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Pharmacoeconomics of linezolid

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Background: New antibiotics efficacious in infections caused by resistant Gram-positive microorganisms and with acceptable costs for national health systems per unit of effectiveness are needed. *Objective*: This paper aimed to summarize all available evidence regarding the pharmacoeconomics of linezolid. *Methods*: A systematic review of pharmacoeconomic analyses through a non-restricted literature search was conducted. *Results/conclusions*: Linezolid, as compared to vancomycin and teicoplanin, results in a reduction of the necessary resources for the treatment of infections caused by Gram-positive microorganisms. These benefits are attributable to clinical outcomes and to savings associated with the ease of switching from intravenous to oral administration, the shorter duration of intravenous therapy and earlier hospital discharge. Likewise, linezolid, compared to vancomycin and teicoplanin, is a cost-effective treatment.

Keywords: cost analysis, Gram-positive bacterial infections, linezolid, teicoplanin, vancomycin

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1. Introduction

1.1 Resistance among Gram-positive microorganisms

The incidence of serious infections that are caused by Gram-positive microorganisms has significantly increased since the early 1990s worldwide [1,2]. The increase in resistance among these microorganisms is a reason for concern, since they are responsible for one-third of nosocomial infections [3]. In recent years, one of the resistant microorganisms with a more markedly increased incidence in hospital environments is methicillin-resistant *Staphylococcus aureus* (MRSA). Although the incidence of this microorganism in community-acquired infections has increased in many geographic areas, most MRSA strains are isolated in hospital- and nursing home-acquired infections [4]. Currently, MRSA is the most frequently isolated antibiotic-resistant microorganism in US hospitals [5]. In addition, 25.9% of *S. aureus* strains isolated in outpatients are methicillin resistant [6] and most are from individuals who probably became infected in a healthcare environment [7]. A distinction was made recently between infections caused by hospital-related strains and those caused by community-acquired strains, these latter ones being in subjects with no direct or indirect relationship with healthcare environments, thus creating an important health problem [8,9]. The prevalence of MRSA in Europe is widely variable, ranging from < 1% in northern European countries to > 40% in southern European countries [10].

Available data appear to indicate that MRSA infections are related to higher mortality rates when compared to infections caused by methicillin-susceptible *S. aureus* (MSSA) strains [11-14]. Similarly, the presence of MRSA infections, as compared to MSSA infections, was related to significant increases in the length of hospital stay and costs, even after adjustment for the severity of infection and appropriate antibiotic treatment [15].

For over 40 years vancomycin was the treatment of choice for methicillin-resistant staphylococci infections. However, in recent years, MRSA strains of intermediate or total vancomycin resistance have appeared [8,16,17]. This has resulted in a decrease in the Clinical and Laboratory Standards Institute cutting-point

values for determining the susceptibility to vancomycin of this microorganism [18]. The frequency of vancomycin-resistant enterococci (VRE) also increased, rising to 27.5% in the US in the year 2002 [1]. On the contrary, this is an anecdotal problem in Europe.

1.2 Economic impact of resistant infections

Bacterial resistance is related to human lives and financial costs, since it results in increased levels of morbidity and mortality, length of hospital stay and significant addition to direct costs (due to longer antibiotic treatments and an increased number of complementary tests), indirect costs (due to loss of working days) and greater possibilities of spreading the infection [19].

In studies conducted in the US the differences in costs between MRSA and MSSA infections ranged from US$2500 to US$17,000 per episode [11,20,21]. In accordance with a retrospective case–control study, hospitalization of patients with MRSA infections was more prolonged compared to patients with MSSA infections (15.5 versus 11 days) ($p = 0.05$) and the cost per episode was higher ($16.575 versus $12.862) ($p = 0.11$) [22]. These results have been confirmed in many other studies [23-27].

The higher costs of VRE infections were also confirmed in a retrospective study in which longer lengths of hospital stay and higher rates of intensive care unit stay were observed when compared to episodes caused by non-resistant strains. However, the most important difference was found in mortality rates, with 17% for VRE infections versus 6% for non-VRE infections (RR = 2.13 and $p = 0.04$) [28].

