Cost-Effectiveness of Linezolid *versus* Vancomycin in Mechanical Ventilation-Associated Nosocomial Pneumonia Caused by Methicillin-Resistant *Staphylococcus aureus*

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Linezolid, an oxazolidinone-class antimicrobial agent, is a new drug; its use has frequently been questioned due to its high price. However, recent trials have demonstrated that the use of linezolid in mechanical ventilation-associated nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus* (VAP-MRSA) may be justified due to its improved efficacy compared to vancomycin. Price and cost have different magnitudes, and clinical efficacy should always be considered in the decision-making process. Our objective was to determine whether linezolid treatment was more cost-effective than vancomycin for treating VAP-MRSA. Methodology: Elaboration of an economic model from a metanalysis of previous clinical trials comparing both drugs, through a cost-effectiveness analysis. Costs of the treatments were calculated using Brazilian parameters and were compared to the results obtained in the metanalysis. In order to compare the results with real life conditions, costs were calculated for both name brand and for generic vancomycin. Results: The cost (May/2004) per unit (vial, ampoule or bag) was R$ 47.73 for the name-brand vancomycin, R$ 14.45 for generic vancomycin and R$ 214.04 for linezolid. Linezolid's efficacy in VAP-MRSA according to the metanalysis was 62.2% and vancomycin's efficacy was 21.2%. The total cost per cured patient was R$ 13,231.65 for the name-brand vancomycin, R$ 11,277.59 for generic vancomycin and R$ 7,764.72 for linezolid. Conclusion: Despite the higher price per unit, linezolid was more cost-effective than vancomycin.

Key Words: Linezolid, vancomycin, *Staphylococcus aureus*, pneumonia, ventilator, cost, pharmacoeconomic.

Pneumonia is considered the most important nosocomial-acquired infection due to its high frequency and morbidity-mortality characteristics [1]. In a study conducted in 99 hospitals in Brazilian capitals, pneumonia was responsible for 28.9% of all nosocomial-acquired infection; approximately 50% were detected in Intensive Care Units (ICU's) [2].

Mechanical ventilation increases the risk of pneumonia (ventilation-associated pneumonia – VAP) 3 to 21 times [3]. Rello et al. retrospectively evaluated 9,080 patients maintained under mechanical ventilation for more than 24 hours and found that 9.3% of the patients developed pneumonia, with an average period of 3.3 days between the beginning of ventilation and the diagnosis [4].

Medeiros, in a study conducted in the ICU of the UNIFESP (Universidade Federal de São Paulo) São Paulo Hospital, found that mortality in patients with pneumonia was 53.3%, versus 28.3% in patients admitted for other diagnoses (attributed lethality 25%, confidence interval (CI) 7.3 to 42%) [5].

From January 1997 to December 1999, the "SENTRY *Antimicrobial Surveillance Program*" monitored the pathogens responsible for community-

Received on 09 February 2005; revised 08 June 2005.
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The Brazilian Journal of Infectious Diseases 2005;9(3):191-200

and nosocomial-acquired infections and their resistance to antimicrobial agents in five geographic areas (United States, Latin America, Europe and the West Pacific). In all these geographic areas, *Staphylococcus aureus* was the most prevalent pathogen identified in blood stream, skin and soft tissue infections and in pneumonias. The frequency of methicillin-resistant *S. aureus* (MRSA) varied amongst the areas: 46% in the West Pacific region, 35% in Latin America, 34% in the US, 26% in Europe and 6% in Canada [6].

In Brazil, the SENTRY Program assessed the strains responsible for infection in 12 hospitals in four Brazilian capitals; *S. aureus* also was, independent of the infected site, the most prevalent agent, being found in 22.8% of isolates. Among the strains obtained from patients with pneumonia, *S. aureus* was the second-most-frequent agent (21%), surpassed only by *Pseudomonas aeruginosa* (29.4%). Among all the *S. aureus* strains isolated, 34% were resistant to methicillin, while in strains isolated from patients with pneumonia, the percentage was 29.4% [7].

