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CLINICAL THERAPEUTICS

Cost-Effectiveness of Ceftazidime-Avibactam for Treatment of Carbapenem-Resistant *Enterobacteriaceae* Bacteremia and Pneumonia

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ABSTRACT Ceftazidime-avibactam (CAZ-AVI) may improve outcomes among patients with carbapenem-resistant *Enterobacteriaceae* (CRE) infections compared to those with conventional therapies. However, CAZ-AVI's cost-effectiveness is unknown. We used a decision analytic model to estimate the health and economic consequences of CAZ-AVI-based therapy compared to colistin-based therapy (COL) for a hypothetical cohort of patients with CRE pneumonia or bacteremia over a 5-year horizon. Model inputs were from published sources and included CRE mortality with COL (41%), CAZ-AVI's absolute risk reduction in CRE mortality (23%), daily cost of CAZ-AVI ($926), risk of nephrotoxicity with COL (42%), and probability of discharge to long-term care (LTC) following CRE infection (56%). Outcomes included quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios (ICER; dollars/QALY). One-way and probabilistic sensitivity analyses were performed and ICERs were compared to willingness-to-pay standards of $100,000/QALY and $150,000/QALY. In the base case, CAZ-AVI had an ICER of $95,000/QALY. At a $100,000/QALY threshold, results were sensitive to a number of variables, including the probability and cost of LTC, quality of life following CRE infection, CAZ-AVI's absolute risk reduction in mortality, all-cause mortality, daily cost of CAZ-AVI, and health care costs after CRE infection. The ICER did not exceed $150,000/QALY after all model inputs were varied across a wide range of plausible values. In probabilistic sensitivity analysis, CAZ-AVI was the optimal strategy in 59% and 99% of simulations at $100,000/QALY and $150,000/QALY thresholds, respectively. In conclusion, CAZ-AVI is a cost-effective treatment for CRE bacteremia and pneumonia based on accepted willingness to pay standards in the United States.

KEYWORDS ceftazidime-avibactam, carbapenem-resistant *Enterobacteriaceae*, cost-effectiveness, polymyxins

The Centers for Disease Control and Prevention (CDC) has designated carbapenem-resistant *Enterobacteriaceae* (CRE) an urgent public health threat (https://www.cdc.gov/drugresistance/biggest_threats.html#cre). The treatment of CRE infections is challenging, and these infections are associated with mortality rates ranging from 30 to 60% (1). Prior to 2015, the best available treatment regimens for CRE infections consisted of polymyxins (colistin or polymyxin B) with or without additional agents such as carbapenems, tigecycline, and aminoglycosides. However, these regimens have demonstrated poor efficacy and high rates of nephrotoxicity.

In 2015, the U.S. Food and Drug Administration (FDA) approved ceftazidime-avibactam (CAZ-AVI), a novel β-lactam–β-lactamase inhibitor, for treatment of compli-

Citation Simon MS, Sfeir MM, Calfee DP, Satlin MJ. 2019. Cost-effectiveness of ceftazidime-avibactam for treatment of carbapenem-resistant *Enterobacteriaceae* bacteremia and pneumonia. Antimicrob Agents Chemother 63:e00897-19. https://doi.org/10.1128/AAC.00897-19.

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Received 30 April 2019
Returned for modification 27 July 2019
Accepted 15 September 2019
Accepted manuscript posted online 23 September 2019
Published 21 November 2019

TABLE 1 Base-case cost-effectiveness results[a]

Strategy	Cost ($)	No. of life yrs	No. of QALYs	Incremental cost ($)	No. of incremental QALYs	ICER ($/qALY)
COL based	108,800	1.82	1.26			
CAZ AVI based	156,300	2.53	1.76	47,500	0.50	95,000

[a]QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio; COL, colistin; CAZ-AVI, ceftazidime-avibactam.

cated intra-abdominal and complicated urinary tract infections (2). In 2018, the approved indications were expanded to include hospital-acquired and ventilator-associated pneumonia. CAZ-AVI has demonstrated potent *in vitro* activity against *Klebsiella pneumoniae* carbapenemase (KPC)-producing CRE, which is the most common mechanism of carbapenem resistance among *Enterobacteriaceae* in the United States (3). Recent observational studies of CRE treatment have demonstrated higher rates of clinical cure, reduced risk of mortality, and reduced risk of nephrotoxicity with CAZ-AVI-based therapy compared with colistin (COL)-based therapy (4–6). However, CAZ-AVI is more expensive than COL, with an estimated cost of $7,500 to $15,000 for a 7- to 14-day course of therapy (7). To date, no cost-effectiveness analysis has been performed to determine the health economic value of CAZ-AVI compared with that of the best alternative therapy. We aimed to analyze the cost-effectiveness of CAZ-AVI-based therapy versus COL-based therapy for CRE pneumonia and bloodstream infections to inform implementation decisions in the United States.

