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Original Article

Comparing ceftolozane/tazobactam versus piperacillin/tazobactam as empiric therapy for complicated urinary tract infection in Taiwan: A cost-utility model focusing on gram-negative bacteria

Guan-Jhou Chen [a,b], Sung-Ching Pan [b,*], Jason Foo [c], Chaienna Morel [c], Wei-Ting Chen [d], Jann-Tay Wang [b]

[a] *Department of Internal Medicine, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan*
[b] *Department of Internal Medicine, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan*
[c] *Global Health Economics, ICON plc, Houten, the Netherlands*
[d] *Global Medical Affairs, Merck Sharp & Dohme (I.A.) LLC, Taiwan*

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Abstract *Background:* Complicated urinary tract infection (cUTI) is often associated with drug-resistant pathogens and requires therapy with broad-spectrum antibiotics. Choice of empiric therapy should be based on an evaluation of clinical efficacy and medical costs. We used a cost-utility model to compare the empiric use of a new antibiotic, ceftolozane/tazobactam with piperacillin/tazobactam in patients with cUTI.
Methods: The analysis was conducted using a decision tree and patient-level simulation approach. Patients in the model received empiric antibiotic treatment with ceftolozane/tazobactam or piperacillin/tazobactam. Outcomes included mortality, medical costs and quality-adjusted life years (QALYs). Parameters related to pathogen distribution, length of hospital stay and medical costs, were estimated based on a cohort of patients with cUTI admitted during July 1st, 2015 to August 31st, 2016 to the National Taiwan University Hospital, a teaching hospital in Taiwan. Isolates used for the patient-level simulation to determine susceptibility to either drug were taken from the Study for Monitoring Antimicrobial Resistance Trend database.
Results: The analysis was performed on a simulation of 1000 patients. Empiric use of ceftolozane/tazobactam leads to higher total medical costs (USD 4199.01 per patient versus USD 3594.76, respectively) but also more discounted QALYs (4.80 versus 4.78, respectively). The

* Corresponding author. Department of Internal Medicine, National Taiwan University College of Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Rd, Taipei, Taiwan.
E-mail address: scpbpan@gmail.com (S.-C. Pan).

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additional cost per discounted QALY gained associated with empiric ceftolozane/tazobactam was 32,521.08 USD (956,282 NTD).
Conclusions: Our results suggest that empiric use of ceftolozane/tazobactam for the treatment of cUTI could be a cost-effective choice in Taiwan.

Introduction

Complicated urinary tract infection (cUTI), defined as UTIs with factors known to compromise host immunity or urinary tract anatomy,[1] is an important cause of hospitalization and is associated with high rates of morbidity and mortality as well as significant economic burden to the healthcare system.[2,3] According to surveillance from the Centers for Disease Control in Taiwan, UTIs account for 35.7% and 37.5% of healthcare associated infections (HAIs) in intensive care unit (ICU) patients from medical centers and regional hospitals, respectively.[4] In terms of the causative micro-organisms for cUTI, most literature suggests that Enterobacteriaceae remained the most common.[1,5] Other gram-negative bacteria, including *Pseudomonas aeruginosa*, gram-positive bacteria and *Candida species* have also been identified as causative micro-organisms for cUTIs.

Furthermore, HAIs are most commonly caused by drug resistant gram-negative bacteria with limited options for antimicrobial agents in Taiwan.[6,7] Apart from healthcare associated cUTIs, the frequency of drug resistant isolates causing community-acquired UTIs has also increased in recent years.[8,9] In a prospective cohort investigating the antimicrobial resistance of Enterobacteriaceae responsible for community-acquired UTI, the overall rate of extended beta-lactamase (ESBL) producing organisms was 13.5%.[8] The data from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) and the Study for Monitoring Antimicrobial Resistance Trend (SMART) also revealed around 30% of ESBL producing Enterobacteriaceae.[10–13] To curb the adverse outcome related to antimicrobial resistance in cUTI, a beta-lactam/beta-lactamase inhibitor or carbapenem is often needed for successful treatment.[5]