1.3 Treatment options and unmet medical needs

Even though numerous antibiotics are active against Gram-positive cocci, those with greater antibacterial activity, including vancomycin, teicoplanin and linezolid, are now preferably recommended [29]. Daptomycin has recently been included in the therapeutic arsenal. Linezolid is a synthetic antibiotic belonging to a new class of antimicrobials, the oxazolidinones, which offers flexible intravenous/oral formulations with high tissue penetration. Linezolid is active against a wide variety of Gram-positive bacteria. Linezolid has been approved for the treatment of nosocomial pneumonia (NP) and community-acquired pneumonia when known or suspected to be caused by susceptible Gram-positive bacteria and complicated skin and skin structure infections (CSSTIs) only when susceptible Gram-positive bacteria are known to have caused the infection [30,31].

As previously mentioned, vancomycin had been the antibiotic of choice for the treatment of resistant Gram-positive microorganisms for years. However, the appearance of resistance to this glycopeptide revealed the need for therapeutic alternatives providing a response to this incipient phenomenon. This is the case of NP due to MRSA, for which increases in survival and clinical cure rates were observed with linezolid compared to vancomycin [32,33]. The greater efficacy of linezolid was observed for pneumonia related to mechanical ventilation (ventilation-associated pneumonia [VAP]) caused by MRSA as well, with 84.1 versus 61.7% ($p = 0.02$) survival rates for linezolid and vancomycin, respectively [34].

Linezolid has been demonstrated to be well tolerated in CSSTIs and equivalent to vancomycin, with a strong microbiological success rate in MRSA CSSTIs [35]. In a subset of the Weigelt *et al.* [36] study, intravenous/oral linezolid proved to be a suitable alternative to vancomycin in the treatment of patients with suspected MRSA surgical site infections (SSIs).

Finally, due to the previously mentioned reasons, new antibiotics efficacious in infections caused by resistant Gram-positive microorganisms and with acceptable costs for national health systems per unit of effectiveness are necessary.

2. Review of pharmacoeconomic analyses

2.1 Objective of the review

The objective of this review was to summarize all available evidence regarding the pharmacoeconomics of linezolid.

2.2 Selection of studies

A non-restricted literature search in Medline and Embase was conducted for linezolid as a free term and 1469 references were obtained. Likewise, the search was extended to the following databases: Cochrane Plus Library, DIMDI Health Technology Assessment databases, NHS Economic Evaluation Database (Centre for Reviews and Dissemination), CEA Registry, Medscape and in the journals *Value in Health* and *Health Technology Assessment*. Finally, the references of all original papers were reviewed. This search was carried out in November 2007.

Economic evaluations of linezolid obtained in the literature review were selected and different types of analyses (cost, cost consequence, cost minimization, cost-effectiveness, cost-utility and cost-benefit) were distinguished.

After removing duplicate publications, a total of 41 references were chosen, corresponding to 31 studies, 16 of which were studies of resource utilization, costs and/or cost minimization analyses and 15 of which were cost-effectiveness analyses.

3. Economic analyses

3.1 Use of health resources studies

Nine studies were available on the use of health resources associated with antimicrobial treatment with linezolid [37-47] compared to vancomycin or teicoplanin (**Table 1**). Seven of them were based on randomized clinical trials [37-40,41,46] and the other two were retrospective studies [41,47]. The primary variables measured in most of these studies were the length of hospital stay and duration of intravenous antibiotic treatment. This was due to the oral formulation

Table 1. Pharmacoeconomics of linezolid: health resources use studies.