(Preliminary findings were presented at IDWeek 2018 on 6 October 2018 in San Francisco, CA.)

RESULTS

Base-case results are displayed in Table 1. Over a 5-year horizon, the COL-based treatment strategy cost $108,800, with an average life expectancy of 1.82 years and 1.26 quality-adjusted life-years (QALYs) per CRE case. The CAZ-AVI-based treatment strategy cost $156,300, with an average life expectancy of 2.53 years and 1.76 QALYs per CRE case. The incremental cost-effectiveness ratio (ICER) for CAZ-AVI compared to COL-based therapy was $95,000/QALY. Considering CRE bacteremia and pneumonia cases separately, the ICERs were $99,000/QALY for bacteremia and $87,000/QALY for pneumonia. If COL plus meropenem was considered as the comparator therapy (and not other combination drugs such as tigecycline), the ICER was $98,000/QALY. The cost to prevent 1 CRE-related death was $206,400.

Figure 1 depicts results of 1-way sensitivity analyses of model inputs, illustrating the change in the ICER across a range of possible values for each input. At a $100,000/QALY willingness-to-pay threshold, results were sensitive to a number of variables (Fig. 1). The most influential variables in the model were the probability of discharge to long-term care, the annual cost of long-term care, and the quality of life after CRE infection. Other model inputs that led to an ICER greater than $100,000/QALY included the absolute risk reduction in CRE mortality, all-cause mortality in the initial year or subsequent years after CRE infection, the daily cost of CAZ-AVI, and initial year health care costs after surviving CRE infection. Threshold values for each of these variables that would result in an ICER greater than $100,000/QALY are shown in Table 2. The model was also sensitive to assumptions regarding the time horizon. The ICER was greater than $100,000/QALY when the time horizon was ≤3 years and ranged from $85,000/QALY to $123,000/QALY with time horizons of 10 and 1 years, respectively. At a $150,000/QALY threshold, results were stable to a wide range of plausible values for all model inputs but could be greater than $150,000/QALY at extreme values (Table 2).

In probabilistic sensitivity analysis, CAZ-AVI-based therapy was the optimal strategy in 59% of simulations at a willingness-to-pay threshold of $100,000 and in 99% of simulations at a willingness-to-pay threshold of $150,000/QALY (Fig. 2A). The ICER ranged from $66,000/QALY to $142,000/QALY in 95% of simulations representing the 2.5th and 97.5th percentiles of the probabilistic sensitivity analysis. If the time horizon

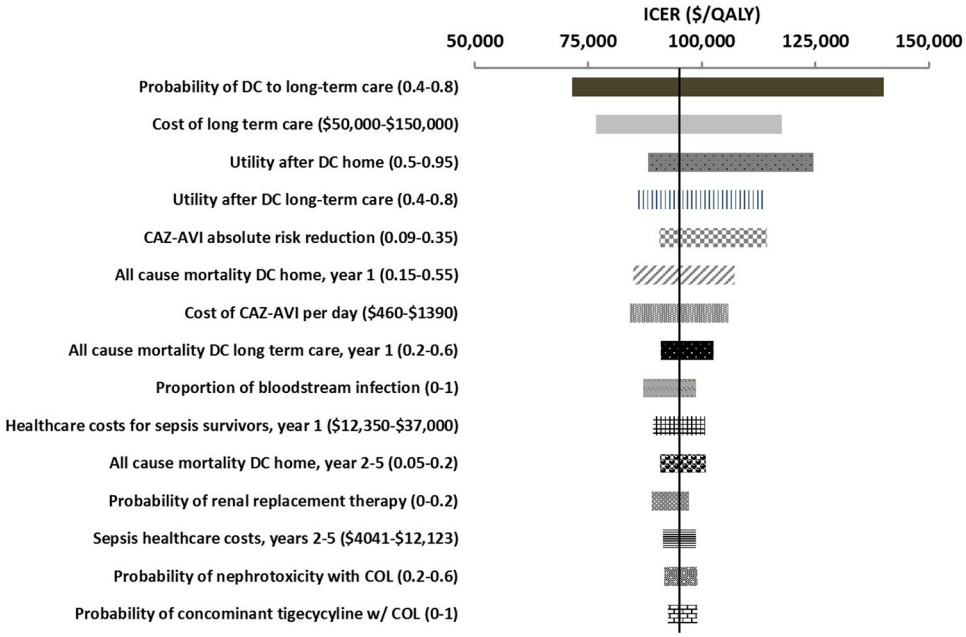

FIG 1 Tornado analysis depicting results of one-way sensitivity analysis of key variables. The horizontal bars represent the change in the incremental cost-effectiveness ratio (ICER) across plausible ranges. The vertical line represents the ICER in the base case analysis ($95,000/QALY). CAZ-AVI, ceftazidime-avibactam; COL, colistin; DC, discharge; QALY, quality-adjusted life-year.