To help combat the growing resistance of gram-negative bacteria, new medications with different mechanisms of action have been investigated.[14] Ceftolozane/tazobactam, a recently marketed antibiotic with an ability to inhibit ESBL producing Enterobacteriaceae and multidrug-resistant *P. aeruginosa*,[15,16] has been associated with higher rates of clinical cure than comparators in clinical trials in the first-line treatment of cUTI.[17] Although the introduction of a new antibiotic with a better resistance profile, such as ceftolozane/tazobactam, might improve the clinical outcome of therapy, its role in an antimicrobial stewardship (AMS) program must also be carefully considered. In some cases, it may be expedient to reserve it for treating patients with bacterial infection caused by pathogens which are resistant to commonly prescribed antimicrobials. It can also be used as empiric therapy to improve clinical outcomes for patients at high risk of drug-resistant infection.

The benefit of a new antibiotic, however, must be balanced with its cost. A number of cost-effectiveness models have been used to demonstrate the cost-effectiveness of ceftolozane/tazobactam versus comparators in many countries. Kauf et al. demonstrated that empiric therapy with ceftolozane/tazobactam was cost-effective, using a cost-utility model comparing ceftolozane/tazobactam and piperacillin/tazobactam as empiric therapy for hospitalized patients with cUTI in the US.[18] However, this and other results may not be applicable in Taiwan, where the costs of health care and medication are significantly different from those in the US. In this study, we developed a patient-level simulation model to assess the cost-effectiveness of ceftolozane/tazobactam as empiric therapy for hospitalized patients with cUTI in Taiwan.

Method

Model structure

We used a cost-effectiveness model to assess the economic impact of ceftolozane/tazobactam as empiric therapy among patients with cUTIs. Piperacillin/tazobactam, a commonly recommended broad-spectrum antibiotic for empiric therapy in patients at high risk of drug resistance pathogens, was selected as the comparator.[5] The cost-effectiveness analysis was conducted using a decision tree and patient level simulation approach. Quality-adjusted life years (QALYs) and medical costs were estimated using patient level information for both treatments. The model used in our study was adopted for Kauf et al. from their study evaluating the cost-effectiveness of using ceftolozane/tazobactam as empiric antibiotics for cUTI in the United States.[18] The model structure and all treatment pathways are shown in Fig. 1.

Patients enter the model when they are admitted to hospital with a diagnosis of cUTI, which is assumed to be concurrent with the initiation of empiric antibiotic therapy and the collection of blood and urine samples for culture. Each patient in the model receives empiric therapy with either ceftolozane/tazobactam or piperacillin/tazobactam and continues treatment until culture results and antimicrobial drug susceptibility are available. In the patient-level simulation, all patients are distributed between three different groups according to culture results: culture-negative, gram-positive infection, gram-negative infection (with or without concurrent gram-positive isolates). The proportion of these three