Countries and ref.	Infection type	Study design	Antibiotics	Sample size	Variable	Results (linezolid versus controls)	Statistical significance
Multinational [37]	MRSA – all infections	Randomized clinical trial	Linezolid Vancomycin	240 220	Hospital length of stay (days) – all infections (median and 95% CI)	14 (9 – 17) versus 15 (13 – 17)	0.19
	MRSA – CSSTIs		Linezolid Vancomycin	122 108	Duration of antibiotic treatment (days) – all infections (mean) Hospital length of stay (days) – CSSTIs (median and 95% CI) Duration of antibiotic treatment (days) – CSSTIs (mean)	6.7 versus 11.3 (intravenous only) 12.6 versus 11.3 (intravenous and oral) 9 (8 – 16) versus 14 (12 – 18) 5.8 versus 12.6 (intravenous only) 14.2 versus 12.6 (intravenous and oral)	0.0001 0.05 0.052 0.0001 0.09
Multinational [38]	MRSA – all infections	Randomized clinical trial	Linezolid Vancomycin	240 220	Adjusted hospital length of stay reduction with linezolid (days) (median) (multivariate analysis)	2.53	0.04
Multinational [39]	MRSA – CSSTIs	Randomized clinical trial	Linezolid Vancomycin Intent to treat Clinically evaluable SSIs	122 108 230 144 114	Adjusted hospital length of stay reduction (days) with linezolid (median) (multivariate analysis) Intent to treat Clinically evaluable SSIs	3.1 6.5 2.5	< 0.01 < 0.01 < 0.10
South America and Mexico [40]	Serious Gram-positive	Randomized clinical trial	Linezolid Teicoplanin	97 106	Adjusted hospital length of stay reduction (days) (median) (multivariate analysis)	1.6	0.049
USA [41]	MRSA – all infections	Retrospective chart review	Intravenous vancomycin Switching to oral administration linezolid Eligible for early discharge	177 103 55	Length of stay decrease with linezolid (mean and SD) due to early discharge (days)	3.3 (2.9)	–
Europe [42]	Serious Gram-positive	Randomized clinical trial	Linezolid Teicoplanin	118 109	Hospital length of stay (days) (median and quartile 1 – quartile 3) Duration of intravenous antibiotic treatment (days) (mean)	11 (5 – 23) versus 10 (6 – 28) 6.3 versus 9.5	0.79 0.0001
Multinational [43]	MRSA – CSSTI	Randomized clinical trial	Linezolid Vancomycin	592 588	Hospital length of stay (days) (mean) – Iintent to treat Hospital length of stay (days) (mean) – MRSA Duration of intravenous antibiotic treatment (days) – intent to treat Duration of intravenous antibiotic treatment (days) – MRSA	7.4 versus 9.8 8.1 versus 10.7 1.9 versus 9.0 1.8 versus 12.6	< 0.0001 0.0026 < 0.0001 < 0.0001

Table 1. Pharmacoeconomics of linezolid: health resources use studies (continued).

Countries and ref.	Infection type	Study design	Antibiotics	Sample size	Variable	Results (linezolid versus controls)	Statistical significance
USA [44]	MRSA – CSSTI	Randomized clinical trial	Oral administration linezolid lintravenous vancomycin	30 30	Length of stay decrease with linezolid (mean and SD) due to early discharge (days)	3.0	0.003
USA [45]	MRSA – CSSTI	Randomized clinical trial	Linezolid Vancomycin	366 351	Hospital length of stay (days) (mean ± SD) – intent to treat Hospital length of stay (days) (mean ± SD) – MRSA Duration of intravenous antibiotic treatment (days) – intent to treat Duration of intravenous antibiotic treatment (days) – MRSA	1.7 ± 2.6 versus 9.7 ± 5.5 1.6 ± 2.7 versus 11.0 ± 5.6 5.5 ± 6.4 versus 7.7 ± 7.7 5.5 ± 6.5 versus 8.0 ± 8.6	0.001 0.001 < 0.001 0.005
USA [46]	MRSA – CSSTIs (elderly)	Randomized clinical trial	Linezolid Vancomycin	87 76	Length of stay decrease with linezolid (mean) Duration of intravenous antibiotic treatment with linezolid (days)	3.5 9.5	< 0.001 < 0.001
USA [47]	CSSTIs	Retrospective (database)	Oal administration linezolid Intravenous vancomycin	205 205	Physician office visits (mean ± SD) Laboratory/Diagnostic claims (mean ± SD) Pharmacy claims (mean ± SD) Emergency room visits (mean ± SD) Hospitalizations (mean ± SD)	4.1 ± 5.7 versus 8.4 ± 13.8 6.3 ± 18.0 versus 10.4 ± 15.2 7.3 ± 8.1 versus 13.6 ± 17.4 9.7 versus 13.9% 15.3 versus 19.1%	< 0.001 < 0.001 < 0.001 0.003 0.024

of linezolid, thereby allowing the introduction of a sequential therapy, that is intravenous followed by oral administration, which is a characteristic that permits the reduction of the length of hospital stay by speeding up the discharge and continuation of the patient's treatment at home. This is not feasible with intravenously administered vancomycin and is more difficult to carry out with intramuscularly administered teicoplanin. In this sense, the studies concluded that, in most cases, oral treatment with linezolid results in a reduction of the length of hospital stay. In the case of MRSA, the reduction ranged from a minimum of 1 day to a maximum of 9.4 days of hospitalization when compared to vancomycin [37,45]. When compared to teicoplanin in serious Gram-positive infections, the reduction in the length of hospital stay with linezolid was 1.6 days [40]. On the contrary, no reduction was observed in another study (**Table 1**) [42].

