Original Research

Cost-effectiveness Comparison of Ceftazidime/Avibactam Versus Meropenem in the Empirical Treatment of Hospital-acquired Pneumonia, Including Ventilator-associated Pneumonia, in Italy

Eszter Tichy, MSc[1]; Antoni Torres, MD, PhD[2]; Matteo Bassetti, MD, PhD[3]; Thitima Kongnakorn, PhD[4]; Roberto Di Virgilio, MD[5]; Paurus Irani, MD[6]; and Claudie Charbonneau, PhD[7]

[1]Evidera, Budapest, Hungary; [2]Servei de Pneumologia. Hospital Clinic, Universitat de Barcelona, Barcelona, Spain; [3]Department of Medicine, University of Udine and Azienda Sanitaria, Universitaria Integrata di Udine, Udine, Italy; [4]Evidera, London, United Kingdom; [5]Pfizer, Rome, Italy; [6]Pfizer, Abbots Langley, United Kingdom; and [7]Pfizer, Paris, France

ABSTRACT

Purpose: Ceftazidime/avibactam (CAZ-AVI) is a fixed-dose combination antibiotic approved in Europe and the United States for patients with hospital-acquired pneumonia, including ventilator-associated pneumonia (HAP/VAP). The economic benefits of a new drug such as CAZ-AVI are required to be assessed against those of available comparators, from the perspective of health care providers and payers, through cost-effectiveness and cost-utility analyses. The objective of this analysis was to compare the cost-effectiveness of CAZ-AVI versus meropenem in the empirical treatment of appropriate hospitalized patients with HAP/VAP caused by gram-negative pathogens, from the perspective of publicly funded health care in Italy (third-party perspective, based on the data from the REPROVE (Ceftazidime-Avibactam Versus Meropenem In Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia) clinical study; ClinicalTrials.gov NCT01808092).

Methods: A patient-level, sequential simulation model of the HAP/VAP clinical course was developed using spreadsheet software. The analysis focused on direct medical costs. The time horizon of the model selected was 5 years, with an annual discount rate of 3% on costs and quality-adjusted life-years (QALYs). Clinical inputs for treatment comparisons were mainly obtained from the REPROVE clinical study data. In addition to clinical outcomes observed in the trial, the model incorporated impact of resistance pathogens, based on data from published studies and expert opinion. Certain assumptions were made for some model parameters due to a lack of data.

Findings: The analysis demonstrated that the intervention sequence (CAZ-AVI followed by colistin + high-dose meropenem) versus the comparator sequence (meropenem followed by colistin + high-dose meropenem) provided a better clinical cure rate (+13.52%), which led to a shorter hospital stay (−0.40 days per patient), and gains in the number of life-years (+0.195) and QALYs (+0.350) per patient. The intervention sequence had an estimated net incremental total cost of €1254 ($1401) per patient, and the estimated incremental cost-effectiveness ratio was €3581 ($4000) per QALY gained, well below the willingness-to-pay threshold of €30,000 ($33,507) per QALY in Italy.

Implications: The model results showed that CAZ-AVI is expected to provide clinical benefits in

☆ The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Accepted for publication March 24, 2020
https://doi.org/10.1016/j.clinthera.2020.03.014
0149-2918/$ - see front matter

hospitalized patients with HAP/VAP in Italy at an acceptable cost compared to meropenem. (*Clin Ther*. 2020;42:802−817)

Key words: avibactam, CAZ-AVI, ceftazidime, cost-effective analysis, hospital-acquired pneumonia, ventilator-associated pneumonia.

INTRODUCTION

Hospital-acquired pneumonia (HAP) is a nosocomial pulmonary infection that occurs in patients after >2 days of hospitalization, irrespective of their stay in the intensive care unit (ICU) or general ward.[1,2] Ventilator-associated pneumonia (VAP) occurs after 2−3 days of tracheal intubation and mechanical ventilation in hospitalized patients in the ICU.[1−3] The incidence of HAP ranges from 5 to >20 cases per 1000 admissions, while the incidence of VAP ranges from 2 to 16 cases per 1000 ventilation days.[1,4] HAP/VAP is associated with considerable mortality, with the greatest risk in the elderly, along with an increased burden on health care systems. Economic burden associated with HAP/VAP is high. In the United States, mean hospitalization costs were ~$100,000 and $60,000 for a single episode of HAP with and without VAP, respectively (costing year 2008 and 2009).[5] In a UK study, a conservative estimate of the additional cost of treating HAP with VAP was ~£10,000 ($13,127) (costing year 2008 and 2009) compared to HAP without VAP; while in a Turkish publication, the costs of HAP per episode were $2832 with and $869 without VAP (costing year 2000−2002).[6]

The common pathogens associated with HAP/VAP differ per an ICU patient's characteristics, length of hospital stay and ICU stay, and local risk factors. *Staphylococcus aureus* (including methicillin-resistant *S aureus* [MRSA]), *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* and Enterobacteriaceae (such as *Klebsiella* spp, *Enterobacter* spp) are the major bacterial strains that cause HAP/VAP.[2,7−9]

Treatment guidelines for HAP recommend empirical treatment with combinations of antibiotics based on patient-specific considerations and local risk factors, such as the resistance pattern within a specific hospital, until the results of microbiological testing are available after 2−3 days.[2,7] However, there is increased resistance to existing antibiotics, due to the evolution of multidrug-resistant pathogens in HAP/VAP causing the failure of initial empirical therapy in 20%−40% of patients with HAP.[2] Increased antibiotic resistance has resulted in a significant unmet need for antibiotics that are effective against these resistant pathogens and that can reduce lengths of hospital stays, costs, and resource utilization.[7]

Ceftazidime/avibactam (CAZ-AVI) is a fixed-dose combination antibiotic, containing a third-generation cephalosporin ceftazidime and a non−β-lactam, β-lactamase inhibitor avibactam, that has been approved in the European Union and the United States for patients with HAP/VAP. This approval was based on the results of a Phase III, multicenter, randomized, double-blind, parallel-group, noninferiority study in patients with HAP, including VAP (the REPROVE study [Ceftazidime-Avibactam Versus Meropenem In Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia]; ClinicalTrials.gov NCT01808092). The study results demonstrated the noninferiority of CAZ-AVI to meropenem in clinical cure rates at the test-of-cure (TOC) visit and supported the role of CAZ-AVI in treating serious gram-negative infections as a carbapenem-sparing strategy with no new safety concerns.[10]

The incidence of infection with gram-negative pathogens is high in Italy. In ~25%−50% of cases are the result of *Klebsiella pneumoniae* isolates resistant to carbapenems, in 25%−50% of the cases are *P aeruginosa* isolates resistant to carbapenems, and 10%−50% of strains are classified as multidrug resistant; furthermore, in up to 50% of cases *Acinetobacter baumannii* have combined resistance to fluoroquinolones, aminoglycosides, and carbapenems.[11] In Italy, the consumption of antibiotics out-of-hospital is high, ranking fifth in Europe, with 27.8 doses per 1000 inhabitants.[12]

Per economic evaluation guidelines in Italy, the economic benefits of a new drug are required to be assessed from the perspective of health care providers and payers through cost-effectiveness and cost-utility analyses, comparing the new drug to available first- and second-line treatments.[13] Similar to other clinical trials of antibiotics, the REPROVE study was conducted with a noninferiority design due to ethical

reasons and thus was not designed to show superiority of CAZ-AVI versus the comparator. In addition, most clinical trials do not include patients with suspected resistance to the study drugs, which limits the interpretation of the true economic value of a new antibiotic, such as CAZ-AVI, which could be an alternate treatment option against resistant pathogens, given the rise of antimicrobial resistance in clinical practice. Health economic evaluation assists in understanding the balance between the incremental health and economic outcomes provided by CAZ-AVI versus incremental drug cost. The objective of this study was to compare the cost-effectiveness of CAZ-AVI versus meropenem in the empirical treatment of appropriate hospitalized patients with HAP/VAP from the publicly funded (third-party payer) perspective in Italy.