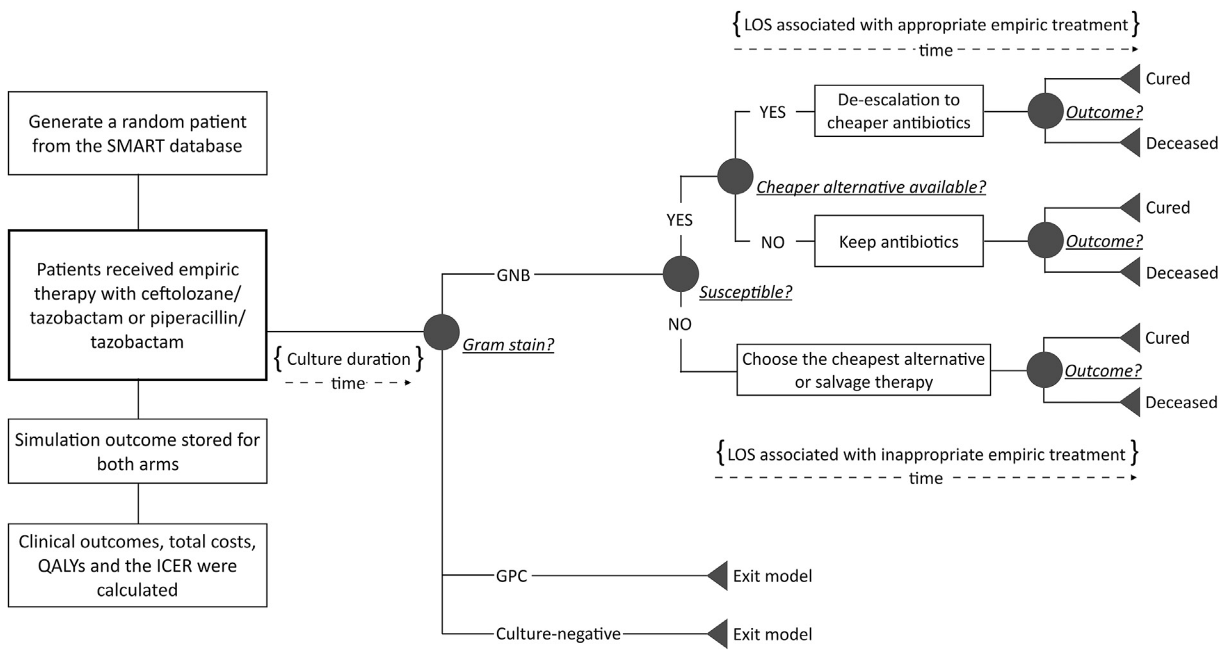

Figure 1. Model structure. Abbreviations: SMART, Study for Monitoring Antimicrobial Resistance Trend study; LOS, length of stay; GNB, gram-negative bacteria; GPC, gram-positive cocci.

categories were based on a real-life cUTI cohort from the National Taiwan University Hospital (NTUH), a teaching hospital in Taiwan which provides both primary and tertiary medical care. Patients with gram-positive infections or culture-negative results exit the model after the culture results are available (Fig. 1), for these patients, the appropriateness of empiric therapy cannot be assessed. Patients with mixed gram-positive and gram-negative infection will be evaluated for the appropriateness of empiric therapy based on the isolated gram-negative bacteria. Since gram-negative bacteria including Enterobacteriaceae and non-fermatative gram-negative bacteria are responsible for a majority of cUTI, we hypothesized that additional costs and outcomes would be similar across both arms in terms of gram-positive isolates.

For patients with gram-negative infection, the model continued with a randomly selected clinical isolate from the Taiwanese subset of the SMART database, and each selected pathogen will represent a single patient.[19] Pathogens isolated from patients with cUTI in 2016 were included in this model. If the isolated pathogen was susceptible to the initial empiric therapy, the patient would be either switched to the least expensive antibiotic to which the causative pathogen was susceptible or continued empiric therapy if there was no cheaper alternative available. Among patients where the empiric therapy was inappropriate, the patients would escalate to the least expensive drug to which the pathogen was susceptible. If the pathogen was not susceptible to any of the antibiotics tested, the patient would be switched to salvage therapy, which is assumed to be high-dose fosfomycin (intravenously, 8000 mg every 8 h with adjustment according to renal function). Available antibiotics for de-escalation and escalation are listed in Table 1. Bacterial resistance emerging during the course of treatment was not considered in this model. In total, 1000 patients are simulated to receive either ceftolozane/tazobactam or piperacillin/tazobactam.