Costa et al. studied the incidence and etiology of nosocomial pneumonias between January 1995 and October 1997 at the Hospital das Clínicas of the Faculdade de Medicina da Universidade de São Paulo. During this period, 16,024 patients were admitted to the institution, and 2.4% (397) developed pneumonia; the etiology was determined in 25% (101) of the cases. Gram-negative agents were responsible for 54% of the pneumonias; individually, *S. aureus* was the most prevalent pathogen (34%), followed by *Acinetobacter baumannii* (29%), *P. aeruginosa* (7%) and *Klebsiella pneumoniae* (7%). Among the *S. aureus* strains that were isolated, 68% were MRSA [8].

At the Hospital das Clínicas of the Universidade Federal de Uberlândia, Sadoyama et al. evaluated, by means of univariate analysis, the risk factors for MRSA infection; these were: age, preexistent infection, length of in-hospital stay, prior use of three or more antimicrobial agents and presence of three or more invasive devices (mostly vascular or urinary), as has also been found in studies in other countries [9].

In the case of nosocomial-acquired infections, besides the elevated morbidity-mortality, the costs are very high for both society and for health-care providers. Since nosocomial infections are the most important cause, pneumonia is one of the clinical entities that most contributes to increased costs [10,11]. In Germany, Kappstein et al. found that nosocomial pneumonias increased the length of ICU stay by 10.13 days and the costs by US$ 8.800 per patient [12]. In the US, Boyce et al. described an additional cost of US$ 5.800 per patient due to nosocomial pneumonia [13]. There have been no cost estimates associated with nosocomial pneumonia in Brazil; however, it is estimated that such infections increase the length of hospital stays 17.2 days, independent of the outcome (death or not); when only surviving patients were evaluated, the number of additional days in the ICU was 13.3 [5].

The continuous increase in microorganisms' resistance reduces the efficacy of antimicrobial treatment, leading to a new increment in morbidity-mortality and costs. In the United States, approximately two million nosocomial infections are diagnosed annually, 60% of them involving microorganisms resistant to antimicrobial agents, generating an increase of approximately 30 billion dollars in costs per year [14].

There is evidence that decreases in VAP-related mortality are associated with adequate empirical antimicrobial therapy, defined as: "administration of at least one antimicrobial agent that, *in vitro*, is effective against bacterial pathogens isolated from respiratory secretion of the patient" [1,4,8,15,16]. In the light of the present stage of microbiological analyses, it is impossible for the physician to determine which pathogen is causing the infection and its resistance profile to antimicrobial agents at the time of the diagnosis and prescription of initial therapy. To wait for test results, especially in pneumonias, results in an unacceptable risk of death. Consequently, empiric antimicrobial coverage must be initiated as early as possible, and the consensus guidelines recommend that the therapy be adjusted to the local patterns of prevalence of the microbiota [1,17-19]. Brazilian data indicate that empiric therapy must include coverage for MRSA [3,7,8].

Vancomycin is the drug of choice for the treatment of MRSA infections [20]. However, Sanduimenge et al. emphasized that vancomycin, using the dosages and the application routes recommended for the treatment of VAP-MRSA, is often associated with unsatisfactory results [21]. Cruciani et al. found that a vancomycin IV infusion at 1 gram per hour does not maintain the pulmonary concentration above the Minimum Inhibitory Concentration (MIC) for staphylococci for 12 hours [22]. Additionally, vancomycin concentration in intraepithelial pulmonary fluid does not reach 20% of the plasma concentration [23]. Golstein and Kitzis reported that approximately 40% of the patients treated with vancomycin (with the standard dosage - 1 gram per 12 hours) did not maintain adequate plasma levels [24]. Additionally, a recent study demonstrated that in MRSA bacteremia the rate of clinical cure is related to the vancomycin MIC: when the MIC was 0.5 µg/mL or less, the outcome was favorable in 55.6% of the cases, against only 9.5% success if MIC was 1 µg/mL or more [25]. Staphylococci with vancomycin MICs up to 4 µg/mL are considered susceptible to the drug according to laboratory criteria. In Brazil, vancomycin plasma concentration is normally not monitored during therapy, and the true cost and clinical benefits of this antibiotic are not well known.