was limited to 1 year, CAZ-AVI was optimal in 10% and 82% of simulations at willingness-to-pay thresholds of $100,000/QALY and $150,000/QALY, respectively (Fig. 2B). If the time horizon was expanded to 10 years, CAZ-AVI was optimal in 75% and 99% of simulations at willingness-to-pay thresholds of $100,000/QALY and $150,000/QALY, respectively (Fig. 2B).

DISCUSSION

Our study is the first to evaluate the cost-effectiveness of a novel β-lactam–β-lactamase inhibitor (CAZ-AVI) for CRE bacteremia and pneumonia. In our base case analysis, we found that CAZ-AVI increased both costs and QALYs but had an acceptable cost-effectiveness ratio ($95,000/QALY) based on current U.S. health care willingness-to-pay standards. These findings suggest that CAZ-AVI is a cost-effective therapy for CRE pneumonia and bacteremia in the United States.

The CDC estimates that approximately 9,000 CRE infections occur annually in the United States, and data suggest that approximately 46% of these are either bacteremia or pneumonia (https://www.cdc.gov/drugresistance/biggest_threats.html#cre) (8). Extrapolating these estimates to our model, if CAZ-AVI was used as first-line therapy for

TABLE 2 Threshold values for variables that could increase ICER above $100,000/QALY or $150,000/QALY

Model input	Base case value	Uncertainty range	Threshold value (ICER > $100,000/QALY)	Threshold value (ICER > $150,000/QALY)
Probability of discharge to long-term care	0.56	0.4–0.8	>0.59	No value in range (>0.85)
Annual cost of long-term care	$94,696	±50%	>$107,000	No values in range (>$228,000)
Quality of life after discharge to home	0.84	0.5–0.95	<0.77	No values in range (<0.31)
Quality of life after discharge to long-term care	0.64	0.4–0.8	<0.57	No values in range (<0.1)
Absolute risk reduction in CRE[a] mortality	0.23	0.09–0.35	<0.16	No values in range (<0.04)
All-cause mortality, yr 1 (discharge home)	0.36	0.15–0.55	>0.44	No values in range (>0.97)
All-cause mortality, yrs 2–5 (discharge home)	0.11	0.05–0.25	>0.19	No values
Daily cost of CAZ-AVI	$926	±50%	>$1,138	No values in range (>$3,260)
All-cause mortality, yr 1 (discharge to long-term care)	0.48	0.2–0.6	<0.3	No values
Health care costs after CRE infection, yr 1	$24,700	±50%	>$35,600	No values in range (>$144,000)

[a]CRE, carbapenem-resistant *Enterobacteriaceae*.

