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Cost-minimization analysis of oral and intravenous administration of linezolid in a public hospital in southern Brazil

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ABSTRACT

Due to the paucity of cost-minimization studies about linezolid, the aim of this study was to estimate the cost differential between intravenous and oral administration. A retrospective cohort study and cost-minimization analysis was conducted between August 2009 and August 2013 in a public hospital in southern Brazil. Inpatient records were evaluated for 152 patients who received linezolid intravenously or orally. Over two-thirds of the patients (103, 67.8%) received the antibiotic by the intravenous route only (IV group), and the remainder received the antibiotic both routes sequentially (mixed group). In the IV group, 33 patients (31.7%) were eligible to receive the antibiotic orally. The total cost per patient (mean) after changing from intravenous to oral administration was significantly lower than the real cost paid per patient (mean) ($p<0.001$). The cost savings associated with switching to oral linezolid administration would be US$14,328.32 over four years. Pharmacoeconomic analyses of linezolid therapy can inform hospitals' decisions about the rational use of therapeutics and economic resources.
Keywords: Administration, Oral. Economics, Pharmaceutical. Administration, Intravenous. Linezolid.

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INTRODUCTION

Linezolid was the first antibiotic of the oxazolidinone class to be approved for clinical use (Butler et al., 2013). It stops the growth of bacteria by disrupting their production of protein by a unique mechanism of action, thus reducing the likelihood of cross resistance (Pigrau, 2003; Butler et al., 2013). Linezolid was introduced to contain the emergence of the multidrug resistant gram-positive bacteria that were know at the time of its discovery, mainly *Staphylococcus aureus* and *Enterococcus faecium* (Pigrau, 2003). It was approved for human use in 2000 for the treatment of adults with hospital- and community-acquired pneumonia, complicated and uncomplicated skin and soft-tissue infections, caused by Gram-positive microorganisms, including infections due to methicillin-rersistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecium* (VRE) (Food, 2000; Plouffe, 2000; Eckmann, Dryden, 2010; Guillard et al., 2014).

Linezolid should be used strictly to infections caused by multi-resistant gram-positive microorganisms (Pérez-Cebrian et al. 2015). For MRSA infections, the gold-standard therapy continues to be based on vancomycin, thus linezolid is recommended as an alternative to vancomycin to treat MRSA in nosocomial pneumonia especially in patient with renal failure, because no dose adjustment is needed when there is moderate renal derangement, for whom vancomycin (which obeys a concentration-dependent kinetics and whose dosage should be based on creatinine clearance) is frequently underdosed (Dryden, 2011; Pérez-Cebrian et al., 2015).

Linezolid has almost 100% bioavailability, and food does not affect its absorption. These special characteristics allow for changing between the intravenous (IV) and oral (PO) administration routes without impacting the effectiveness of the medication (Dryden, 2011).

The use of linezolid in the treatment of infections caused by gram-positive bacteria has been evaluated in many pharmacoeconomic analyses in the USA and elsewhere. These studies have been divided into two categories: A)

assessment of the health care resource use and/or total costs associated with linezolid and other antibiotics and B) cost-effectiveness analyses (Plosker & Figgit, 2005). However, none of these studies directly compared the costs of IV linezolid with the costs of PO linezolid.

Therefore, this study aimed to conduct a cost-minimization analysis in a public hospital setting among inpatients who met the criteria for switch therapy – exchanging PO or nasogastric tube (NG) administration for IV administration – and to measure the financial resources that could be saved with this hypothetical exchange. A retrospective cohort study design was used to identify the social and clinical characteristics of the inpatients in the sample.

MATERIALS AND METHODS

The study was conducted in a 195-bed public hospital in southern Brazil that provides a wide range of health care services (Hospital, 2013). The sample comprised inpatients age 12 and above who were hospitalized between August 1, 2009 and August 31, 2013 and who received linezolid for at least 72 hours during their hospital admission. After the selection of subjects, we extracted the relevant demographic and clinical data from the patient records. The dates were divided in social, clinical and relating to the linezolid use. Only the data from the first administration of linezolid during a single hospitalization was used. The study duration was four years, and findings related to cost and resource use are reported from the hospital's perspective.

