

A Vancomycin Drug Use Evaluation and Economic Analysis in a Cancer Treatment Centre

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ABSTRACT

Princess Margaret Hospital is a 140-bed university affiliated cancer treatment centre. Vancomycin was the only formulary agent available for the treatment of methicillin-resistant gram-positive organisms. The high cost and potential toxicity of this drug warranted a closer examination of its use. The purpose of this study was to evaluate vancomycin use and to determine the economic impact when it was used contrary to newly developed hospital guidelines.

A sample of 100 vancomycin orders was randomly selected from all prescriptions filled in 1992. The indication, dose, and duration of therapy for each order were compared against the hospital guidelines. The cost savings associated with altering the sample of prescriptions to meet hospital guidelines were then determined.

Nine percent of the prescriptions were for non-approved indications. The actual dose used did not meet criteria in 32% of cases and the length of therapy was beyond the approved duration in 45% of the orders. If the cases had been altered to meet the guidelines then a total savings of \$13,581 would have been realized. The projected savings for the entire year (1992) would have been \$100,907.

The critical problem areas in vancomycin prescribing were the duration of therapy and dose. The results have provided the impetus to initiate a hospital wide prospective Drug Utilization Evaluation (DUE) study to optimize vancomycin prescribing. The program costs would be easily covered by the expected savings.

Key Words: *drug use evaluation, economic analysis, vancomycin*

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RÉSUMÉ

Le Princess Margaret Hospital est un centre de traitement anticancéreux universitaire de 140 lits. La vancomycine est le seul agent de lutte contre les organismes Gram positifs résistants à la méthicilline qui figure sur le formulaire. Le coût élevé et la toxicité éventuelle du médicament justifie un examen plus attentif de son utilisation. La présente étude vise à évaluer l'usage de la vancomycine et à déterminer les répercussions économiques en cas de prescription contraire aux lignes directrices de l'hôpital.

Parmi les ordonnances exécutées en 1992, on a choisi au hasard 100 prescriptions de vancomycine. Pour chacune, on a comparé l'indication, la dose et la durée du traitement aux lignes directrices de l'hôpital, puis déterminé qui aurait été réalisée si on avait modifié l'échantillon pour le rendre conforme à ces dernières.

Pour 9 % des prescriptions, l'indication n'est pas approuvée. Dans 32 % des cas, la dose administrée ne respecte pas les critères établis et, pour 45%, la durée du traitement dépasse celle approuvée. La correction des prescriptions non conformes aux lignes directrices aurait abouti à une économie de 13 581 \$. Par extrapolation, l'économie (pour 1992) serait de 100 907 \$.

La durée du traitement et la dose sont les éléments critiques de la prescription de la vancomycine. Ces résultats ont déclenché le lancement d'une revue prospective de l'utilisation de ce médicament (RUM) afin d'en optimiser la prescription. Les économies escomptées couvriront aisément les dépenses liées au programme.

Mots-clés: *analyse économique, revue de l'utilisation des médicaments, vancomycine.*

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INTRODUCTION

The Princess Margaret Hospital (PMH) is a 140-bed University of Toronto affiliated cancer treatment centre. A wide range of medical services are provided at PMH. These include chemotherapy for solid organ tumours, lymphoma and leukemia, radiation oncology, and bone marrow transplantation (BMT).

A common side effect of cancer chemotherapy is the development of neutropenia¹. Although the neutrophil count of many patients returns to normal without the development of infection, other patients develop fever associated with severe life-threatening infections. Neutropenia can also occur secondary to invasion of the bone marrow by the tumour and is particularly common after systemic chemotherapy or BMT for acute leukemias². Radiation therapy may also suppress the immune system, resulting in an increased risk of infection³.

The risk of infection rises dramatically after the neutrophil count drops below 1,000 cells per cubic millimetre of blood⁴. When the neutrophil count drops below 100 cells/mm³, severe life-threatening infections can occur^{4,5}. The risk of serious infection is also related to the duration of the patient's neutropenia. Leukemic patients undergoing BMT are more likely to experience febrile episodes than those undergoing chemotherapy for solid organ tumours because the former group can remain neutropenic for up to four weeks, while the latter group remains neutropenic for only a few days².

Empiric treatment of febrile neutropenia begins with broad spectrum antibiotic(s). If the patient remains febrile at 72 hours, vancomycin is usually added empirically¹. Vancomycin is also

the only commercially available drug for the treatment of documented infections due to methicillin-resistant, gram-positive organisms. In our hospital, 50-60% of gram-positive isolates are coagulase-negative Staphylococcus, and most are methicillin-resistant. This is common in patients receiving chemotherapy through a central venous access².

