Empiric Vancomycin Use in Febrile Neutropenic Oncology Patients

Jessica Libuit,[1] Andrew Whitman,[1] Rebecca Wolfe,[1] and Casey S. Washington[1,2]

[1]Virginia Commonwealth University School of Pharmacy, Falls Church, Virginia, [2]Department of Pharmacotherapy and Outcome Sciences

Vancomycin is commonly added as empiric therapy for febrile neutropenia. A retrospective chart review was conducted at a large community teaching institution to evaluate vancomycin use in oncology patients. The results revealed that a majority of empiric vancomycin therapy was inappropriate, raising concern for antibiotic resistance and prompting opportunities for improvement.

Keywords. febrile neutropenia; oncology; vancomycin; empiric; antibiotics.

Vancomycin is a glycopeptide antibiotic that is one of the most widely used antibiotics in the United States for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. Neutropenic fever in oncology patients is a medical emergency in which Gram-positive organisms are the predominant bacterial pathogens. Febrile neutropenia (FN) requires rapid administration of empiric antibiotic therapy; however, studies do not support the addition of vancomycin to the initial antibiotic regimen in all patients [2]. The Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America (IDSA) stated 7 specific criteria for the appropriate use of empiric vancomycin, which include instances that a Gram-positive infection should be suspected. Despite this update, vancomycin use continues to be widespread and often inappropriate [3].

The results of a large, retrospective study assessing compliance with guideline-based recommendations for FN in cancer patients over the last decade indicated that patients at teaching hospitals that treat ≥14.6 cases of FN per year were more likely to adhere to guideline-based recommendations [4]. The authors also concluded that empiric vancomycin, administered in 36.9% of patients, did not improve patient outcomes, which is consistent with previous literature [2]. Likewise, the aim of this study was to assess the appropriateness of vancomycin therapy in oncologic FN patients at a large, community teaching hospital.

METHODS

Study Design and Patient Population

A retrospective, systematic review of patient medical records from November 1, 2010 to November 1, 2012 at a large, community teaching hospital was conducted to assess appropriateness of indication and duration of therapy according to current IDSA guidelines in adult cancer patients with a diagnosis of FN [3]. Patients included in the study were 18 years of age or older, and they had an inpatient stay ≥72 hours. These patients were also diagnosed with FN, and their initial empiric treatment included vancomycin. The IDSA definition of FN was used to identify patients: an absolute neutrophil count (ANC) <1000 cells/mm^3 or expected to decrease to <500 cells/mm^3 within 48 hours and a temperature >38.3°C (101°F) or a sustained temperature >38°C (100.4°F) for at least 1 hour [3]. The author's concluded that if patients required in-patient admission for their FN, their ANC would likely drop below 500 cells/mm^3 if not already below 500 on admission.

We considered evidence of at least 1 of the following: hemodynamic instability or other evidence of severe sepsis, assessed according to the 2012 Surviving Sepsis Guidelines; pneumonia documented radiographically; positive blood culture for Gram-positive bacteria before final identification and susceptibility testing if available; clinically suspected, serious, catheter-related infection; skin or soft-tissue infections at any site; known colonization with MRSA or penicillin-resistant *Streptococcus pneumoniae*; or severe mucositis if fluoroquinolone prophylaxis had been given and ceftazidime had been used as empirical therapy, as an appropriate indication for empiric vancomycin therapy [3, 5].

Of the patients determined to have an appropriate indication, as outlined above, appropriate duration of vancomycin was assessed, defined as either discontinuation of vancomycin within 3 days of therapy if the patient did not have evidence of Gram-positive bacteria in the blood or continuation with a "clinically appropriate" indication. Group consensus determined clinically appropriate indications and included cases of persistent fever, symptoms of

DOI: 10.1093/ofid/ofu006

Table 1. Distribution of Appropriate Vancomycin Indications

Indication	Percentage
Hemodynamic instability or other evidence of severe sepsis	37%
Clinically suspected, serious, catheter-related infection	15%
Positive blood culture for Gram-positive bacteria before final identification and susceptibility testing if available	11%
Known colonization with MRSA or penicillin-resistant *Streptococcus pneumoniae*	11%
Pneumonia documented radiographically	8%
Skin or soft-tissue infections at any site	7%
Severe mucositis if fluoroquinolone prophylaxis had been given and ceftazidime had been used as empirical therapy	0%
Multiple indications	11%

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*.

sepsis, pneumonia documented radiographically, or any evidence of clinical instability. The secondary outcome was to evaluate appropriateness of the initial vancomycin-dosing regimen based on a dose of 15–20 mg/kg (actual body weight) given every 8–12 hours for patients with normal renal function [6]. For purposes of data collection, vancomycin administration every 12 hours for patients whose creatinine clearance (CrCl) was ≥50 mL/min or once daily if their CrCl was <50 mL/min was documented as appropriate.

Descriptive statistical analysis was conducted using Microsoft Excel 2011. The primary outcome was appropriateness of indication and duration, and the secondary outcome was appropriateness of initial dosing regimen.

