Cost-minimization in Health: Linezolid versus vancomycin with serum monitoring in patients with incipient renal failure – a simulation and real-life

Minimização de custos em Saúde: Linezolida versus vancomicina com monitoramento sérico em pacientes com insuficiência renal incipiente - uma simulação e vida real

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ABSTRACT
Vancomycin serum levels (VSL) were measured to prevent dose-dependent side effects. However, the cost of VSL is high, therefore in some cases alternative antibacterial treatments, such as linezolid, can be used. The aim of this study was to perform an economic analysis of the cost of linezolid compared to vancomycin plus therapeutic drug monitoring. This is an ecological, retrospective, quantitative study, conducted in a Brazilian public university hospital. The study period was from January 2018 to January 2019. First part from January/18 - July/18 based on pre-linezolid data (T1) and another after the introduction of linezolid from August/18 - January/19 (T2). A breakeven analysis to vancomycin substitution was performed following 3 scenarios: (i) in all patients, (ii) in critically ill patients with renal failure or (iii) only in patients in hemodialysis. The DDD/1000-patients day, MRSA incidence, costs with VSL, as well as the costs of drugs (vancomycin and linezolid) and infusion kits were evaluated. Vancomycin was substituted in critically ill patients with renal failure from T1 to T2. The incidence of MRSA infections did not vary between T1 and T2. Vancomycin consume maintained constant (p=0.157); while linezolid consuming increased (0 DDD/1000PD versus 33.4 DDD/1000PD; p=0.002). Vancomycin and linezolid costs was lower in T1 than T2 (USD 9202,00 versus 11331,00; p=0.015). Linezolid implementation as a strategy to avoid vancomycin plus VSL was not cost-effective in critically ill patients with renal failure. More studies are needed to understand if linezolid implementation may be cost-effective in different scenarios.

Keywords: Vancomycin, Linezolid, Antimicrobial Stewardship, Economy.

RESUMO
Os níveis de soro de vancomicina (VSL) foram medidos para evitar efeitos colaterais dose-dependentes. Entretanto, o custo da VSL é alto, portanto em alguns casos podem ser utilizados tratamentos antibacterianos alternativos, como o linezolida. O objetivo deste estudo foi realizar uma análise econômica do custo da linezolida em comparação com a vancomicina mais o monitoramento de drogas terapêuticas. Este é um estudo ecológico, retrospectivo, quantitativo, realizado em um hospital público universitário brasileiro. O período do estudo foi de janeiro de 2018 a janeiro de 2019. Primeira parte de janeiro/18 a julho/18 com base em dados pré-

linezolida (T1) e outra após a introdução da linezolida de agosto/18 a janeiro/19 (T2). Uma análise do breakeven para a substituição da vancomicina foi realizada seguindo 3 cenários: (i) em todos os pacientes, (ii) em pacientes críticos com insuficiência renal ou (iii) somente em pacientes em hemodiálise. Foram avaliados o dia DDD/1000-paciente, a incidência de MRSA, os custos com VSL, bem como os custos de medicamentos (vancomicina e linezolida) e os kits de infusão. A vancomicina foi substituída em pacientes criticamente enfermos com insuficiência renal de T1 a T2. A incidência de infecções por MRSA não variou entre T1 e T2. O consumo de vancomicina se manteve constante (p=0,157); enquanto o consumo de linezolida aumentou (0 DDD/1000PD contra 33,4 DDD/1000PD; p=0,002). Os custos de vancomicina e linezolida foram menores em T1 do que em T2 (USD 9202,00 versus 11331,00; p=0,015). A implementação de linezolida como estratégia para evitar a vancomicina mais VSL não foi econômica em pacientes críticos com insuficiência renal. São necessários mais estudos para entender se a implementação de linezolida pode ser rentável em diferentes cenários.

Palavras-Chave: Vancomicina, Linezolid, Administração Antimicrobiana, Economia.

1 INTRODUCTION

Prevalence of methicillin-resistant Staphylococcus aureus (MRSA) infections is different according with the country [1]. Infections can be classified as healthcare-associated community-onset (HACO), hospital-onset (HO) and community-associated (CA) [2]. The Emerging Infections Program – Active Bacterial Core Surveillance (EIPABCs) at the Centers for Disease Control and Prevention (CDC) reported 11% annual decline in incidence of hospital-onset MRSA bloodstream infections between 2005 and 2008 in 9 diverse metropolitan areas in United States [3].

