Cost-Effectiveness of Linezolid vs Vancomycin in Suspected Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia in Germany

E. De Cock, W. A. Krueger, S. Sorensen, T. Baker, J. Hardewig, S. Duttagupta, E. Müller, A. Piecyk, E. Reisinger, A. Resch

Abstract

Background: The oxazolidinone antibiotic linezolid has demonstrated efficacy in treating infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). In a retrospective analysis of two prospective randomized clinical trials in patients with nosocomial pneumonia (NP), initial therapy with linezolid produced significantly better clinical cure and survival rates than vancomycin in the subset of patients with documented MRSA infection. This study was designed to evaluate the economic impact of these clinical outcomes from the perspective of the German health care system to determine the use of these regimens in the light of limited resources and rising costs.

Methods: A decision–analytic model using clinical trial data was developed to examine the costs and outcomes of treatment with linezolid or vancomycin in hospitalized patients with NP caused by suspected MRSA. The model followed an average patient from initiation of empiric treatment until treatment success, death, or second-line treatment failure. Local treatment patterns and resource use were obtained from a Delphi panel. Costs were taken from published sources. Outcomes included total cost per patient, cost per additional cure, cost per death avoided, and cost per life-year gained.

Results: The model calculated that linezolid was associated with an 8.7% higher cure rate compared with vancomycin (73.6% vs 64.9%, respectively). Average total costs per episode for linezolid- and vancomycin-treated patients were €12,829 and €12,409, respectively. Death rates were 13.2% lower with linezolid than with vancomycin (20.7% vs 33.9%), resulting in an average of 2.3 life-years gained per linezolid-treated patient in a 65-year-old cohort (14.0 life-years vs 11.7 life-years). With linezolid, incremental costs per death avoided and per patient cured were €3,171 and €4,813, respectively. The base case estimated a similar mean length of stay for both drugs (11.2 vs 10.8 days). One-way sensitivity analyses did not change the overall results.

Conclusion: The model estimated a higher clinical cure (+8.7%) and survival (+13.2%) for linezolid compared with vancomycin at an incremental cost of €420 per treatment episode. The cost–benefit profile suggests that linezolid could be considered a cost-effective alternative to vancomycin in the treatment of patients with NP caused by suspected MRSA in Germany.

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Introduction

Pneumonia is the most common nosocomial infection in intensive care units (ICUs) in the USA and Europe,

E. De Cock *(corresponding author)*
Health Economics, United BioSource Corporation, Carrer Torrent del Remei, 5-11, 40-2a, 08023, Barcelona, Spain; Phone: (+34/93) 285 4640, Fax: 213 2076,
e-mail: erwin.decock@unitedbiosource.com

W.A. Krueger
Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinik Tübingen, Tübingen, Germany
(*present address*)
Klinik für Anästhesiologie und Operative Intensivmedizin, Klinikum Konstanz, Konstanz, Germany

S. Sorensen, T. Baker
United BioSource Corporation, Bethesda, USA

J. Hardewig
Pfizer Pharma GmbH, Karlsruhe, Germany

S. Duttagupta
Pfizer Inc, New York, USA

E. Müller
Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie, Knappschaftskrankenhaus Bochum-Langendreer, Universitätsklinik, Bochum, Germany
(*present address*)
Thoraxzentrum Ruhrgebiet, Klinik für Anästhesiologie, Intensiv- und Notfallmedizin, Ev. Krankenhausgemeinschaft Herne/Castrop-Rauxel gGmbH, Herne, Germany

A. Piecyk
Klinik Hirslanden, Abteilung für Allgemeine Innere Medizin, Zurich, Switzerland

E. Reisinger
Klinik und Poliklinik für Innere Medizin, Abt. Tropenmedizin und Infektionskrankheiten, Universitätsklinikum Rostock, Rostock, Germany

A. Resch
IM Nonnengarten 49, Bad Dürkheim, Germany

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including Germany [1–4]. German surveillance data captured from 274 ICUs between 1997 and 2002 have shown that *Staphylococcus aureus* caused 24.1% of cases of ventilator-associated pneumonia (VAP) [5]. During this same period, infections due to methicillin-resistant *S. aureus* (MRSA) increased remarkably in Germany [5–7]. One study reported a MRSA rate in ICUs of 4.9% in 1997–1998 [6], which had increased to 27% in 2005 [7]. According to the European Antimicrobial Resistance Surveillance System (EARSS), the 2005 MRSA rate in Germany was 21% [7].