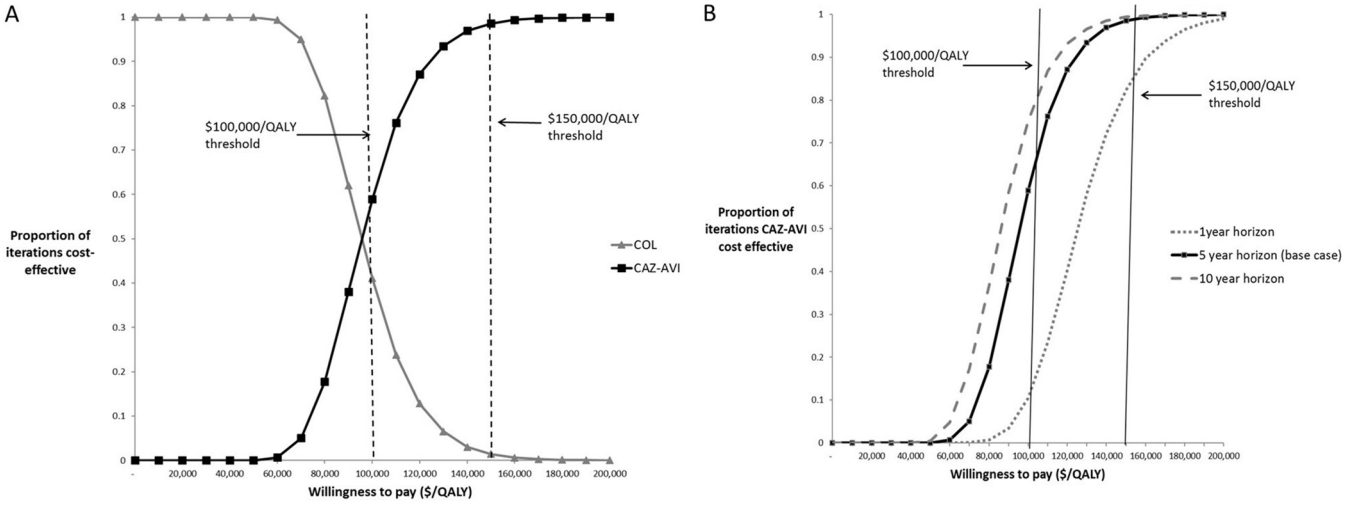

FIG 2 (A) cost-effectiveness acceptability curve showing the probability that ceftazidime-avibactam (CAZ-AVI)- or colistin (COL)-based therapy is cost-effective for a given willingness-to-pay value. (B) Separate probabilistic sensitivity analyses were conducted for scenarios with 1-year, 5-year (base case), and 10-year time horizons. The curves represent the probability that CAZ-AVI is optimal for a given willingness-to-pay threshold for each time horizon assumption.

CRE bacteremia and pneumonia, instead of COL, there could be gains of 2,939 life-years and 2,070 QALYs and increased health care costs of $197 million. Although current utilization of CAZ-AVI for treatment of CRE infection has not been well described, preliminary data suggest increased overall use of CAZ-AVI in the United States between 2015 and 2017 (9). Further study of CAZ-AVI utilization practices for CRE infections would assist in refining projections of CAZ-AVI's health economic impact.

A key assumption of our model was that CAZ-AVI reduces mortality in CRE bacteremia and pneumonia. The high mortality rate for invasive CRE infection with conventional therapy is well established (1). In contrast, outcomes data for CAZ-AVI in CRE infection are less robust, but three recent observational studies have compared CAZ-AVI with the best available alternative therapy and found a reduced risk of death (4–6). van Duin et al. conducted a prospective, multicenter observational study and found a 23% reduced risk of death and a 64% probability of better overall outcome with CAZ-AVI than with COL-based therapy (4). Shields et al. conducted a single-center observational study with a historical control group that found improved clinical success (85% with CAZ-AVI versus 40% with COL-based treatment) and reduced 30-day mortality (8% with CAZ-AVI versus 30% with COL-based therapy) (5). Lastly, Tumbarello et al. examined CAZ-AVI as salvage therapy for KPC-producing CRE infections and found significantly lower mortality with CAZ-AVI than with other regimens (36.5% versus 55.8%) (6). Our model based CRE mortality with COL-based therapy (40.9%) on pooled data from multiple studies. However, because mortality was not always stratified by treatment in these studies, other treatment combinations were included in this estimate. However, if we used COL-specific mortality rates from the work of Shields et al. (30%) or van Duin et al. (32%), the ICER did not exceed $100,000/QALY. In the base case, we assumed a 23% absolute risk reduction in mortality for CAZ-AVI and found that this would need to be $\leq$16% or $\leq$4% for the ICER to exceed $100,000/QALY or $150,000/QALY, respectively. Since a randomized controlled trial is unlikely to be conducted to answer this question, larger observational studies of CAZ-AVI for CRE infections would improve confidence in our findings.

We found that long-term-care costs and quality of life after surviving CRE infection were highly influential variables in the cost-effectiveness model. Although no data are available on the long-term health and economic consequences of CRE infection, at least 50% of patients with CRE infection or colonization are discharged to long-term-care facilities (10). van Duin et al. found an increased, but not statistically significant, proportion of CAZ-AVI-treated patients, compared with COL-treated patients, who were

discharged to home (4). We conservatively assumed no difference in the likelihood of discharge to home between these treatment strategies. However, if CAZ-AVI improved the likelihood of discharge to home, cost-effectiveness results would be even more favorable.

Readmissions are a costly and common complication following CRE infection, occurring for up to 20% of patients with CRE infection (11). We incorporated the costs associated with readmissions in our estimate of $24,700 for 1-year costs for survivors of CRE infection. We found that the ICER only increased to >$100,000/QALY and $150,000/QALY when these costs exceeded $35,600 and $144,000, respectively. The impact of CAZ-AVI, compared to COL-based therapy, on readmission rates is unknown and was not explicitly incorporated into this analysis because of lack of data for this outcome.