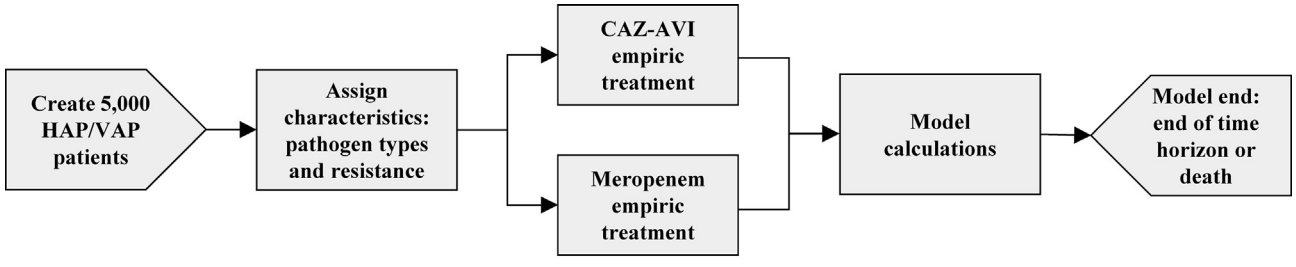
MATERIALS AND METHODS

No human subjects were enrolled in this study; therefore, the study was exempted from regulations guiding the protection of human subjects.

Model Overview and Structure

A patient-level, sequential simulation model of the clinical course of HAP/VAP following the initiation of anti-infective empirical treatment (ie, CAZ-AVI or meropenem) was developed using Excel 2016 software (Microsoft Corporation, Redmond, Washington). Each patient's pathway is described in the model structure depicted in Figs. 1 and 2. Patient-level simulation allowed the management of patient characteristics, particularly treatment switching, to be simulated at detailed levels, as opposed to Markov-type models, which require many simplifying assumptions.

At the beginning of the model, 5000 patients with HAP/VAP were created, and Monte Carlo sampling was used to assign clinical characteristics based on pathogen type, including resistant pathogens. In the next step, 2 identical cohorts were generated by duplicating simulated patients, with 1 cohort receiving CAZ-AVI and the other receiving meropenem as an empirical treatment, which ensured that factors other than treatment did not affect the comparisons. Patients were then assigned times for all possible events by sampling whether or not the event occurred, based on the probability of the event (eg, probability of adverse event [AE] or death) and if the event occurred, the time of the event was assigned based on uniform distribution of the time window of the particular event (eg, during



Assumptions:

- Patients with resistant pathogens will switch to the next line of treatment at time of microbiological test results.
- Patients with no response at EOT will switch to the next line of treatment, and if already discharged, will be re-hospitalized.
- Patients with no cure at TOC will start the next line of treatment and be re-hospitalized.
- After EOT, those who show response will discontinue treatment.
- Patients who discontinue treatment are no longer exposed to adverse event risks.
- The efficacy inputs are based on the clinically evaluable population of the trial and assumed data are reflective of real-world Italian population.
- Utilities are assumed to be constant from the end of the infection episode until the end of time horizon.

Figure 1. Model structure. CAZ-AVI = ceftazidime/avibactam; HAP/VAP = hospital-acquired pneumonia including ventilator-associated pneumonia; EOT = end of treatment; TOC = test-of-cure.

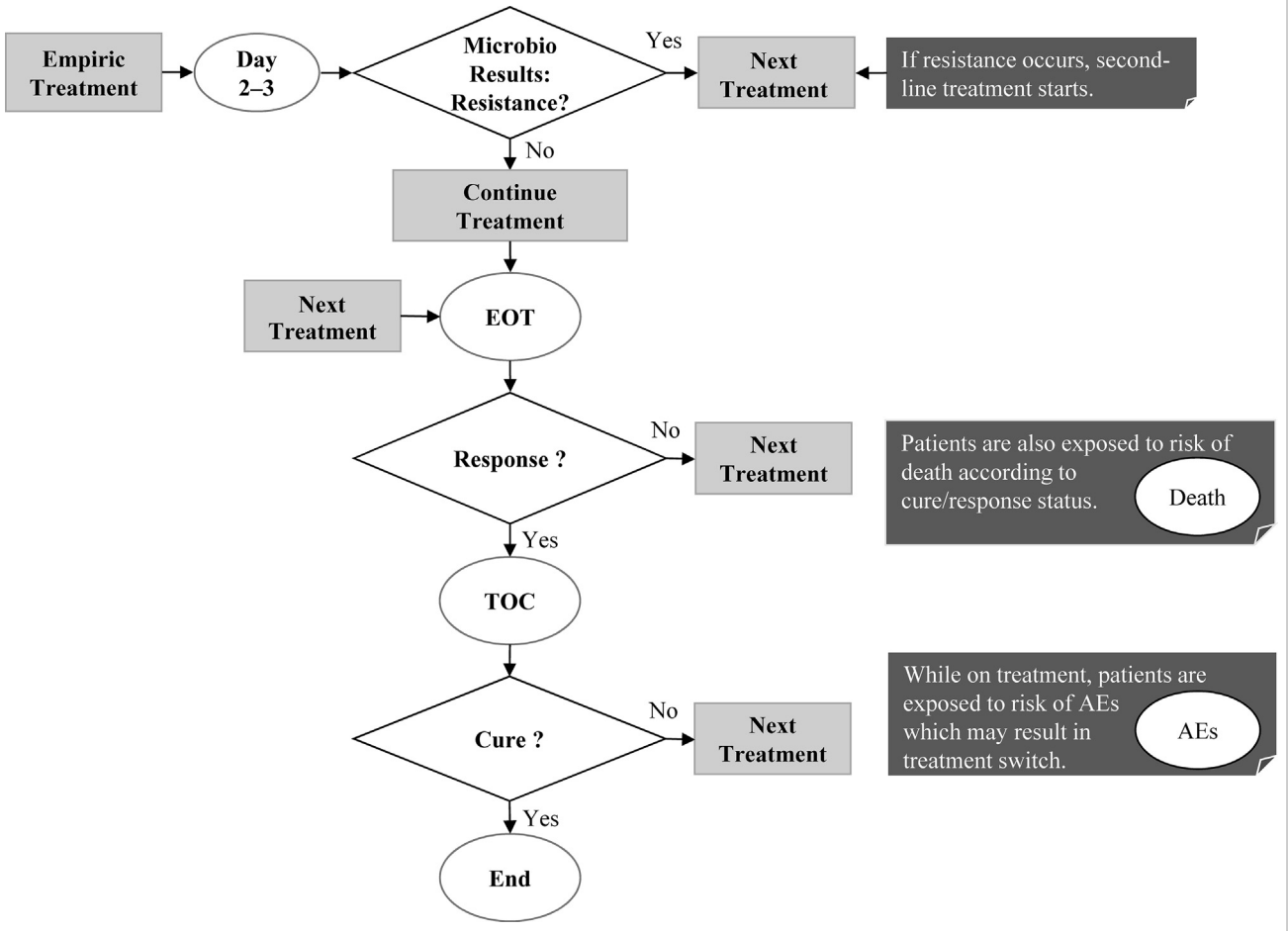


Figure 2. Overview of the patient flow. AE = adverse event; EOT = end-of-treatment visit; TOC = test-of-cure visit (21−25 days following the initiation of treatment).

treatment duration for AE, during time in hospital for in-hospital death). As these events were expected to occur randomly over a short time period, equal probability during the time window was assumed. For some events, the times assigned were based on the treatments received (eg, time to AE, time to end of treatment [EOT]).