RETROSPECTIVE COHORT STUDY

The study population was divided into two groups: patients who received only IV linezolid (IV group) and patients who received linezolid by more than one administration route, as they initiated the therapy by one route but finished with another (PO, NG or IV). The groups were compared using statistical measures of central tendency.

COST ANALYSIS

The direct medical costs of linezolid use were analyzed. The identified costs of administration included the cost of the drug in its two pharmaceutical forms (tablet and intravenous solution) and the cost of the necessary medical materials.

The indirect and intangible costs were not discussed. The resources that were used in a similar way between the two pharmaceutical forms of the drug were not considered because they did not represent an additional cost for either product. For this reason, exams and other hospitalization expenses were not considered. Similarly, human resource costs were not considered because hospital staff received a fixed salary.

COST-MINIMIZATION ANALYSIS

Cost-minimization analyses are appropriate when the therapeutic alternatives in question have equivalent efficacy levels and differ only in cost (Drummond et al., 1997). Linezolid meets these criteria; therefore, this study evaluated changing the administration route from IV to PO or NG according to criteria adapted from Conly et al. (2003) and also measured the financial impact of this change. The following criteria were used to identify patients eligible for the change from intravenous therapy to oral therapy or by nasogastric tube (all criteria must be met): a) Patient is tolerating oral or nasogastric (NG) nutrition or receiving medications by mouth or NG tube; b) Patient has a functioning gastrointestinal tract; c) Signs and symptoms related to the infection have resolved or are improving, d) Patient does not fall within the exclusion parameters. However, the following exclusion criteria for the switch therapy were used: e) Patient has an infection in which continuation of intravenous therapy is indicated, such as infections related to line sepsis with *Staphylococcus aureus* bacteremia; f) Patient is neutropenic (absolute neutrophil count < 500/mm3) and febrile (temperature > 38°C); g) Response to oral medication may be unreliable, for example, in the presence of continuous NG suction, malabsorption syndrome, ileus, protracted vomiting or severe diarrhea (Conly et al., 2003).

To standardize whether subjects could receive linezolid orally or via an NG tube after the hypothetical switch, we determined that those patients who were receiving food or drugs through the NG tube during linezolid treatment would switch from IV to NG. However, if they met the criteria for the switch therapy but were not using an NG tube during linezolid treatment, they would switch from IV to PO.

To calculate the real cost (RC) per patient for linezolid treatment during hospitalization, the daily costs related to the administration route used by the subjects were multiplied by the number of the days that the subjects received linezolid. The same calculations were used to determine the costs after the hypothetical switch therapy (adjusted costs - AC). During the first three days of treatment in subjects who were eligible to receive the switch therapy, linezolid would be administered by IV, and the remaining treatment would be delivered via the PO or NG route. This decision was based on a previous study (Lelekis, Gould, 2001).

The amount of resources that could be saved with the switch therapy was determined by calculating the difference between the RC and the AC. For those subjects who did not meet the criteria for the switch therapy, there was no difference between the RC and the AC.

STATISTICAL ANALYSIS

The quantitative variables were characterized by mean and standard deviation, while the absolute and relative frequencies were calculated for the qualitative variables. The quantitative variables without normal distributions were compared using the Wilcoxon test (Mann-Whitney), and Student's t-test was used for variables with normal

distributions. The proportions test was used for proportions. A 5% level of statistical significance was established, and decisions about the hypothesis were based on the p-value. The statistical software R Core Team was used (R Core, 2014).

SENSITIVITY TEST

Sensitivity analyses were conducted to verify that the results obtained were robust. For this purpose, we applied the sensitivity analysis of extremes. This technique tests the best and worst scenarios from the technology in the analysis. Therefore, we added and subtracted 10% to the amounts paid by the hospital to purchase the items that contributed to the direct medical costs of linezolid treatment, and we used the Wilcoxon test to determine whether there was a statistically significant difference between the expenses before and after the hypothetical change of linezolid administration route.

EXCLUSION CRITERIA

The following exclusion criteria were used: linezolid treatment for less than 72 hours, age less than 12 years old because dose adjustments are necessary for younger patients, and incomplete or illegible patient records.

ETHICAL ASPECTS

This study was approved by the Ethics Committee on Human Research at the Universidade Estadual do Oeste do Paraná – Brazil under document number 126/2013.