Meropenem-vaborbactam (MVB) is another newly approved β-lactam–β-lactamase inhibitor with potent *in vitro* activity against KPC-producing CRE (12). A randomized clinical trial that compared MVB to best available therapy for CRE infections suggested improved outcomes with MVB (13). However, a diverse group of agents were used as best available therapy (not solely COL-based therapy), and there were only 27 patients with CRE bacteremia or pneumonia in the study. Thus, insufficient data were available to conduct a cost-effectiveness analysis of MVB compared to COL-based or CAZ-AVI-based therapy for CRE bacteremia and pneumonia. Given a number of novel antibiotics in the developmental pipeline with activity against CRE (e.g., imipenem-relebactam and cefiderocol), future studies should compare not only important clinical outcomes, such as mortality, but also quality of life, length of hospital stay, readmissions, and discharge disposition, as these are likely to be important determinants of cost-effectiveness for these novel agents.

The interpretation of cost-effectiveness studies requires an explicit determination of willingness to pay. In health economic studies, QALYs are the gold standard measure of effectiveness because they capture both morbidity and mortality associated with a condition and provide a standardized metric for comparison across diseases (14). In the United States, there is no universally agreed upon standard for willingness to pay per QALY. A recent expert panel recommended using a range of willingness-to-pay thresholds in reporting cost-effectiveness analysis results (14). Historically, $50,000/QALY was a commonly used threshold, but current evidence suggests that this is too low and that a $100,000/QALY or $150,000/QALY threshold is more appropriate in the United States (15, 16). Because our base-case ICER of $95,000/QALY was so close to the $100,000/QALY threshold, small variations in a number of model inputs increased the ICER to above $100,000/QALY. However, no variables caused the ICER to exceed $150,000/QALY across plausible ranges in our model. Furthermore, in probabilistic sensitivity analysis, CAZ-AVI was the preferred strategy in 58% and 99% of simulations at $100,000/QALY and $150,000/QALY thresholds, respectively. Overall, our results suggest CAZ-AVI's health economic value is in line with currently accepted cost-effectiveness standards in the United States.

Our findings are subject to limitations. First, as with any modeling study, our model inputs are constrained by the quality of existing data. Specifically, CAZ-AVI's effectiveness is based on a small number of observational studies and long-term health and economic outcomes were based on the literature for sepsis and are not specific to CRE infection. To account for this uncertainty, we conducted extensive sensitivity analyses and varied model inputs across a wide range of plausible values. Second, we limited our analysis to CRE bacteremia and pneumonia because these conditions are well established to cause significant morbidity and mortality. We did not consider nonbacteremic urinary tract infection for which CAZ-AVI treatment could be used in clinical practice. It is possible that cost-effectiveness results would be less favorable for this indication. Third, our findings are not applicable to geographic regions outside the United States where metallo-β-lactamases are more common causes of carbapenem resistance, as CAZ-AVI is not active against organisms with these enzymes. Fourth, we did not assess CAZ-AVI's budget impact for hospital pharmacies; rather, we considered cost-effectiveness from a health care system perspective. However, we would not expect