As foreseen, the duration of intravenous antibiotic treatment with linezolid was shorter compared to vancomycin (2.2 – 10.2 days) [37,43,45,46] and teicoplanin (3.2 days) (**Table 1**) [42].

McKinnon *et al.* [47] conducted a retrospective study using a US health database comprising 10,962 patients, from which two cohorts of 205 patients were selected with CSSTIs treated with oral linezolid or intravenous vancomycin, respectively. This study evaluated the use of other health resources, including medical visits, diagnostic tests, pharmacological treatments, visits to emergency departments and the rate of hospitalizations. In all cases, the treatment with oral linezolid resulted in a statistically significant lower use of resources compared to intravenous treatment with vancomycin (**Table 1**).

3.2 Cost analyses

Fifteen cost or minimization of cost studies were available [40-44,47-56] with linezolid compared to vancomycin, teicoplanin, flucloxacillin, oxacillin and imipenem (**Table 2**). Six of these studies were randomized clinical trials [40,42,44,45,49,53], five were pharmacoeconomic models [48,51,54-56] and four were retrospective studies [41,47,50,52]. Four studies collected data from various countries [40,42,49,53], while the rest of the studies were conducted in single countries (six in the US, two in the UK, one in Germany, one in Mexico and one in Hong Kong). As foreseen, the cost of sequential therapy with linezolid (intravenous therapy during hospitalization followed by oral therapy at home) was lower than the cost of the other antibiotics mentioned above: this was a consequence of a reduced length of hospital stay and duration of intravenous administration. In the case of MRSA infections, the saving per patient treated with oral linezolid instead of intravenous vancomycin ranged between a minimum of €121 and a maximum of €1125 [41,44,45,53,54]. In a comparison with teicoplanin, savings with linezolid ranged between $335 and $1286 (**Table 2**) [40,42].

In the treatment of cellulitis, linezolid indicated lower costs than vancomycin for all rates of MRSA resistance and, compared to flucloxacillin and oxacillin, generated lower costs per patient for 24.1 and 18.7% rates of MRSA resistance, respectively [48,51].

In a comparison against imipenem conducted in Mexico in patients with mechanical VAP caused by *S. aureus*, a 12-week treatment with linezolid resulted in a saving of $4053 per patient [55].

Compared to linezolid, home-infusion vancomycin was only related to lower direct medical costs under the perspective of the national health system in a study conducted in Hong Kong [56]. The cost of outpatient therapy with linezolid was analyzed against 6-week in-hospital (or intravenous administration in a rehabilitation center) or outpatient (home parental administration) therapy with vancomycin for the treatment of prosthetic joint infections. The results indicated that outpatient therapy with vancomycin was related to mean savings of $2313 (95% CI 2188 – 2438) and $4881 (95% CI 4869 – 4893) versus linezolid and hospital vancomycin therapies, respectively. The linezolid group was less costly than the group receiving vancomycin in the inpatient setting (in hospital or in a rehabilitation center).

3.3 Cost-effectiveness analyses

Fifteen cost-effectiveness studies of linezolid compared to vancomycin and teicoplanin were available (**Table 3**) [40-45,47-55]. Only one of these studies was a randomized clinical trial [57] and the other 14 were pharmacoeconomic models [58-71]. In the clinical trial, data from six European and seven South American countries were collected [57], while the rest of the studies were limited to analysis of the efficiency of linezolid in single countries (five in Spain, three in the US, two in France, one in Germany, one in Italy, one in Brazil and one in Argentina).

According to the cost-effectiveness clinical trial conducted by Li *et al.* [57], the probability of linezolid dominance over teicoplanin (i.e., linezolid being more efficacious and with lower costs versus teicoplanin) for the treatment of serious Gram-positive infections was 65.3% in European countries and 86.9% in South American countries.