Infections caused by MRSA are associated with a higher mortality rate than infections caused by methicillin-susceptible *S. aureus* (MSSA) [2, 4, 8, 9]. The increasing prevalence of nosocomial infections caused by MRSA not only has severe implications for patient mortality but also on morbidity and hospital length of stay (LOS) [10–12]. *Cosgrove* et al. [10] reported that the mean duration of hospitalization after *S. aureus* bacteremia for patients who survived was significantly increased in MRSA patients (7 days vs 9 days, $p = 0.045$). Another study [11] showed a significantly longer median ICU LOS for patients with MRSA infections (33 days vs 22 days, $p = 0.011$). These results reinforce the findings that preventing infection and decreasing the prevalence of MRSA can lead to substantial cost savings to the health system [11].

The role of vancomycin in the treatment of MSSA and MRSA infection has become controversial due to its poor tissue penetration, relatively weak antibacterial activity, and poor therapeutic performance [13–15]. Linezolid, the first oxazolidinone antibiotic, has demonstrated efficacy in proven or suspected Gram-positive infections, including those caused by MRSA [16–20]. Linezolid has a unique mechanism of action, and the potential for cross-resistance with other agents is considered to be low [21]. It is available in iv and oral forms, with an oral bioavailability of 100%. A switch from iv to oral therapy may decrease both the duration of the iv treatment in some infections, allowing an earlier discharge from the hospital, and the costs associated with the treatment [22].

In two multicenter, randomized, double-blind studies involving a total of 1,019 patients, both linezolid and vancomycin were effective and well tolerated in the treatment of patients with Gram-positive nosocomial pneumonia (NP) [18, 19]. A retrospective analysis of the combined subsets of patients with confirmed MRSA NP [20] showed that initial therapy with linezolid compared with vancomycin produced significantly higher survival rates (80% vs 63.5%, respectively; $p = 0.03$) and significantly higher clinical cure rates (59.0% vs 35.5%, respectively; $p < 0.01$). Similar results have been reported in patients with ventilator-associated pneumonia (VAP) [16]. Of note, only iv linezolid was allowed in these clinical trials.

Based on the improved clinical outcomes reported for linezolid compared with vancomycin, we hypothesized that empiric linezolid would be a cost-effective alternative to empiric vancomycin in the treatment of suspected MRSA NP in Germany. The objective of this study was to evaluate the economic impact of these clinical outcomes from the perspective of the German hospital system to determine the best use of these regimens in the light of limited available resources and rising costs.

Methods

Model Design

A decision–analytic model was developed to simulate the clinical outcomes and costs of empiric linezolid or vancomycin for hospitalized patients with MRSA NP (Figure 1) [23, 24]. The model followed patients until success of the first- or second-line treatment or failure of the second-line treatment. Clinical data for linezolid and vancomycin were obtained from a retrospective analysis [20] of two prospective, randomized, double-blind clinical trials in patients with NP [18, 19]. Gram-negative coverage was provided by aztreonam, which could be discontinued if Gram-

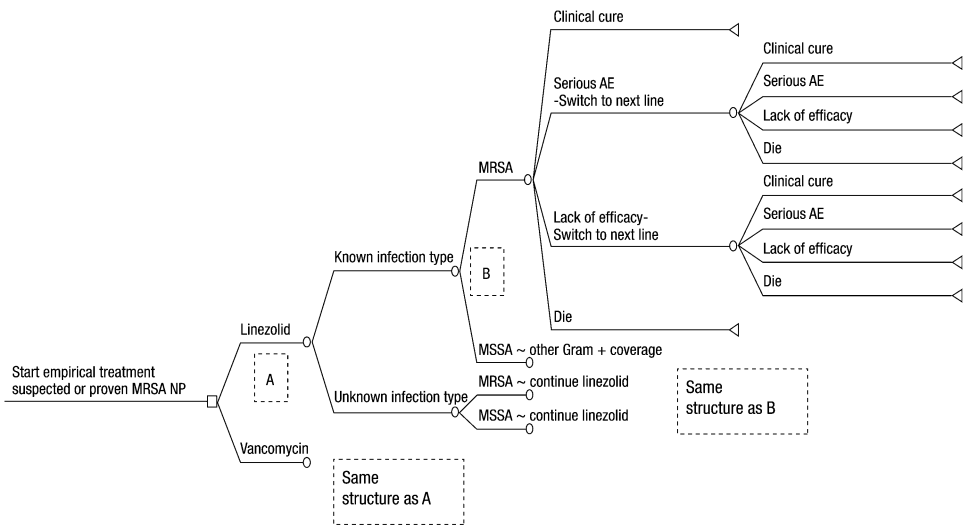


Figure 1. Model design. AE: adverse event; MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-susceptible *S. aureus*; NP: nosocomial pneumonia.