Each patient who entered the model received empirical treatment with either CAZ-AVI or meropenem. Patients continued the empirical treatment until microbiological test results were available (at 48−72 h). If microbiological results revealed that at least 1 of the pathogens was resistant to the empirical treatment, the patient was switched to the next treatment and was counted as a clinical failure. The empirical treatment was continued if no resistance was observed.

At the EOT, each patient's response was assessed. In cases of response, the patients continued to follow-up and were assigned a time to first follow-up visit, which was equivalent to the TOC visit in the clinical trial (21−25 days post-initiation of treatment). In cases of nonachievement of response, patients were considered as treatment failures and were switched to the next treatment.

At the first follow-up visit (TOC visit), achievement of clinical cure was assessed in patients. If clinical cure was again not achieved, the patient was switched to the next line of treatment. Patients were also exposed to risk for in-hospital death due to HAP/VAP. In cases

of AE, the medical cost of managing the AE was accrued and patients may have been switched to the next treatment line. In cases of death, the drug and hospitalization costs were accrued along with life-years (LYs) and quality-adjusted (QA) LYs, and these patients were exited from the model.

To take into account the additional burden of resistant pathogens in empirical treatment, the base-case analysis assumed that in these cases response/cure rates in subsequent treatment would be reduced by 10%; this percentage was based on experts' opinion (A.T. and M.B.). In addition, 10% higher hospital daily costs were accrued for the increased health care resource utilization to treat patients with antibiotic resistance (eg, additional nursing care, diagnostic testing, and use of isolation rooms).[14] Patients with pathogens resistant to empirical treatment were also assigned a 20% increase in mortality compared to patients who did not have resistance but did receive inappropriate treatment.[14–16] These numbers were tested in scenario analyses.

Treatment Comparison

The base-case analysis compared treatment (intervention and comparator) sequences that consisted of the empirical treatment followed by a second-line treatment based on current routine clinical practice in Italy. The empirical treatments considered in the model were CAZ-AVI (intervention sequence) and meropenem (comparator sequence). The second-line treatment consisted of a combination of colistin (IV delivery assumed) and high-dose meropenem for both the intervention and comparator treatment sequences.

Model Inputs and Data Sources

Baseline and resistant pathogens

The base-case inputs were derived from the top 5 most frequently identified baseline pathogens in the REPROVE study: *K pneumonia* (37%), *P aeruginosa* (26%), *Enterobacter cloacae* (14%), *Escherichia coli* (12%), and *Hemophilus influenzae* (9%). The rate of resistance to CAZ-AVI was based on data from the published literature, with 7% resistance for *P aeruginosa* and 1% each for *K pneumonia*, *E cloacae*, and *E coli*.[17] Rates of resistance to the meropenem were based on rates of resistance to carbapenems from the 2017 resistance data observed in patients from Italy for *K pneumonia* (52%), *P aeruginosa* (24%), and *E coli* (1%) calculated in a forecast model based on data from the European Centre for Disease Prevention and Control[18] and the resistance rates were validated by clinical experts (A.T. and M.B.). Furthermore, the rate of resistance of *K pneumonia* to carbapenems, which had the highest resistance rate among others, was tested in scenario analysis.

Clinical inputs

Treatment efficacy in the model was characterized as the response achieved at the EOT visit and clinical cure achieved at the TOC visit from the REPROVE clinical trial.[10] The model inputs are summarized in Table I.[19–28]

In terms of AEs, only serious AEs (SAEs) were considered due to their relevant cost impact and because they could result in treatment switches or discontinuations. The probability of treatment discontinuation due to AEs (assuming all AEs were SAEs) was set at 21%, based on REPROVE study data.

Since the REPROVE study showed a low mortality rate, model inputs for in-hospital deaths from HAP/VAP were obtained from another published study.[4] In-hospital deaths were categorized based on whether a patient had received appropriate empirical treatment and whether a patient was infected with a pathogen(s) resistant to the empirical treatment.

Economic inputs

Model inputs on treatment duration were obtained from the EU-approved product labels, and it was assumed that each patient completed the course of treatment per the label-specified duration, except in cases of resistance to empirical treatment or an AE that resulted in treatment discontinuation or the death of a patient.

The hospitalization costs were calculated as a mean of the ICU costs and general ward costs, using time spent in ICU or general ward as weights. Analysis of data on health care resource utilization from the REPROVE study provided the inputs for the percentage of hospitalization days in ICU versus in general ward and the total length of hospital stay. These data were further estimated based on whether a patient was cured at the first follow-up visit.

Model inputs on the costs of SAEs were derived as a weighted mean cost based on different SAEs reported

Table I. Model inputs and data sources.

Inputs	Value	Source
Clinical cure, %		
CAZ-AVI	77.4	REPROVE clinical study data[10]
Meropenem	78.1	
Colistin + high-dose meropenem	58.0	Expert opinion
AE frequencies, %*		
CAZ-AVI	8.6	REPROVE clinical study data[10]
Meropenem	6.5	REPROVE clinical study data[10]
Colistin + high-dose meropenem	6.5	Assumed to be same as meropenem in REPROVE study
In-hospital death, %		
Appropriate empirical treatment	14.02	Wilke et al (2011)[4]
Inappropriate empirical therapy	26.36	
Resistant to empirical therapy†	31.63	
Daily drug costs‡ (average daily dose)		
CAZ-AVI	€300 ($335; 7500 mg)	Assumption provided by Pfizer
Meropenem	€55 ($62; 3000 mg)	AIFA[19] (except for the cost of colistin, which was taken from BNF,[20] then converted to Euros using an exchange rate of £1 = €1.36 [$1.52])
Colistin + high-dose meropenem	€120 ($134; 5 mg for colistin; 6000 mg for meropenem)	
Treatment duration, d		
CAZ-AVI	10.5	CAZ-AVI EU label[21]
Meropenem	12.0	Doripenem EU label, assumed same as doripenem data given the same drug class[22]
Colistin + high-dose meropenem	9.5	Doripenem EU label, assumed same as doripenem data given the same drug class[22]
Hospital cost per day		
General ward	€309 ($345)	Italian hospital diagnosis-related groups (2013 and 2015)[23,24]
ICU	€1383 ($1545)	Tan et al (2012)[25]
Hospital length of stay, d		
With clinical cure	16.4	REPROVE clinical study data[10]
With clinical failure	19.1	REPROVE clinical study data[10]
Percentage of hospitalization days in ICU, %		
With clinical cure	43.90	REPROVE clinical study data[10]
With clinical failure	56.02	REPROVE clinical study data[10]

(*continued on next page*)

Table I. (*Continued*)

Inputs	Value	Source
Cost of SAE in the base case		
SAE cost	€3424 ($3824)	Italian hospital diagnosis-related groups (2013 and 2015)[23,24]
Utility (quality of life)		
With clinical response/cure	0.92	Song et al (2012)[26]
Without clinical response	0.61	Delate et al (2001)[27]