The following variables were analyzed in pharmacoeconomic models: the cost of quality-adjusted life year gained (QALY), cost of life year gained (LYG) with the most efficacious treatment, cost per avoided death and/or, finally, cost per additional clinically cured patient.

Only two of these models were cost–utility analyses [59,60]. In both studies, which were carried out with the same decision tree, the efficiency of treatment with linezolid (intravenous 600 mg/12 h for 10 days) was compared to vancomycin (intravenous 1000 mg/12 h for 10 days) in VAP patients. A retrospective cost–utility model with a decision analysis was designed. A 10-day duration of the antibiotic treatment was considered for the analysis of costs.

Table 2. Pharmacoeconomics of linezolid: cost and cost-minimization analyses.

Countries and ref.	Infection type	Study design	Antibiotics	Sample size	Variable	Results (linezolid versus controls)	Statistical significance
UK [48]	Cellulitis	Decision-analytic model	Linezolid Flucloxacillin Vancomycin	–	To assess the clinical and economic consequences of using linezolid for the empiric treatment of cellulitis versus flucloxacillin and vancomycin	Linezolid is likely to be less costly compared with vancomycin at all resistance rates and with flucloxacillin when the risk of infection with MRSA is greater than 24.1%	–
Multinational [49]	MRSA – all infections	Randomized clinical trial	Linezolid Vancomycin	240 220	Hospital costs comparison	The total costs were higher for linezolid patients than vancomycin patients	NS
South America and Mexico [40]	Serious Gram-positive	Randomized clinical trial	Linezolid Teicoplanin	97 106	Total cost reduction per patient treated with linezolid ($) (mean) (multivariate analysis)	$335	NS
USA [41]	MRSA – all infections	Retrospective chart review	Intravenous vancomycin Switching to oral administration linezolid Eligible for early discharge	177 103 55	Total annual cost reduction per patient of switching from intravenous vancomycin to oral administration linezolid ($) (mean) (minimum – maximum)	$5359 ($649 – 10069)	–
UK [50]	Bone and joint infections	Retrospective study	Teicoplanin (or hypothetical linezolid)	55	Total cost per patient of treatment with teicoplanin (outpatient or home setting) or hypothetical oral linezolid (home setting) (£) (mean)	Teicoplanin (inpatient) = £11,400 Teicoplanin (ambulatory) = £1749 Linezolid (home) = £2546	–
USA [51]	Cellulitis	Decision-analytic model	Linezolid Oxacillin Vancomycin	– – –	To assess the clinical and economic consequences of using linezolid for the empiric treatment of cellulitis versus oxacillin and vancomycin	Linezolid is likely to be less costly compared with vancomycin at all resistance rates and with oxacillin when the risk of infection with MRSA is > 8.7%	–
USA [52]	All infections	Retrospective study and pharmacoeconomic model	Intravenous vancomycin (or hypothetical oral administration Linezolid)	72	Treatment-related cost savings per patient of switching from intravenous vancomycin to hypothetical oral administration linezolid (both at home setting)	$2413	–

NS: Non-significant.

Table 2. Pharmacoeconomics of linezolid: cost and cost-minimization analyses (continued).

