



Randomized prospective study comparing cost-effectiveness of teicoplanin and vancomycin as second-line empiric therapy for infection in neutropenic patients

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ABSTRACT

Background and Objective. The current health-care philosophy dictates that new therapies should always be evaluated for their economic impact. Along with acquisition cost, the cost of delivery, monitoring, adverse effects and treatment failure must also be considered when determining the total cost of therapy. These auxiliary costs can be significant and greatly alter the overall cost of a drug treatment. We conducted a prospective randomized study to evaluate the efficacy, safety and cost of vancomycin and teicoplanin therapy in patients with neutropenia, after the failure of empirical treatment with a combination of piperacillin/tazobactam and amikacin.

Design and Methods. Seventy-six febrile episodes from 66 patients with hematologic malignancies under treatment, neutropenia (neutrophils $<500/\text{mm}^3$) and fever (38°C twice or 38.5°C once) resistant to the combination piperacillin/tazobactam and amikacin were included in the study.

Results. Primary success of second-line therapy was obtained in 35 cases (46%) with no significant difference between vancomycin (17/38) and teicoplanin arms (18/38). No difference in renal or hepatic toxicity related to the antibiotic therapy was observed. The average cost per patient according to glycopeptide used was $\$450\pm 180$ for the teicoplanin group and $\$473\pm 347$ for the vancomycin group. Interestingly, in the teicoplanin arm, drug acquisition accounted for 97% of the total cost, while in the vancomycin arm administration and monitoring play an important role in overall costs.

Interpretation and Conclusions. In conclusion, our pharmaco-economic analysis demonstrates that teicoplanin and vancomycin can be administered in neutropenic hematologic patients with similar efficacy and direct costs.

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Key words: vancomycin, teicoplanin, febrile neutropenia, cost-effectiveness

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The introduction of new drugs usually results in improved efficacy of the therapeutic regimens for infectious diseases but also in an increase in the costs of health care. Antimicrobial agents make up a large proportion of hospital drug expenditure in Europe and USA (15% to 40% of the total pharmacy drug acquisition budget).¹⁻³ Although it is difficult to determine the costs that nosocomial infections incur, several studies reveal their significance within different sanitary systems.¹⁻⁴ Thus, during the last decade in the USA, the annual cost of nosocomial infections was estimated to be greater than \$10 billion.¹ Economic studies carried out in France showed that the costs related to nosocomial infections were 3.2 times higher than the average cost of community-acquired infections, and those that were caused by resistant staphylococci were the most expensive to treat.² Bacteremia caused by methicillin-resistant staphylococci incurred an average cost 7.4 times higher than that of methicillin-sensitive staphylococci.^{3,4}

Reducing costs associated with antibacterial agents may help to control hospital expenditure.¹ The introduction of teicoplanin, a glycopeptide with a similar spectrum of activity to vancomycin,^{5,6} effective against both methicillin-resistant staphylococci and mainly enterococci has promoted many comparative trials related to efficacy, safety and cost.⁷ Although, vancomycin is a highly effective and widely used drug it has some inconveniences such as the side effects and need to monitoring serum concentrations during treatment.⁸⁻¹⁰ We have recently reported on the cost-effectiveness of monitoring serum vancomycin concentration in patients with hematologic malignancies.^{11,12} Teicoplanin has a longer half-life than vancomycin, can be given not only as an intravenous bolus but also by intramuscular injection, and nephrotoxicity and ototoxicity are relatively uncommon.¹³

The cost of one drug alone does not provide a complete picture, and it is often outweighed by the costs associated with laboratory monitoring, treatment of adverse effects, and administration.¹⁴ A model for evaluating costs and effectiveness is required to allow useful comparisons between stan-

dard and new antibiotics.^{7,15}

Several randomized studies have compared the efficacy and safety of vancomycin and teicoplanin^{6,15,16} and the impact of glycopeptide therapy after hospital discharge on treatment costs.¹⁴ However, to the best of our knowledge no appropriate study has been conducted using a comprehensive, pharmacoeconomic evaluation to compare all costs derived from teicoplanin versus vancomycin treatments in neutropenic in-patients using the glycopeptide as second-line therapy. We conducted a prospective, randomized study to evaluate the efficacy, safety and cost of vancomycin and teicoplanin therapy in patients with neutropenia, after the failure of empirical treatment with a combination of piperacillin/tazobactam and amikacin.