negative pathogens were not detected at baseline [18–20]. Costs for Gram-negative coverage were not included in the model.

The model specified that a specimen be taken for bacterial culture and sensitivity testing at the start of the empiric antibiotic therapy. The initial therapy for MRSA was continued in the case of proven MRSA or an unknown pathogen or switched to appropriate therapy for MSSA. The possible treatment outcomes to first- or second-line therapy were (1) cure (resolution of symptoms or clinical improvement), (2) failure due to serious adverse events, (3) failure due to lack of efficacy, or (4) death. In the case of first-line failure, the patient underwent a second series of microbiological tests (Gram stain, PCR, blood culture, bronchoalveolar lavage or tracheal aspirate if pathogen unknown, polymicrobial infection test if the pathogen was known) and was switched to the appropriate second-line therapy.

Delphi Panel

A Delphi panel, consisting of five German physicians chosen for their expert knowledge of the treatment of NP, was used to identify real-life treatment patterns and associated health care resource use. We conducted structured interviews, and the members remained anonymous to each other. One expert reviewed the model design and assumptions and assisted in the development of the survey instrument. The panel members were asked to familiarize themselves with the definition of NP that was used in the clinical trials: an infection caused by a suspected Gram-positive organism and resulting in a clinical picture compatible with pneumonia acquired after 48 h in an inpatient facility. This definition ensured that the collection of data was consistent with the inclusion criteria from the clinical trials. Data collected included hospital LOS by ward type, length of antibiotic treatment, use of concomitant medications, laboratory tests, patient isolation, adverse event management, and therapy switches in response to failure of first-line therapy. Each physician was provided with his individual answers together with the average panel results. Major differences between individual responses and the average panel results were discussed during individual follow-up interviews.

The switching patterns were provided by the Delphi panel. Patients with known MSSA were switched after an average of 2.6 days of empiric therapy. The most frequently mentioned antibiotics targeting MSSA infections were first-generation cephalosporins (cefazolin) or a carbapenem (imipenem was considered a second-line option only after failure of cefazolin). The panel estimated that 30% of laboratory test results would remain unknown. Fifty percent of patients would receive empiric vancomycin in combination with rifampicin. After failure of vancomycin in the case of known MRSA, patients would be switched to linezolid. No concomitant medications were to be given with first-line linezolid. After failure of linezolid in the case of known MRSA, patients would be switched to vancomycin in combination with rifampicin. After failure in the case of an unknown pathogen and following a second series of microbiologic tests, patients would be switched to linezolid in combination with imipenem. The panel estimated 3.4 and 4.6 days of first-line therapy before the chosen therapy was determined to be a failure due to a lack of efficacy and due to serious adverse events, respectively. In patients with MRSA, the panel estimated an average length of successful first-line treatment of 12.6 days for linezolid and 14.2 days for vancomycin. LOS was 17.0 days for linezolid and 20.8 days for vancomycin. The panel estimated that the patient would spend 60% of the time in the ICU and 75% in isolation. Patients with proven MSSA standardly do not remain isolated beyond the first few days before therapeutic switch. The panel estimated slightly more hematology tests for linezolid, which is in line with recommendations on testing for myelosuppression, but slightly fewer biochemistry tests for linezolid than for vancomycin; a serum concentration of vancomycin was expected due to the potential risk of nephrotoxicity. The daily frequencies of other tests were similar for both drugs.