Euros converted to USD using an exchange rate of €1 = $1.1169 as of November 1, 2019.[28]
AE = adverse event; AIFA = Agenzia Italiana del Farmaco, BNF = British National Formulary; CAZ-AVI = ceftazidime-avibactam; EU = European Union; ICU = intensive care unit; REMOVE = Ceftazidime-Avibactam Versus Meropenem In Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia.
* AEs considered in the model included only serious AEs, as these have relevant cost impact and can result in treatment discontinuation or treatment switch.
† Mortality of patients with resistant pathogens are assumed to be 20% higher than mortality of patients with inappropriate empirical therapy without resistance.
‡ AIFA, Agenzia Italiana del Farmaco, 2014 (except for cost of colistin, which was taken from British National Formulary, converted to Euros using an exchange rate of £1 = €1.36 [$1.52]).

in the REPROVE study. Health utilities, key components in estimating QALYs, were based on data obtained from the published literature, as these were not captured in the REPROVE study, and published data on utility in nonresponding patients with HAP/VAP were not identified.

Analyses

The model compared the cost-effectiveness of empirical treatment with CAZ-AVI (intervention sequence) versus meropenem (comparator sequence), followed by second-line treatment of colistin + high-dose meropenem, from the perspective of publicly funded health care in Italy, with only direct medical costs considered. The selected time horizon of the model in the base-case analysis was 5 years, to cover the episode of the infection and to evaluate the long-term impact. An annual discount rate of 3% on costs and health benefits was applied.[13]

Cost-effectiveness and cost-utility were analyzed, and the following health outcomes were evaluated: percentages of cured patients, LYs gained, and QALYs gained. These outcomes were combined with cost data to calculate the incremental cost-effectiveness ratio (ICER) as the incremental cost per QALY gained.

The robustness of the results with respect to the uncertainty in the model input parameters was evaluated by probabilistic sensitivity analysis (PSA) using second-order Monte Carlo simulation. Each parameter (costs and outcomes) was assigned a probability distribution, and cost-effectiveness results associated with simultaneously selecting random values from those distributions were generated. Health care resource utilization and costs were assumed to follow a γ distribution, while inputs restricted between 0 and 1 (eg, utilities) were assumed to follow a β distribution. The SE of the input parameters was available only for the treatment duration and for the time of microbiological results. Assumptions had to be performed at all other inputs to estimate the SEs, as there was no information on the variability of these parameters. The variability in the risks for AEs was assumed to be high; therefore, the SEs of the AE risks were calculated to be 20% of the means. For all other inputs, the SEs were assumed to be 10% of the means. Results of the PSA were plotted on the cost-effectiveness plane, and cost-effectiveness acceptability curves were calculated.

One-way deterministic sensitivity analyses were conducted by varying each parameter as ±20% of the base-case values while holding all other parameters

constant to examine the impact of each input parameter and to define the most influential parameters. The *incremental net benefit* (INB) was defined as the difference between the incremental QALYs, multiplied by a threshold (willingness to pay), and the incremental costs were summarized in a tornado diagram. If the INB was positive, then the intervention was considered cost-effective; if the INB was negative, then the intervention was not considered cost-effective versus the comparator, at the given threshold.

Scenario analyses were performed, first, as a conservative case in which the additional burden due to resistance (ie, reduction in efficacy of second-line treatment, increase in daily hospital costs, and increase in mortality) was removed; second, where the rate of resistance of *K pneumonia* to carbapenems was reduced to 30%; and third, where the efficacy of second-line treatment was set to 100% (ie, assuming patients were switched to the "correct" treatment in the second line after the microbiological test results).

RESULTS

Base-Case Results

In the base case (Table II), patients treated with the intervention sequence had better clinical outcomes compared to those treated with the comparator sequence, as a higher proportion of patients had a clinical cure (+13.52%), which led to a shorter mean hospital stay (–0.40 days per patient), and gains in number of LYs (+0.195) and QALYs (+0.350) per patient. The intervention sequence had an estimated incremental total cost of €1254 ($1401) per patient compared to the total costs estimated for the comparator sequence; this finding was primarily due to higher costs of drugs (€3067 [$3426] vs €741 [$828]) and AEs (€296 [$331] vs €172 [$192]), despite lower hospitalization costs (€15,030 [$16,787] vs €16,228 [$18,125]) due to shorter length of hospital stay. The estimated ICER was €3581 ($4000) per QALY gained, which was well below the willingness-to-pay threshold of €30,000 [$33,507] per QALY in Italy (Table II and Fig. 3).

Scenario Results

A scenario in which the additional burden of resistance was removed (ie, the reduced efficacy, increased probability of death and additional hospital costs) was tested. In this scenario, the ICER was increased by 63% (€5851 [$6535] per QALY) compared to the base-case scenario (€3581 [$4000]). Similarly, in the scenario in which patients receiving second-line treatment were assumed to have 100% response/cure rates, the ICER was increased by 37% (€4922 [$5497] per QALY). Also, in the scenario in which the rate of resistance of *K pneumonia* to carbapenems was decreased from that in the base case (ie, 30% vs 52%), the ICER was increased by 145% (€8766 [$9791] per QALY). However, in all scenarios, the ICERs were <€30,000 (<$33,507) per QALY, the acceptable willingness-to-pay threshold in Italy.

Probabilistic Sensitivity Analysis Results

The incremental costs and incremental QALYs of the intervention versus comparator sequence at the simulation points calculated in the PSA were plotted on a cost-effectiveness plane (Fig. 4A). The PSA results showed that the groupings on the cost-effectiveness planes had a cluster around the northeast quadrant, suggesting that the intervention sequence (ie, CAZ-AVI) was more effective and costlier than was the comparator sequence (ie, meropenem) in 52% of the iterations performed in the PSA. In 30% of the iterations, intervention sequence (CAZ-AVI) was found to be dominant (ie, providing better clinical outcomes at lower costs compared to sequence initiating with meropenem).

The cost-effectiveness acceptability curve (Fig. 4B) depicted that at a willingness-to-pay threshold of >€9000 ($10,052) per QALY, the intervention sequence was an optimal treatment option representing the maximum net benefit compared to that of the comparator sequence. Below this threshold (€9000 [$10,052] per QALY), the comparator sequence had a higher probability of being an optimal treatment option.

Deterministic Sensitivity Analysis Results

The tornado graph (Fig. 5) represents the 1-way deterministic sensitivity analysis results of outcomes of INB based on a willingness-to-pay threshold of €30,000 ($33,507) per QALY. The intervention sequence depicted cost-effectiveness (positive INB of €9249 [$10,330]) as compared to the comparator sequence based on the INB from the base case. The results were based on the top 10 parameters by order of their influence on the outcomes. The INB was most influenced by the variation in the response rates

Table II. Base-case outcomes (discounted by 3%).

Outcomes	CAZ-AVI Followed by Colistin + High-Dose Meropenem	Meropenem Followed by Colistin + High-Dose Meropenem
Clinical outcomes, %		
Percentage of patients with cure	72.42	58.90
Percentage of patients who died in hospital	16.32	20.54
Percentage of patients with adverse events	8.66	5.02
Hospital length of stay, mean, d	18.28	18.68
Discounted life-years	3.889	3.694
Discounted QALYs	3.439	3.089
Discounted cost outcomes		
Drug costs	€3067 ($3426)	€741 ($828)
Hospitalization costs	€15,030 ($16,787)	€16,228 ($18,125)
Adverse event costs	€296 ($331)	€172 ($192)
Total costs	€18,394 ($20,544)	€17,140 ($19,144)
ICERs		
Incremental cost per QALY gained	€3581 ($4000)	

CAZ-AVI = ceftazidime-avibactam; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-year.