Design and Methods

Eligibility

All patients included in the study were older than 18 years, had hematologic malignancies under treatment, neutropenia (neutrophils <500/mm³) and fever (38°C twice or 38.5°C once) resistant to the combination of piperacillin/tazobactam and amikacin. Patients were excluded before randomization if they were allergic to glycopeptides or if their serum creatinine level was >1.5 mg/mL.

Patient characteristics and randomization

Seventy-six febrile episodes from 66 patients were randomized to be treated with either teicoplanin or vancomycin. Randomization was carried out using sequential sealed envelopes. The characteristics of these patients are summarized in Table 1. There were no significant differences between groups in terms of age, type of intestinal decontamination or duration of marrow aplasia. The distribution of the hematologic malignancies was as follows: 20 acute leukemias, 17 non-Hodgkin's lymphomas and Hodgkin's disease, 33 bone marrow transplants, and 6 multiple myelomas (Table 1).

Protocol

All the patients were hospitalized in single rooms with reverse phase isolation. They received sterile food and selective intestinal decontamination (ofloxacin). All patients had an indwelling central venous catheter. When neutropenic patients became febrile, clinical examination and a chest X-ray were performed and bacteriological samples were taken. The first-line parenteral antibiotics used in all the 76 episodes were: piperacillin/tazobactam 4 g every 6 h intravenously plus amikacin 20 mg/kg/day intravenously. In the absence of clinical resolution after 72 h (primary failure) or when a second case of fever occurred after some time (secondary failure), the still neutropenic patients received associated vancomycin (scheduled by a nomogram)¹¹ intravenous infusions over 2 h or teicoplanin 400 mg twice a day on three infusions, and then 400 mg once a day (infused over 30 min).

Vancomycin doses were prepared, using standard minibags, in 100 mL of glucose 5% or normal saline and the diluted solution infused over 120 minutes. Teicoplanin doses were prepared in a syringe and administered by intravenous bolus injection.

Microbiological study

At the time of admission to hospital, once a week during the marrow aplasia, and also at the onset of each episode of fever, bacteriological samples were taken from the following sites: oropharynx, stools, urine, blood, and any relevant lesions or site (e.g. central catheter access, cutaneous lesion, sputum, bronchoalveolar lavage, lumbar puncture).

Evaluation criteria

Clinical efficacy was evaluated according to whether or not apyrexia was obtained (success/failure) after 48h (primary success or failure), after 7 days (secondary success or failure) or at the conclusion of aplasia (definitive success or failure).^{17,18}

Classification of infection

Infections were classified into four categories:

- *microbiologically documented infection with bacteremia*: febrile episode accompanied by clinical signs and symptoms of infection plus microbiological confirmation from blood cultures;
- *microbiologically documented infection without bacteremia*: febrile episode accompanied by clinical signs and symptoms of infection plus microbiological confirmation from the original site of infection;
- *clinically documented infection*: febrile episode accompanied by definite clinical signs and symptoms of infection but without specific microbiological proof. The sites of origin of infection included: *mucositis or gingivitis*, defined by the presence of periapical erythema and induration along the gums; *throat infection*, defined by erythema and ulceration of the oropharynx and the tonsils; *cel-*

Table 1. Patients' characteristics.