Countries and ref.	Infection type	Study design	Antibiotics	Sample size	Variable	Results (linezolid versus controls)	Statistical significance
Europe [42]	Serious Gram-positive	Randomized clinical trial	Linezolid Teicoplanin	118 109	Total cost reduction per patient treated with linezolid ($) (mean) (adjusting for baseline variables)	Adjusted for outpatient/home parenteral antibiotic therapy effect = $555 Unadjusted for outpatient/home parenteral antibiotic therapy effect = $1286	0.76 0.47
Multinational [53]	MRSA – CSSTIs	Randomized clinical trial	Linezolid Vancomycin	592 588	Total cost reduction per patient treated ($) (mean)	$511	< 0.0001
USA [44]	MRSA – CSSTI	Randomized clinical trial	Oral administration linezolid Intravenous vancomycin	30 30	Total cost per patient treated with linezolid ($) (mean)	$227 versus $160 $103 versus $200	0.069 0.001
Germany [54]	MRSA – CSSTIs	Decision-analytic model	Linezolid Vancomycin	– –	Total cost reduction per patient treated with Linezolid (€) (mean)	€121	–
Mexico [55]	Ventilator-associated pneumonia due to *S. aureus*	Decision-analytic model	Linezolid Vancomycin Imipenem	– – –	Total cost per patient ($) (mean and 12-week period)	$38182 $39345 $42235	– – –
USA [45]	MRSA – CSSTIs	Randomized clinical trial	Linezolid Vancomycin	366 351	Total cost per patient ($) (mean ± SD) – intent to treat Total cost per patient ($) (mean ± SD) – MRSA	$4865 ± 4367 versus $5738 ± 5190 $4881 ± 3987 versus $6006 ± 5039	0.017 0.041
USA [47]	CSSTIs	Retrospective (database)	Oral administration linezolid Intravenous Vancomycin	1.048 1.048	Total cost reduction per patient treated with linezolid ($) (mean)	$4707	< 0.001
Hong Kong [56]	Prosthetic joint infections	Decision-analytic model	Linezolid Vancomycin	– –	Total cost per patient ($) (mean) Total cost per patient ($) (mean) – rehabilitation Total cost per patient ($) (mean) – outpatient/home parenteral antibiotic therapy	$17,877 $19,980 $14,470	– – –

NS: Non-significant.

Table 3. Pharmacoeconomics of linezolid: cost-effectiveness and cost-utility analyses.

Countries and ref.	Infection type	Study design	Antibiotics	Sample size	Variable	Results (linezolid versus controls)
Europe and South America [57]	Serious Gram-positive	Randomized clinical trial	Linezolid versus teicoplanin	227 (European countries) and 203 (South American countries)	Probability of dominance (lower cost and superior effectiveness) with linezolid*	European countries – 65.3% South American countries – 86.9%
Germany [58]	MRSA – NP	Decision-analytic model	Linezolid Vancomycin	– –	Cost per life year gained with linezolid Cost per death avoided with linezolid	€371 €124
USA [59]	Ventilator-associated pneumonia due to *S. aureus*	Decision-analytic model	Linezolid Vancomycin	–	Cost per QALY gained with linezolid	$29,945 (95% CI $23,637 – 42,785)
Spain [60]	Ventilator-associated pneumonia due to *S. aureus*	Decision-analytic model	Linezolid Vancomycin	–	Cost per QALY gained with linezolid – all patients Cost per QALY gained with linezolid – Gram-positive Cost per QALY gained with linezolid – *S. aureus* Cost per QALY gained with linezolid – MRSA	€1804 €997 €1149 €349
Spain [61]	Bacteremia by Gram-positive	Decision-analytic model	Linezolid Teicoplanin	–	Cost per cured patient	€6279 (95% CI €5960 – 6510) versus €11159 (95% CI €10,865 – 12,647) Linezolid is the dominant option*
Brazil [62]	MRSA – VAP	Decision-analytic model	Linezolid Vancomycin	–	Cost per cured patient	Brazilian real 7765 versus 11,277
Argentina [63]	Nosocomial pneumonia	Decision-analytic model	Linezolid Vancomycin	–	Cost per life year gained with linezolid Cost per death avoided with linezolid	$482 $7299
Italy [64]	MRSA – CSSTIs	Decision-analytic model	Linezolid Vancomycin Teicoplanin	–	Cost per cured patient versus vancomycin Cost per cured patient versus teicoplanin	€22,404 €17,100
USA [65]	MRSA – NP	Decision-analytic model	Linezolid Vancomycin	–	Cost per life year gained with linezolid	$3600
France [66]	MRSA – NP	Decision-analytic model	Linezolid Vancomycin	–	Cost per life year gained with linezolid Cost per death avoided with linezolid	€685 €12,727
France [67]	MRSA – CSSTIs	Decision-analytic model	Linezolid Vancomycin	–	Cost per cured patient (€)	Linezolid is the dominant option*

*Dominant option: less costly and more effective than the comparator.

Table 3. Pharmacoeconomics of linezolid: cost-effectiveness and cost-utility analyses (continued).

