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Cost-effectiveness analysis of ceftazidime/avibactam compared to imipenem as empirical treatment for complicated urinary tract infections

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ABSTRACT

Ceftazidime/avibactam (CAZ-AVI) is a novel, fixed-dose combination antibiotic that has been approved in Europe and the United States for patients with complicated urinary tract infections (cUTIs) based on results of a Phase III, randomized, comparative study (RECAPTURE study). The present analysis evaluated cost-effectiveness of CAZ-AVI as an empirical treatment for hospitalized patients with cUTIs from the Italian publicly funded healthcare (third-party payer) perspective. A sequential, patient-level simulation model was developed that followed the clinical course of cUTI and generated 5000 pairs of identical patients (CAZ-AVI or imipenem as empirical treatment). The model included additional impact of resistant pathogens; patients who did not respond to empirical treatment were switched to second-line treatment of colistin+high dose carbapenem in both groups. The time horizon of the model was five years, with an annual discount rate of 3% applied to both costs and quality-adjusted life-years (QALYs). The analysis demonstrated that an intervention sequence (CAZ-AVI followed by colistin+high dose carbapenem) compared with a comparator sequence (imipenem followed by colistin+high dose carbapenem) was associated with a net incremental cost of €1015 per patient but provided better health outcomes in terms of clinical cure (97.65% vs. 91.08%; $\Delta = 6.57\%$), shorter hospital stays (10.65 vs. 12.55 days; $\Delta = 1.90$ days), and QALYs gained per patient (4.190 vs. 4.063; $\Delta = 0.126$). The incremental cost-effectiveness ratio was €8039/QALY, which is well below the willingness-to-pay threshold of €30 000/QALY in Italy. The results showed that CAZ-AVI is expected to be a cost-effective treatment compared with imipenem for cUTI in Italy.

1. Introduction

Complicated urinary tract infections (cUTIs) involve structural or functional abnormalities of the genitourinary tract, relevant for infection, including urinary catheterization [1,2]. The majority of cUTIs are caused by Gram-negative bacteria, including *Escherichia coli, Klebsiella pneumoniae, Enterobacter* species, and *Pseudomonas aeruginosa* [3-5]. Many of these bacterial infections are resistant to

Abbreviations: AE, adverse event; AIFA, Italian Medicines Agency (Agenzia Italiana del farmaco); CAZ-AVI, ceftazidime and avibactam; CBP, carbapenem; CEAC, cost-effectiveness acceptability curve; cUTI, complicated urinary tract infections; DSA, deterministic sensitivity analysis; EOT, end of treatment; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; INB, incremental net benefit; LFU, long-term follow-up; LY, life-year; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SAE, serious adverse event; SE, standard error; TOC, test-of-cure.

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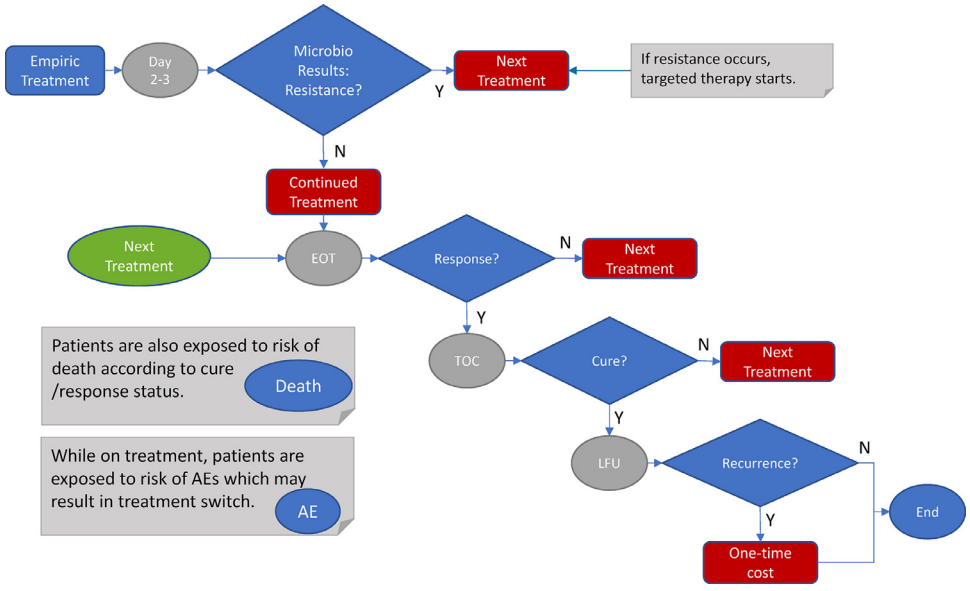

Fig. 1. Overview of the model structure depicting patient flow.
Footnote: AE, adverse event; EOT, end-of-treatment visit; LFU, late follow-up visit (45–52 days following initiation of treatment); N, no; TOC, test-of-cure visit (21–25 days following initiation of treatment); Y, yes.

antibiotics, resulting in prolonged stays in hospital and critical care units, and are a serious threat to public health, thus highlighting the urgent requirement for new treatments [6-8].

Ceftazidime/avibactam (CAZ-AVI) is a fixed-dose combination antibiotic containing ceftazidime, an approved broad-spectrum, third-generation cephalosporin, and avibactam, a first-in-class, non-β-lactam, β-lactamase inhibitor that has been approved in Europe and the United States for patients with cUTI. CAZ-AVI has been developed to treat a broad range of Gram-negative bacterial infections that are resistant to current antibiotics and pose an increasing threat to public health. This drug combination has shown promising results in the treatment of multidrug-resistant infections [7,9].