In Latin America, specifically in Brazil and Argentina, epidemiology is not clearly and comprehensively described since a large part of the population is served by basic health facilities, which do not have a well-defined surveillance and etiology of infections[36]. A study published in 2017 of 1,185 hospital samples isolated from 9 Latin American countries, including Brazil, found that Brazil had the highest rate of bloodstream MRSA infection [4].

Despite the acquired resistance of MRSA, there is still a comprehensive susceptibility profile. The last Infectious Diseases Society of America (IDSA) guidelines for MRSA treatment, vancomycin, linezolid, sulfamethoxazole, clindamycin, daptomycin are some options available [5]. Among the treatments presented, vancomycin is the first option in almost all MRSA infections; as it is the most widely used, there is more experience with the antibiotic medication[6]. Vancomycin can cause dose-dependent side effects, therefore plasma serum concentrations are measured. Particularly, this monitoring is indicated in cases of patients receiving high doses of vancomycin to reduce

the risks of nephrotoxicity, as well as for patients who use other concomitant nephrotoxic drugs and who have unstable renal function [7]. However, the cost of serum analysis is high, therefore, in some cases alternative antibacterial treatments can be used when serum dosage is needed, such as patients with nephropathy and critically ill patients. Among medications with activity against MRSA, linezolid is an alternative to vancomycin [5]. In this regard, given the lack of knowledge and pharmacoeconomic studies evaluating the relationship between the cost of vancomycin, serum vancomycin analysis, and the cost of new drugs such as linezolid, this study aims to evaluate the cost of minimizing linezolid versus vancomycin in patients with MRSA infections and renal dysfunction.

The aim of this study was to perform an economic analysis of the cost of linezolid compared to vancomycin plus therapeutic drug monitoring in different panorama, including critically-ill patients and those with renal failure.

2 METHODS

Study design and setting

This is an ecological, retrospective, quantitative study, conducted in a Brazilian public university hospital with 207 beds, a reference in trauma and surgery. The study period was from January 2018 to January 2019 and it evaluated two phases, one part (January 2018 to July 2018) based on pre-linezolid data (T1) and another after the introduction of linezolid (August 2018 to January 2019) (T2).

Antimicrobial Stewardship Program (ASP) was implemented in 2017, including two infectious disease physicians and a clinical pharmacist. All patients under treatment with vancomycin were evaluated by the clinical pharmacist, and vancomycin serum level (VSL) monitoring were performed in patients using vancomycin in the intensive care unit. In the protocol used during T1, vancomycin was always used in continuous infusion and VSL evaluated after 24h of first day and regular monitoring according to previous results. In patients under hemodialysis, the vancomycin was used in intermittent infusion after hemodialysis, according to vancomycin though level after hemodialysis. Dose, length of treatment adjustment, de-escalation of route of administration and side effects are all determined under the guidance of the clinical pharmacist. After July 2018 (T2), all patients with indication of VSL monitoring changed the treatment to linezolid, due to increasing costs of the kit to perform VSL. Thus, in July 2018, a protocol for the use of linezolid was created in our hospital. This protocol states that patients on hemodialysis or

those with creatinine greater than 1.5 mg/dL (Cr > 1.5 mg/dL). The protocol favored financial optimization, without prejudice to patient treatment.

Two steps study

Consume of vancomycin and linezolid were evaluated during T1 and T2. The costs with VSL, the infusion kit (lines, pump for infusion, material for dilution) as well as the costs of drugs (vancomycin and linezolid) were evaluated in both periods. The costs were fixed along the time, considering the values in January 2018. After analysis of costs of T1, a simulation was performed, considering three hypothetical situations: 1) substitute of vancomycin to linezolid for all patients in the hospital; 2) substitute vancomycin to linezolid in all patients with incipient acute renal failure (serum Cr level >1.5 mg/dL in the intensive care unit); and 3) substitute vancomycin to linezolid only in patients under hemodialysis.

After this simulation, the ASP in accord with the administration of the hospital, decide to change vancomycin to linezolid in all patients with serum creatinine level >1.5 mg/dL in the intensive care unit. Thus, an analysis of the real costs was performed during the T2. The costs related to each drug, vancomycin (USD 0.58) and linezolid (USD 14.79), vancomycin infusion kit (USD 0.50), linezolid infusion kit (USD 0.22), and VSL (USD 15.61), were expressed in United States dollar (USD)

Assessment and Outcomes

In T1 and T2, the costs previously described were evaluated, as well as the monthly incidence and number of cases of infection/colonization of methicillin-resistant Staphylococcus aureus (MRSA). These data were included to correlate the consume of both anti-MRSA drugs (linezolid and vancomycin) and MRSA rated during both periods.