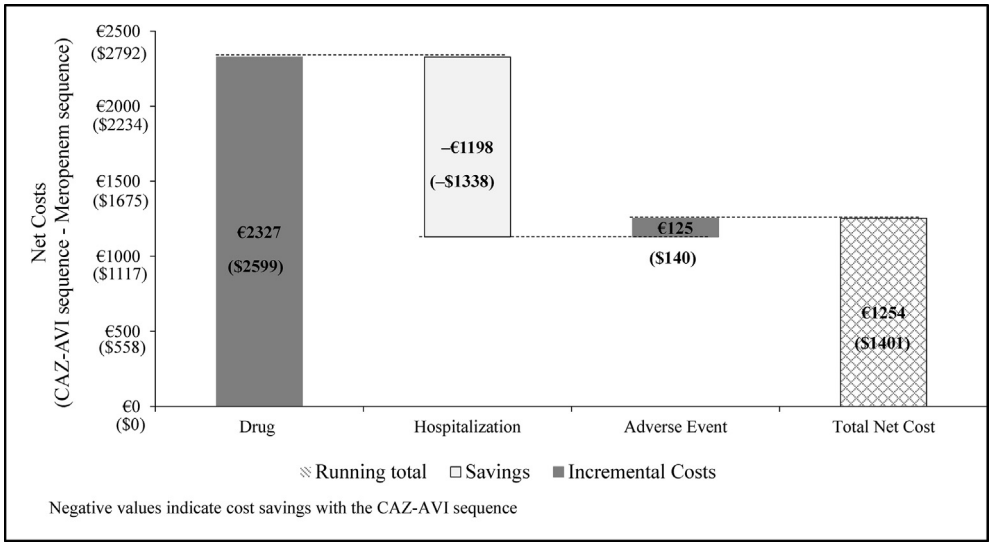


Figure 3. Incremental cost outcomes per patient for ceftazidime/avibactam (CAZ-AVI) sequence versus meropenem sequence. Euros converted to USD using an exchange rate of €1 = $1.1169 as of November 1, 2019.[28]

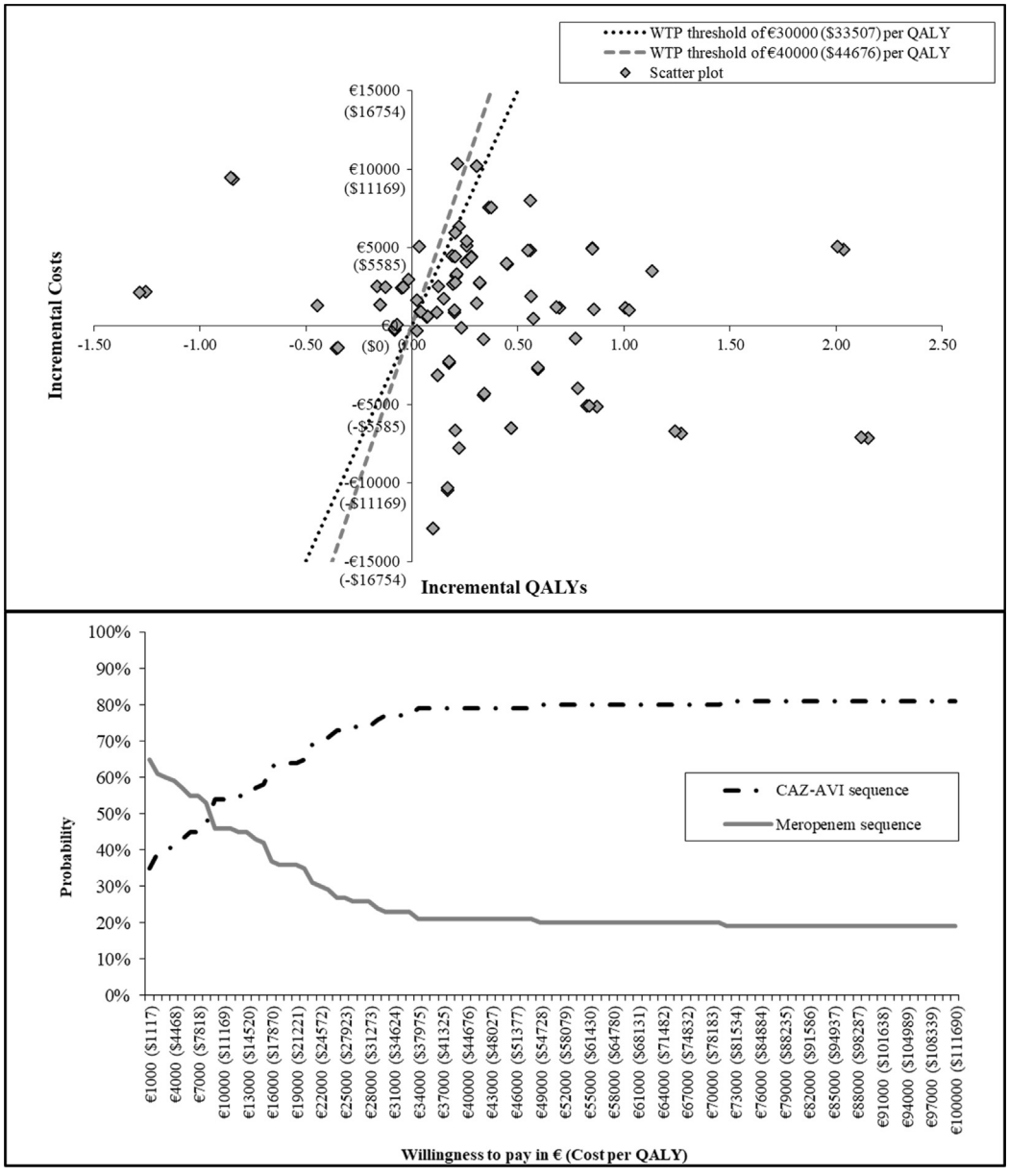


Figure 4. Results from probabilistic sensitivity analysis for ceftazidime/avibactam (CAZ-AVI) versus meropenem in the treatment of hospital-acquired pneumonia including ventilator-associated pneumonia (HAP/VAP), cost per quality-adjusted life-year (QALY). A, On cost-effectiveness plane B, On cost-effectiveness acceptability curve. Each dot represents cost-effectiveness outcome from each iteration. The threshold lines represent cost-effectiveness thresholds (€30,000 [$33,507] per QALY); the maximum amount society is willing to pay for a QALY gain. In cases that fall to the right and below this line, the intervention (CAZ-AVI) is cost-effective compared to the comparator (meropenem). In cases that fall to left and above this line, the intervention is not cost-effective compared to the comparator. Euros converted to USD using an exchange rate of €1 = $1.1169 as of November 1, 2019.[28] WTP = willingness to pay.