RESULTS

Linezolid was administered in 152 inpatients from August 01, 2009 to August 31, 2013. Of these 152 patients, 103 (67.8%) were in the IV group, and the remainder were in the mixed group. The daily direct medical costs of drugs and materials, both per patient and total, and the characteristics of each group are shown in table 1 and in table 2, respectively.

The groups showed similar characteristics with significant differences only in the length of stay and the reason for discharge. The inpatients in the mixed group had a shorter length of stay ($p<0.05$), and the majority of them were discharged due to improvement in health condition ($p<0.05$).

There was no statistically significant difference between the groups for any variables related to the utilization of linezolid; the groups were similar in terms of posology and reason for linezolid administration, microbiologic identification and antibiogram testing. The costs of treatment were also similar between groups. The per-patient cost was US$1991.33 ± 946.39 in the IV group and US$1874.18 ± 763.20 in the mixed group ($p>0.05$).

In the cost-minimization analysis, 33 of the 103 patients in the IV group (32.0%) met the criteria for the hypothetical switch therapy (i.e., modified linezolid administration route). When the subjects were not divided into two groups, the real per-patient cost of the treatment was US$1953.57 ± 844.68. Using the hypothetical switch therapy, the adjusted per-patient cost of therapy was US$1851.32 ± 778.77. This difference is statistically significant ($p<0.001$). The results were maintained over the sensitivity analysis in both the best scenario ($p<0.001$) and the worst scenario ($p<0.001$). These results indicate the robustness of the findings and confirm that the switch therapy is economically feasible. Adoption of the switch therapy could yield total savings of US$15542.02 or US$102.25 per patient over four years.

Table 1. Daily direct medical costs associated with the use of linezolid by intravenous, oral, and nasogastric tube route in patients admitted between August 2009 and August 2013 in a public hospital in southern Brazil.

Materials and drugs	Price (US$)	Daily use	Daily Cost (US$)	Total cost (US$)
Intravenous				
Linezolid – intravenous solution	85.92	2	171.84	177.79
Photosensitive system for infusion pump	5.95	1	5.95	
Oral				
Linezolid - tablet	64.10	2	128.20	128.20
Nasogastric				
Linezolid - tablet	64.10	2	128.20	128.60
Distilled water (10mL)	0.03	4	0.12	
Disposable syringe (20mL)	0.14	2	0.28	

DISCUSSION

The rational use of economic resources is as important as the consistent use of clinical resources, and this importance is especially significant for antibiotics, which represent a significant portion of health care expenses (Sipahi, 2008).

This study evaluated the medical records of 152 inpatients over four years. Similar studies were performed in Spain (Rivas et al., 2008), Canada (Walker, 2006), France (Duhalde et al., 2007; Aubin et al., 2011), Ireland (McNicholas et al., 2006) and the United Kingdom (Ziglam et al., 2005). The average age of the subjects in this analysis was approximately 46 years old, which was slightly younger than the average age of participants in similar studies (57.8 to 69.5 years old). This difference may be due to disparities in life expectancy between developed and developing countries. In all the studies, males comprised the majority of the study sample, often close to 60%.

The IV form of linezolid was the most prescribed, and the PO form was prescribed least often. Patients received linezolid exclusively by IV in 103 cases (67.8%), whereas only six patients were treated using exclusively PO linezolid. The remaining subjects received by PO, NG or IV route, sequentially. In other studies, the oral route was

Table 2. Characterization of patients admitted to a public hospital in southern Brazil between August 2009 and August 2013 according to the route of administration of linezolid