Countries and ref.	Infection type	Study design	Antibiotics	Sample size	Variable	Results (linezolid versus controls)
Spain [68]	Infections caused by Gram-positive	Decision-analytic model	Linezolid Teicoplanin	–	Cost per cured patient	€8445 (95% CI €8196 – 8709) versus €9963 (95% CI €9466 – 10,502)
Spain [69]	MRSA – SSIs	Decision-analytic model	Linezolid Vancomycin	–	Cost per cured patient (€)	Linezolid is the dominant option*
Spain [70]	MRSA – NP	Decision-analytic model	Linezolid Vancomycin	–	Cost per life year gained with linezolid Cost per death avoided with linezolid	€406 €4730
USA [71]	MRSA – SSIs	Decision-analytic model	Linezolid Vancomycin	–	Cost per cured patient – oral administration linezolid Cost per cured patient – intravenous vancomycin plus oral administration linezolid Cost per cured patient – intravenous vancomycin	$10,292 $14,486 $17,653

*Dominant option: less costly and more effective than the comparator.

For the calculation of gained LYG and QALY, the survival of VAP patients was estimated to be 50% of life expectancy at the age of 62 years (9 years). Four patient subgroups were analyzed and included all patients with a diagnosis of VAP, VAP caused by a Gram-positive microorganism, VAP caused by *S. aureus* and VAP caused by MRSA. The rates of clinical cure and survival were obtained in a retrospective analysis [35] of two randomized and double-blind clinical trials comparing linezolid versus vancomycin in VAP [33,34]. The following health costs were considered: the cost of antibiotic acquisition, cost of vancomycin monitoring, diagnostic tests due to clinical failure and intensive care unit stay. Utilities were collected from a study conducted using the time trade-off technique. In accordance with the model results, in the Spanish study [60] linezolid was more effective than vancomycin and resulted in a greater number of LYGs (0.471, 0.829, 0.729 and 2.175) and QALYs (0.392, 0.688, 0.606 and 1.805) in the four above-listed groups of VAP patients, respectively. Due to the higher cost of acquisition, linezolid generated more costs than vancomycin (€707.12, 686.11, 696.29 and 629.68, respectively). As a consequence, the additional costs per LYG with linezolid compared to vancomycin were €1501.31, 827.63, 955.13 and 289.51, respectively. The costs per gained QALY with linezolid were €1803.87, 997.25, 1149.00 and 348.85, respectively. In most scenarios of the model linezolid was more cost-effective than vancomycin for the treatment of VAP due to its greater efficacy (both in clinical cure and survival), thereby providing more life years and QALYs and with an acceptable additional cost. The results of the US model confirmed the greater cost-effectiveness of linezolid in VAP [59]. However, comparing the results obtained in the Spanish study [60] with those in the study by Shorr *et al.* [59] is of interest. When applied to the US the incremental costs per LYG or additional QALY in patients with VAP for *S. aureus* treated with linezolid were $22,027 and $29,945, respectively. The absolute cost would be higher than in the Spanish model, possibly due to the differences in the health system costs and to the fact that, in the US study, long-term costs were also considered [59].

In four [58,65,66,70] out of five studies [63] the cost per LYG with linezolid, compared to vancomycin in the treatment of NP caused by MRSA was, in general, low, between €337 and 685, updated to the year 2007. The highest cost per LYG was €2518.

In three [58,66,70] out of four studies [63] the costs per avoided death with linezolid compared to vancomycin in the treatment of NP caused by MRSA ranged between €4730 and 5616, updated to the year 2007. The highest cost per avoided death was €12,727.

Regarding the cost per additional cure, in most studies linezolid compared to teicoplanin was the leading treatment in Gram-positive infections [68], in particular bacteremia [61]: similar results were obtained when compared to vancomycin in SSIs [69,71], VAP [62] and CSSTIs [67] caused by MRSA. However, in an Italian study of MRSA CSSTIs, the cost of each additional cure obtained with linezolid was €17,100 compared to teicoplanin and €22,404 compared to vancomycin (**Table 3**) [64].

4. Conclusions

The increase in resistance among Gram-positive microorganisms constitutes an important problem in public health, resulting in increased levels of morbidity, length of hospital stay, mortality and costs. Thus, there is a need for new antibiotics that are efficacious against resistant Gram-positive microorganisms and have acceptable costs for national health systems per additional effectiveness unit.