Approval of CAZ-AVI was based on the results of a Phase III, randomized, comparative study to determine the efficacy, safety and tolerability of CAZ-AVI vs. doripenem followed by appropriate oral therapy in hospitalized adult patients with cUTI (RECAPTURE study). The study was a non-inferiority design for ethical reasons because the use of placebo was impractical and the new drug must be shown to be non-inferior to the gold standard/standard-of-care treatment to minimize risk to patients. The study met its primary endpoints to assess the non-inferiority of CAZ-AVI compared with doripenem with respect to the per-patient microbiological response at the test-of-cure (TOC) visit in Europe and the rest of the world and the symptomatic resolution rate of UTI-specific symptoms [7,9].

In the real world where antibiotic resistance is rising, traditional clinical evaluation does not show the true value of new antibiotics because of the non-inferiority design of studies and the exclusion of patients with suspected resistance to study drugs. Antibiotic resistance leads to prolonged hospital stay and increases the cost and economic burden for the payers [10-12]. Italy has a high prevalence of resistant Gram-negative bacteria (e.g., in 2014 the resistance rate of fluoroquinolones in *E. coli* was 44% and in *K. pneumonia* was 56%) [13]. Furthermore, antibiotic consumption outside of hospital was 27.8 doses per 1000 inhabitants, ranking Italy as the fifth highest country in terms of antibiotic use in Europe [14]. The clinical and economic benefits of CAZ-AVI need to be assessed against increasing drug treatment costs from the perspective of healthcare providers and payers. Thus, the objective of the current study was to compare the cost-effectiveness of CAZ-AVI as an empirical treatment for cUTI with that of imipenem from the Italian publicly funded healthcare (third-party payer) perspective.

2. Methods

2.1. Model structure

A sequential, patient-level simulation model of the clinical course of cUTI after initiation of empirical treatment (i.e., CAZ-AVI or imipenem) was developed in Microsoft Excel® to estimate the cost-effectiveness of CAZ-AVI in the target patient population. Based on data from the RECAPTURE study, the model tracks index patients through different phases of cUTI from diagnosis until clinical resolution or death. A graphical representation of the model structure with all treatment pathways is provided in Fig. 1. The model structure fulfils the requirements of the Italian health economic agency and is generalisable for other countries with similar clinical practice and epidemiology.

The model started with the creation of 5000 cUTI patients; each one was assigned clinical characteristics based on pathogen(s) and resistance status by Monte Carlo sampling. Hospitalized patients entered the model at the time of cUTI diagnosis, which was assumed to be concurrent with collection of urine culture and initiation of empirical antimicrobial therapy. The model then generated two identical cohorts: one cohort received empirical treatment with CAZ-AVI and the other received imipenem, an antibiotic widely used in Europe for cUTI, as suggested by Italian clinical experts. Identical cohorts ensured the comparisons were not affected by any differences in baseline characteristics of the infection and that random chance events (non-treatment effects) were treated equally across the groups. As displayed in Fig. 1, each patient received empirical treatment upon entering the model. The patient continued empirical treatment until his/her microbiological results were available (2–3 days). The patient was counted as having clinical failure and switched to the next treatment line if microbiological results revealed that at least one of the pathogens was resistant to empirical treatment. If no resistance was observed, empirical treatment was continued as definitive therapy.

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Once the patient completed the treatment course, he/she was assessed to evaluate for response at the end-of-treatment (EOT) assessment. If there was no response, the patient was counted as having a failure and switched to the next treatment. If there was a response, the patient was continued to follow-up and had the next assessment at the first follow-up visit, equivalent to the TOC visit in the clinical study (i.e., 21–25 days after initiation of treatment). At the TOC visit, patients were assessed for clinical cure. If there was no clinical cure, the patient was switched to the next line of treatment. If clinical cure was achieved, the patient proceeded to the second follow-up visit, which was equivalent to a long-term follow-up (LFU) visit in the clinical study (i.e., 45–52 days after initiation of treatment), where recurrence of infection (i.e., equivalent to clinical failure observed at the LFU visit in the randomized controlled studies) was assessed. If the patient had a recurrence, a one-time recurrence cost was accrued; this cost was assumed to include all medical costs associated with management of the recurrence.

During the model time horizon, patients were also exposed to risk of death and risk of treatment-related adverse events (AEs). The cost of managing any AE that occurred was accrued and the patient could switch to the next treatment line. Life-years (LYs) and quality-adjusted life years (QALYs) were evaluated when the patient died or reached the end of the time horizon.

Considering the increase in antibiotic resistance and the character of non-inferiority studies of antibiotics, the model included the additional impact of resistant pathogens to evaluate the real value of antibiotics. Patients infected with a pathogen resistant to empirical treatment were considered to have a 10% increase in hospitalization daily cost to account for increased healthcare resource use [10]; a 20% higher mortality than patients with susceptible pathogens but inappropriate treatment to account for the increased risk of mortality [10-12]; and a 10% reduced efficacy in subsequent treatment (based on expert opinion).

2.2. Treatment comparison

The treatment sequences consisted of an empirical treatment followed by second-line treatment and were based on current Italian clinical practices. The analysis compared an intervention sequence, which included empirical treatment with CAZ-AVI and second-line treatment with a combination of colistin and high dose carbapenem (colistin+high dose CBP), with a comparator sequence, which included empirical treatment with imipenem followed by second-line treatment with colistin+high dose CBP.