The consume of the antibiotics were evaluated in DDD (Defined Daily Dose – DDD)/1000 patients-day; the costs were evaluated in United States dollars (USD), and incidence of MRSA in number of cases/1000-patients-day.

A breakeven graph was developed to simulate the possible breakeven price of linezolid if we consider a fixed cost of vancomycin [8].

Statistical analysis

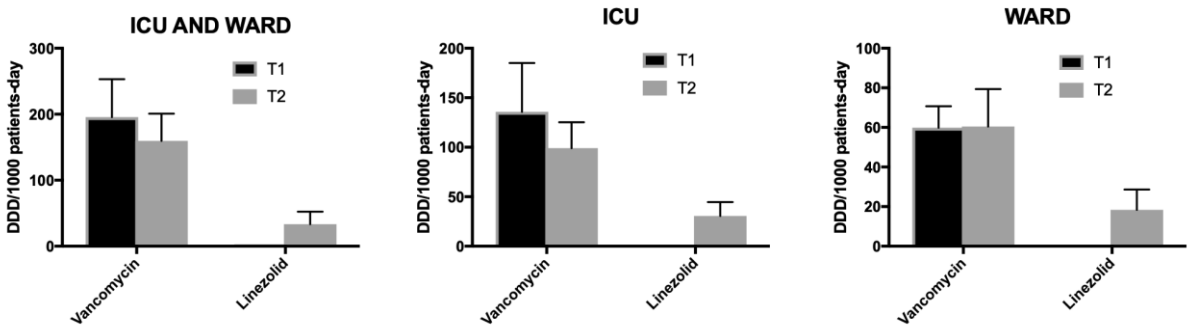
We used the Student's t-test or Mann-Whitney test to compare utilization and costs for vancomycin and linezolid between the two periods and MRSA infection/colonization. For all analyses, $p<0.05$ was considered statistically significant. All tests were performed using SPSS 21.0 and descriptive statistics and graphs were designed in Prism GraphPad 7.

3 RESULTS

Antibiotic use

During T1, consume of vancomycin was 195.5 DDD-1000-patients day and linezolid 0 DDD-1000-patients day. In T2, consume of vancomycin was 159.5 DDD-1000-patients day and linezolid only 33.4 DDD-1000-patients day (Figure 1).

Figure 1. Comparison of consume in DDD of vancomycin and linezolid 6 months before and after implementation of routine linezolid use for incipient acute renal failure.

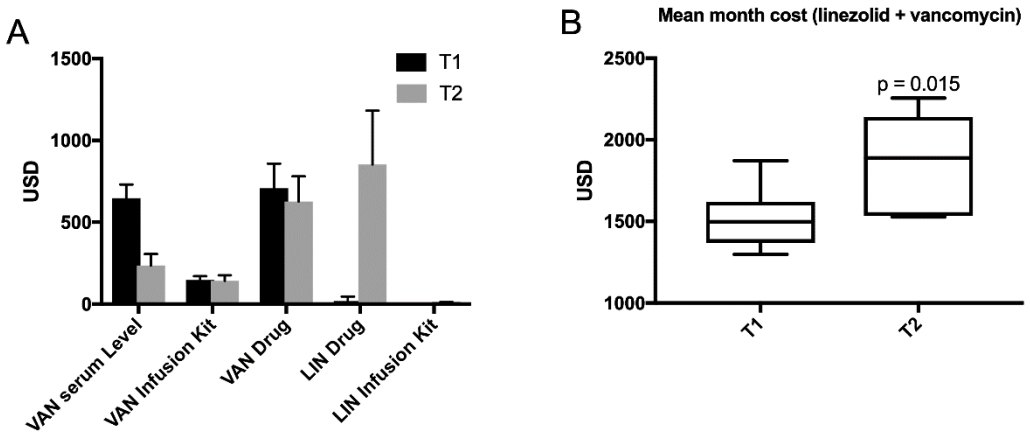


There was statistical difference in consume of linezolid between T1 and T2 (p=0.002); but not to vancomycin between T1 and T2 (p=0.157). Even though linezolid was used in ICU, some patients continued the treatment in the ward.