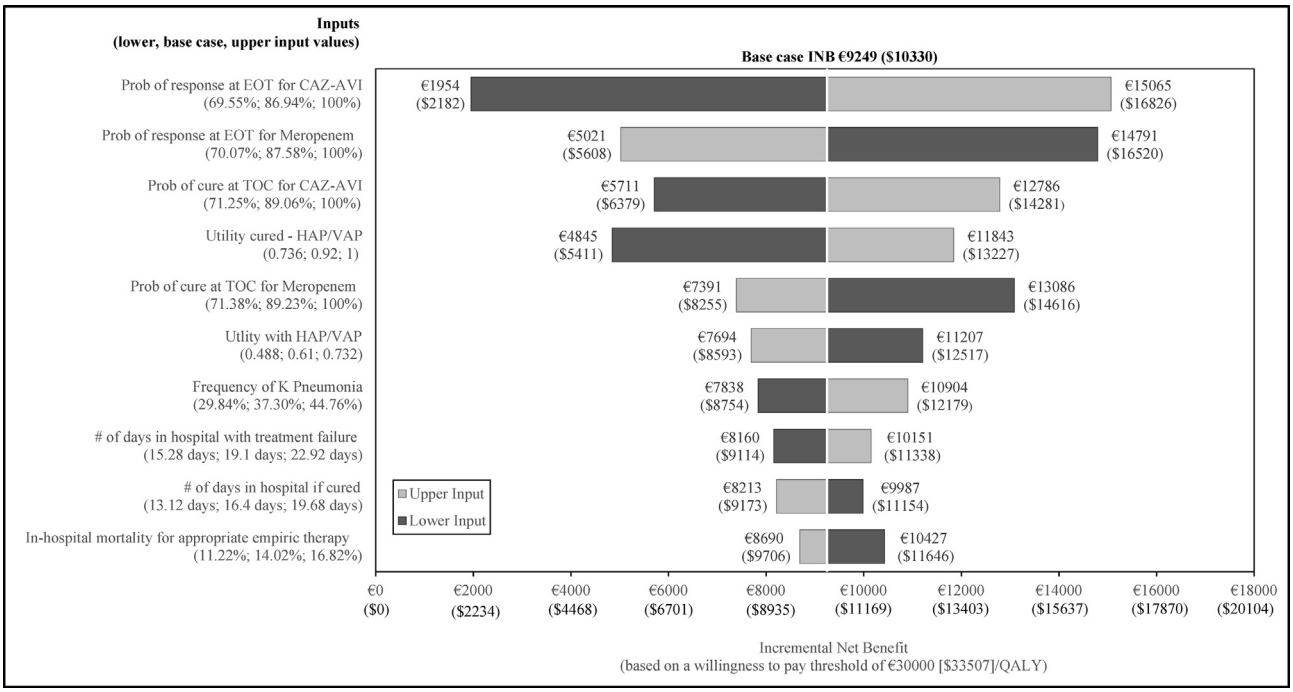


Figure 5. Results from 1-way deterministic sensitivity analyses for ceftazidime/avibactam (CAZ-AVI) versus meropenem in hospital-acquired pneumonia including ventilator-associated pneumonia (HAP/VAP): incremental net benefit (INB) based on willingness-to-pay threshold. Positive INB indicates the intervention (CAZ-AVI) is cost-effective versus the comparator (meropenem), and vice versa. Euros converted to USD using an exchange rate of €1 = $1.1169 as of November 1, 2019.[28] EOT = end of treatment; Prob = probability; TOC = test-of-cure.

at EOT and the cure rates at the TOC assessment for CAZ-AVI and for meropenem but remained below the maximum willingness-to-pay threshold in all instances.

DISCUSSION

The present study is the first economic evaluation of CAZ-AVI versus meropenem in the empirical treatment of hospitalized patients with HAP/VAP from the perspective of publicly funded health care (third-party payer) in Italy. The base-case analysis results showed that the intervention sequence (CAZ-AVI followed by colistin + high-dose meropenem) versus the comparator sequence (meropenem followed by colistin + high-dose meropenem) was associated with an increase in the clinical cure rate, shorter hospital stays, and higher QALYs at an acceptable incremental cost of €1254 ($1401) per patient with HAP/VAP in Italy. The higher drug and AE costs per patient were offset by reduced hospitalization costs. Furthermore, CAZ-AVI was cost-effective compared to meropenem at an ICER of €3581($4000) per QALY gained, well below the threshold of €30,000 ($33,507) per QALY in Italy. The introduction of CAZ-AVI to hospital formularies in the treatment of HAP/VAP was expected to have a minimal impact on the health care budget in Italy, with an estimated increase of just 0.5% over 3 years.[29]

The current study was the first to look at the cost-effectiveness of CAZ-AVI compared to that of meropenem in the treatment of HAP/VAP, although other studies of the cost-effectiveness of HAP/VAP treatments[29–33] and of CAZ-AVI have been previously published.[29,34,35] The previously published cost-effectiveness studies showed CAZ-AVI to be cost-

effective compared to the comparator (ie, colistin-based therapy or imipenem) in the treatment of bacteremia, pneumonia, and complicated urinary tract infection.

In the present study, the model inputs for treatment comparison were obtained from data from the REPROVE clinical study, other published studies, expert opinion, and local databases, with assumptions being made due to a lack of data on some model parameters. This approach is consistent with those from other published studies that have been compared the cost-effectiveness of antibiotic treatments of HAP/VAP.[29,31,33]

In our evaluation, a willingness-to-pay threshold of €30,000 per QALY was used. A recent publication by Woods et al (2016)[36] suggested an alternate approach to determine willingness-to-pay threshold in a specific country in which the relationship between health care spending and health outcomes is taken into account. Using the approach suggested, the estimated threshold calculated for Italy was €15,114 per QALY (using the following values: gross domestic product of the United Kingdom = $42,986[37]; gross domestic product of Italy = $35,391.70[38]; elasticity = 0.7[36]; euros − British £ exchange rate = 1.2009[39]). With the reduced willingness-to-pay threshold, our cost-effectiveness results including base case and all scenarios evaluated still remained below the threshold.

The model analysis had certain limitations. The REPROVE study was planned as a noninferiority study and hence lacked the statistical power to show superiority of CAZ-AVI to meropenem. The noninferiority study design could have affected the clinical inputs of the base-case analysis. The model was thus designed to include the impact of resistant pathogens, considering the additional economic burden associated with antibiotic resistance that cannot be captured in clinical trials (ie, reduction in cure rates with the second-line treatment, increase in daily hospitalization costs, and increase in mortality). In a conservative scenario in which this additional impact was removed, as expected the ICER was increased compared to the base case (€5851 [$6535] vs €3581 [$4000] per QALY); however, it was still well below the willingness-to-pay threshold of €30,000 ($33,507) per QALY in Italy.