	Intravenous (n=103)		Mixed (n=49)		p-value
Demographic characteristics					
Sex					
Male	68	66.0%	26	53.1%	0.1743
Age (mean ± SD) (years)	46.3 ± 18.8		46.7 ± 21.2		0.9717
Clinical characteristics					
Length of stay (mean ± SD) (days)	52.4 ± 68.4		35.3 ± 21.5		0.04091
Comorbidities					
Yes	68	66.0%	30	61.2%	0.6921
Comorbidities – Types					
HIV/AIDS	4	3.9%	0	0	0.3921
Liver disease	3	2.9%	1	2.0%	1.0000
Hematological disorders	0	0	0	0	NA
Nephropathy	6	5.8%	3	6.1%	1.0000
Dialysis	2	1.9%	0	0	0.8255
Others	64	62.1%	29	59.2%	0.8642
None	30	29.1%	18	36.7%	0.4493
No information	5	4.9%	1	2.0%	0.6988
Reason for hospitalization					
Surgical	60	58.3%	23	46.9%	0.2563
Nonsurgical	43	41.7%	26	53.1%	0.2563
Reason for discharge					
Improvement	59	57.3%	37	75.5%	0.04576
Death	44	42.7%	12	24.5%	0.04576
Inpatient ward					
Medical/Surgical Clinic	24	23.3%	15	30.6%	0.4437
Orthopedics/Neurology	9	8.7%	2	4.1%	0.4855
ICU – General	35	34.0%	15	30.6%	0.8193
Pediatrics	1	1.0%	1	2.0%	1.0000
ICU – Pediatric	1	1.0%	0	0	1.0000
Emergency room	8	7.7%	1	2.0%	0.3028
Multiple	25	24.3%	15	30.6%	0.5270
Before or after the hospitalization, the patient has been in ICU - G?					
Yes	77	74.8%	34	69.4%	0.6159
Length of stay at ICU (mean ± SD) (days)	23.5 ± 45.3		16.2 ± 19.6		0.3266
Route of administration					
Intravenous	103	100%			
Oral			6	12.2%	
Mixed			43	87.8%	
Dose					
600 mg	102	99.0%	49	100%	1.0000
Frequency					
12/12 h	102	99.0%	48	98.0%	0.7030
Length of treatment (mean ± SD) (days)	10.5 ± 4.9		11.5 ± 4.4		0.1506
Cost per patient (mean ± SD) (US$)	1991.33 ± 946.39		1874.18 ± 763.20		0.4973

Table 2 , continued. Characterization of patients admitted to a public hospital in southern Brazil between August 2009 and August 2013 according to the route of administration of linezolid

	Intravenous (n=103)		Mixed (n=49)		p-value
Reason for use					
Community-acquired pneumonia	0	0	1	2.0%	0.7030
Nosocomial pneumonia	37	35.9%	16	32.7%	0.8312
Complicated and noncomplicated skin and soft tissue infections	12	11.7%	4	8.2%	0.7099
Bone and joint infections	1	1.0%	1	2.0%	1.0000
Enterococcus infections	1	1.0%	0	0	1.0000
Sepsis	35	35.9%	13	26.0%	0.4612
Others	13	12.6%	10	26.5%	0.3125
Not mentioned	4	3.9%	4	8.2%	0.4741
Type of infection					
Nosocomial	93	90.3%	44	89.8%	1.0000
Non-nosocomial	10	9.7%	5	10.2%	
Has antibiogram?					
Yes	59	57.3%	25	51.0%	0.5816
No	44	42.7%	24	49.0%	
Associated micro-organism					
Staphylococcus aureus	23	22.3%	15	30.6%	0.3672
Enterococcus faecium	3	2.9%	0	0	0.5600
Enterococcus faecalis	3	2.9%	0	0	0.5600
Coagulase-negative Enterococcus	15	14.6%	8	16.3%	0.9670
Gram-negative bacilli	12	11.6%	1	2.0%	0.09497
Other	3	2.9%	1	2.0%	1.0000
Not identified	44	42.7%	24	49.0%	0.5816
Micro-organism was linezolid-sensitive?					
Yes	42	40.8%	22	55.1%	0.7602
No	0	0	0	0	NA
Not available	61	59.2%	27	44.9%	0.7602
Micro-organism was methicillin-sensitive?					
Yes	10	9.7%	11	22.4%	0.06065
No	25	24.3%	9	18.4%	0.5430
Not available	68	66.0%	29	59.2%	0.5227
Micro-organism was vancomycin- sensitive?					
Yes	20	19.4%	12	24.5%	0.6142
No	0	0	0	0	NA
Not available	83	80.6%	37	75.5%	0.6142
The patient met the intravenous to oral switch therapy criteria?					
Yes	33	32.0%			

prescribed in between 50% and 62% of the cases (Walker, 2006; Aubin et al., 2011). This difference can be attributed to variability between hospitals in terms of antibiotic administration characteristics and protocols. One of the main purposes of the protocols and guidelines to promote the rational use of antibiotics is the precise compliance with their indications (Pérez-Cebrian et al. 2015). Guidelines will help physicians to prescribe rationally and to choose the best effective, most appropriate empiric antibiotic for the patient (Anand et al., 2016) and could, including, reduce the length of hospital stay. In a study that comprised two cohorts: the prospective cohort to assess the effectiveness of a sequential intravenous-to-oral linezolid switch algorithm and early discharge, and a retrospective cohort in which the algorithm had not been applied, used as the comparator, the duration of hospitalization was significantly shorter in the prospective cohort compared to the retrospective group that did not switch to oral drugs ($p < 0.001$) (Rodriguez-