2.3. Model inputs and data sources

Model inputs and data sources are presented in Table 1 [15,17–26]. The model included up to five baseline pathogens. The frequency of the pathogens was based on the top five most frequently identified baseline pathogens in the RECAPTURE study [7].

Model inputs on resistance rate of CAZ-AVI were obtained from a published paper [15]; patients with resistant pathogen were excluded, as in the RECAPTURE study. Resistance rates of other drugs were derived from the 2017 resistance data of Italian patients [16]. Treatment efficacy included response achieved at the EOT visit, clinical cure at the first follow-up visit (i.e., TOC visit), and recurrence of infection at the second follow-up visit (i.e., LFU visit). The inputs for response and clinical cure for CAZ-AVI were based on data from the RECAPTURE study [7], and those for imipenem were clinical cure probabilities extracted from a published clinical study [16]. Probability of response at EOT and cure at TOC of the second-line treatment colistin+high dose CBP was assumed to be the same as the results of doripenem in the RECAPTURE study (same drug class).

Probabilities of recurrence for CAZ-AVI were based on data from clinical failures at the LFU visit in the RECAPTURE study in patients who achieved clinical cures at TOC, and recurrence data for imipenem and colistin+high dose CBP were assumed to be the same as for doripenem in the RECAPTURE study.

AEs in the base case included only serious adverse events (SAEs) that had relevant cost impact and could have resulted in treatment switch or discontinuation. Model inputs on SAEs were obtained from the RECAPTURE study. As the RECAPTURE study had low mortality, model inputs for in-hospital deaths were obtained from published clinical studies. In-hospital death was categorized based on appropriateness of treatment and resistance to empirical treatment.

Drug costs for CAZ-AVI and imipenem were available on the official site of the Italian Medicine Agency (AIFA); the cost of colistin was based on the United Kingdom price (from the British National Formulary) as the AIFA database did not have this information [23,27]. Hospitalization costs were calculated as an average of intensive care unit (ICU) costs [26] and general ward costs [24,25], weighing the duration in each location.

Inputs for total length of hospital stay and proportion of time spent in the ICU vs. general ward were obtained from analysis of healthcare resource use data from the RECAPTURE study. Costs of SAEs were calculated as a weighted average cost based on different SAEs reported during the RECAPTURE study. Costs of SAEs in the base case and the recurrence costs modelled as a one-off cost at the time of recurrence were based on the Italian hospital DRG costs [24,25]. Health utilities were based on data obtained from published literature [21,22] as this information was not included in the RECAPTURE study.

2.4. Analyses

The model compared the cost-effectiveness of an intervention sequence (empirical treatment with CAZ-AVI followed by colistin+high dose CBP) with that of a comparator sequence (empirical treatment with imipenem followed by colistin+high dose CBP) from the perspective of publicly funded healthcare (third-party payer) in Italy. The analysis focused on direct medical costs. The model included patient-level simulation that followed the clinical course of cUTI after initiation of empirical treatment for 5000 cUTI patients. The time horizon of the model was five years to cover the infection episode and to evaluate long-term impact. The model applied an annual discount rate of 3% on costs and health benefits [28].

Comparison of the two treatment strategies was based on the following outcomes from the model: proportions of patients cured, LYs, QALYs, and total costs. Differences in these outcomes between the two treatment strategies were calculated, along with an incremental cost-effectiveness ratio (ICER) as incremental cost per QALY gained.

Uncertainty of the results in the model was evaluated by probabilistic sensitivity analysis (PSA), applying second-order Monte Carlo simulation. Each parameter (costs and efficacy) was assigned a probability distribution, and cost-effectiveness results associated with simultaneously selecting random values from those distributions were generated. Healthcare resource use costs were assumed to follow gamma distributions. As there was no information on the variability of some of these parameters, the standard error (SE) was assumed to equal 10% of the mean. Results of the probabilistic analysis were plotted on the cost-effectiveness plane and were used to calculate cost-effectiveness acceptability curves (CEACs).

One-way deterministic sensitivity analyses were conducted to identify key model parameters, where each parameter was varied ± 20% of the base case values while holding all other parameters constant. Incremental net benefit (INB) was summarized as a tor-

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Table 1
Model inputs and data source.

Baseline pathogens and resistance rates by pathogen for each treatment			
		Resistance rates by pathogen for each treatment	
Pathogens	Frequency of baseline pathogens[a]	CAZ-AVI[b]	Imipenem[c]
Escherichia coli	76%	1%	1%
Klebsiella pneumoniae	12%	1%	52%
Pseudomonas aeruginosa	4%	7%	24%
Proteus mirabilis	3%	0%	0%
Enterobacter cloacae	3%	1%	0%