González et al. reported that in bacteremic pneumonia due to staphylococci, patients with infection caused by oxacillin-susceptible staphylococci had a 0% mortality rate when treated with this beta-lactamic antibiotic and a 47% mortality rate when treated with vancomycin. In the same study, treatment with vancomycin was found to be an independent risk factor for death in a multiple logistic regression analysis [26].

On the other hand, linezolid (an antimicrobial agent of the oxazolidinone class) has excellent activity against Gram-positive pathogens, including those resistant to methicillin and vancomycin [27-30]. Linezolid given at the usual doses of 600 mg every 12 hours, maintains adequate serum and pulmonary levels (for 16 hours) and alveoli levels (for 30 hours) above the linezolid MIC_{90} for *S. aureus* (≤ 4 mg/L), *S. viridans* or β-hemolyticus (2 mg/L), methicillin-resistant *S. epidermidis* (2mg/L), vancomycin-resistant enterococcus (2 mg/L) and penicillin-resistant *S. pneumoniae* (1 mg/L) [27, 30-34]. Another important factor is the identical bioavailability of this drug when administered by oral versus intravenous routes [27-30].

Wunderink et al. showed, in a retrospective analysis of data from two prospective, double-blind, randomized studies [25,36], that clinical cure rates achieved by linezolid (59%) were significantly higher than those achieved by vancomycin (35.5%) in cases of nosocomial pneumonia due to MRSA. In the same study, a multivariate analysis indicated that use of linezolid was the only predictive modifiable factor (OR: 3.3) that increased clinical cure rates [37]. Using the same studies, Kollef et al. performed an analysis of VAP-MRSA. Again, they found that clinical cure rates with linezolid (62.2%) were significantly higher than those with vancomycin (21.2%). Also, linezolid was the only predictive modifiable factor (OR: 20) for increased clinical cure rates in MRSA-VAP [38].

Nevertheless, clinical prescription of linezolid is often avoided due to the difference of prices per unit of this medication compared to a unit of vancomycin. One vial of vancomycin costs R$ 47.73 (reference brand), while one dose of injectable solution of linezolid costs R$ 214.04 - prices May 2004 [39]. In a scenario of cost rationalization currently found in health systems management, it is crucial to justify the use of a more expensive product.

Pharmacoeconomic analyses are tools used to compare the of costs of different technologies used in health care versus the economic, clinical and humanistic benefits that they are able to deliver [40, 41]. The ethical and philosophical essentials of this science are that it is not enough to keep expenditures under control if the impacts of this attitude towards human health are not measured, due to the risk that medicine may become a purely financial science.

Additionally, it is also necessary to know the real cost of drug use, since the straightforward price comparison per unit has little impact in the set of factors that compose costs for the health system. Some apparently cheap drugs carry a large number of "unseen" costs (administration, treatment of adverse events, cost of inefficacy, monitoring and others), which may increase the total cost of treatment to levels comparable or superior to those of apparently more expensive alternatives [42].

Drummond, currently one of the most respectable specialists in health economics, states that although the high costs of health assistance have often been attributed to drug prices, these drugs are only a fraction of the total healthcare cost. He indicated that though some prescription drugs appear to be excessively expensive, their use may result in net savings [43].

Based on clinical studies, linezolid has clinical advantages over vancomycin. Since vancomycin use has additional costs that usually are not evaluated, we decided to determine if linezolid, when used as the drug of first choice for VAP-MRSA therapy, would be cost-effective compared to vancomycin.