In a recent meta-analysis of clinical trials, the efficacy of linezolid was equivalent to those of vancomycin and teicoplanin (OR 1.05 and 95% CI 0.75 – 1.46) in the treatment of NP and greater than that of glycopeptides in CSSTIs (OR 2.24 and 95% CI 1.12 – 4.48) [72].

The present systematic review identified 31 pharmacoeconomic studies of linezolid. From these studies, the following conclusions are inferred.

1. Use of linezolid has been proven to reduce the duration of intravenous therapy, resulting in shorter hospital stays in CSSTI patients with MRSA compared with patients on vancomycin and teicoplanin. The shorter duration of intravenous therapy may decrease intravenous administration costs and result in earlier hospital discharge.
2. Linezolid has the advantage of an oral formulation, thereby facilitating outpatient usage.
3. As expected, these effects reduce the treatment costs of linezolid compared to glycopeptides.

The costs of one life year gain, adjusted or not to quality and per additional cure obtained with linezolid versus glycopeptides seem to be acceptable for national health systems. In some cases, linezolid may be the leading treatment (i.e., more efficacious, with lower costs) compared to vancomycin and teicoplanin.

The differences in the results of the pharmacoeconomic studies reviewed (hospital length of stay, duration of antibiotic treatment, cost per patient, cost per life year gained, cost per QALY and cost per cured patient) could be explained by taking into account the different designs of the studies (randomized clinical trials, retrospective studies and decision-analytic models) and the different countries involved (North America, Latin America and Europe) in the which gross domestic products, national health systems and, as a consequence, health resource uses are very different (**Tables 1 – 3**).

5. Expert opinion

When analyzing the financial impact of an antibiotic treatment, in addition to the acquisition cost, many other

factors should be considered, which, in general, are cost drivers, including the length of hospital and intensive care unit stay, complications of the disease and the development of resistance [73]. A suboptimal empirical treatment of Gram-positive infections, in particular those caused by MRSA, due to the use of inappropriate antibiotics delays the implementation of an optimal treatment and results in a therapeutic failure with a longer length of hospital stay, administration of rescue antibiotics, an increase in total costs and the likelihood of transmitting the infection to other patients and health professionals in the hospital or in the community after hospital discharge [74]. As a consequence, an appropriate empiric antibiotic treatment is critical. Until recently, therapeutic options for the treatment of MRSA infections were limited to glycopeptides (vancomycin and teicoplanin). However, a considerable increase in the incidence of enterococci and, occasionally, vancomycin-resistant staphylococci has been observed.

Linezolid is efficacious for the treatment of CSSTIs, NP and VAP caused by MRSA. Compared to vancomycin, linezolid has been proven to reduce the duration of intravenous therapy and facilitates the switch to an oral formulation after hospital discharge. The shorter duration of intravenous therapy results in a decrease of intravenous administration costs and, as a consequence, in earlier hospital discharge. This was demonstrated in 31 pharmacoeconomic studies carried out in various countries. In most health systems, the treatment with linezolid was cost-effective, due to its greater rates of clinical cure and survival (in NP), lower treatment costs (in complicated CSSTIs) and acceptable costs per LYG in VAP [75]. Only one study of prosthetic joint infections, which was conducted in Hong Kong, indicated lower direct medical costs for outpatient home parental treatment with vancomycin, but not vancomycin administered in rehabilitation centers or in hospitals, compared with the costs related to therapy with linezolid. However, this experience is difficult to extrapolate to other countries with higher home medical care costs.

It would be interesting to conduct studies comparing linezolid with cotrimoxazole in the treatment of MRSA infections, since cotrimoxazole, like linezolid, allows the prescription of sequential therapy, with intravenous followed by oral administration. However, limited clinical experiences have compared both antibiotics, thus hampering the design of pharmacoeconomic models derived from these experiences. To date, the only newly approved agent with MRSA activity and demonstrated economic advantage over vancomycin is linezolid.

When selecting an empiric antibiotic treatment, the appearance of bacterial resistance, as well as the probability of success of the different therapeutic options, should be considered, with the objective of reducing morbidity and mortality, in the most efficient way for national health systems. In the near future it would be interesting to conduct new pharmacoeconomic analyses in order to evaluate the pharmacoeconomic impact of linezolid selection (over vancomycin) as first-line therapy in patients at risk for MRSA.

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