Although vancomycin played a critical role in the management of febrile neutropenia, its high cost and potential toxicity warranted a closer examination of its use. In 1992, PMH spent approximately \$200,000 on vancomycin which was approximately 3% of the total drug budget. In this study, we examined retrospectively the actual use of vancomycin against newly-developed hospital guidelines. In addition, the economic impact of not prescribing vancomycin in accordance with the guidelines was calculated.

METHODS

The study began with the development of guidelines for the use of vancomycin in our patient population. Hospital guidelines did not exist prior to the study. However, a three-day stop date policy for negative cultures was in place (see criteria # 4 in Appendix A) before the guidelines were prepared. A subcommittee of the Pharmacy and Therapeutics (P&T) Committee was formed to develop vancomycin guidelines. Subcommittee members consisted of two clinical pharmacists, the DUE pharmacist, an infectious diseases specialist, a medical and radiation oncologist, and a clinician from the bone marrow transplant unit.

After the guidelines were approved by the P&T and Medical Advisory Committees (Appendix A), 100 vancomycin orders were randomly selected from all orders

dispensed by the Department of Pharmacy in 1992. Patient charts were then retrieved from the Department of Medical Records.

Each order was evaluated using the approved guidelines for indication, dose, and duration of therapy by the DUE pharmacist in collaboration with the infectious diseases physician. The initial dosage was compared to a calculated dosage, estimated by the method of Matzke et al⁶ (Appendix B). When discrepancies were identified, the corresponding vancomycin level was examined and categorized as normal, high, or low. Dosage was considered inappropriate if the level was above or below the therapeutic range.

The results were expressed as the proportion of orders failing to meet the guidelines. The gathering of this information was facilitated by the development and use of a standardized data collection sheet (Appendix C). The guidelines became available to the Pharmacy and Medical Staff after the retrospective audit.

Cost Analysis: A cost analysis from a hospital perspective was then performed to determine the economic impact of non-approved vancomycin prescribing. The cost analysis included pharmacy time required for IV admixing, nursing time to administer the drug, cost of mini-bags used, and cost of supplies (i.e., needles, syringes, etc.) (Table I). For each non-approved dose of vancomycin, the total cost of that dose was determined using the above as well as the acquisition cost of the drug. In situations where a therapeutic alternative for vancomycin was indicated, the total cost of the appropriate alternative (e.g., ceftazolin/cloxacillin) was subtracted from the cost of vancomycin. If an initial vancomycin dose resulted in serum levels below the therapeutic index,

Table I: Cost Components

Item	Cost(\$)
Vancomycin acquisition cost	48.04/g
Preparation time ^a	2.25/dose
Administration time ^a	3.30/dose
Cost of mini-bags	1.55/dose
Cost of supplies (needles, syringes, etc)	0.73/dose
Cost of alternative antimicrobials:	
Cefazolin	2.08/g
Cloxacillin	0.88/g

^aObtained from nursing and pharmacy workload measurement statistics.

Table II: Disease Site Distribution for 100 Vancomycin Orders

Disease Site	Distribution (%)
Leukemia/BMT	64
Lymphoma	16
Myeloma	7
Breast	4
Gastrointestinal	2
Gynaecological	2
Ear-Nose-Throat	1
Genitourinary	1
Other	3

Table III. Vancomycin Use and Cost of Inappropriate Use

Criteria	Criteria Met (%)	Criteria Not Met (%)	Associated Costs (\$)
Indication	91	9	1,926.79
Dosage ^a	68	32	4,214.00
Duration	55	45	8,590.46
Overall^b	35	65	14,731.25

^aSerum vancomycin concentrations were either inappropriately high or low.

^bAll of the above three criteria must be met.

Table IV: Cost Analysis of Vancomycin Orders Not Meeting Criteria

Item	Vancomycin (\$)	Cefazolin/Cloxacillin (\$)
Acquisition cost	12,666.71	234.00
Preparation time	593.26	263.25
Administration time	870.11	386.10
Cost of mini-bags	408.69	181.35
Cost of supplies	192.48	85.41
Total Costs	14,731.25	1,150.11^a
Cost Avoidance (65 orders)^b		13,581.14
1992 Projected Cost Avoidance		100,907.87

^aCost of cefazolin/cloxacillin where indicated in seven vancomycin orders.

^bCost of inappropriate vancomycin prescribing corrected by cost of alternative therapy.

the cost of an additional drug was incorporated into the analysis.