	Teicoplanin		Vancomycin	
	n=38	%	n=38	%
Men/women	15/23	39/61	21/17	55/44
Mean age (years)	51		47	
Underlying disease				
AML	10	26	10	26
HD/NHL	10	26	7	18
BMT	15	39	18	47
MM	3	6	3	8

AML: acute myeloblastic leukemia; HD/NHL: Hodgkin's diseases/non Hodgkin's lymphomas; BMT: bone marrow transplantation; MM: multiple myeloma.

lulitis, diagnosed by the existence of erythema, induration and pain with or without a positive puncture or biopsy; *chest infection*, defined by changes on auscultation and a modification of the chest X-ray or respiratory symptoms which could not be attributed to another cause, with or without microbiological confirmation; *diarrhea*, defined by abnormally frequent and liquid stools. Septic shock was defined by deterioration of the clinical condition with cardiovascular collapse even if blood cultures were negative;

- *fever was considered to be of unknown origin* if the clinical and microbiological evaluation did not reveal a pathogen site or agent within 72 h following the onset of fever and the start of parenteral therapy.^{16,19,20}

Cost analysis

In the cost analysis we considered the following partial costs: drug price, preparation and administration costs, monitoring costs, treatment of adverse events and treatment failure.^{7,12}

Drug acquisition cost: the costs of drug acquisition were based on the official prices in Spain in 1996, without consideration of the discounts sometimes offered by pharmaceutical manufacturers.

Preparation and administration cost: all patients were followed during the preparation and administration of each dose of vancomycin and teicoplanin to determine the costs associated with the drug. All materials used in preparing a dose and administering it and the nursing time required were recorded. Personnel costs were calculated by multiplying the average wage per minute by the number of minutes spent for each dose.

Monitoring cost: although costs of laboratory-monitoring of parameters, such as serum creatinine and white blood cell count, are also an important part of the cost of drug therapy, we did not include them, as we could not be sure that these were not measured for other reasons. However, the cost of monitoring vancomycin serum concentrations is an important expense that should be included in determining the cost of treatment. This cost was determined from the cost of serum vancomycin assays (drug assay kits, calibration, quality control, and other medical supplies) and the derived costs of time spent by nurses and clinical pharmacists performing these monitoring activities.^{11,12}

Cost of treatment of adverse effects: we have only considered those adverse effects that cause relevant economic expenses.

Cost of treatment failure: in order to evaluate the costs produced by therapeutic failure, the method for global cost calculation (acquisition, administration, preparation, and monitoring costs) and the cost of total antibiotic therapy was applied from the beginning of treatment with glycopeptide.

Statistical analysis

A descriptive statistical analysis was performed after testing for a normal distribution using the SPSS

software (SPSS Inc., Chicago, IL, USA). Logistic regression was performed for the total cost outcome and the following independent variables: age, diagnosis, hospitalization days, parenteral nutrition and hematopoietic growth factors. Statistical significance was defined as $p < 0.05$.

Results

Efficacy and safety

The types of infections and offending pathogens were similar in the teicoplanin and vancomycin arms. Of the 76 febrile episodes included in the study, 25 (10 vancomycin/15 teicoplanin) were microbiologically documented (12 Gram-positive cocci, 8 Gram negative bacilli, 4 mycosis and 1 Herpes virus) including 18 septicemias (6 vancomycin/12 teicoplanin). The septicemia were caused by *Staphylococcus aureus* (1), *S. coagulase-negative* (8), *Streptococcus viridans* (1), *P. aeruginosa* (1), *Escherichia coli* (3), *Candida albicans* (3) and *M. morgani* (1) (Table 2). Two out of the 8 infections due to Gram-negative bacilli, were primary failures of piperacillin/tazobactam plus amikacin.

Primary success of second-line therapy was obtained in 35 cases (46.1%) with no significant difference between the vancomycin (17/38) and teicoplanin arms (18/38) ($p = n.s.$). In all primary successes resolution of fever was maintained until the end of marrow aplasia. The details of the 41 primary failures, 20 in the teicoplanin arm and 21 in the vancomycin arm are shown in Figure 1 and Table 3. Within the group treated with vancomycin, failures with infections microbiologically documented (6 cases) were due to septicemia (4 patients), caused by *Streptococcus viridans* (1), *Escherichia coli* (1) or *Candida albicans* (2), to an oral *Herpes virus* infection (one patient) and to urinary infection caused by *Escherichia coli* (one patient). In the group treated with teicoplanin, there were 12 failures with microbiologically documented infections, in eight patients due to septicemia caused by *S. epidermidis* (1), *Staphylococcus aureus* (1), *S. xylosus* (1), *Escherichia coli* (2),

Table 2. Clinical and microbial documentation of febrile neutropenic episodes.