Pharmacoeconomic Analysis

We modelled the data using straightforward decision analysis, considering the occurrence of VAP-MRSA, two treatment alternatives (linezolid versus vancomycin) and two simple outcomes - death or survival. The decision tree is shown in Figure 1.

The costs for each treatment option were calculated by taking into account the drugs and material used for administration of each alternative, while treatment success probabilities came from comparative studies with linezolid and vancomycin for the treatment of VAP-MRSA.

The list of materials (with prices) used for administration of each drug was obtained by interviews with nurse teams from a reference institution in São Paulo (Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) (Table 1) [39]. In order to reproduce the conditions of daily practice, we considered the prices of a brand-name vancomycin (Vancocina CP, Eli Lilly) and of a generic product (Vancomycin, Eurofarma), for separate analyses.

Drug dosages are those presented in the literature and recommended by manufacturers. These were used for the estimation of direct daily costs (Table 2).

To determine the duration of antibiotic therapy in patients with VAP-MRSA, we adopted the results of a study conducted by Kollef et al. [26], who retrospectively evaluated data of two prospective, randomized and double-blind studies in 134 sites, involving 1,019 patients with nosocomial pneumonia, including 160 with identified MRSA and 91 with VAP-MRSA. In the second group, treatment duration for the 44 patients who received linezolid and the 47 patients who received vancomycin was 11.4 (±4.9) and 11.2 (±3.4) days, respectively [38]. Therefore, for the purpose of this study, the treatment period was standardized to 11 days for both drugs. Based on this treatment duration, direct costs for one course of therapy using each drug were calculated (Table 3). Other figures that usually should be included in the calculation of direct total cost of treatment, such as cost of in-hospital stay, were excluded because they were equivalent for the two drugs (since the length of stay was estimated taking into account the same duration of in-hospital stay).

Cost-effectiveness analyses determine which treatment option is able to achieve the greatest proportion of positive clinical results, taking into account the financial investment necessary for implementation. Therefore, it is necessary to calculate the expenditures to treat the population and divide by the number of benefited patients.

Using the data of Kollef et al. [38], we deduced that treating 100 patients resulted in approximately 62 cured with linezolid and 21 with vancomycin. By dividing the hypothetical expenditure to treat 100 patients by the number of cured patients for each drug, it is possible to determine the option with the best performance, i.e., with the best relationship between cost and effectiveness (Table 4).

Discussion

Brazil, and other countries all over the world, is facing a challenge of huge proportions: how to control health expenditures and simultaneously improve or at least maintain the clinical results. Although enormous

Figure 1. Decision tree for treatment of mechanical ventilation-associated nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus* with linezolid or vancomycin. The values of "pLin" and "$Lin" show the probabilities of successful therapy and costs associated with the use of linezolid, and "pVan" and "$Van" represent the same items for vancomycin, respectively.