Clinical Data and Costs

The clinical data for the model are shown in table 1. Data for the efficacy rates of other antibiotics were obtained from a controlled clinical trial by *Zanetti* et al. [25]. The model considered the perspective of the German hospital system and included only direct medical costs associated with hospitalization. Costs were obtained from published sources and were inflated to 2006 levels (Tables 2, 3) [26–30]. Costs for bacterial culture and sensitivity testing were not included because they were identical across model arms. The cost per day in a general ward was calculated from D-DRG data and included only hotel costs [27]. In the absence of an estimate for ICU cost calculated from G-DRG data, we used the 2002/2003 daily rate from the Privaten Krankenversicherung as the best available proxy [30]. The cost for isolation was calculated from the bottom up to reflect the increased resource use associated with this level of care. The cost for each day in isolation was added to the standard daily cost by type of ward. We calculated additional hospital-based costs for adverse events using management patterns obtained from the physician panel and unit costs.

Table 1
Clinical parameters.

Parameter	MSSA value (%)	MRSA value (%)	Source
Cure rate			
Linezolid	51.5	59.0	[20]
Vancomycin	43.4	35.5	[20]
Carbapenem	74.0		[25] [a]
First-generation cephalosporin	70.0		[25] [a]
Serious adverse event rate requiring therapy switch: MRSA and MSSA (%)			
Linezolid	5.2	5.2	[20]
Vancomycin	6.5	6.5	[20]
Carbapenem	0.0	0.0	[25] [a]
First-generation cephalosporin	0.9	0.9	[25] [a]
Mortality rate (MSSA and MRSA)			
Linezolid	22.0	20.0	[20]
Vancomycin	29.2	36.5	[20]
Carbapenem	4.0	4.0	[25] [a]
First-generation cephalosporin	9.3	9.3	[25] [a]
Length of stay [b] for patients who die during vs after first-line treatment (days)			
Linezolid and vancomycin	5.8	13.4	[18, 19]
Total duration of second-line therapy for patients who die (days)			
Linezolid and vancomycin	7.0	7.0	[18, 19]

MRSA: Methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; [a] In the absence of data for first-generation cephalosporin and carbapenem, data were obtained from the clinical trial of cefepime vs imipenem-cilastin; [b] Total duration of ICU and isolation

Table 2
Drug dosage and costs [26].

Drug	Dosage (mg)	Daily drug cost (€)	iv cost (€)
Linezolid			
iv	600 b.i.d.	182.12	32.92
Oral	600 b.i.d.	176.40	–
Vancomycin monotherapy	1,000 b.i.d.	53.12	32.92
Vancomycin plus rifamycin	600 b.i.d.	39.40	32.92
First-generation cephalosporin (cefazolin)			
iv	2,000 t.i.d.	30.23	49.39
Oral	1,000 t.i.d.	12.92	–
Imipenem [a]	1,000 t.i.d.	144.16	49.39

Vancomycin cost represents the weighted average by pack size and volume based on February 2007 sales data; [a] Monotherapy or in combination with linezolid

Table 3
Hospital and adverse event costs [27–30].

Parameter	2002 Cost (€)	2006 Cost (€)
ICU (without ventilator) (per day)	870.64	927.05 [a]
ICU weighted average (per day)		954.55 [b]
General ward (per day)	256.28	264.31
Isolation (per day)		302.42
iv infusion longer than 30 min		16.46
Adverse event management [c]		
Thrombocytopenia		914
Renal insufficiency		3,052
Fever		2,470
Diarrhea		702

ICU: Intensive care unit; [a] Assumed an extra €50 per day for connection to a ventilator; [b] Cost weighted for an estimated proportion of time with ventilator (55%) and without ventilator (45%); [c] Calculated from estimated resource use data (Delphi panel)

Model Outcomes and Analyses

Clinical outcomes (clinical cure rate, survival rate, and life-years gained post-treatment) and predicted cost outcomes (total cost per patient) were calculated for a base case and two expert case scenarios. Total costs were divided into costs due to hospitalization, antibiotics, tests, and treatment for adverse events. Incremental cost effectiveness ratios (ICERs), calculated as the difference between linezolid and vancomycin treatment divided by the difference in effect, were established for cost per death avoided, cost per life-year gained, and cost per additional cure.

Base Case Analysis

It is unclear whether NP increases LOS since patients are hospitalized for underlying reasons, such as trauma or cardiovascular conditions. Therefore, in the base case scenario, the duration of therapy for vancomycin was based on data provided by the Delphi panel. The base case was kept conservative by assuming a similar treatment duration for linezolid and vancomycin, and we assumed that LOS was equal to the length of treatment (Table 4).