	Teicoplanin	Vancomycin
Microbiologically documented		
With septicemia*	12 (31%)	6 (15.8%)
Without septicemia	3 (7.9%)	4 (10.5%)
Clinically documented	22 (57.9%)	22 (57.9%)
Possible Infection	1 (2.6%)	1 (2.6%)
Unrelated infection (FUO)	0 (0%)	5 (13.2%)

**S. coagulase negative* (8), *S. aureus* (1), *S. viridans* (1), *E. coli* (3), *P. aeruginosa* (1), *M. morgani* (1), *C. albicans* (3).

Table 3. Failures: microbiologically isolated.

	Teicoplanin	Vancomycin
Microbiologically documented		
with septicemia	8	4
without septicemia	4	2
Clinically documented	7	9
Possible infection	1	1
Unrelated infections	0	5

Table 4. Toxicity.

	Teicoplanin	Vancomycin	p
Red man syndrome	0 (0%)	4 (10%)	0.04
Renal toxicity	1 (3%)	1 (3%)	n.s.
Hepatotoxicity	3 (8%)	7 (18%)	n.s.
Diarrhea	4 (10%)	5 (13%)	n.s.
Phlebitis	1 (3%)	1 (3%)	n.s.
Ototoxicity	0 (0%)	0 (0%)	n.s.
Other	1 (3%)	1 (3%)	n.s.

Candida albicans (1), *Pseudomonas aeruginosa* (1), Herpes virus (1), in two patients due to cutaneous infections by *S. simulans* (1) and *S. xylosum* (1), in one patient due to urinary infection caused by *Pseudomonas aeruginosa* and in another patient due to an oral infection by *Candida albicans*. The incidence of failures due to clinically documented infections was similar in the teico-

planin and vancomycin arms (7 and 9 respectively). Seven patients (5 teicoplanin/2 vancomycin) died of septicemia: two due to fungal infections (*Candida albicans*) – one in the vancomycin arm and the other in the teicoplanin arm – and one patient in the vancomycin arm, due to pseudomonas infections; the fatal infections in the remaining four patients were not documented microbiologically. All severe oral infections due to a coagulase-negative staphylococcus that were susceptible to vancomycin/teicoplanin *in vitro* were resistant to amikacin. No differences in renal or hepatic toxicity related to the antibiotic therapy was observed but the incidence of red man syndrome was significantly higher ($p < 0.05$) in the group treated with vancomycin (11%) than in that treated with teicoplanin (0%) (Table 4).

Cost analysis

The total cost of purchasing, preparing and administering a dose of vancomycin ranged between \$12.67 and \$22.15, depending on the dose used (500 mg or 1000 mg), while the total cost for a dose of 400 mg of teicoplanin came to \$49.33 (Table 5).

The total cost of vancomycin monitoring (only through plasma) was \$22, and includes personnel, assay material, and equipment depreciation. Vancomycin serum concentrations were monitored in 26 patients (68%). Adjustments to the dose of vancomycin were made in 4 patients, three patients needed two determinations and in one case it was necessary to perform three assays. The total cost of monitoring vancomycin levels in these 26 patients was \$682.