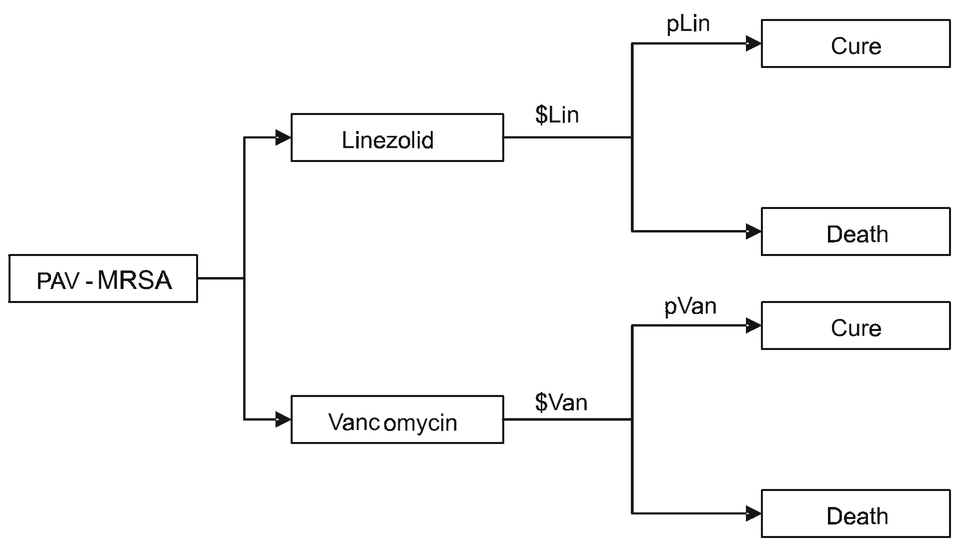

Figure 2. Comparison between total cost per patient *vs* invested amount per cured patient.

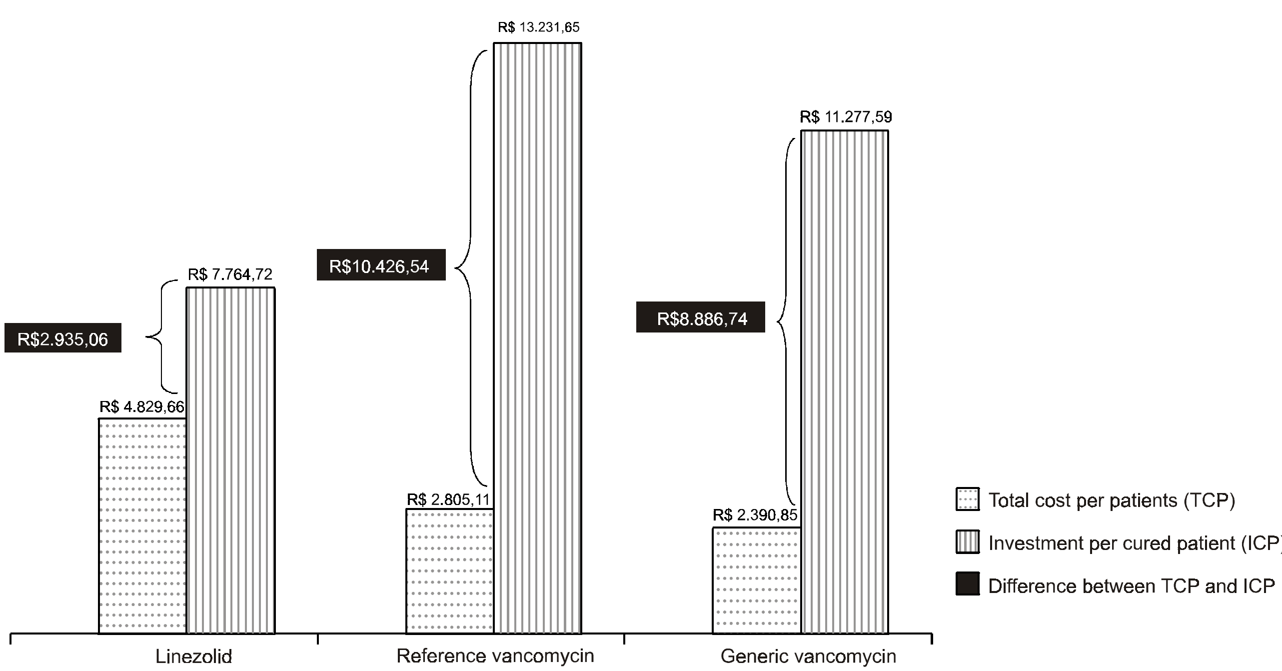

Table 1. List of medications, material, and prices [39]