Pardo et al., 2016). For this reason, we highly recommend elaboration of institutional antibiotic policy and guideline in place which should be based on preview studies about therapeutics indications, criteria to identify patients eligible for the change of route of administration, local characteristics of linezolid use and susceptibility pattern of pathogens.

There was no significant difference between the groups in the length of treatment: 10.5 ± 4.9 days for the IV group and 11.5±4.4 days for the mixed group (p = 0.1506). The duration of antibiotic therapy reported in other studies is comparable to the findings of this study, and there were few cases where therapy exceeded the recommended maximum duration of 28 days (Ziglam et al., 2005; McNicholas et al., 2006; Duhalde et al., 2007; Rivas et al., 2011). Only one patient in this study met that criterion.

In published studies, the main reasons for linezolid administration were skin and soft tissue infections (Ziglam et al. 2005; Walker et al. 2006; Aubin et al., 2011; Rivas et al., 2011). Additional reasons included nosocomial pneumonia and ventilator-associated pneumonia (Ziglam et al., 2005; Walker, 2006; Duhalde et al., 2007; Aubin et al., 2011; Rivas et al., 2011), bone and joint infections (Ziglam et al., 2005; Aubin et al., 2011) and bacteremia (Walker, 2006). Researchers highlight the growing use of linezolid for infections of the lower respiratory tract, especially in intensive care units (ICUs), possibly due to clinical failure, renal dysfunction and lack of efficacy of glycopeptide antibiotics in cases of nosocomial pneumonia due to methicillin-resistant *Staphylococcus aureus* (MRSA). In this research, both the IV and the PO groups had high prevalences of nosocomial pneumonia (35.6% and 32.7%, respectively) and sepsis (34.6% and 26.0%, respectively). Furthermore, approximately 70% of the patients were in the ICU before or during linezolid treatment.

The literature shows that the pathogens most frequently isolated in patients receiving linezolid are MRSA (Ziglam et al., 2005; McNicholas et al., 2006; Walker, 2006; Rivas et al., 2011), methicillin-resistant *Staphylococcus* epidermidis (Duhalde et al., 2007; Aubin et al., 2011) and coagulase-negative *Staphylococcus* species (CNS) (Rivas et al., 2008), with rates between 29% and 56%. Our results are consistent with these findings. Microbiological cultures identified *Staphylococcus aureus* in 22.1% of patients in the IV group and 30.6% of patients in the mixed group and CNS in 14.4% of patients in the IV group and 16.3% of patients in the mixed group. The prevalence of MRSA was not verified in this study, but approximately 20% of the micro-organisms isolated in the microbiological cultures were characterized as methicillin resistant.

More than 40% of the medical records used in this study reported no microbiological data when linezolid was prescribed. In the IV group, 12.5% of microbiological cultures identified gram-negative bacilli, with which linezolid is ineffective. Moreover, 19.2% and 25.0% of susceptibility profiles in the IV and the mixed group, respectively, were susceptible to vancomycin. An audit by McNicholas et al. (2006) found that linezolid use without microbiologic justification is frequent, and the authors propose that linezolid has been used as a first-line alternative when vancomycin could be more effective. These data suggest the possibility of inappropriate linezolid use. In order to combat this problem, that cause antimicrobial resistance, increases morbidity, mortality and costs, the development of programmes to enhance antimicrobial stewardship is recommended. (García-Martínez et al., 2016).