Antibiotic – related costs

The costs with vancomycin (including drug, infusion kit and VSL) and linezolid (drug and infusion kit) in T1 and T2 were USD 9202 and USD 11331, respectively (difference of + USD 2,128). The detailed cost with drugs, infusion kits, VSL are detailed in the figure 2A.

Figure 2. A- Detailed costs with vancomycin (including drug, infusion kit and VSL) and linezolid (drug and infusion kit) in T1(black) and T2 (gray). B – The mean month cost of vancomycin (including drug, infusion kit and VSL) and linezolid (drug and infusion kit) in T1(left) and T2 (right).

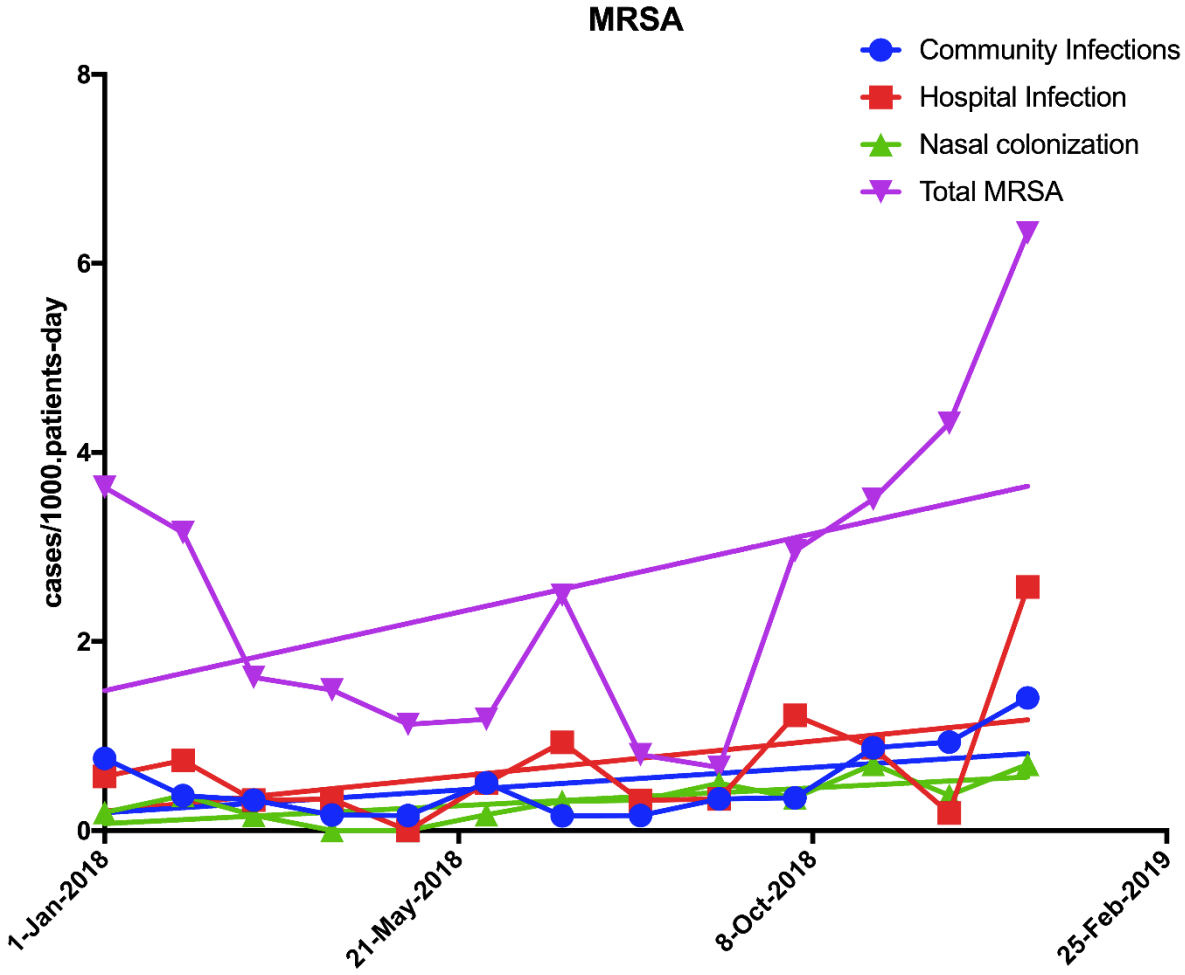


The consume of vancomycin maintained during both periods (p = 0.984), and the consume of linezolid increased (p < 0.001). The mean month cost of vancomycin and linezolid was higher in T2 than T1 (p = 0.015) (figure 2B).