Other model inputs and data sources			
	CAZ-AVI	Imipenem	Colistin + high-dose CBP
Probability of clinical cure	97.3%[d]	80.6%[e]	93.6%[f]
Probability of AE[g]	1.8%[d]	1.0%[f]	1.0%[f]
Probability of recurrence	5.6%[d]	7.2%[f]	7.2%[f]
Treatment duration	7.5 days[h]	9.5 days[i]	9.5 days[i]
Probability of in-hospital death[j]	Appropriate empirical treatment: 1.80% Inappropriate empirical treatment: 7.20% Resistant to empirical treatment: 8.64%[k]		
Utility (quality of life)	With clinical response/cure: 0.92[l] Without clinical response: 0.61[m]		
Hospital length of stay[d]	With clinical cure: 10.40 days With clinical failure: 14.20 days		
Daily drug costs[n], (€) (average daily dose)	€300.00 (7500 mg)	€39.00 (2000 mg)	€68.13 (colistin [IV] 5 mg; CBP [imipenem] 3000 mg)
Hospital cost per day	General ward: €308.74[o]; ICU €1383.00[p]		
Cost of SAE in the base case	€ 1970		
Cost of recurrence	€ 2155		

AE, adverse event; BNF, British National Formulary; CAZ-AVI, ceftazidime-avibactam; CBP, carbapenem; ICU, intensive care unit; IV, intravenous, SAE, serious adverse event
[a] Top five most frequently identified baseline pathogens based on the RECAPTURE clinical study data.
[b] 2017 resistance data for Italy, derived from Kazmierczak et al. 2017 [13].
[c] Expert opinion. The same resistance rates are used at colistin+high dose CBP (at second line).
[d] RECAPTURE clinical study data [7].
[e] Vazquez et al. 2012 [15].
[f] Assumed to be the same as doripenem in RECAPTURE trial, given the same drug class.
[g] AEs considered in the model included only serious AEs, as these have relevant cost impact and can result in treatment discontinuation or treatment switch.
[h] Zavicefta (CAZ-AVI) EU label, ANNEX I Summary of Product Characteristics [16].
[i] Doribax (Doripenem) EU label, ANNEX I Summary of Product Characteristics, assumed same as doripenem data, given the same drug class [17].
[j] MacVane et al. 2014 [18].
[k] Assumed to be 20% higher than mortality among patients with susceptible pathogens but had inappropriate empirical therapy.
[l] Song et al. 2012 [19].
[m] Delate et al. 2001 [20].
[n] AIFA, Agenzia Italiana del Farmaco (except for cost of colistin which was taken from BNF, converted to Euros using an exchange rate of £1 = €1.36) [21].
[o] Italian hospital diagnosis-related groups (DRGs 2013 and 2015) [22,23].
[p] Tan et al 2012 [24].

nado diagram where INB was calculated as:

$$INB = (QALYs1 - QALYs2) \times threshold - (Costs1 - Costs2)$$

where QALYs1 = QALYs generated with Treatment 1; QALYs2 = QALYs generated with Treatment 2; Costs1 = Total costs associated with Treatment 1; Costs2 = Total costs associated with Treatment 2; and threshold = willingness-to-pay.

Scenario analyses were performed: the first was a conservative case where no adjustments due to resistance were made; in the second, treatment efficacy of second-line treatment was set to 100% (i.e., assuming patients were switched to the 'right' treatment in the second line).

3. Results

3.1. Base case results

The key base case results obtained from the model are presented in Table 2 and Fig. 2. The analysis revealed that the intervention sequence provided better health outcomes, including a 6.57% increase in proportion of patients cured, average of 0.062 LYs, and 0.127 QALYs gained per patient vs. the comparator sequence (Table 2). This led to a reduction in the average length of hospital stay with the intervention sequence by 1.90 days per patient compared with the comparator sequence. The proportion of patients who died in hospital was lower with the intervention sequence compared with the comparator sequence (1.68% vs. 3.03%), although the proportion of patients with AEs was comparable (1.00% vs. 1.03%) for the two treatment sequences (Table 2).

The model predicted an incremental cost of €1015 per patient with the intervention sequence. Most of the incremental cost was generated from the average drug cost (€2238 vs. €561) due to the higher acquisition cost of CAZ-AVI. However, incremental costs were partially offset by savings in hospitalization cost (€3350 vs. €3990) because of the reduced length of hospital stay with the intervention sequence. In addition, the average recurrence cost was predicted to be lower in patients treated with the intervention sequence (€124 vs. €146). The average SAE cost was similar in the

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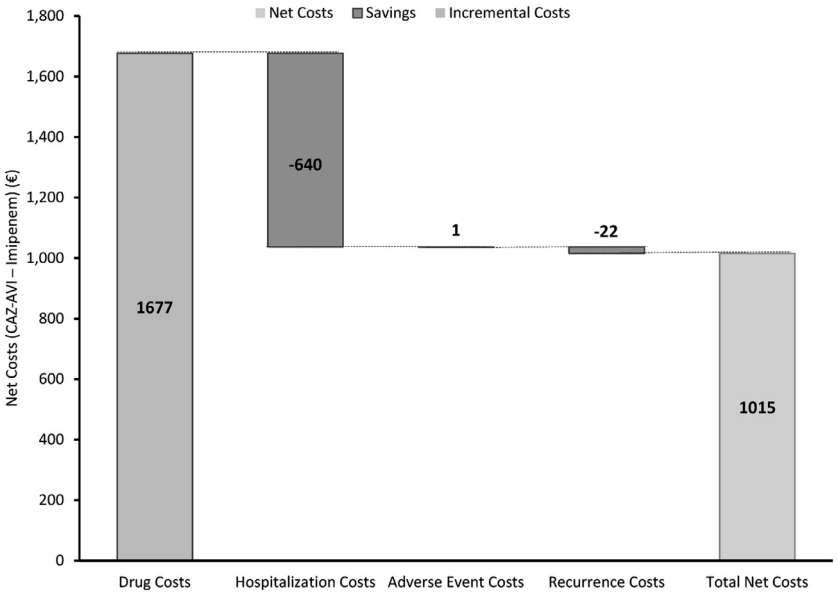

Fig. 2. Incremental cost outcomes per patient.
Footnote: Negative values indicate cost savings with the intervention sequence.