Scenario Analyses

In the first model scenario, treatment durations for iv-administered vancomycin and for oral- and iv-administered linezolid were based on estimates obtained from the Delphi panel, but we maintained the assumption that LOS equaled the length of treatment. Cure rates for oral and iv linezolid were assumed to be identical. In the second model scenario, we further relaxed the assumptions by using the length of treatment and LOS data as reported by the Delphi panel (Table 5).

Sensitivity Analyses

A series of one-way sensitivity analyses was carried out to evaluate the effect of varying key parameters by 25% around the baseline readings for the model. A tornado chart was generated, showing the absolute impact on incremental cost of changes in selected parameters with all other parameters held constant. Parameters considered in sensitivity analyses were time in isolation for vancomycin vs linezolid, resistance rate (MRSA), unknown infection rate, LOS for patients who die on first-line treatment, LOS for patients who die after first-line treatment, days on empiric treatment before switch vs failure, ICU on a daily basis, and isolation on a daily basis. For the MRSA population, the following additional parameters were evaluated: ICU days with vancomycin vs linezolid (first-line treatment), days on iv vancomycin, days on oral linezolid, and days on IV linezolid. A two-way sensitivity analysis simultaneously explored the effect on the incremental cost and cure of resistance and the rate of unknown infection.

Model Assumptions

The following key assumptions were made in the model:

1. Patients were assumed to have a Gram-positive infection and suspected MRSA [20].
2. Approximately 50% of patients with suspected MRSA infection were assumed to have proven MRSA infection. Variations in this rate were explored in the sensitivity analyses.
3. In the absence of published evidence showing different rates of resistance for patients with conclusive vs inconclusive test results, we assumed identical resistance in both groups.
4. In the absence of efficacy rates for first-generation cephalosporin (cefazolin) and imipenem in NP, we assumed the efficacy to be similar to that observed in the clinical trial of cefepime vs imipenem-cilastin [25].
5. In the absence of published data, the efficacy rate for the combination of linezolid and carbapenem was assumed to be the same as that for linezolid monotherapy.
6. In the absence of published data on the efficacy of second-line therapy, the rate of cure with first-line therapy and second-line therapy was assumed to be the same.
7. In the clinical trials, no significant difference was seen between linezolid and vancomycin in the length of treatment. Therefore, the model base case conservatively assumed that length of successful first-line (and second-line treatment) would be the same.
8. Because of the uncertainty surrounding the extent to which NP prolongs hospital LOS, the base case model assumed that all antibiotic treatment days were hospital days due to NP and that no difference in LOS by model comparator was expected.

Table 4
Length of treatment and hospital length of stay (LOS) parameters: base case.

	MSSA			MRSA		
	Length of treatment		LOS	Length of treatment		LOS (isolation)
	iv	Oral		iv	Oral	
First-line treatment (days)						
Linezolid	10.4	0.0	10.4	14.2	0.0	14.2 (10.9)
Vancomycin	10.4	0.0	10.4	14.2	0.0	14.2 (10.9)
First-generation cephalosporin	7.5	2.2	9.7			
Second-line treatment (days)						
Linezolid				13.6	0.0	13.9 (10.8)
Vancomycin				13.9	0.0	13.9 (10.8)
First-generation cephalosporin	5.9	2.1	8.0			
Carbapenem	8.0	0.0	8.0			
Linezolid in combination with carbapenem				13.9	0.0	13.9 (10.8)

Table 5
Length of treatment and hospital LOS parameters: scenarios 1 and 2.

	MSSA				MRSA			
	Length of treatment		LOS		Length of treatment		LOS	
	iv	Oral	Scenario 1	Scenario 2	iv	Oral	Scenario 1	Scenario 2
First-line treatment (days)								
Linezolid	6.3	2.1	8.4	10.8	8.0	4.6	12.6	17.0
Vancomycin	10.4	0.0	10.4	13.0	14.2	0.0	14.2	20.8
First-generation cephalosporin	7.5	2.2	9.7	11.6				
Second-line treatment (days)								
Linezolid					7.5	3.7	11.2	17.8
Vancomycin					13.9	0.0	13.9	22.4
First-generation cephalosporin	5.9	2.1	8.0	12.2				
Carbapenem	8.0	0.0	8.0	12.2				
Linezolid-carbapenem					6.3	4.3	10.6	17.8

Scenario 1 uses the length of treatment provided by the Delphi panel and assumes that LOS equals the length of treatment; scenario 2 uses the length of treatment and LOS data provided by the Delphi panel

