Effect of Pharmacists’ Interventions on the Appropriateness of Empiric Vancomycin Therapy in Oncology Patients with Febrile Neutropenia

Nour Baghdady¹,², PharmD, BCPS, MPH, Daniel Voit², PharmD, Anne M. McDonnell², PharmD, MBA, BCOP, CPPS, David W. Kubiak², PharmD, BCPS
¹Clinical Pharmacy Department, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia
²Department of Pharmacy, Brigham and Women’s Hospital, Boston, Massachusetts, U.S.A.

Abstract
The purpose of this observational study is to evaluate the effect of an active pharmacy intervention to facilitate timely discontinuation of empiric vancomycin therapy in oncology patients with febrile neutropenia who lack objective evidence of a Gram-positive infection. This was a two-phase study. Vancomycin use was evaluated retrospectively on all oncology patients with febrile neutropenia over four weeks (phase I). In a parallel four weeks a year later, vancomycin use in this patient population was evaluated prospectively (phase II). In the absence of evidence of Gram-positive infection after 72 hours of treatment initiation, the team was contacted by a pharmacist to encourage discontinuation. Usage was compared between both phases. Forty-three patients in phase I and 25 patients in phase II were treated with vancomycin with no evidence for Gram-positive infections. Pharmacists’ interventions were documented on 18 patients in phase II. Of these, 56% of interventions to discontinue vancomycin were accepted, but only 33.3% of patients had treatment stopped within 72 hours of initiation. Although not significant, a trend in more appropriate use of vancomycin in oncology patients with febrile neutropenia was observed. Pharmacist’s interventions might have played a role in this observation.

Keywords
Vancomycin; De-escalation; Febrile neutropenia

Introduction
Neutropenia is a complication of chemotherapy which can predispose cancer patients to infections and cause significant morbidity and mortality[1]. The magnitude and duration of neutropenia puts patients at a higher risk of developing infections[2]. Often times, fever is the only sign of infection due to impaired cell-mediated immunity and inflammatory responses in these patients[3]. Febrile neutropenia (FN) is a medical emergency in oncology patients, early recognition and initiation of empiric broad spectrum antimicrobials is of critical importance[1,2]. Clinical practice guidelines by the National Comprehensive Cancer Network
(NCCN) and the Infectious Disease Society of America (IDSA) recommend empiric treatment with broad spectrum antimicrobials with antipseudomonal beta lactams, e.g., an antipseudomonal beta lactam or a carbepenam typically as monotherapy\[1,3\]. Treatment with glycopeptide antibiotics such as vancomycin, on the other hand, should be reserved for patients with cultures growing Gram-positive pathogens or indications suggesting likelihood of a Gram-positive infectious process (GPI) such as: hemodynamic instability, skin and soft tissue infection, infections suspected to be related to catheter, or pneumonia\[1\]. Current data show that empiric treatment with vancomycin without evidence of a GPI did not improve outcomes in FN\[3,4\]. On the contrary, it put patients at risk of unnecessary side effects and increased the likelihood of promoting resistance in pathogens such as *Enterococcus spp*. and *Staphylococcus spp.*\[1\].

Over the past few years, the use of vancomycin has been increasing significantly, particularly in patients with FN\[2\]. Recent data shows that vancomycin initiation for FN increased from 17.2% in 2000 to 54.9% in 2010\[2\]. We observed this increase at our 793-bed tertiary care academic medical center, the Brigham and Women's Hospital, in the form of a steady increase in defined daily doses (DDD) of vancomycin per 100 patient days admitted to oncology and hematopoietic stem cell transplant (HSCT) wards and in general hospital wards as shown in Figure 1. A guideline for antimicrobial use in patients with FN was created based on published national guidelines and implemented at our institution in 2007. This guideline specifies that vancomycin should only be used in patients with an indication suggesting the likelihood of GPI. It also recommends the discontinuation of vancomycin if cultures remain negative after 48- to 72-hours of therapy. At our institution, promoting adherence to treatment guidelines, including FN guidelines, and antimicrobial stewardship is one of the clinical pharmacists’ daily duties. This has been established based on the evidence proving the benefits pharmacists can provide in discontinuation of unnecessary antibiotics, reduction in overall exposure to antimicrobials and decreased infection-related length of stay\[5\].