Pharmacy preparation and nursing administration times were obtained from hospital workload measurement statistics. The costs

of mini-bags and supplies were obtained from the current Pharmacy Ordering Catalogues.

RESULTS

A total of 100 vancomycin orders

were examined from 96 patients with a mean age of 46 years and a 56:40 male:female distribution. The patient disease sites included leukemia/BMT, lymphoma, breast and other solid organ tumours (Table II). The majority of patients treated with vancomycin were from the leukemia/BMT and lymphoma group. This distribution of vancomycin use was consistent with our patient population.

At least one of the three outcome criteria (indication, dose, and duration) were not met in 65% of the orders examined (Table III). Overall, 9% of the orders did not meet hospital approved indications. More specifically, 7% of orders had blood cultures indicating sensitivity of cefazolin/cloxacillin (violates criteria #1), and 2% were for surgical prophylaxis (not an approved use).

An analysis of the duration of therapy revealed that 45% of the orders examined did not meet hospital guidelines (Table III). This was due to the failure to discontinue therapy at 72 hours (36%) when cultures were negative and in the absence of clinical signs of a central venous access infection and in some cases continuing therapy well beyond the approved 10-14 days (9%).

Of the 100 orders reviewed, the initial estimated dosage (Appendix B) was compared to the actual dosage and the vancomycin serum level. The audit of dosing and serum levels revealed that 22% of the orders had drug serum concentrations above and 10% below the desired therapeutic concentration.

Cost Analysis: The dose and duration guidelines were less often met than indication guidelines. The dose and duration problems accounted for a greater proportion (90%) of the overall avoidable ex-

penditure (Table III). The cost breakdown of vancomycin included both personnel and supply costs associated with all doses which were ordered outside of guidelines (Table IV). For the 100 vancomycin cases, \$13,581 would have been saved if 65 orders had been modified to meet hospital guidelines. If this cost saving were projected over the entire year (1992), it would translate to more than \$100,000 in expenditures that could have been avoided (Table IV).

DISCUSSION

In the face of decreased government funding for hospitals, DUE is becoming an increasingly important quality assurance process for controlling hospital costs and optimizing drug therapy. Einarson and colleagues⁷ recently conducted a comprehensive review of the Canadian DUE literature. In their analysis, they included several categories of drugs, including antibiotics. The investigators reported that the overall average rate of inappropriate drug prescribing was 42.7%. This was lower than the overall rate (65%) reported in this study. The difference may be related to the type of drugs evaluated and the nature of our hospital.

In this study, only 9% of the orders examined failed to meet the indication criteria. These results differ from those of Nightingale et al⁸, who reported that 42% of vancomycin prescriptions, when ordered empirically, were for inappropriate uses. Their results revealed that the required signs and symptoms for empiric therapy were not present in 49% of the cases examined. The lower percentage of problems involving indications for vancomycin in this cancer hospital may be a result of the limited number of possible indications where vancomycin can be used.

Due to the lack of published DUE studies in cancer hospitals, a comparison to similar hospitals was not possible.

The two major problem areas of vancomycin prescribing were duration of therapy and dosage. Generally, orders were not discontinued after negative cultures were reported. In one case, vancomycin therapy was continued for seven weeks. If these two problems alone were corrected, they would account for approximately 90% of the projected annualized savings of \$100,907. This amounts to almost one-half of the entire annual vancomycin budget. In addition, the dosage and duration problems may be less difficult to correct than indication related issues.

A limitation in retrospective DUE studies in general, is that patient outcomes are difficult to assess. This is especially true with cancer patients where outcomes are influenced by many variables. Another drawback of this study related to the frequency of ordering serum vancomycin concentrations (SVC). This was another cost component of vancomycin therapy. However, guidelines for ordering SVCs were not available which made it difficult to determine the number of unnecessary SVCs ordered. As a result, the cost of unnecessary SVCs was not included in the cost analysis.

This retrospective study revealed that inappropriateness in vancomycin prescribing was predominately related to dosage and duration of therapy. The methodology used in this report was successful for defining the drug-related problems more clearly. To tackle these issues, the first phase of our intervention included a dissemination of the results through a "Grand Rounds" presentation, a pharmacy newsletter, and a poster presentation at a professional conference.

This study was instrumental in securing the needed hospital-wide support for the second phase of intervention which included a prospective DUE program to improve the clinical and economic use of vancomycin. Overall, it is recommended that future DUE studies or programs employ a similar methodology to identify specific drug-related problems, thus assuring that pharmacist intervention is more focused and efficient. ☐

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Appendix A: Hospital Guidelines for Vancomycin Prescribing^a.