The average cost per patient according to the glycopeptide used was \$450±180 for the teicoplanin group and \$473±347 for the vancomycin group (Figure 2). These figures refer to the cost of acquisition, administration and monitoring. The 38 patients treated with vancomycin received 1,165 doses, with a direct drug related cost of \$17,959, including \$13,483 for acquisition, \$3,794 for preparation and administration and \$682 for monitoring serum concentrations. The total cost of treating 38 patients with teicoplanin (341 doses), was similar (\$17,073) although drug acquisition accounted for 97 % of the total cost. Accordingly the total costs were not significantly different, although marginally lower in the teicoplanin group (Figure 2). Moreover, although no significant differences were found in the cost of additional antibiotics from the start of glycopeptide therapy, these were lower for the teicoplanin group (\$2,112±1,427) than for the vancomycin group (\$2,891±2,708).

Sensitivity analysis. Because of effect of frequency of administration in the cost, we performed a sensitivity analysis modifying the intervals of 6 and 8 hours to 12 hours. The average cost per patient for vancomycin decreased by 10% – 423±311 – but no significant differences were found with patients treated with teicoplanin.

Teicoplanin (n=20)		Vancomycin (n=21)																
Microbiologically documented with septicemia	8	<table border="1"> <tr><td>3</td><td>Gram(+)</td><td>1</td></tr> <tr><td>3</td><td>Gram(-)</td><td>1</td></tr> <tr><td>1</td><td>Virus</td><td>0</td></tr> <tr><td>1</td><td>Fungal</td><td>2</td></tr> </table>	3	Gram(+)	1	3	Gram(-)	1	1	Virus	0	1	Fungal	2	4			
3	Gram(+)	1																
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1	Fungal	2																
Microbiologically documented without septicemia	4	<table border="1"> <tr><td>2</td><td>Gram(+)</td><td>0</td></tr> <tr><td>1</td><td>Gram(-)</td><td>1</td></tr> <tr><td>0</td><td>Virus</td><td>1</td></tr> <tr><td>1</td><td>Fungal</td><td>0</td></tr> </table>	2	Gram(+)	0	1	Gram(-)	1	0	Virus	1	1	Fungal	0	2			
2	Gram(+)	0																
1	Gram(-)	1																
0	Virus	1																
1	Fungal	0																
Clinically documented	7	<table border="1"> <tr><td>4</td><td>Lung</td><td>2</td></tr> <tr><td>1</td><td>Catheter</td><td>1</td></tr> <tr><td>2</td><td>Skin</td><td>1</td></tr> <tr><td>0</td><td>Mucositis</td><td>4</td></tr> <tr><td>0</td><td>Urinary</td><td>1</td></tr> </table>	4	Lung	2	1	Catheter	1	2	Skin	1	0	Mucositis	4	0	Urinary	1	9
4	Lung	2																
1	Catheter	1																
2	Skin	1																
0	Mucositis	4																
0	Urinary	1																
Possible infection	1		1															
Unrelated Infection (FUO)	0		5															

Figure 1. Flow chart of the failures in the two study arms.

Table 5. Summary of the costs associated with preparing and administering a dose of vancomycin or teicoplanin.

	Cost (\$) Vancomycin				Cost (\$) Teicoplanin
	500 mg	600 mg	750 mg	1000 mg	400 mg
<i>Materials</i>					
Drug	8.12	10.10	13.60	17.60	47.60
Minibag	0.93	0.93	0.93	0.93	-
Syringe, needle, Intravenous set	0.52	0.52	0.52	0.52	0.10
<i>Nursing labor</i>	3.10	3.32	3.32	3.10	1.63
Total cost/dose	12.67	14.87	18.37	22.15	49.33

Discussion

The current health-care philosophy dictates that new therapies should always be evaluated for their economic impact. Along with acquisition cost, the cost of delivery, monitoring, adverse effects and treatment failure must also be considered when determining the total cost of therapy. These auxiliary costs can be significant and greatly alter the overall cost of a drug treatment.