We conducted a pilot observational study to evaluate the impact of pharmacists’ interventions on the discontinuation of empiric vancomycin therapy in oncology patients with FN lacking evidence of GPI within 72 hours of drug initiation.

**Materials and Methods**

This observational study was conducted over two phases. The first phase (phase I) is the pre-intervention phase. Data was collected retrospectively over a period of four weeks starting January 1, 2012 through February 1, 2012 and was used as baseline data to identify the current practice at our institution. Data from this phase was used as a comparative arm for the intervention phase. In the second phase (phase II), the intervention phase, data was collected prospectively over four weeks starting January 1, 2013 through February 1, 2013, one year later.

During both phases, all oncology patients with FN on receiving systemic vancomycin were evaluated. Inclusion criteria included patients with neutropenia and fever admitted to our oncology and HSCT wards. Fever was defined as a body temperature of more than 38 degrees Celsius. Neutropenia was defined as an absolute neutrophil count (ANC) of less than or equal to 0.5 x 10^3 cells per mm^3. Patients with an ANC between 0.5 to 1.5 x 10^3 cells per mm^3 with an anticipated decline to less than 0.5 x 10^3 cells per mm^3 within 48 hours were also evaluated to capture patients trending into neutropenia. Reasons for exclusion were ages less than 18 years or treatment with vancomycin for an indication approved by our institution’s guidelines including cultures growing Gram-positive bacteria, hemodynamic instability, skin and soft tissue infection, infections suspected to be related to catheter, or pneumonia.

During the intervention phase (Phase II), patients with FN admitted to an oncology service and started on vancomycin therapy were monitored for the
Effect of Pharmacists’ Interventions on the Appropriateness of Empiric Vancomycin Therapy in Oncology Patients with Febrile Neutropenia
N. Baghdady et al.

confirmation of an indication within the following 48 hours. If patients were found not to have an indication approved by our guideline, the responding clinician was paged to discuss the indication of vancomycin therapy and to consider discontinuation. An intervention was considered accepted if treatment was discontinued before the next day. If treatment continued and the pharmacist did not receive a call back from the covering team, another page was sent as a reminder. No more than two pages were sent per case. Interventions were considered not accepted if therapy continued beyond 72 hours. Vancomycin use in concordance with our guidelines, i.e., where an indication was present or if de-escalated within 72 hours, was defined as “appropriate”. Otherwise, use was deemed “inappropriate”.

The number of pharmacist-led clinically appropriate vancomycin discontinuations within 72 hours was assessed. In addition, we evaluated the overall vancomycin days on therapy (DOT) and the combined number of appropriate versus inappropriate therapy.

The sample size in this study is small and, therefore, assumed to be not normally distributed; medians and interquartile ranges were used for descriptive statistics and Wilcoxon signed-rank test were used to compare differences in medians. We used chi-squared for categorical data and all p values were two-tailed and were significant if < 0.05.

This observational study was approved by the Partners Human Research Committee (PHRC), the Institutional Review Board of Partners HealthCare, for adherence to ethical, federal and institutional guidelines. As this was an observational study of pharmacists’ standard practice, a waiver of informed consent was approved by the PHRC.

Results
In total, 119 patients were evaluated; 65 in phase I and 54 in phase II. Fifty-one cases, 22 in phase I and 29 in phase II, were excluded because vancomycin was used for indications consistent with our guidelines (Fig. 2). Baseline characteristics and allergy profiles were similar in both phases (Table 1A and 1B).