Furthermore, the model had treatment pathways as predefined and thus the subsequent treatment choices cannot be controlled for patients. Hence, in the case of no microbiological resistance, the model assumed continuation of empirical treatment with CAZ-AVI or meropenem and did not allow consideration for de-escalation of broad-spectrum empirical therapy or dose adjustment, which could be followed in clinical routine. Had the model considered de-escalation, that would have lowered the costs of treatment sequence with CAZ-AVI, given that more patients responded to the empirical therapy (mainly due to lower rates of resistance) and thus lowering the ICER. Therefore, our analysis can be considered as conservative. In addition, the clinical inputs for the model were sourced from REPROVE and other published multicenter, multinational clinical studies, and it was assumed that the data were reflective of the population of Italy. Similarly, the assumption for efficacy of the combination colistin + high-dose meropenem specifically in second-line treatment (ie, cure rate = 58%), was based on expert opinion due to the unavailability of published evidence. However, one may argue that, by that time, microbiological test results are available, so clinicians should be able to switch patients to the "correct" antibiotic, and thus the success rate with the second-line treatment should be high. A scenario analysis that assumed clinical cure rates with second-line antibiotics would be 100% revealed an increase in the ICER compared to that in the base case (€4922 [$5497] vs €3581[$4000] per QALY); however, it was still well below the willingness-to-pay threshold of €30,000 [$33,507] per QALY. The model also did not include the impact of disease transmission in HAP/VAP. Treating with an appropriate medication early in an infection can decrease the risk for transmission. Furthermore, a reduction in the length of stay in-hospital also decreases this risk. Additionally, the change in resistance incidence over time was not considered and was assumed to have been constant. It was assumed that the distribution of different AEs observed with other treatments would be similar to that observed in clinical studies of CAZ-AVI, since AEs were included as an aggregated AE. Furthermore, the frequency of AEs with colistin + high-dose meropenem was considered similar to the frequency of AEs with

meropenem, although additional AEs, due to the colistin treatment, were expected. Given that the AE rates for both treatment sequences and also for the second-line treatment were very low, these assumptions were not expected to have had a significant impact on the cost-effectiveness results. The sensitivity analysis also revealed AE costs to have had little impact on the ICER outcome (not even on the top 10 most influential parameters). Also, the model inputs were based on Italy-specific data. Therefore, the model results are applicable to Italy. To calculate the results in other countries, the model inputs should be replaced by county-specific inputs. Furthermore, the model evaluated data from only patients infected with gram-negative pathogens, which was the target population for CAZ-AVI treatment. The majority of the HAP/VAP infections are caused by gram-negative pathogens.[40–42] In a European, Serbian study, the percentage of gram-negative agents in HAP/VAP patients was 95.2%.[40] Because the percentage of gram-positive patients among those with HAP/VAP is small, the inclusion of gram-positive patients in the analyses would not have modified the results considerably. Finally, as the antibiotics are used over time, the resistance rates can evolve. Therefore, the results of the analysis in the present study may have to be updated in the long run. Furthermore, the introduction of CAZ-AVI can increase diversity in prescribing and provide early appropriate empirical treatment, with a subsequent reduction in levels of resistance.[43,44]

The strengths of the present study ability to included its capture of the impact of different resistant pathogens and the evaluation of the whole course (response, cure, treatment length, hospital discharge, adverse events) of HAP/VAP experienced by patients. The efficacy inputs were considered in detail, with modeling of both cure of patients and probability of response before the cure, which allowed nonresponder patients to be switched between treatments at EOT in the model. Additionally, the individual patient simulation approach provided a means to a more realistically modeled treatment pathway, allowing the effects of treatment switch and resistance to have been captured in the cost-effectiveness outcomes despite the noninferiority nature of the REPROVE study.

One of the challenges with novel antibiotics lies in getting them into the focus of society, payers, and decision makers. As this study shows, the introduction of novel antibiotics such as CAZ-AVI can save lives, preventing HAP/VAP-related deaths due mainly to inappropriate empirical treatment, with only minimal incremental costs. However, novel antibiotics do not seem to get the attention given to new drugs in other therapeutic areas, such as oncology, which get media attention even if they offer relatively little clinical benefit at high incremental costs.

CONCLUSIONS

The choice of an optimal antibiotic in patients with HAP/VAP should involve careful consideration of local resistance data, treatment efficacy, treatment—resistance profile, and resource burden associated with management of the infection. The present study demonstrated that CAZ-AVI, when compared with meropenem, provided better health outcomes (ie, clinical cures), shorter times in-hospital, and thus higher QALYs per patient, at an acceptable cost. CAZ-AVI was demonstrated as a cost-effective alternative to meropenem in HAP/VAP in Italy, based on the willingness-to-pay threshold, resistance levels, and efficacy data. These findings further support the use of CAZ-AVI as an alternative treatment in patients with HAP/VAP.

DISCLOSURES

This research and its publication were supported by Pfizer Inc. The sponsor had a co—lead role in conceptualization of the study design. The sponsor supported the methodology, validation, and formal analysis of the data. The sponsor supported writing, review, and editing of the manuscript. The sponsor also funded medical writing assistance by Evidera.

E.T. and T.K. are employees of Evidera, which received funding from Pfizer in connection with conducting the study, developing the manuscript, and medical writing. A.T. is an employee of IRB Barcelona Institute for Research in Biomedicine, Pulmonology Hospital Clinic (Barcelona, Spain), and M.B. is an employee of the Department of Medicine, University of Udine and Azienda Sanitaria Universitaria Integrata di Udine (Udine, Italy), each of which received research funding from Pfizer. R.D., P.I., and C.C. are employees of, and hold stock and/or stock options in, Pfizer. The authors have

indicated that they have no other conflicts of interest with regard to the content of this article.

ACKNOWLEDGMENTS

The authors thank Nathalie Baillon-Plot (Pfizer Inc., Paris, France) for medical guidance provided during the development of the model. They also thank medical writer Saurabh Aggarwal, PhD, of Evidera.

E.T. and T.K. were involved in the study conceptualization, methodology, software, and validation; formal analysis of the data; investigation; and writing, review, and editing of the manuscript. A.T. and M.B. provided support in conceptualization, methodology, and investigations of the manuscript. R.D., P.I., and C.C. participated in the study conceptualization, methodology, and validation; formal analysis of the data; and writing, review, and editing of the manuscript.

REFERENCES

1. Barbier F, Andremont A, Wolff M, Bouadma L. Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management. *Curr Opin Pulm Med*. 2013;19:216–228.
2. Montravers P, Harpan A, Guivarch E. Current and future considerations for the treatment of hospital-acquired pneumonia. *Adv Ther*. 2016;33:151–166.
3. Hunter JD. Ventilator associated pneumonia. *Postgrad Med J*. 2006;82:172–178.
4. Wilke M, Grube RF, Bodmann KF. Guideline-adherent initial intravenous antibiotic therapy for hospital-acquired/ventilator-associated pneumonia is clinically superior, saves lives and is cheaper than non-guideline adherent therapy. *Eur J Med Res*. 2011;16:315–323.
5. Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. *Infect Control Hosp Epidemiol*. 2012;33:250–256.
6. Erbay RH, Yalcin AN, Zencir M, Serin S, Atalay H. Costs and risk factors for ventilator-associated pneumonia in a Turkish university hospital's intensive care unit: a case-control study. *BMC Pulm Med*. 2004;4:3. https://doi.org/10.1186/1471-2466-4-3.
7. Awad SS, Rodriguez AH, Chuang YC, et al. A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. *Clin Infect Dis*. 2014;59:51–61.
8. Weber DJ, Rutala WA, Sickbert-Bennett EE, Samsa GP, Brown V, Niederman MS. Microbiology of ventilator-associated pneumonia compared with that of hospital-acquired pneumonia. *Infect Control Hosp Epidemiol*. 2007;28:825–831.
9. Luyt C-E, Hekimia G, Koulenti D, Chastre J. Microbial cause of ICU-acquired pneumonia: hospital-acquired pneumonia versus ventilator-associated pneumonia. *Curr Opin Crit Care*. 2018;24:332–338.
10. Torres A, Zhong N, Pachl J, et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. *Lancet Infect Dis*. 2018;18:285–295.
11. Bassetti M, Pecori D, Peghin M. Multidrug-resistant gram-negative bacteria-resistant infections: epidemiology, clinical issues and therapeutic options. *Ital J Med*. 2016;10:364–375.
12. Scarafile G. Antibiotic resistance: current issues and future strategies. *Rev Health Care*. 2016;7:3–16.
13. Capri S, Ceci A, Terranova L, Merlo F, Mantovani L. Members of the Italian Group for Pharmacoeconomic. Guidelines for economic evaluations in Italy: recommendations from the Italian group of pharmacoeconomic studies. *Drug Inf J*. 2001;35:189–201.
14. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. *Clin Microbiol Infect*. 2016;22:416–422.
15. Liu Q, Li X, Li W, et al. Influence of carbapenem resistance on mortality of patients with *Pseudomonas aeruginosa* infection: a meta-analysis. *Sci Rep*. 2015;5:11715.
16. Marquet K, Liesenborgs A, Bergs J, Vleugels A, Claes N. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. *Crit Care*. 2015;19:63. https://doi.org/10.1186/s13054-015-0795-y. https://ccforum.biomedcentral.com/articles/10.1186/s13054-015-0795-y.
17. Kazmierczak K, Jonge BLM, Stone G, Sahm D. In vitro activity of ceftazidime/avibactam against isolates of Pseudomonas aeruginosa collected in European countries: INFORM global surveillance 2012-15. *J Antimicrob Chemother*. 2018;73:2777–2781.
18. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2016. Available at:(update May 2016) https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2016. Accessed November 15, 2018.
19. Agenzia Italiana del Farmaco. Available at: http://www.agenziafarmaco.gov.it/. Accessed November 15, 2018.
20. British National Formulary. Committee joint formulary. British national formulary (BNF) 66. Pharmaceutical press. Available at: https://www.bnf.org/; 2013. Accessed November 15, 2018.