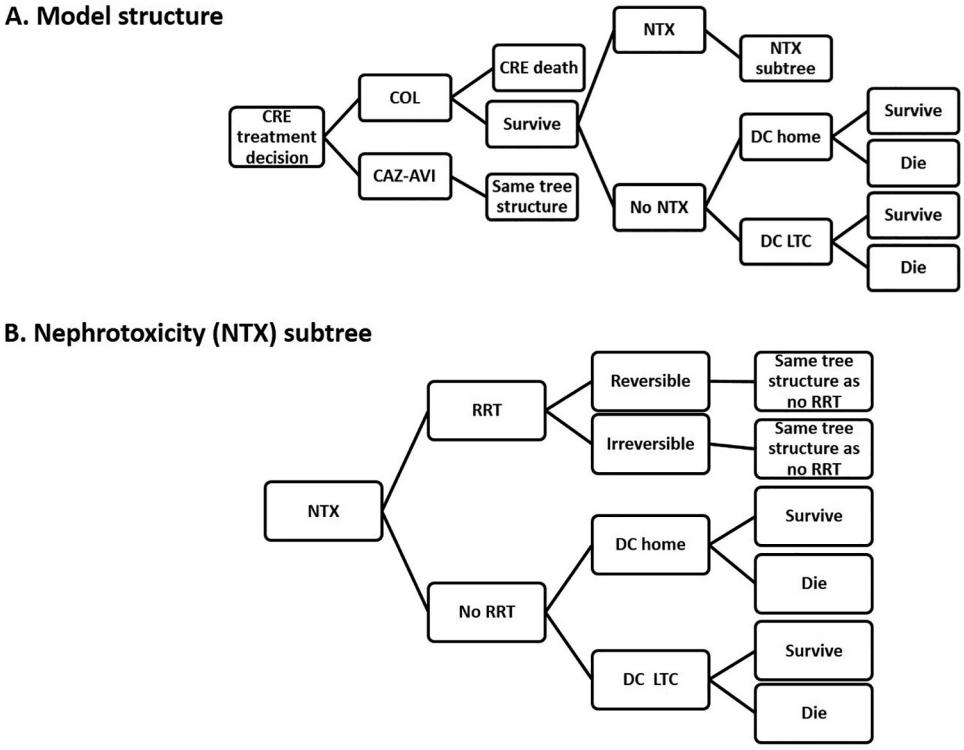

FIG 3 Decision tree structure for treatment of carbapenem-resistant *Enterobacteriaceae* (CRE) bacteremia and pneumonia. Branches in the model are linked by probabilities and are used to calculate expected costs, life-years, and quality-adjusted life-years for each treatment strategy. NTX, nephrotoxicity; LTC, long-term care; DC, discharge; RRT, renal replacement therapy.

affordability to be a significant issue for the majority of hospitals given the overall infrequency of invasive CRE infection in the United States. Lastly, our data source for drug prices was based on acquisition costs reported from the U.S. Department of Veterans Affairs (VA) and may not reflect acquisition costs of U.S. hospitals. However, the Federal Supply Schedule (FSS) is the recommended source for drug prices for cost-effectiveness analysis and when drug costs were increased by as much as 50% in sensitivity analysis, the ICER remained below $150,000/QALY (14).

In summary, CAZ-AVI, a novel β-lactam–β-lactamase inhibitor, is a promising but considerably more expensive therapy for CRE infection than COL-based therapy. Based on limited comparative effectiveness data from observational studies, we found CAZ-AVI to be a cost effective treatment for CRE bacteremia and pneumonia at commonly accepted willingness-to-pay thresholds in the United States.

MATERIALS AND METHODS

Model overview. We constructed a decision analytic model (Fig. 3) to evaluate the clinical and economic consequences of CAZ-AVI-based therapy compared to COL-based therapy for a hypothetical cohort of patients with CRE pneumonia or bacteremia. Patients in the model are assigned a probability of CRE pneumonia or bacteremia and may survive or die from CRE infection. Patients who survive may develop nephrotoxicity which could be reversible or irreversible, requiring long-term dialysis. After hospitalization, patients may be discharged to home or to long-term care and have an annual probability of all-cause mortality stratified by their discharge disposition. CRE-related mortality and nephrotoxicity risk differ depending on treatment with CAZ-AVI or COL, whereas discharge disposition and long-term all-cause mortality were assumed to be equivalent regardless of treatment with COL or CAZ-AVI. Model inputs and sensitivity analysis ranges are reported in Table 3. The model was programmed in TreeAge Pro 2017 (TreeAge Software, Inc., Williamstown, MA).

The model calculates quality-adjusted life-years (QALYs), life-years, CRE deaths, and costs associated with COL-based therapy and CAZ-AVI based-therapy. In the base case analysis, we adopted a 5-year time horizon and used a Markov model cycle length of 1 year. Costs and QALYs were projected for each strategy and used to calculate incremental cost-effectiveness ratios (ICERs; dollars/QALY). To determine cost-effectiveness, ICERs were compared to willingness-to-pay standards of $100,000/QALY and

TABLE 3 Model inputs, ranges used in one-way sensitivity analyses, and distributions applied in probabilistic sensitivity analysis