Results

Base Case Analysis

The modeled clinical cure rate was 8.7% greater for patients beginning treatment with linezolid than for those beginning treatment with vancomycin (Table 6). The difference in the modeled clinical cure rate between linezolid and vancomycin was greatest after first-line therapy (61.7 vs 48.7%). The model calculated that patients receiving second-line therapy following treatment with linezolid contributed an additional 11.9% in cure rate, compared with an increase of 16.1% with vancomycin. The greater number of failures on first-line treatment with vancomycin allowed for a greater increase in cure on second-line therapy in patients switching to linezolid. In-hospital mortality was 13.2% lower in patients on linezolid therapy than in those receiving vancomycin (20.7% vs 33.9%), resulting in an expected 2.3 life-years gained per linezolid-treated patient in a 65-year-old cohort (14.0 life-years vs 11.7 life-years).

Despite the assumed equivalence in the length of the iv treatment and LOS for successful first-line treatment with linezolid and vancomycin (14.2 days if MRSA and 10.4 days if MSSA, respectively), the modeled total average LOS was slightly longer for linezolid therapy than for vancomycin therapy (11.2 days vs 10.8 days). The higher modeled survival rate of linezolid compared with vancomycin resulted in linezolid-treated patients accumulating more hospital days.

Average total costs per episode for linezolid- and vancomycin-treated patients were €12,829 and €12,409, respectively (Table 6). The increased costs for antibiotics in the linezolid arm were partly offset by the expected cost savings for monitoring tests and adverse event management. Hospitalization had a minimal impact on incremental cost. The main component of costs was hospitalization, followed by antibiotics (77% and 16% for patients starting on linezolid and 79% and 12% for patients

Table 6
Comparison of cure rates, survival, and costs by treatment arm.

	Linezolid	Vancomycin	Difference
Cure rates (%)			
Overall	73.6	64.9	8.7
First-line	61.7	48.7	13.0
Second-line	11.9	16.1	–4.3
Survival (%) [a]	79.3	66.1	13.2
Expected life years [b]	14.0	11.7	2.3
Costs (€)			
Hospitalization	9,884	9,808	76
Antibiotic drug (inpatient)	2,067	1,526	541
Tests	655	803	–148
Adverse event management	222	271	–49
Total	12,829	12,409	420

[a] Survival rate refers to the modeled proportion of patients surviving infection; [b] Expected remaining life years were based on gender-specific life expectancy tables from the Federal Statistical Office Germany for a 65-year-old population, which represents the mean age of patients in the trials. Results were weighted for the gender distribution observed in the trials (66% male and 34% female)

Table 7
Incremental effectiveness, incremental cost, and incremental cost-effectiveness ratio (ICER).

Scenario	Incremental effectiveness [a]	Incremental cost (€)	ICER (€)
Base case		420	
Cost per life year gained [b]	2.34		180
Cost per death avoided	13.2%		3,171
Cost per additional cure	8.7%		4,813
Scenario 1		–139	Dominant
Cost per life year gained [b]	2.34		
Cost per death avoided	13.2%		
Cost per additional cure	8.7%		
Scenario 2		–222	Dominant
Cost per life year gained [b]	2.34		
Cost per death avoided	13.2%		
Cost per additional cure	8.7%		

[a] Life years gained/deaths avoided/incremental cure; [b] In a 65-year-old cohort

on vancomycin, respectively). The costs of monitoring tests and adverse events accounted for 5%–6% and 2% of the total costs, respectively.

Effectiveness and cost results for linezolid and vancomycin translated into ICERs of €4,813 per cure, €3,171 per death avoided, and €180 per life-year gained (Table 7). However, results for life-years gained have to be treated with caution as future costs (post-discharge) were not included in the analysis.

Scenario Analyses

In scenario 1 (Table 5), modeled mean LOS for the cohort was 10.50 days for linezolid and 10.53 days for vancomycin. The costs were €11,908 for patients initiating treatment with linezolid vs €12,048 for patients starting on vancomycin (–€139). Higher antibiotic treatment costs (€405) were more than offset by savings in costs of hospitalization (–€322), laboratory testing (–€173), and management of adverse events (–€49).