Our study did not find differences between teicoplanin and vancomycin in total treatment costs, despite marked differences in acquisition cost per dose in favor of vancomycin. However, as shown in Figure 2, the costs derived from administering vancomycin and monitoring its serum levels finally led to teicoplanin treatment having a similar or even lower cost. One cost-minimization analysis from the Netherlands showed a slight cost advantage for vancomycin compared with teicoplanin therapy. In that study vancomycin was administered every 12 hours.¹ A French study which compared two empirical antibacterial regimens in 88 children with febrile neutropenia demonstrated that combination therapy with teicoplanin and ceftriaxone was less costly than treatment

with vancomycin and ceftazidime. The vancomycin plus ceftazidime regimen was administered every 8 hours and teicoplanin and ceftriaxone were administered once daily.²¹ In our study, the initial vancomycin dosage and interval was selected according to a previously obtained nomogram specifically designed for this patient population.¹¹ The most common dosages were 600 mg and 750 mg intravenously every 8 hours (14 and 11 times, respectively) although intervals ranging between 6 and 24 hours were also used. Route and frequency of administration have a substantial effect on delivery costs of a drug. Intravenous bolus or push injections cost considerably less to deliver than intravenous infusions and daily delivery costs increase with increasing frequency of administration. The cost saving related to decreased frequency of antibiotics administration were clearly demonstrated by Foran *et al.*,²² to be due mainly to additional labor and materials required to prepare and administer extra doses of an antibacterial agent. However, as we have previously shown, with some antibiotics, and particularly with vancomycin, it is important to take into account the pharmacokinetics of the drug and dosage regimens to define the best patient-specific regimen, instead of using a standard dosage for all individuals.

The occurrence of vancomycin-associated nephrotoxicity is a relatively infrequent side-effect, occurring in approximately 5-10% of patients on monotherapy²³ and over 20% in-patients receiving vancomycin with an aminoglycoside.²⁴ In our study only one patient (3%) developed nephrotoxicity; this low incidence is probably due to the use of the nomogram based dosage¹¹ and to the careful monitoring of vancomycin serum concentrations. In a prospective randomized study in immunocompromised febrile patients we demonstrated that individualized prescription of vancomycin, basing the initial dosage on a nomogram and the subsequent doses on results of the monitoring of the serum concentrations, was associated with a decreased incidence of nephrotoxicity.¹² Signs and symptoms suggestive of severe red man syndrome occurred in only one patient, but this syndrome can occur due to increasing infusion duration or administration of smaller and more frequent doses of vancomycin.

In conclusion, our pharmacoeconomic analysis demonstrates that teicoplanin and vancomycin can be administered in neutropenic hematologic patients with similar efficacy and direct costs. With increasing pressure on health systems to control costs, using home therapy and its associated cost savings, teicoplanin may be an attractive agent because of its once daily administration, bolus intravenous injection and the possibility of intramuscular injection. The possible benefits to quality of life associated with teicoplanin use should be investigated.

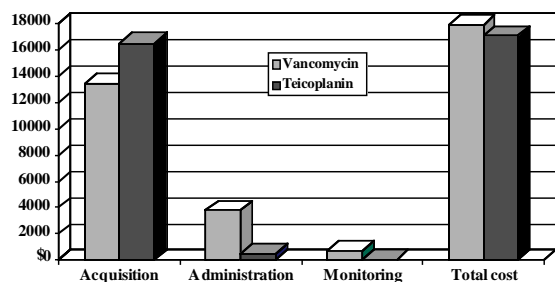


Figure 2. Distribution of the total costs associated with vancomycin or teicoplanin in the patients of the study.

Contributions and Acknowledgments

LV was the main investigator and designed the study, reviewed clinical data and performed the literature revision; she wrote the article with RG-S, and both were responsible for the data interpretation, direct supervision, funding and day-to-day contact with participants. PV, NG and DC were responsible for the inclusion of patients, clinical management and direct clinical data acquisition. MP-E, LSM and AD-GH carried out the vancomycin monitorization and evaluation of the protocol costs. JFSM was the main coordinator of the group and reviewed the article to obtain the final form in which it was sent for submission.

The order tries to take into account the time work and scientific contribution of all authors.

The authors thank Mark Anderson for his technical assistance.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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