![Figure 2. Study enrollment.](image-url)

Table 1a. Baseline characteristics (Medians [Interquartile Range])

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Phase I (n = 43)</th>
<th>Phase II (n = 22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55 [20.5]</td>
<td>62 [20.25]</td>
<td>0.12</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>21 (48.84%)</td>
<td>10 (45.5%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>67.3 [28.05]</td>
<td>78.5 [20.13]</td>
<td>0.1</td>
</tr>
<tr>
<td>ANC (x10^3 cells/mm³)</td>
<td>0.44 [0.94]</td>
<td>0.12 [0.62]</td>
<td>0.23</td>
</tr>
<tr>
<td>WBC (x10^3 cells/μm³)</td>
<td>0.8 [1.3]</td>
<td>0.91 [1.97]</td>
<td>0.76</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.69 [0.49]</td>
<td>0.73 [0.46]</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Table 1b. Allergies to antibiotics (Some patients had more than one allergy so number)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Phase I</th>
<th>Phase II</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any allergy</td>
<td>51.16%</td>
<td>45.45%</td>
<td>0.66</td>
</tr>
<tr>
<td>Penicillin</td>
<td>18.60%</td>
<td>13.04%</td>
<td>0.61</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>16.28%</td>
<td>8.70%</td>
<td>0.43</td>
</tr>
<tr>
<td>Quinolones</td>
<td>6.98%</td>
<td>1.90%</td>
<td>0.7</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>4.65%</td>
<td>0.00%</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Effect of Pharmacists’ Interventions on the Appropriateness of Empiric Vancomycin Therapy in Oncology Patients with Febrile Neutropenia

N. Baghdady et al.

In phase II, interventions occurred on 18 patients (Fig. 3) of which 10 (56%) were accepted; 6 (33%) were successfully implemented within the 72-hour window. Interventions were not accepted on 8 patients: in 3 cases, an indication was present but not documented in the patient’s medical record at the point of intervention. Documentation occurred later on at which point it was considered an appropriate indication and excluded from our statistics. The team decided to continue therapy despite recommendation to discontinue in 5 patients. This leads to a total of 13 (7 spontaneously and 6 upon pharmacist’s recommendation) discontinuations within 72 hours in phase II (13/22; 59.1%) compared to 23 (23/43; 53.5%) in phase I with no statistical significance (p = 0.86).

The median vancomycin DOT was not significantly different between phases I and II (3 [IQR = 3.25] days vs. 3 [IQR = 2] days; p = 0.81). The median length of hospitalization was also similar between both groups (17 [30.5] vs. 8 [9] days; p = 0.08).

Table 2. Overall appropriate therapy

<table>
<thead>
<tr>
<th></th>
<th>Phase I (n = 65)</th>
<th>Phase II (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate</td>
<td>45 (69.3%)</td>
<td>45 (83.3%)</td>
</tr>
<tr>
<td>Non-appropriate</td>
<td>20 (30.7%)</td>
<td>9 (16.7%)</td>
</tr>
</tbody>
</table>

Of the total 119 FN patients receiving vancomycin therapy, use was appropriate in 45 (69.3%) of 65 patients during phase I and 45 (83.3%) of 54 patients during phase II (Table 2; p = 0.07).

**Discussion**

Although vancomycin is an effective antibiotic, its use in patients with FN should be reserved for those with appropriate indications to decrease the risk of adverse events and the risk of adverse events and resistance\(^\text{[1]}\). In our study, we did not see significant results between both phases; however, we observed a slight non-significant towards more appropriate use of vancomycin in accordance with our institutional guidelines in phase II. This appropriateness was demonstrated through initiation of vancomycin in patients with approved indications (22 in phase I vs. 29 in phase II; Figure 2) and discontinuation within 72 hours of absence of indications (23 [53.5%] in phase I vs. 13 [59.1%] in phase II). Pharmacists’ vigilance and active interventions might be a contributing factor to this improvement.

Our study has some limitations. First, this study is a pilot study that evaluated a small sample over a short period of time. The number of patients captured was lower than expected, which contributed heavily to the lack statistical significance. Second, phase I and phase II are separated by one year. The reason this was conducted was to prevent the introduction of potential confounding factors with the month
Effect of Pharmacists’ Interventions on the Appropriateness of Empiric Vancomycin Therapy in Oncology Patients with Febrile Neutropenia

N. Baghdady et al.

Although our study sample was not large enough to show a statistically significant difference in the benefit measured, there was an improvement in hospital admissions and lengths of stay[6,7]. This aligns with the growing body of evidence that demonstrates pharmacists are integral to antibiotic stewardship[10]. Current guidelines emphasize the need of pharmacists’ involvement in antimicrobial stewardship in all patient populations including those that are immunocompromised[10,11]. In this study, two main methods of antibiotic stewardship were exercised: development and implementation of facility specific treatment recommendations and prospective audit and feedback on specific antibiotics. Both methods are described as stewardship methods in patients in the Center of Disease Prevention and Control Core Elements of Hospital Antibiotic Stewardship Programs document[12].