Item	Brand	Presentation	Price per unit	
Linezolid IV 600 mg	Zyvox (Pfizer)	Packages w/10 bags 600 mg	R$2,140.47	R$214.04
Reference vancomycin	Vancomycin (Eli Lilly)	Vials 1 g	R$ 47.73	R$ 47.73
Generic vancomycin	Vancomycin (Eurofarma)	Vials 500 mg	R$ 14.45	R$ 14.45
Discarded syringes with needle (primary dilution)	BD	uni	R$ 1.50	R$ 1.50
Sterile water for injection	Becker	Ampoulle with 20 mL	R$ 0.56	R$ 0.56
Saline solution 0.9% for infusion		Baxter PVC bag with 250 mL	R$ 3.94	R$ 3.94
Device for infusion pump	Life Care	unit	R$ 76.82	R$ 76.82
Simple device for infusion	Intrafix AIR	R$ 10.98 with filter (B Braun) unit	R$ 10.98	
Infusion pump*		Daily rate	R$ 70.73	R$ 70.73

*Rate used at INCOR – Instituto do Coração do HC/FMUSP in May 2004.

Table 2. Direct daily cost of antimicrobial agents

Item	Price	Daily consumption	Item price	Total
Linezolid IV 600 mg	R$214.04	2	R$ 428.08	R$ 439.06
Simple device for infusion	R$ 10.98	1	R$ 10.98	
Brand-name vancomycin				
Vancomycin 1 g	R$ 47.73	2	R$ 95.46	R$ 255.01
Discarded syringe with needle	R$ 1.50	2	R$ 3.00	
Sterile water for dilution	R$ 0.56	2	R$ 1.12	
0.9% Saline solution for infusion	R$ 3.94	2	R$ 7.88	
Device for infusion pump	R$ 76.82	1	R$ 76.82	
Infusion pump	R$ 70.73	1	R$ 70.73	
Generic vancomycin				
Vancomycin 500 mg	R$ 14.454 (2 g/day)	R$	57.80	R$ 217.35
Other items*		R$	159.55	

* Described in item "brand-name vancomycin".

Table 3. Direct total cost of antibiotic therapy

Product	DDC	TD [38]	TCp=DDC x TD
Linezolid	R$ 439.06	11 days	R$ 4,829.66
Brand-name vancomycin	R$ 255.01	11 days	R$ 2,805.11
Generic vancomycin	R$ 217.35	11 days	R$ 2,390.85

DDC: direct dayly cost (see Table 2); TD: treatment duration; TCp: total cost per patient.

Table 4. Cost-effectiveness of vancomycin *versus* linezolid in mechanical ventilation-associated nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*

	TCp	E [38]	Iacp= TCp x 100
Linezolid	R$ 4,829.66	62.2%	R$ 7,764.72
Brand-name Vancomycin	R$ 2,805.11	21.2%	R$ 13,231.65
Generic Vancomycin	R$ 2,390.85	21.2%	R$ 11,277.59

TCp: total cost per patient (see Table 3); E: effectiveness; Iacp: invested ampunt per cured patient.

progress has been achieved in the outcomes of sanitary interventions over the last years, we are still far from attaining "state-of-art" in therapy, as most therapies are neither entirely effective nor safe. On the other hand, we must recognize that, with the current trend of increasing health costs, the best therapies are not currently available for everyone. Although this is undesirable, there are some important considerations to be made:

1. The inclusion of high-price technologies could result in a reduction in global costs, as they may avoid or decrease the use of resources that would be necessary if they were not adopted.
2. Restricted access to these technologies may be an ethical problem, as it excludes patients from the potential benefits of good health and quality of life.
3. To block the inclusion of new technologies condemns the progress of medical science and prevents the development of new options that gradually induce decreases in the costs of existing treatments, as has happened with various technologies launched in the past at apparently unbearable prices but that nowadays constitute available tools for diagnosis, treatment and palliative care.
4. Although the health system has its own point of view, it cannot be forgotten that it is part of a society; in the initial and in the final analysis, better health care can even influence productivity capacity and the achievement of economic objectives.