21. European medicines agency: annex I: summary of product characteristics (Zavicefta). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004027/WC500210234.pdf. Accessed November 15, 2018.
22. European medicines agency: annex I: summary of product characteristics (Doribax). Available at: https://www.ema.europa.eu/documents/product-information/doribax-epar-product-information_en.pdf. Accessed November 15, 2018.
23. della Salute Ministero. Rapporto SDO 2013 - Tavola 2.2.6 - Descrizione dell'attività per DRG (versione 24) - attività per acuti in Regime ordinario - anno 2013 [in Italian]. Available at: http://www.salute.gov.it/portale/home.html. Accessed November 15, 2018.
24. della Salute Ministero. Direzione generale della programmazione sanitaria. Tariffe delle prestazioni di assistenza ospedaliera per acuti, per tipo di ricovero (Euro) [in Italian]. Available at: http://www.salute.gov.it/portale/home.html. Accessed November 15, 2018.
25. Tan SS, Bakker J, Hoogendoorn ME, et al. Direct cost analysis of intensive care unit stay in four European countries: applying a standardized costing methodology. *Value Health*. 2012;15:81−86.
26. Song Y, Tai JH, Bartsch SM, Zimmerman RK, Muder RR, Lee BY. The potential economic value of a *Staphylococcus aureus* vaccine among hemodialysis patients. *Vaccine*. 2012;30:3675−3682.
27. Delate T, Coons SJ. The use of 2 health-related quality-of-life measures in a sample of persons infected with human immunodeficiency virus. *Clin Infect Dis*. 2001;32:e47−e52.
28. Board of Governors of the Federal Reserve System. Foreign exchange rates- H.10. Nov 1, 2019 data (Release date November 4, 2019). Available at: https://www.federalreserve.gov/releases/h10/current. Accessed November 7, 2019.
29. Kongnakorn T, Wagenlehner F, Falcone M, et al. Cost-effectiveness analysis of ceftazidime/avibactam compared to imipenem as empirical treatment for complicated urinary tract infections. *Int J Antimicrob Agents*. 2019;54:633−641.
30. Collins CD, Schwemm AK. Linezolid versus vancomycin in the empiric treatment of nosocomial pneumonia: a cost-utility analysis incorporating results from the ZEPHyR trial. *Value Health*. 2015;18:614−621.
31. Patel DA, Shorr AF, Chastre J, Niederman M, Simor A, Stephens JM. Modeling the economic impact of linezolid versus vancomycin in confirmed nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Crit Care*. 2014;18:R157.
32. McKinnell JA, Corman S, Patel D, Leung GH, Gordon LM, Lodise TP. Effective antimicrobial stewardship strategies for cost-effective utilization of telavancin for the treatment of patients with hospital-acquired bacterial pneumonia caused by *Staphylococcus aureus*. *Clin Ther*. 2018;40:406−414. e2.
33. McGarry LJ, Merchant S, Nathwani D, et al. Economic assessment of doripenem versus imipenem in the treatment of ventilator-associated pneumonia. *J Med Econ*. 2010;13:142−147.
34. Simon MS, Sfeir MM, Calfee DP, Satlin MJ. Cost-effectiveness of ceftazidime-avibactam for treatment of carbapenem-resistant Enterobacteriaceae bacteremia and pneumonia. *Antimicrob Agents Chemother*. 2019 Sep 23. https://doi.org/10.1128/AAC.00897-19 [Epub ahead of print].
35. Kongnakorn T, Eckmann C, Bassetti M, et al. Cost-effectiveness analysis comparing ceftazidime/avibactam (CAZ-AVI) as empirical treatment comparing to ceftolozane/tazobactam and to meropenem for complicated intra-abdominal infection (cIAI). *Antimicrob Resist Infect Control*. 2019;8:204. https://doi.org/10.1186/s13756-019-0652-x.
36. Woods B, Revill P, Sculpher M, Claxton K. Country-Level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health*. 2016;19:929−935.
37. Trading Economics. United Kingdom GDP per capita (1960-2018 data). Available at: https://tradingeconomics.com/united-kingdom/gdp-per-capita. Accessed February 18, 2020.
38. Trading Economics. Italy GDP per capita (1960-2018 data). Available at: https://tradingeconomics.com/italy/gdp-per-capita. Accessed February 18, 2020.
39. Bank of England. Daily spot exchange rates against Sterling. Available at: https://www.bankofengland.co.uk/boeapps/database/Rates.asp?TD=19&TM=Feb&TY=2020&into=GBP&rateview=D. Accessed February 18, 2020.
40. Djordjevic ZM, Folic MM, Jankovic SM. Distribution and antibiotic susceptibility of pathogens isolated from adults with hospital-acquired and ventilator-associated pneumonia in intensive care unit. *J Infect Public Health*. 2017;10:740−744.
41. Eades C, Hughes S, Heard K, Moore LSP. Antimicrobial therapies

for Gram-positive infections. *Clin Pharm*. 2017;9(9). https://doi.org/10.1097/MCP.0000000000000042.
42. Enne VI, Personne Y, Grgic L, Gant V, Zumla A. Aetiology of hospital-acquired pneumonia and trends in antimicrobial resistance. *Curr Opin Pulm Med*. 2014;20:252–258.
43. Karam G, Chastre J, Wilcox MH, Vincent JL. Antibiotic strategies in the era of multidrug resistance. *Crit Care*. 2016;20:136. https://doi.org/10.1093/jac/dkl097.
44. Sandiumenge A, Diaz E, Rodriguez A, et al. Impact of diversity of antibiotic use on the development of antimicrobial resistance. *J Antimicrob Chemother*. 2006;57:1197–1204.

Address correspondence to: Eszter Tichy, Evidera, Bég u. 3-5 / 520, 1022, Budapest, Hungary. E-mail: eszter.tichy@evidera.com