Table 2
Base-case results.

Outcomes	Intervention sequence [CAZ-AVI; Colistin+high dose CBP]	Comparator sequence [Imipenem; Colistin+high dose CBP]
Clinical Outcomes		
% of patients with cure	97.65%	91.08%
% of patients died in hospital	1.68%	3.03%
% of patients with AE	1.00%	1.03%
Average days in hospital	10.65	12.55
Discounted LYs	4.565	4.503
Discounted QALYs	4.190	4.063
Discounted Cost Outcomes		
Drug costs	€ 2,238	€ 561
Hospitalization costs	€ 3,350	€ 3,990
SAE costs	€ 20	€ 20
Recurrence costs	€ 124	€ 146
Total costs	€ 5,732	€ 4,717
Incremental Cost-Effectiveness Ratios		
Incremental cost per QALY gained	€ 8,039	

AE, adverse event; CAZ-AVI, Ceftazidime-avibactam; CBP, carbapenem; LY, life year; QALY, quality-adjusted life year; SAE, serious adverse event

two treatment sequences because there was a similar proportion of patients with AEs (Fig. 2). The incremental cost-effectiveness ratio was €8039 per QALY gained, which was well below the willingness-to-pay threshold of €30 000 per QALY in Italy.

3.2. Scenario results

A moderate impact on the ICERs (+21%) was estimated in a scenario with 'no resistance adjustments' and in a scenario with patients receiving second-line treatment, the assumption of 100% response/cure rates had only a small impact (+6%) on the results (Table 3). In both scenarios, the ICERs remain below the acceptable willingness-to-pay threshold of €30 000 per QALY.

3.3. Probabilistic sensitivity analysis (PSA) results

PSA results are presented on the cost-effectiveness plane, where incremental costs and incremental QALYs of CAZ-AVI vs. imipenem followed by colistin+high dose CBP are shown (Fig. 3a). In most simulations, the groupings on the cost-effectiveness planes had a cluster around the North-East quadrant, indicating that the intervention sequence was more effective and costlier than the comparator sequence.

Table 3
Scenario analysis.

Scenario	Incremental cost per QALY gained (% change from base case)
Base case	€ 8,039
Resistance adjustments	
No adjustments	€ 9,757 (+21%)
Second line efficacy	
Assumed 100% response/cure rates in treatment	€ 8,517 (+6%)

QALY, quality-adjusted life year

The cost-effectiveness acceptability curve (Fig. 3b) depicted that the intervention sequence (i.e., sequence with CAZ-AVI) was an optimal treatment option representing the maximum net benefit compared with the comparator sequence, at a willingness-to-pay threshold above €16 000 per QALY.

3.4. Deterministic sensitivity analysis (DSA) results

The results from one-way DSA for cUTI representing outcomes of INB based on a willingness-to-pay threshold of €30 000 per QALY are presented in Fig. 4. Based on INB from the base case, the intervention sequence (i.e., sequence with CAZ-AVI) depicted cost-effectiveness (positive INB of €2772) compared with the comparator sequence at a willingness-to-pay threshold of €30 000 per QALY. The results were based on the top 10 parameters by order of their influence on the outcomes. Variation in response rates at the EOT assessment for imipenem influenced INB the most, followed by utility value of clinical cure.

4. Discussion

The primary objective of the analysis was to compare the cost-effectiveness of CAZ-AVI as an empirical treatment with that of imipenem for hospitalized patients with cUTI. The analysis results showed that CAZ-AVI provided better health outcomes (increase in

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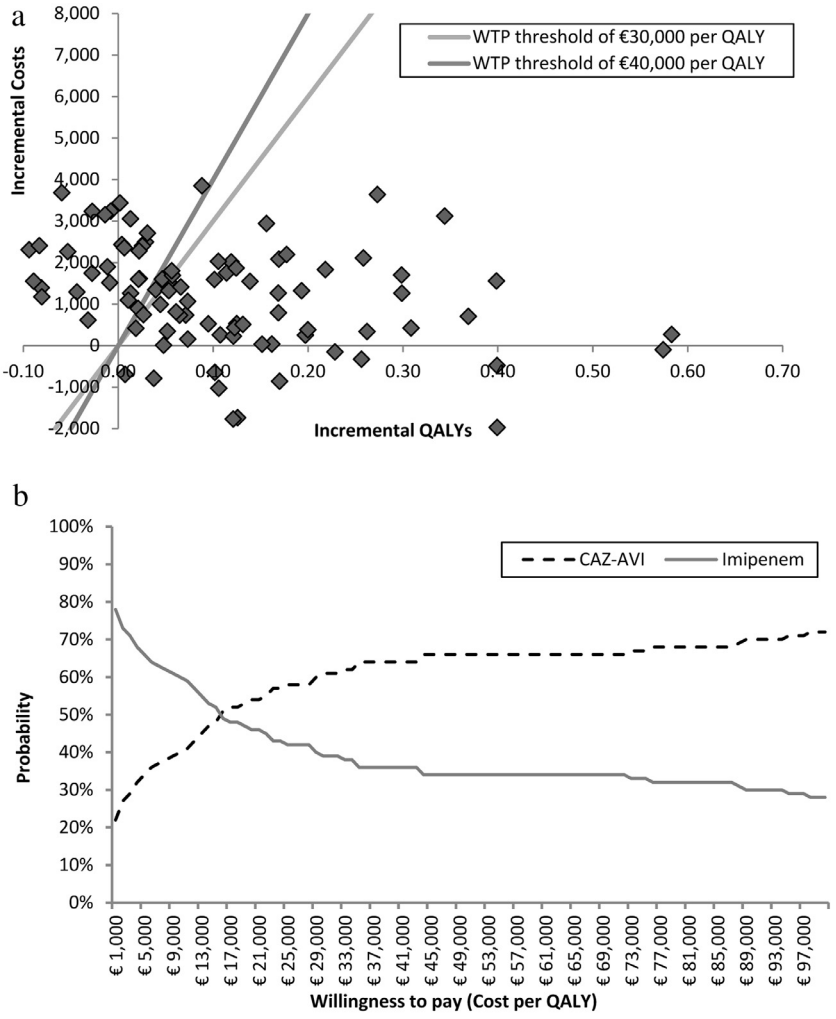