Model input	Base-case value	Uncertainty range	Distribution	Reference(s)
Probability values				
CRE BSI	0.68	0–1	Beta	4
CRE attributable mortality				
Bacteremia	0.409	0.2–0.6	Beta	Table S1
Pneumonia	0.407	0.2–0.6	Beta	Table S2
Absolute risk reduction with CAZ-AVI	0.23	0.09–0.35	Beta	4
Nephrotoxicity				
Colistin	0.42	0.2–0.6	Beta	17
CAZ-AVI	0.08	0.04–0.2	Beta	4, 5
Nephrotoxicity requiring in-hospital RRT[a]	0.052	0–0.2	Beta	Table S3
Nephrotoxicity requiring chronic RRT	0.024	0–0.05	Beta	17
Discharge to long-term care	0.559	0.4–0.8	Beta	10
All-cause mortality, yr 1				
Home	0.356	0.15–0.55	Beta	20
Long-term care	0.479	0.2–0.6	Beta	20
All-cause mortality, yrs 2–5				
Home	0.112	0.05–0.25	Beta	20
Long-term care	0.217	0.1–0.3	Beta	20
Relative risk of death on chronic RRT	3.15	2.78–3.58	Lognormal	18
Relative risk of discharge to facility with RRT	3.0	1.0–6.0	Lognormal	19
Cost (2017 U.S. dollars)				
COL-based therapy (daily)[b]	$235	±50%	Gamma	4, 6
CAZ-AVI-based therapy (daily)[c]	$1,038	±50%	Gamma	4, 6
Nephrotoxicity				
Without RRT	$8647	±50%	Gamma	Table S4
With RRT	$23,013	±50%	Gamma	Table S4
Chronic dialysis (annual)	$90,410	±50%	Gamma	U.S. Renal Data System Report[d]
Long-term care (annual)	$94,696	±50%	Gamma	U.S. HHS[e]
Sepsis subsequent care				
Yr 1	$24,709	±50%	Gamma	21
Yrs 2–5	8,082	±50%	Gamma	21
Utility value[f]				
Home (recovered)	0.84	0.5–0.95	Beta	22, 24
Hospitalization[g]	0.73	0.4–0.95	Beta	25
Nephrotoxicity (reversible)[h]	0.66	0.4–0.8	Beta	26
Long-term care[i]	0.64	0.4–0.8	Beta	28
Chronic dialysis[i]	0.59	0.4–0.8	Beta	27

[a]RRT, renal replacement therapy.
[b]Calculated as weighted average of colistin therapy ($26 [100% of patients]), tigecycline ($274 [61%]), meropenem ($74 [51%]), amikacin ($15 [23%]), and gentamicin ($2 [14%]).
[c]Calculated as weighted averages of ceftazidime-avibactam ($926 [100% of patients]), tigecycline ($274 [32%]), gentamicin ($2 [32%]), meropenem ($74 [29%]), and amikacin ($15 [16%]).
[d]https://www.usrds.org/2017/view/Default.aspx.
[e]U.S. HHS, U.S. Department of Health and Human Services (https://longtermcare.acl.gov/costs-how-to-pay/costs-of-care.html).
[f]Utility values represent quality of life weights for health states ranging from 0 (death) to 1 (perfect health).
[g]The hospitalization health state was applied for the average lengths of stay for CRE pneumonia and bacteremia, 23 and 28 days, respectively (23).
[h]Reversible nephrotoxicity health states were assumed to incur increased lengths of stay, an additional 2 and 5 days, for non-RRT and RRT, respectively, based on the literature (Table S4).
[i]The joint health state of dialysis and long-term care (0.45) was estimated using the multiplicative method (29).

$150,000/QALY (14, 15). Future costs and QALYs were discounted at 3% annually (14). The analysis was conducted from a health care system perspective.

Sensitivity analyses. To assess individual parameter uncertainty, inputs were varied individually in one-way sensitivity analyses across plausible ranges based on the literature (Table 3). Results of the one-way sensitivity analyses are displayed as a tornado diagram which demonstrates the change in the ICER when one model input is varied across a plausible range and all other variables are held constant. Overall model uncertainty was evaluated in probabilistic sensitivity analysis by simultaneously conducting 10,000 random draws from probability distributions specified for each variable as described in Table 3. The probabilistic sensitivity analysis generates a distribution of ICERs, and results of this analysis are displayed as a cost-effectiveness acceptability curve. This curve plots a range of willingness-to-pay thresholds against the probability that a treatment strategy is cost effective at that threshold.

Probabilities. (i) CRE bacteremia and pneumonia and associated mortality. For patients in the hypothetical cohort, the probability that the CRE infection was bacteremia (68%) or pneumonia (32%) was based on the proportions of patients with each of these types of infection observed in a multicenter observational study (4). Mortality from CRE bacteremia (40.9%) and pneumonia (40.7%) with COL-based

therapy was based on pooled data of in-hospital or up to 30-day mortality from multiple studies of patients treated with conventional therapies (see Tables S1 and S2 in the supplemental material). To model the effect of CAZ-AVI on CRE mortality, we used the absolute risk reduction in mortality (23%) based on van Duin et al's prospective multicenter observational study of CAZ-AVI versus COL for treatment of CRE infections (4).