1. Treatment of bacteraemia with organisms not sensitive to other antibiotics (e.g. cloxacillin/cephalosporin-resistant staphylococci, ampicillin-resistant enterococci). Treatment is usually for 7-14 days.
2. Treatment of serious infections due to gram-positive bacteria in patients with documented allergies which precluded the use of penicillin/cephalosporins. Treatment is usually for 10-14 days.
3. Treatment of culture-negative, soft-tissue infections (excluding facial and perianal infections) in febrile neutropenic patients likely colonized with resistant, gram-positive organisms. Treatment is usually for 7-10 days or until lesions are completely healed or significantly improved and neutropenia has resolved.
4. Empiric treatment of febrile, severely neutropenic patients who have not responded to initial therapy or who become febrile while on other antibiotic therapy. Therapy should be discontinued at 72 hours if cultures are negative, and no clinically evident central venous access, soft-tissue infection is present.
5. Empiric treatment of serious central venous catheter line infections, until culture results are available.

^aThe initial dose was determined by the method of Matzke et al. (1984).

Appendix B: Method for Estimating Vancomycin Dose Adjustments

1. Initial dose = weight (kg) x 15 mg/kg
2. Estimation of creatinine clearance:
Clcr(mL/min) = (140-age) x total body weight (kg) / (50 x Scr(umol/L)) x 60 sec/min
3. Initial interval

Estimated Clcr (mL/min)	Dose Interval ^a
>80	Q12H
50 - 80	Q24H
30 - 50	Q36H
<30 mL/min	give initial dose, check serum concentrations at 24 hours

^aTarget concentrations for vancomycin at PMH are: peak 30-40 ug/mL, trough 5-12 ug/mL

4. **Estimation of half-life ($T_{1/2}$)**
 $K = \ln(\text{observed peak} - \text{observed trough}) / (\text{time between samples})$
 $T_{1/2} = 0.693/k$
5. **Estimation of distribution volume (V_d)**
 $V_d = (\text{observed peak} - \text{observed trough}) / \text{dose}$
 Corrected for fast excretors if half-life is less than 4 hrs as follows:
 Actual peak = observed peak / (e^{-kt_1}) where t_1 = time peak sampled after dose.
 Trough remains the same.
6. **Calculation of dose**
 Dose = (desired peak - desired trough) x V_d
7. **Calculation of interval**
 Interval = approximately (2-3 x $T_{1/2}$), in order to achieve a peak to trough ratio of approximately 4:1

Appendix C: Data Collection Sheets for Vancomycin

Date: _____ Name: _____ Age (yrs): _____ Weight (kg): _____

Scr (mmol/L): _____ T#: _____ Nursing Unit: _____ Name of Doctor: _____

Approved Vancomycin Therapy in Clinical Gram Positive Infections**Y****N****A) Indications and Duration:** Please check (Y/N) where indicated

- 1) Treatment of bacteremia with organisms not sensitive to other antibiotics (e.g., staphylococci resistant to cloxacillin/cephalosporins, ampicillin resistant Enterococci, corynebacterium JK).

Treatment was for 14 days or less.

2. Treatment of serious infections due to gram positive bacteria in patients with **documented allergies** precluding the use of penicillins/cephalosporins.

Treatment was for 14 days or less.

- 3) Treatment of culture negative soft tissue infections (excluding facial and perianal infections) in febrile neutropenic patients likely to be colonized with resistant gram positive organisms.

Treatment is 10 days or less or until lesions are completely healed or significantly improved and neutropenia has resolved.

- 4) Empiric treatment of febrile, severely neutropenic patients not responding to initial therapy or who become febrile while on other antibiotic therapy.

Was a culture taken?

The drug was reordered because cultures indicated the presence of bacteria sensitive only to vancomycin.

The drug was reordered, even though cultures were negative, because there was clinical evidence of a CVA soft tissue infection.

Treatment was reordered for 10 days or less.

Therapy was discontinued at 72 hours because cultures were negative and there was no clinical evidence of a CVA soft tissue infection.

5. Empiric treatment of serious central venous catheter line infection, until culture results are available.

Was a culture taken?

The drug was reordered because cultures indicated the presence of bacteria sensitive only to vancomycin.

The cultures were negative but there was clinical evidence of a central venous line infection.

Treatment was reordered for 10 days or less.

B) Dosage

The maintenance dose was 1 g q12h.

The dosage interval was reduced because of decreased renal function.

C) Drug Monitoring

Vancomycin levels were ordered for this patient.

D) Clinically Incorrect (please describe):