Additional research has assessed regional and institutional adherence to established guidelines for linezolid therapy and verified that between 40% and 54% of prescriptions were outside the standards (Ziglam et al., 2005; Aubin et al., 2011; Rivas et al., 2011). Similarly, further evaluation of the appropriateness of linezolid prescriptions at this public hospital could contribute to a better understanding of the antibiotic's utilization. That is because development of linezolid guidelines and policy is not enough to ensure rational use. To increase adherence with protocol, training of prescriber, regular audit with active feedback, as the inclusion of clinical pharmacologist and microbiologist in the management team should be implemented (Anand et al. 2016).

In this cost-minimization study, we found that 33 of the 103 patients (32.0%) who received IV linezolid exclusively met the criteria for switch therapy. In a study by Ziglam et al. (2005) conducted in a teaching hospital, just 18 of the 88 subjects (14.8%) met the criteria to change the administration route. Though pharmacoeconomic analyses were not conducted in this study, the authors did conclude that the hypothetical switch therapy could save more than US$13,000.00 over four years. In addition, it was verified that the costs before adjusting for the administration route were significantly higher than the costs after this process ($p<0.05$).

We found two studies that used cost-minimization methodology to analyze the use of linezolid. The first study compared linezolid with vancomycin as the initial treatment of skin and soft tissue infections due to MRSA in a Brazilian setting. Despite the lower acquisition price of glycopeptide antibiotics, the cost of inpatient treatment with linezolid was US$804.10 less than the cost with brand name or generic vancomycin. The authors suggest that the cost differential is due to the ability to offer oral and outpatient treatment with linezolid (Grinbaum et al., 2005).

The second study compared linezolid with vancomycin for treatment of bone and joint infections and concluded that when the alternatives were utilized in outpatient settings, linezolid was US$1326.56 more expensive. However, when the use of an oxazolidinone antibiotic in an outpatient setting was compared with a glycopeptide antibiotic in a hospital setting, linezolid saved US$14,681.70. The hypothesis is that the outpatient administration of teicoplanin in a single daily dose could help to reduce costs (Nathwani et al., 2003).

CONCLUSION

This analysis of resources use in the treatment of infections with linezolid is relevant because it can contribute to better clinical and economical utilization of this therapy, which despite its high price, is considered one of the last available strategies for the treatment of multidrug-resistant gram-positive bacteria. In this cost-minimization study, we found that changing the route of linezolid administration from IV to PO/NG could reduce the costs of treatment in this hospital setting. This result was confirmed by a sensitivity analysis for the best and worst scenarios ($p<0.001$), confirming the robustness of the findings. Over four years, adoption of the switch therapy could yield total savings more than US$1500.02. These results, which demonstrate the cost savings that can be achieved by switching the administration route of linezolid without compromising the quality of treatment patient, can contribute to the rational use of linezolid in the study hospital and other health care institutions. For this reason, we highly encourage elaboration of institutional antibiotic policy and guideline to support use of linezolid in compliance with their indications and criteria to switch route of administration.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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RESUMO

Análise de custo-minimização entre as vias de administração oral e endovenosa de linezolida em um hospital público da região sul do Brasil

Devido à escassez de estudos de custo-minimização a cerca da linezolida, o objetivo deste estudo foi estimar a diferença de custo entre a administração intravenosa e oral desse antibiótico. Um estudo de coorte retrospectiva e uma análise de custo-minimização foram realizados entre agosto de 2009 e agosto de 2013, em um hospital público do sul do Brasil. Foram avaliados os prontuários médicos de 152 pacientes que receberam linezolida por via intravenosa e / ou oralmente. Mais de dois terços dos pacientes (103, 67.8%) receberam o medicamento exclusivamente por via intravenosa (grupo IV), e o restante (grupo misto) recebeu o antibacteriano por via intravenosa e por via oral sequencialmente. No grupo IV, 33 pacientes (31.7%) eram elegíveis para receber o antibiótico por via oral. O custo médio total por paciente após a troca hipotética da via de administração intravenosa para oral foi significativamente mais baixo do que o custo médio real pago por cada tratamento com linezolida ($p <0.001$). A economia de custos associados com a mudança para a administração oral de linezolida seria de US $ 14,328.32 ao longo de quatro anos. A análise farmacoeconômica da terapia com linezolida pode orientar as decisões dos hospitais quanto ao uso racional de terapêuticas e de recursos econômicos.

Palavras-chave: Administração oral. Farmacoeconomia. Administração intravenosa. Linezolida.

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