(ii) Risk of nephrotoxicity. Nephrotoxicity with COL-based therapy (42%) was determined from a meta-analysis of colistin and polymyxin B for the treatment of multidrug-resistant Gram-negative infections (17). Among patients who developed nephrotoxicity, the probability of in-hospital reversible renal replacement therapy (RRT) (5.2%) was estimated by pooling multiple studies from the literature that reported this outcome for patients receiving COL or polymyxin B (Table S3). The risk of long-term RRT (2.5%) was based on the number of patients with loss of renal function from the meta-analysis (17). Nephrotoxicity occurring among patients receiving CAZ-AVI (8%) for treatment of CRE infection was derived from observational studies that reported this outcome (4, 5). For patients who developed nephrotoxicity on CAZ-AVI, we assumed that the risk of in-hospital RRT and long-term dialysis was equivalent to that for COL-based therapy. Dialysis was assumed to confer a 3.15-fold increase in the relative risk of all-cause mortality (18) and a 3-fold increase in the likelihood of discharge to long-term care (19).

(iii) Discharge disposition and all-cause mortality. The probability of discharge to long-term care following CRE infection (55.9%) was based on a multicenter population-based surveillance study of CRE incidence in the United States (10). Since no long-term mortality data exist for CRE, long-term survival was extrapolated from the literature on sepsis. Specifically, all-cause mortality at 1 year and the annual mortality risk thereafter were modeled using the results of a Medicare claim-based retrospective cohort study of survivors of severe sepsis and included 5-year mortality risk stratified by discharge home or to a skilled nursing facility (20). We assumed that long-term survival and discharge disposition probabilities did not vary as a function of treatment arm.

Costs. We included costs related to antibiotic therapy, nephrotoxicity, and health care utilization following hospital discharge. Except for antibiotic therapy and incident nephrotoxicity, the costs of the index CRE hospitalization were assumed to be equivalent between the COL and CAZ-AVI strategies because there are no published comparative data on overall hospital costs or length of hospital stay. All medication costs were from the U.S. Department of Veterans Affairs (VA) Federal Supply Schedule (FSS) as per guidelines for cost-effectiveness analysis (https://www.va.gov/opal/nac/fss/pharmPrices.asp) (14). Because FSS pharmaceutical costs are reported to be less than for other U.S. health care delivery sponsors, the listed FSS costs were increased by 21% to more accurately represent the typical cost to the U.S. health care system, as recommended by the VA Health Economics Resource Center (https://www.herc.research.va.gov/include/page.asp?id=pharmaceutical-costs) (6). Since treatment for CRE infection often includes multiple antibiotic combinations (e.g., carbapenems, tigecycline, and aminoglycosides), the costs of COL-based and CAZ-AVI-based therapies were calculated as weighted averages using treatment regimen frequencies reported by van Duin et al. (4). For instance, in the COL-based therapy arm, 61% of patients received concomitant tigecycline. Therefore, the daily cost of tigecycline ($274) was multiplied by 0.61 and added to the daily cost of COL ($26). The daily cost of CAZ-AVI was $926. Treatment durations were 7 days and 14 days for pneumonia and bacteremia, respectively. The cost of nephrotoxicity with and without renal replacement therapy was averaged from multiple published sources (Table S4). The annual cost of chronic dialysis ($90,410) was obtained from the U.S. Renal Data System 2017 annual report (https://www.usrds.org/2017/view/Default.aspx). The annual cost of long-term care ($94,696) was the U.S. national average for a private room reported by U.S. Department of Health & Human Services (https://longtermcare.acl.gov/costs-how-to-pay/costs-of-care.html). Because long-term health care resource utilization following CRE infection has not been studied, the subsequent health care costs for survivors of CRE infection, such as rehospitalizations, emergency room visits, and physician charges, were based on studies of the long-term health care costs of sepsis in the first year ($24,079) and in subsequent years ($8,082) (21). The costs of nephrotoxicity and long-term health care were assumed to be equivalent between COL and CAZ-AVI. All costs were updated to 2017 U.S. dollars using the medical care component of the consumer price index (https://www.bls.gov/cpi/data.htm).

Quality of life. Health states in the model were assigned utility weights using a scale of 0 to 1 where 0 represents death and 1 represents perfect health. QALYs were calculated by multiplying the utility weight by the length of time in the given health state. The utility weight associated with discharge home following CRE infection (0.84) was based on a prior economic analysis of CRE infection and age-based health-related quality of life from the literature assuming a mean age of 61 for CRE infection (4, 22–24). Utility values for hospitalization (0.73) (25), reversible nephrotoxicity (0.66) (26), dialysis (0.59) (27), and long-term care (0.64) (28, 29) were from published sources.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.00897-19.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

ACKNOWLEDGMENTS

M.S.S. has received consulting fees from Roche Diagnostics. M.J.S. has received research grant support from Allergan and Merck through Weill Cornell Medicine and consulting fees from Achaogen and Shionogi.

Allergan had no role in the funding, design, conduct, or reporting of this study.

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