Fig. 3. Results from probabilistic sensitivity analysis for CAZ-AVI vs. imipenem followed by colistin+high dose CBP in cUTI, cost per QALY.
Panel a) On cost-effectiveness plane.
Footnotes: QALY, quality-adjusted life year; WTP, willingness-to-pay.
Note: Each dot represents cost-effectiveness outcome from each iteration. The threshold lines represent cost-effectiveness thresholds (€30 000 or €40 000 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 is cost-effective compared with the comparator. In cases that fall to the left and above this line, the intervention is not cost-effective compared with the comparator.
Panel b) On cost-effectiveness acceptability curve.
Footnote: QALY, quality-adjusted life year.

clinical cure, shorter hospital stays, and higher QALYs gained per patient) at an acceptable net incremental cost of €1015 per patient and an ICER of €8039 per QALY gained, which is well below the threshold of €30 000 per QALY in Italy. Therefore, CAZ-AVI can be considered a cost-effective option compared with imipenem for empirical treatment of cUTI patients. The current study is the first cost-effectiveness analysis of CAZ-AVI from the Italian publicly funded healthcare (third-party payer) perspective.

CAZ-AVI was shown to be as effective as doripenem in treating patients with cUTI infections due to Gram-negative pathogens resistant to ceftazidime, and was well tolerated in the RECAPTURE study [7]. The current analysis used data from the RECAPTURE study and published clinical studies along with local surveillance data to estimate the cost-effectiveness of CAZ-AVI compared with imipenem. In a recent study in the United States, another novel antibiotic – ceftolozane/tazobactam – was found to be cost-effective at an ICER of $6128 per QALY compared with piperacillin/tazobactam for the empirical treatment of adult patients with cUTI [3]. The authors stressed the importance of local data because antimicrobial resistance varies by location and this could impact cost-effectiveness calculations [29-31].

Antibiotic resistance directly affects disease management, leading to prolonged hospitalization, additional drug costs, and nursing and medical care [10,20]. The current model is flexible enough to include the additional impact of resistant pathogens. This helps evaluate the true value of antibiotics as patients infected with pathogens resistant to empirical treatment were assumed to have increased costs of hospitalizations, reduced efficacy of subsequent treatments, and higher mortality. In a conservative scenario where this impact was removed from the analysis (i.e., 'no resistance' adjustments), the estimated ICER, although slightly increased (€9757 vs. €8039 per QALY), was still well below the threshold of €30 000 per QALY. In another scenario analysis, patients receiving second-line treatment were assumed to have 100% response/cure rates and this had only a small impact on the results (€8517 vs. €8039 per QALY) compared with the base case.

In addition to the cost-effectiveness outcome from this study, a recent budget impact analysis revealed that the introduction of

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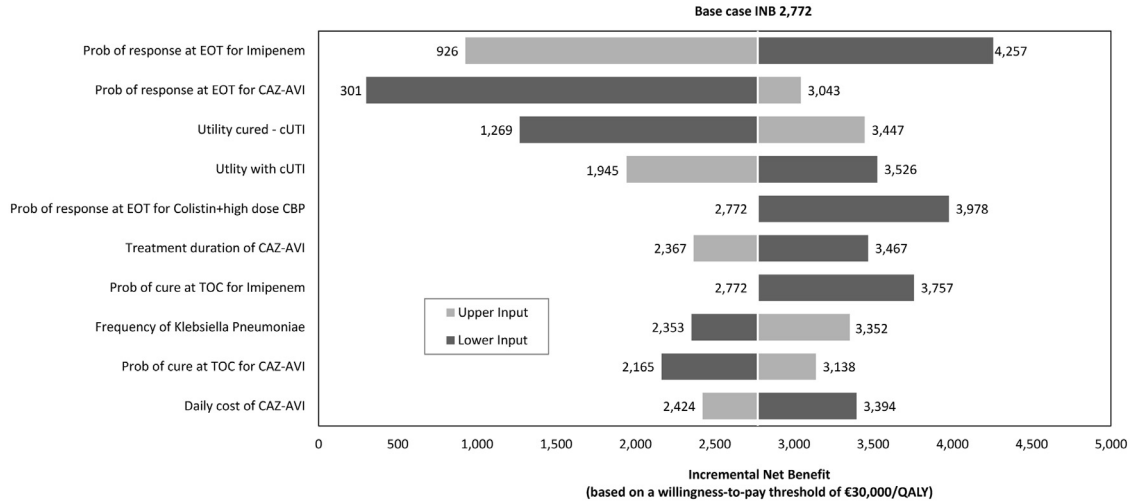

