance with national guideline recommendations and a shorter duration of empiric vancomycin therapy in FN. The largest impact related to pharmacist intervention was de-escalation of empiric vancomycin therapy. The comparability of the total percentage of patients initiated on vancomycin with guideline-recommended clinical indications among phases highlights the valuable role of the pharmacist in de-escalation of empiric antimicrobial therapy in the absence of positive blood cultures. However, the project had significant limitations. Some limitations of this project included the small sample size and short duration, being that the prospective intervention was only three months in duration and occurred during weekdays and business hours. Additionally, compliance with the GDA was reported as an “all-or-nothing” approach, meaning that vancomycin had to be both initiated in a patient with guideline-recommended clinical indications as well as de-escalated appropriately in order to be considered compliant. There was little opportunity to impact initiation in this particular project, and this should be evaluated in the future. Lastly, the expansion of oncology services allowed for disparity in patient volume between phases due to the ability to accommodate more oncology patients in phase II. Currently throughout the health care system, the sepsis protocol drives the use of vancomycin in febrile neutropenia. Therefore, a future direction for this project is to streamline the criteria for vancomycin use in FN to specifically include the clinical indications set forth by NCCN/IDSA guidelines and separate it from the criteria for vancomycin use in sepsis. Moreover, a significant number of patients were excluded from the project due to being one-time orders. Therefore, it may be beneficial to conduct a medication-use evaluation of one-time orders for vancomycin for FN to evaluate whether there is an opportunity to optimize one-time ordering of vancomycin in FN.

CONCLUSION

Pharmacist interventions had an impact in increasing compliance with national guideline recommendations and decreasing the duration of empiric vancomycin therapy in patients with FN. Therefore, clinical pharmacists should routinely evaluate empiric vancomycin orders in patients with FN for the presence of guideline-recommended clinical indications and follow up to ensure optimal duration of therapy.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1*Summary of Guideline Recommendations for Empiric Addition of Vancomycin in Febrile Neutropenia*

Clinical Indication	IDSA	NCCN
Suspected catheter-related infection	✓	✓
Hemodynamic/clinical instability	✓	✓
Known colonization with Penicillin/Cephalosporin-resistant pneumococci or MRSA	✓	✓
Skin or soft tissue infection	✓	✓
Gram positive blood cultures	✓	✓
Pneumonia documented radiographically	✓	
Severe mucositis (if fluoroquinolone prophylaxis <u>AND</u> ceftazidime use empirically)	✓	

Note. This table summarizes the guideline-recommended clinical indications for empiric addition of vancomycin in febrile neutropenia.

IDSA = Infectious Diseases of America, NCCN = National Comprehensive Cancer Network

Table 2*Subject Characteristics*

Characteristic	Phase I (n=48)	Phase II (n=32)
Average age, years	67 (SD 15.9)	60 (SD 13.6)
Median ANC, cells/mm ³	0.26 (IQR 0.7)	0.29 (IQR 0.6)
Average Tmax, °C	38.6 (SD 0.8)	38.6 (SD 0.8)
BMT, n (%)	3 (6.3%)	13 (40.6%)
PCN allergy, n (%)	5 (10.4%)	5 (15.6%)
Median baseline SCr, mg/dL	1.1 (IQR 0.7)	0.97 (IQR 0.5)
Acute kidney injury, n (%)	9 (18.8%)	2 (6.3%)
Positive blood culture, n (%)	12 (25%)	5 (15.6%)
MRSA/MRSE	2 (4.17%)	1 (3.13%)
Selected indication, n (%)		
Febrile neutropenia	32(66.7%)	24 (75%)
Sepsis, no clear source	10 (20.8%)	5 (15.6%)
Other	6 (12.5%)	3 (9.4%)
Disposition n (%)		
Home	33 (68.7%)	30 (93.7%)
Expired	13 (27.1%)	2 (6.3%)
Nursing Facility	2 (4.2%)	—

Note. This table summarizes the subject characteristics in phase I vs. phase II.

SD = Standard deviation, IQR = Interquartile range

Table 3*Percent Compliance with GDA*

Characteristic	Phase I (n=48)	Phase II (n=32)
Initiated with Clinical Indications, n (%)	20 (42%)	13 (41%)
De-escalated within 48 Hours, n (%)	11 (23%)	25 (78%)
Overall compliance with GDA, n (%)	7 (15%)	12 (38%)

Note. This table summarizes the percent compliance with the guideline-driven algorithm as it relates to initiation, de-escalation, and compliance to the algorithm as a whole.

Figure 1*Summary of Guideline-Driven Algorithm*

Figure 2

Duration of Therapy