MRSA incidence

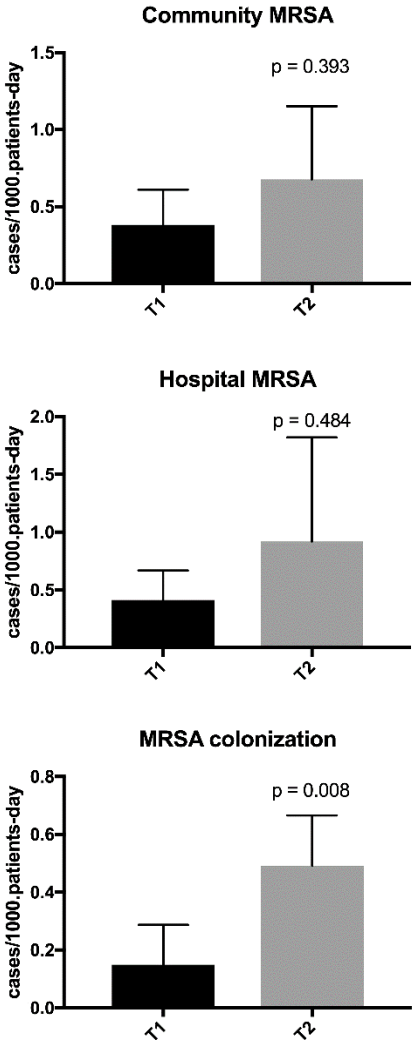
There was a trend of increasing the incidence of MRSA during the period of study with a r2 = 0.51 (figure 3).

Figure 3. Incidence of MRSA according with the site during all study since January 2018 to January 2019.



When we separated the cases of MRSA according with site, there was a significant increase in the incidence of colonized patients (p = 0.008), but not with hospital infection (p = 0.484) and community infection (p = 0.393) (figure 4).

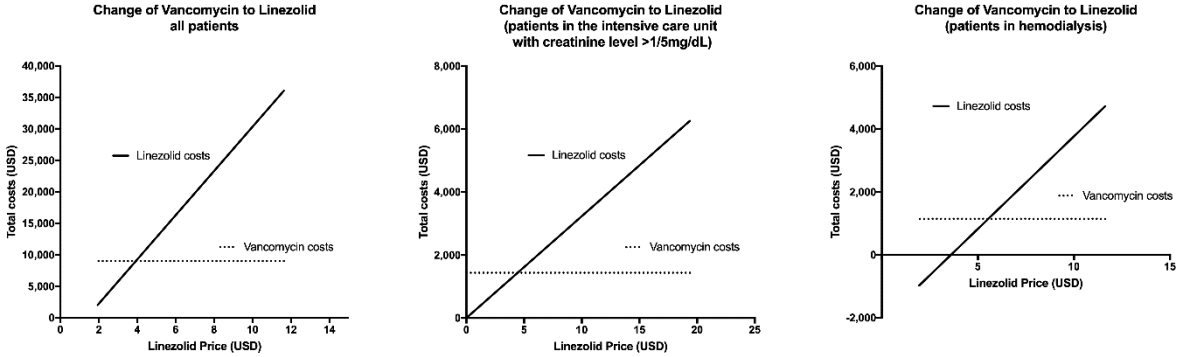
Figure 4. Mean month incidence of MRSA according with the site comparing T1 with T2.



Breakeven analysis

To determine the ideal price of linezolid to achieve similar or lower cost than vancomycin, a breakeven graph was constructed. We created three hypothetical situations: 1) change all vancomycin costs (drug + VSL + infusion kit) to linezolid; 2) change vancomycin costs (drug + VSL + infusion kit) to linezolid only for patients with serum creatinine level >1.5mg/dL in the ICU; 3) change vancomycin costs (drug + VSL + infusion kit) to linezolid for patients under hemodialysis. In the figure 5, the horizontal line is the total vancomycin costs, and the inclined line is the total cost of linezolid according with the price of the drug. When the lines cross, is the ideal price of linezolid to be considered in the hospital[33].

Figure 5. Breakeven simulation of linezolid price according with indications to change of vancomycin.



4 DISCUSSION

This study evaluated different scenarios between costs of vancomycin and linezolid usage. According to breakeven simulation in our hospital, the best scenario would be the replacement of vancomycin with linezolid in patients admitted to ICU and serum Cr levels > 1.5 mg/dL. This is due to our protocol of VSL, once it is recommended to measure only in this group of patients. However, real-life results from T1 versus T2 did not demonstrate cost benefit in replacement vancomycin for linezolid, at least in the hospital evaluated.