In scenario 2 (Table 5), modeled mean LOS was 13.82 days for linezolid and 14.32 days for vancomycin. Overall treatment costs were €222 lower for patients initiating treatment on linezolid (€14,068) compared with those starting on vancomycin (€14,290). Linezolid was considered to be the dominant treatment strategy in both scenarios due to the reduction in cost combined with better clinical outcomes.

Sensitivity Analyses

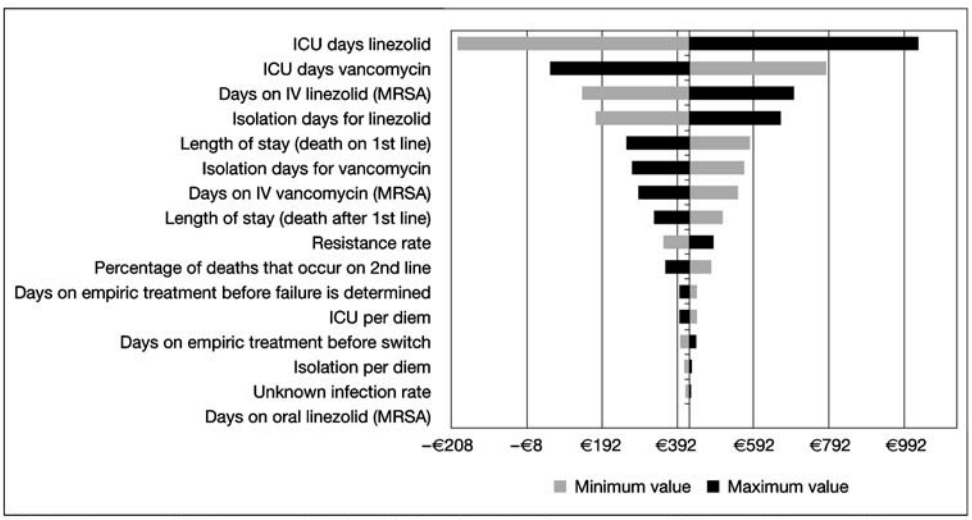
Figure 2 shows that the incremental cost in the base case model was most sensitive to the number of ICU days with linezolid or vancomycin (hospitalization being the main cost driver), the number of isolation days, time on iv therapy, and LOS for patients who died (when death occurred on or after first-line therapy). However, varying these parameters by 25% did not change the overall conclusions.

Discussion

The results of this model showed improved clinical outcomes with linezolid compared with vancomycin in the treatment of patients with suspected MRSA NP, but at a small incremental cost. Under the conservative base case conditions dictated by the clinical trial, an investment of €4813 would be required per additional patient cured, and €3171 per death avoided, when linezolid is compared with vancomycin. A series of one-way sensitivity analyses showed that the model was most sensitive to a change in the number of days in the ICU, days in isolation, and days on iv drug treatment. Although these results tell something about the magnitude of the impact, a change in each of these variables would simultaneously lead to a change in other variables (e.g., a longer duration of treatment increases LOS associated with pneumonia). Scenario 1 relaxed the assumptions by considering increased therapy duration, and scenario 2 further relaxed the assumptions by also considering increased LOS. In these two scenarios, therapy initiated with linezolid appeared to be less costly and more efficacious than therapy initiated with vancomycin; consequently, the former was considered the dominant treatment strategy.

Parameter	Minimum value	Current value	Maximum value
Resistance rate	38%	50%	63%
Unknown infection rate	23%	30%	38%
Days on empiric treatment before switch	2.0	2.6	3.3
Days on empiric treatment before failure is determined	2.6	3.4	4.3
Days on IV linezolid (MRSA)[a]	10.7	14.2	17.8
Days on oral linezolid (MRSA)[a]	0	0	0
Days on IV vancomycin (MRSA)[a]	10.7	14.2	17.8
ICU days linezolid[a]	6.4	8.6	10.7
ICU days vancomycin[a]	6.4	8.6	10.7
Isolation days for linezolid[a]	8.2	10.9	13.6
Isolation days for vancomycin[a]	8.2	10.9	13.6
Length of stay (death on 1st line)	4.3	5.8	7.2
Length of stay (death after 1st line)	10.1	13.4	16.8
ICU per diem	€716	€955	€1193
Isolation per diem	€227	€302	€378
Deaths that occur on 2nd line	17%	23%	29%

[a] First-line treatment.



ICU = intensive care unit; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Figure 2. One-way sensitivity analyses—base case. ICU: Intensive care unit; iv, intravenous.