Moving forward, a larger prospective trial is needed to evaluate the benefit gained from implementing a pharmacist-run stewardship program in this patient population. In such a study, cost-savings would be a useful parameter to evaluate. Overcoming obstacles will require raising awareness to this issue and intensive education of all members of the health care team (including physicians, nurses, and pharmacists). This teaching opportunity is also an area where pharmacists can play an active and effective role.

Conclusion

Prolonged vancomycin use in oncology patients with febrile neutropenia with no evidence of a gram-positive infection is unnecessary. Discontinuation after 72 hours is strongly encouraged. Clinical pharmacists are an integral component of effective antimicrobial stewardship programs.

Conflict of Interest

Nour Baghdady, Daniel Voit, Anne M. McDonnell, David W. Kubiak work at the Brigham and Women’s Hospital. No sponsorship or funding was received by any of the authors in relation to this paper. No editorial or medical writing assistance was received in preparing this manuscript. Authors have no other relevant conflicts of interest to disclose.

Disclosure and Ethical Approval

This observational study was approved by the PHRC, the Institutional Review Board of Partners HealthCare, for adherence to ethical, federal and institutional guidelines. As this was an observational study of pharmacists’ standard practice, a waiver of informed consent was approved by the PHRC.

References


Effect of Pharmacists’ Interventions on the Appropriateness of Empiric Vancomycin Therapy in Oncology Patients with Febrile Neutropenia 
N. Baghdady et al.


تأثير تدخلات الصيدلانية على ملاءمة العلاج التجريبي بالفانكومايسين في مرضى الأورام الذين يعانون من حمى نقص العدائم

نور بغدادي، و دانيال فويت، و وان ماكدونيل، و ديفيد كوبياك

جامعة الملك عبد العزيز، جدة - المملكة العربية السعودية
قسم الصيدلة، مستشفى بريجهام والنساء، بوسطن، ماساتشوستس - الولايات المتحدة الأمريكية

المستخلص: الهدف: الهدف من هذه الدراسة هو تقييم تأثير التدخل الصيدلاني الفعال للمساعدة في إيقاف العلاج المبديي بالفانكومايسين في الوقت المناسب لدى مرضى الأورام المصابين بالحمي، ونقص العدائم في حال عدم وجود دليل لعدوى بيكتريا إيجابية الجرام. الطريقة: كانت هذه الدراسة على مرحلتين. في المرحلة الأولى، تم تقييم استخدام الفانكومايسين بأخذ رجلي على جميع مرضى الأورام الذين يعانون من حمى نقص العدائم في حال عدم وجود دليل على الإصابة ببكتيريا إيجابية الجرام. في المرحلة الثانية، تم تقييم استخدام الفانكومايسين استشرافياً على مرضى الأورام الذين يعانون من حمى ونقص العدائم ومع عدم وجود دليل على الإصابة بالإصابة ببكتيريا إيجابية الجرام. النتائج: تم علاج جميع مرضى في المرحلة الأولى، و 25 مريضا في المرحلة الثانية، بفانكومايسين مع عدم وجود دليل لعدوى بيكتريا إيجابية الجرام. تم توثيق التدخلات على مدى 18 ساعة، حيث كانت نتائج التدخلات خلال 6 ساعات بين 3،33٪ و 63،33٪ من التدخلات. تم رصد دلالة إحصائية لوجود نقص في استخدام ملامح الفانكومايسين لدى مرضى الأورام الذين يعانون من حمى ونقص العدائم في المرحلة الثانية، وعليه فقد يكون تدخلات الصيدلاني دور في هذه الملاحظة.