Vancomycin can be considered the first option to MRSA infection [9]. No drug to date has shown superiority to vancomycin in the treatment of MRSA infections, although some studies have suggested a superiority of linezolid in hospital-acquired pneumonia [10, 11]. Nevertheless, new pharmacokinetics and pharmacodynamics (Pk/Pd) studies improved the use of vancomycin [12]. After 2004, more studies have demonstrated that best AUC_{24h}/MIC ratio is between 350-400 in bacteremic patients [12, 13]. Vancomycin troughs levels between 15-20 mg/dL are demonstrated to be correlated with AUC_{24h}/MIC ratio > 400 when considered Staphylococcus aureus MIC 1mg/dL [14]. Thus, vancomycin costs usage was increased once therapeutic drug monitoring is highly needed to evaluate if target achievement is reached [15]. The greater the need of VSL, the greater the cost of applied therapy.

Linezolid is an alternative option to MRSA infections [16]. Concerning about its bacteriostatic effect in bacteremic patients or with blood stream infection had been raised, however, meta-analysis supported the use of linezolid even in those group of patients [17]. Linezolid cost is high and PD targets (AUC_{24h}/MIC > 80-120) are commonly constant [18], thus, there is low evidence to recommend t a therapeutic drug monitoring program, which may justify cost benefits analysis. Previous publications diverged from our study,

suggesting that linezolid is more cost-effective than glycopeptides [19, 20]. Nevertheless, once hospital epidemiology of bacterial susceptibility is heterogeneous among regions, this pharmacoeconomic analysis must be made in details (i.e. considering different VSL protocols and renal insufficiency incidence).

Therefore, these considerations may explain the divergent results from this study. A retrospective study compared the costs of vancomycin with linezolid in a German model re-imbursement data of real-life patient populations, showing no difference between the drugs [21]. Other authors have also reinforced that all analysis between vancomycin and linezolid requires customization for each national payer's system [22]. In a Chinese perspective, linezolid was more cost-effective than vancomycin, considering adverse effects of this drug [23]. Other studies from different points of view showed similar results with our study [24,25]. The theorical burden of vancomycin related renal failure is questionable in cost-analysis publications [26]. In other extreme, authors affirms that vancomycin must be the first choice treatment for MRSA infections and the cost of linezolid is not justifiable [27].

There is only one study evaluating the cost-effectiveness of linezolid and vancomycin. However, it was a simulation from meta-analysis, showing that linezolid is cost-effective in a Brazilian perspective [28,34].

Variables may be categorized into (i) patient profile, (ii) MRSA incidence and (iii) VSL protocols. Patients profile interferes in the costs of vancomycin according comorbidities (i.e. Charlson index), need of antibiotic association (i.e. piperacillin-tazobactam, aminoglycosides) and renal insufficiency. Higher Charlson comorbidities, association with piperacillin-tazobactam or aminoglycosides, diuretics and previous renal insufficiency are related to vancomycin toxicity and unpredictable serum levels [29,32]. MRSA incidence influence vancomycin use once the greater incidence, the greater usage. Lastly, VSL protocols vary among available economic resources. Hospitals with broader criteria for VSL measurement shall present a breakeven graph different from ours and tending to favor linezolid in general. Thus, we do not recommend extrapolate previous data once scenarios must be cautiously analyzed according population, MRSA incidence and VSL protocols. This was an important issue in our study because there was an increase in the MRSA incidence, increasing the consume of vancomycin and linezolid. This epidemiology chance in the hospital is the prove that studies based only in simulations should be carefully evaluated before implementation in the hospital routine[33].

The best approach is to recognize the local panorama, propose the ideal protocol and test it for a short period.

We performed a retrospective study with common limitations like patients not randomly allocated to treatments and the stratification by diagnoses. The cost-analysis used a fixed cost of the drug, however, in Brazil, the price of medications and laboratorial tests are extremely variables along the year[35,36].

In resume, linezolid implementation as a strategy to avoid vancomycin with VSL is not cost-effective[33,34]. The panorama of each hospital must be carefully evaluated before strategies like we implemented, because the incidence of MRSA can be an important variable and the monitoring of VSL continues to be an important approach to achieve an ide al Pk/Pd parameter for treatment.

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