Cure or failure on second-line treatment was the end of the time horizon for our model, which is consistent with the expert opinion that of those patients surviving hospitalization, the majority would be cured with up to two lines of antibiotic treatment. Although our analysis considered life expectancy of survivors with an average age of 65 years after hospital discharge, we did not include future costs beyond the period of hospitalization. For this reason, the cost per life-year gained results should be interpreted with caution. Interpretation of the ICERs per additional patient cured and per death avoided is more clear-cut, given that the costs and benefits pertain to the model time horizon of hospitalization. Whether a drug is considered cost-effective is subjective and depends on the threshold value for cost-effectiveness (i.e., what a decision-maker would be willing to pay for an additional unit of effect). In the case of cost per death avoided, the ICER of €3,171 in the base case could be considered cost-effective as the willingness to pay to avoid a patient death is expected to be much higher than €24,000–36,000. This value has been referred to by the Organization for Economic Co-operation and Development (OECD) as a

range of the threshold value per quality-adjusted life-year gained in Germany [31].

Previous studies have demonstrated that linezolid can be considered a cost-effective alternative to vancomycin for the treatment of VAP in the USA [32, 33] and Spain [34]. These three studies used the same clinical trial data used in our model [18–20].

Our study has several important limitations. First, the model base case scenario considered the conditions under which the clinical trials were carried out, conditions which are likely to differ in real-life German practice. The trial data were obtained from a defined clinical population, as stipulated in the clinical protocol, which also did not allow oral dosing of linezolid. The use of a Delphi panel was considered appropriate to supplement the clinical trial data and to determine the likely economic effect of a treatment when economic data were not collected within the clinical trial [35–38]. Although the Delphi method has been widely used as a data source in medical research, its application in pharmacoeconomics has been more limited [37, 38]. Limitations to the Delphi method include respondent bias and lack of consensus; it provides the opinions of physicians for particular hospital settings and patient populations and therefore, it may not be representative or generalizable to the country as a whole. While the sample size for Delphi panels has not been established, reliable outcomes can nevertheless be obtained from a relatively small number of experts in a well-defined area of knowledge [37, 38]. Although our sample size was small (only five members), the experts were chosen on the basis of their clinical expertise and diversity of geographic location. The impact of uncertainty surrounding the estimates obtained by the Delphi panel in our study was assessed through sensitivity analyses.

Second, it is important to address the question of whether NP increases LOS, which depends on the nature and severity of the underlying condition, which was the reason for hospitalization. For serious conditions requiring prolonged hospital stay, NP may not have an impact on total LOS. In other cases, where expected LOS for a condition is short, NP may add to hospitalization, and there may be scope for early discharge as a result of a switch to an oral drug. An answer to this question is crucial in order to be able to adequately attribute costs to NP and to demonstrate the cost and cost-effectiveness of pneumonia treatment. *Beyersmann* et al. [39] used a multi-state model to assess the part played by nosocomial infection in prolonging LOS and estimated that the mean prolongation of ICU LOS due to nosocomial infection was 5.3 ± 1.6 days (standard error). In a cost-of-illness analysis conducted in Germany [40], NP was found to increase LOS by up to 7 days compared to controls, with an additional cost to the hospital of €7,467 per patient. In the absence of clarity in the published literature on the expected additional LOS associated with MRSA NP, our model assumed that all antibiotic treatment days are associated with NP, which may have led to an overestimation of the total cost of NP treatment but would not affect the incremental cost difference between linezolid and vancomycin because the model base case assumed equal therapy duration for successful treatment with linezolid and vancomycin. This important model limitation could only be addressed appropriately by conducting a case–control study that captures health care resource use for patients with NP vs a control group without infection.

Nosocomial MRSA infections are expected to increase patient morbidity, mortality, and hospital costs. Any therapeutic intervention against such infections should form part of a comprehensive strategy to combat the infection, including hygienic measures, early detection, patient isolation, and avoidance of inappropriate antibiotic use. Eliminating the source of infection by successful treatment of these patients with the most effective therapy options should be a central part of this strategy.

In conclusion, our cost-effectiveness model shows that linezolid is associated with higher clinical cure and survival, but at a small incremental cost compared with vancomycin. This resulted in acceptable ICERs of cost per death avoided and cost per patient cured. However, further studies are needed in patients with NP to investigate the true impact of linezolid on resource use and hospital LOS.

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