Fig. 4. Results from one-way deterministic sensitivity analysis, incremental net benefit based on a willingness-to-pay threshold.
Footnotes: CAZ-AVI, Ceftazidime avibactam; CBP, carbapenem; cUTI, complicated urinary tract infection; EOT, end of treatment; INB, incremental net benefit; Prob, probability; TOC, test-of-cure.
Note: Positive INB indicates intervention was cost-effective compared with comparator, and vice versa.

CAZ-AVI to the hospital formulary in Italy for treatment of cUTI patients can be expected to have a marginal impact on the total healthcare budget, with an increase in the total budget of approximately 1% over three years [32].

Administering antibiotics that can provide appropriate coverage early on can save lives, as shown by the results from this study: in-hospital deaths were reduced by 1.4% with CAZ-AVI compared with imipenem (Table 2). However, these drugs do not seem to be sufficiently valued by society, payers, and decision makers compared with novel treatments in other therapeutic areas, such as oncology, where costs of treatments can be striking with little gain in life expectancy.

The model analysis had limitations. First, the analysis was based on the results from the RECAPTURE study, which had a non-inferiority design and could not show the superiority of CAZ-AVI [7]. Data to support the impact of antibiotic resistance had to come from other supplemental sources, because patients with resistance were excluded from the RECAPTURE study. Second, due to the model structure, the treatment pathways in the model could only be predefined; therefore, subsequent treatment choices could not be specified for individual patients. Third, the clinical inputs, i.e., clinical data for safety and efficacy for all treatments, were obtained directly from published multicentre clinical studies. No data synthesizing method, such as indirect comparison or mixed-treatment comparison, was performed during the analysis. Testing the response rates at EOT showed that if the imipenem response probability was increased by 10% or the CAZ-AVI response probability was decreased by 10%, the intervention sequence remained cost-effective with the threshold of €30 000, as the INB remained positive (€926 with increased imipenem response, and €301 with decreased CAZ-AVI response probability). Also, the published data were assumed to be applicable for Italy. Fourth, the model envisaged the continuation of the same antimicrobial regimen (imipenem or CAZ-AVI) as definitive therapy if no resistance was found. However, in clinical practice, if the clinical isolate shows no resistance, a de-escalation to a less expensive therapy should be advocated. If the model had included step-down therapy, the results would have favoured CAZ-AVI as a higher proportion of patients was susceptible to CAZ-AVI, and thus treatment costs would have been lower. Therefore, this assumption can be considered conservative. Fifth, AEs were captured as an aggregated AE, with a unit cost of AE calculated based on distribution of different AEs as observed in the CAZ-AVI clinical studies. Thus, it was assumed that a similar distribution of different AEs was observed with other treatments. Lastly, given geographical variations in healthcare resource use and clinical practice across different countries, the results from this study may not be generalisable to other countries unless clinical practice, epidemiology, resource use, and costs are similar to that in Italy.

The study had several strengths, which make the findings more impactful. The study analysis evaluated the entire disease course (response, cure, treatment duration, hospitalization, AEs, recurrence of infections) at the patient level. Multidrug resistance was evaluated in detail by different pathogens, which depicted the real value of the antibiotics to reflect the real-world scenario of increasing antimicrobial resistance. The analysis evaluated the efficacy aspects on a broad level, including clinical response, cure, and recurrence, which provides more meaningful clinical and economical outcomes. The patient-level simulation used by the model is well established and permits the development of realistic models, as it enables simulation of switching patients from treatment to treatment, capturing consequences at detailed levels, such as impact of resistance, while keeping the model logic transparent.

5. Conclusions

Healthcare providers should evaluate local resistance data, treatment efficacy, treatment-resistance profile, and economical aspects of management of the cUTI infection. The choice of an optimal antibiotic treatment for patients with cUTI is key and should be carefully considered. Our findings indicate that use of CAZ-AVI as an empirical treatment is cost-effective, providing better clinical outcomes at an acceptable cost, compared with imipenem in cUTI in Italy. With the rise of antimicrobial resistance, early appropriate treatment along with antimicrobial stewardship would not only optimize clinical outcomes but also help preserve the lifecycle of novel antibiotics and thus, CAZ-AVI should be considered as an alternative to imipenem.

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Declarations

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Declaration of Competing Interests

Thitima Kongnakorn and Eszter Tichy are employees of Evidera, which received funding from Pfizer in connection with the study and the development of this manuscript. Roberto Di Virgilio, Nathalie Baillon-Plot, and Claudie Charbonneau are employees of and shareholders in Pfizer. Florian Wagenlehner is an employee of Justus-Liebig-University, and Marco Falcone is an employee of University of Pisa (Italy); while both have received research funding from Pfizer, neither received any payments from Pfizer for their work on this manuscript.