RESULTS

From November 1, 2010 to November 1, 2012, 128 adult cancer patient registration records were evaluated and 66 patients met the inclusion criteria. Baseline characteristics of our study population included predominantly females (54.5%) averaging 57 years of age with hematologic malignancies (71.2%). Twenty-five patients included in the study were found to have an appropriate indication for empiric vancomycin (37.9%). The most common appropriate indication for the use of empiric vancomycin in this patient population was hemodynamic instability or other evidence of severe sepsis. The distribution of appropriate indications across the study population is displayed in Table 1. Eighteen patients were found to have both appropriate indication and appropriate duration (27.3%) in accordance with IDSA guidelines. Results from the secondary outcome showed that the initial dosing regimen for vancomycin was appropriate in 40 patients (60.6%).

DISCUSSION

We found that the majority of empiric vancomycin therapy in oncologic FN patients at a large, community teaching hospital was inconsistent with current IDSA guidelines because vancomycin use was appropriate in only 27.3% of cases. In comparison, the results of a similar study illustrated that empiric vancomycin was used appropriately in 67% of FN patients [4]. In our study, we found a considerably lower rate of appropriate therapy, which is concerning. Consequently, inappropriate vancomycin use may have deleterious effects such as the development of vancomycin-resistant *Enterococcus* (VRE). Acquisition of VRE has been associated with prolonged or repeated hospitalization, repeat use of broad-spectrum antibiotics, and neutropenia [7]. Vancomycin-resistant *Enterococcus* is an independent risk factor for mortality in neutropenic patients, thus prevention of VRE in oncology patients is important and can be decreased through judicious use of vancomycin [8, 9].

One of the limitations of this study was that the data were collected from only 1 institution and is not representative of care across the country. Second, derivation of our patient list was based on institution-specific diagnosis coding, including subjective group parameters in addition to ICD-9 codes, Diagnosis-Related Group codes, and not based on a standardized coding method for FN. Third, our findings may have been influenced by incomplete documentation, because only patients with a documented indication consistent with IDSA guidelines were considered as appropriate when collecting the data. In efforts to maintain consistency regarding hemodynamic instability, we used the Systemic Inflammatory Response Syndrome criteria to determine whether a patient exhibited hemodynamic instability. Finally, our study only included FN patients who received vancomycin as empiric treatment, yielding a small sample size, and excluded patients that may have been appropriate candidates for vancomycin therapy but did not receive it.

With vancomycin use deviating from IDSA guidelines 73.7% of the time, there is a clear need for improvement at this institution. One strategy for increasing antibiotic stewardship in cancer patients, which would not interfere with rapid administration of empiric antibiotics, would be to implement a 72-hour stop date in the absence of a Gram-positive organism or approval by an infectious disease team member [10]. Another strategy includes utilizing an electronic health record system to adapt institution-specific order sets tailoring antibiotic-ordering parameters to ensure an appropriate indication is considered before antibiotics are given [11]. A final, less time-intensive strategy to increase compliance with guideline recommendations is by educating prescribers that could benefit from IDSA guideline education. Combinations of the above-listed strategies are currently being researched for implementation at this institution.

CONCLUSION

This study was performed to evaluate current practice in empiric vancomycin use in FN oncology patients. Results from this study support that vancomycin use is widespread and often

prematurely added onto empiric antibiotic therapy in FN patients. In light of acquiring VRE through repeated exposure to vancomycin and the increased mortality associated with VRE [11], vancomycin use should be reserved only in those patients who exhibit indications for its use according to the IDSA guidelines [3].

Notes

References

1. Moellering RC Jr. Vancomycin: a 50-year reassessment. Clin Infect Dis **2006**; 42(Suppl 1):S3–4.
2. Paul M, Borok S, Fraser A, et al. Empirical antibiotics against gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother **2005**; 55:436–44.
3. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis **2011**; 52:e56–93.
4. Wright JD, Neugut AI, Anath CV, et al. Deviations from guideline-based therapy for febrile neutropenia in cancer patients and their effect on outcomes. JAMA Intern Med **2013**; 173:559–68.
5. Dellinger PR, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med **2013**; 39:165–228.
6. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm **2009**; 66:82–98.
7. Husni R, Hachem R, Hanna H, Raad I. Risk factors for vancomycin-resistant enterococcus (VRE) infection in colonized patients with cancer. Infect Control Hosp Epidemiol **2002**; 23:102–3.
8. Koc Y, Snydman DR, Schenkein DS, Miller KB. Vancomycin-resistant enterococcal infections in bone marrow transplant recipients. Bone Marrow Transpl **1998**; 22:207–9.
9. DiazGranados CA, Jernigan JA. Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J Infect Dis **2005**; 191:588–95.
10. Tverdek FP, Rolston KV, Chemaly RF. Antimicrobial stewardship in patients with cancer. Pharmacotherapy **2012**; 32:722–34.
11. Kullar R, Goff D, Schulz L, et al. The "Epic" challenge of optimizing antimicrobial stewardship: the role of electronic medical records and technology. Clin Infect Dis **2013**; 57:1005–13.