It is well know that many technologies do not bring benefits proportional to their costs. Therefore, a rational decision-making process involves determining a balance between disbursement for a new therapy and the global advantages offered; this is the role of pharmacoeconomics.

Comparison of one vial of vancomycin to one bag of injectable linezolid reveals a difference of 640% in price (when comparing with the generic product). However, many cost factors are incorporated into the administration of vancomycin, making its final cost only 40% less expensive than linezolid.

Amongst the main factors that add costs to vancomycin is the requirement of an infusion pump for its administration. In some institutions, administration is made through a less accurate method, such as a microdrop device, for instance; but medication errors with this technique (i.e., too fast infusion rate and consequently adverse events) are potentially harmful and add costs to the treatment.

Shah et al. have recently published a study concerning the direct costs associated with the use of vancomycin in MRSA infections. They indicated that the price of one dose of vancomycin (1 g) is US$ 9.01. However, when all secondary costs are considered (monitoring, professional involvement, drug administration and adverse events), each dose has an estimated increment in cost of between US$ 23 and US$ 43 [44].

Unfortunately, there is no published data in Brazil on the occurrence of adverse events related to vancomycin administration errors; this prevents us from incorporating such events into the pharmacoeconomic analysis.

We did not include the costs of monitoring vancomycin plasma levels, which is necessary to obtain optimal results with this treatment [45-48]. We also did not include treatment costs and the impact of adverse reaction outcomes for both products, which could influence the global decision-making process [44]. The risk of catheter infections that may occur in patients submitted to prolonged periods of drug infusion was not considered. It was not the aim of this study to exhaust the subject, but only to improve the comprehension of the relationship between expenditures for each treatment and the clinical effects resulting from each treatment decision.

Another possibility to be explored is a switch in the linezolid administration route, due to the therapeutic equivalence of oral and parenteral routes [27-30]. For patients with good gastrointestinal tolerability, the switch in the route could offer a chance to reduce risks associated with obtaining and maintaining a vascular access, such as phlebitis, puncture accidents and catheter-related infections [17]. As there are no data concerning this option during the evolution of VAP, this possibility should be investigated.

Hospital discharge, optimized by the possibility of completing the treatment with oral linezolid outside the hospital was not tested, because the design of the study did not include this possibility. It is likely that over time this practice will be incorporated into clinical practice, such as for the treatment of community-acquired pneumonia (for instance with fluoroquinolones).

A cost-effectiveness analysis is an evaluation of the productivity of a financial investment made to improve the health of patients. Therefore, the greater the productivity, the smaller the expenditure per beneficiary. We calculated that in order to obtain one cured case, it would be necessary to invest R$ 7,764.72 with linezolid, R$ 13,231.65 with a brand-name vancomycin or R$ 11,277.59 with generic vancomycin (Table 4). These numbers are numerically greater than the direct total cost of antibiotic therapy (Table 3). An understanding of this phenomenon must be translated into the concept of cost-effectiveness; it is easy to understand that the costs of non-cured patients should added to the costs of cured patients. Therefore, the greater the efficacy of a drug, the smaller the additional part added to its cost-effectiveness value (Figure 2), and vice-versa.

The value of linezolid in treating VAP-MRSA, given its clinical efficacy, is approximately 200% greater than treatment with vancomycin, based on the proportion of cured patients (62.2% versus 21.2%, respectively), while vancomycin has only a 40% smaller direct cost of treatment.

Conclusions

In nosocomial pneumonia associated VAP-MRSA, the use of linezolid is cost-effective when compared to vancomycin. Linezolid allows a cost reduction of R$ 5,466.93 when compared to brand-name vancomycin or a cost reduction of R$ 3,512.87 when compared to generic vancomycin, per cured patient. This benefit is due with an increased rate of clinical cure provided by linezolid, which is disproportionately beneficial, considering the incremental costs when compared to vancomycin use.

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