Ethical Approval

Not required

Author Contributions

TK, ET, RDV, NBP, and CC were involved in conceptualization, methodology, analysis of the study, and writing, editing and reviewing the manuscript. FW and MF contributed to clinical validation and writing, reviewing and editing the manuscript. All authors have read and approved the final manuscript.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or Europe or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

References

[1] Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13(5):269–84.
[2] Nicolle LEAMMI Canada Guidelines Committee. Complicated urinary tract infection in adults. Can J Infect Dis Med Microbiol 2005;16:349–60.
[3] Kauf TL, Prabhu VS, Medic G, Borse RH, Miller B, Gaultney J, et al. Cost-effectiveness of ceftolozane/tazobactam compared with piperacillin/tazobactam as empiric therapy based on the in-vitro surveillance of bacterial isolates in the United States for the treatment of complicated urinary tract infections. BMC Infect Dis 2017;17:314.
[4] Gaynes R, Edwards JR. National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by Gram-negative bacilli. Clin Infect Dis 2005;41:848–54.
[5] Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollack DA, et al. NHSN annual update: Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infect Control Hosp Epidemiol 2008;29:996–1011.
[6] Salgado P, Gilsanz F, Maseda E. Resistant gram-negative bacteria. Therapeutic approach and risk factors. Rev Esp Quimioter 2016;29(Suppl.1):26–30.
[7] Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone G, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a Phase 3 randomized trial program. Clin Infect Dis 2016;63(6):754–762.
[8] Golan Y. Empiric therapy for hospital-acquired, Gram-negative complicated intra-abdominal infection and complicated urinary tract infections: a systematic literature review of current and emerging treatment options. BMC Infect Dis 2015;15:313.
[9] Barber KE, Ortwine JK, Akins RL. Ceftazidime/avibactam: who says you can't teach an old drug new tricks? J Pharm Sci 2016;19(4):448–64.
[10] Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. Clin Microbiol Infect 2016;22:416–22.
[11] Liu Q, Li X, Li W, Du X, He JQ, Tao C, et al. Influence of carbapenem resistance on mortality of patients with Pseudomonas aeruginosa infection: a meta-analysis. Sci Rep 2015;5:11715.
[12] 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.
[13] Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary tract infections: a review. J Chemother 2017;29(sup1):2–9.
[14] Scarafile G. Antibiotic resistance: current issues and future strategies. Rev Health Care 2016;7(1):3–16.
[15] Kazmierczak K, Estabrook M, Jonge BLM, Stone G, Sahm D. Activity of ceftazidime-avibactam against isolates of Enterobacteriaceae and Pseudomonas aeruginosa collected in Europe as part of the INFORM global surveillance program, 2015. In: 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 2017. abstract P1295.
[16] European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2016. Available at: https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2016. (Accessed on 16 July 2018)
[17] Vazquez JA, González Patzán LD, Stricklin D, Duttaroy DD, Kreidly Z, Lipka J, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. Curr Med Res Opin 2012;28(12):1921–31.
[18] 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 on 16 July 2018)
[19] European Medicines Agency. Annex I: Summary of Product Characteristics (Doribax). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000891/WC500037148.pdf. (Accessed on 16 July 2018)
[20] MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum β-lactamase–producing organisms on clinical and economic outcomes in patients with urinary tract infection. J Hosp Med 2014;9:232–8.
[21] 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(24):3675–82.
[22] 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:e47–52.
[23] Agenzia Italiana del Farmaco; Available at: http://www.agenziafarmaco.gov.it/. Accessed 25 May 2018.
[24] Ministero della Salute - Direzione generale della programmazione sanitaria. Tariffe delle prestazioni di assistenza ospedaliera per acuti, per tipo di ricovero (Euro). http://www.salute.gov.it/portale/home.html. Accessed September 2015.
[25] Ministero della Salute - Rapporto SDO 2013 - Tavola 2.2.6 - Descrizione dell'attività per DRG (versione 24) - Attività per Acuti in Regime ordinario - Anno 2013. http://www.salute.gov.it/portale/home.html. Accessed September 2015.
[26] Tan SS, Bakker J, Hoogendoorn ME, Kapila A, Martin J, Pezzi A, et al. Direct cost analysis of intensive care unit stay in four European countries: applying a standardized costing methodology. Value Health 2012;15(1):81–6.
[27] Committee Joint Formulary. British National Formulary (BNF) 66. Pharmaceutical Press; 2013 https://www.bnf.org/ .
[28] Capri S, Ceci A, Terranova L, Merlo F, Mantovani L. Guidelines for Economic Evaluations in Italy: Recommendations from the Italian Group of Pharmacoeconomic Studies. Drug Info J 2001;35:189–201.
[29] Kahlmeter G. ECO.SENS An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. J Antimicrob Chemother 2003;51(1):69–76.

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[30] Gupta K, Sahm DF, Mayfield D, Stamm WE. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in women: a nationwide analysis. Clin Infect Dis 2001;33:89–94.
[31] Fluit AC, Jones ME, Schmitz FJ, Acar J, Gupta R, Verhoef J. Antimicrobial susceptibility and frequency of occurrence of clinical blood isolates in Europe from the Sentry Antimicrobial Surveillance Program, 1997 and 1998. Clin Infect Dis 2000;30:454–60.
[32] Kongnakorn T, Tichy E, Merinopoulou E, Berto P, Di Virgilio R, Charbonneau C. budget impact of introducing ceftazidime avibactam (CAZ-AVI) for complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) and Hospital-acquired pneumonia including ventilator-associated pneumonia (HAP/VAP) to a hospital formulary in Italy. In: ISPOR 20th Annual European Congress, Glasgow, Scotland; 2017.

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