In terms of the clinical and economic outcomes, the length of hospital stay and mortality are influenced by the appropriateness of initial antibiotic therapy. The clinical parameters used in the model are listed in Table 1. For patients who survived, their life expectancy was estimated based on data provided by the Department of Statistics of Ministry of Interior of Taiwan.[20]

Input for clinical and economic parameters

A retrospective cohort including patients who presented to the emergency department of NTUH and were subsequently admitted for the treatment of cUTI was used to inform model parameters used in this study (Supplement Table 1). The study was approved by the National Taiwan University Hospital Research Ethics Committee (registration no., 201609019RSC) and informed consent was waived. In the cohort, 15.5% of patients with cUTI were culture-negative and 9.9% had gram-positive infections. The average turnaround time for culture results was 3.9 days (range, 0—9 days). For patients with initially appropriate antibiotic therapy, the average length of hospital stay was 20.9 days (range, 6—51 days) and initially inappropriate antibiotic therapy was associated with a 3.9 day increase in hospital stay. The daily cost of hospitalization was also calculated from the NTUH cohort and was 188.90 United States Dollar (USD) per day (range, 70.85—647.79 USD). The daily costs for included antibiotics were derived based on the highest tolerable dosage on the package inserts and the approved or preliminary unit prices by the Taiwan National Health Insurance. When conversion between USD and New Taiwan Dollar (NTD) is needed, we used the exchange rate on May 7th, 2018, whereas 1 USD were equivalent to 29.405 NTD.

Drug susceptibility results for gram-negative bacteria from the Taiwanese subset of the SMART database were used to evaluate the appropriateness of empiric treatment and any subsequent therapy. Inputs for mortality rates were based on the study by Fraser et al.[21] A health utility value of 0.4 was applied to patients who were cured from the infection for the remainder of their life.[22] Other parameters used in the model are listed in Table 1.

Time horizon and discounting

Although cUTI is an acute illness and likely be cured in a short period of time, hospitalization due to acute infection might results in deconditioning and long-term complications among vulnerable patients with multiple comorbidities, as in our cohort. Therefore, a lifetime horizon was used to capture the health utility and costs of survivors. The costs for hospitalization and antibiotics were not discounted, since all costs were incurred within the first year. QALYs were discounted by 3% every year.[23]

Model analysis

Our model aimed to compare the use of ceftolozane/tazobactam and piperacillin/tazobactam as empiric therapy for hospitalized patients with cUTI in Taiwan. For both treatments, proportions of patients appropriately and inappropriately treated (sensitive/resistant to the initial empiric therapy), cost per QALY gained, costs of antibiotics, costs of hospitalization, and mortality were estimated.

To incorporate uncertainty in the evaluation, one-way sensitivity analyses (OWSA) and probabilistic sensitivity analysis (PSA) were performed to quantify the uncertainty in the model outcomes based on the uncertainty of the input parameters. The model assessed the sensitivity of the model results to all the input data for which uncertainty has been defined one parameter at a time by means of OWSA. The ten parameters with the greatest impact were summarized with tornado diagrams.

With the PSA, new model input parameter values were repeatedly sampled from the estimated (posterior) or defined (prior) distributions for efficacy, safety and costs, and subsequently the corresponding model output was calculated. The output values of 1000 iterations were summarized.

Table 1 Input parameters of the study model.

Variables	Mean	Lower bound	Upper bound	Reference
Mortality				
Mortality rate with IAAT	0.118	0.094	0.147	Fraser et al.[20]
Mortality rate with IIAT	0.201	0.160	0.248	Fraser et al.[20]
Duration of therapy and hospitalization				
Duration of empiric therapy, days	3.9	0.0	9.0	NTUH cohort
Duration of initial appropriate therapy (including empiric therapy)	14.4	5.0	26.0	NTUH cohort
Additional duration of therapy associated with IIAT	0.1	−2.3	2.6	NTUH cohort
LOS for patients with IAAT, days	20.9	6.0	51.0	NTUH cohort
Additional LOS associated with IIAT, days	3.9	−4.3	12.1	NTUH cohort
Economic parameters				
Hospital cost per day (excluding antibiotics), USD (2018)	188.90	70.85	647.79	NTUH cohort
Health utility	0.4	0.32	0.48	Maxwell et al.[21]
Discount rate	3%	3%	3%	Weinstein et al.[22]
Daily cost of drug available for treatment in the model, USD (2018)				
Ceftolozane/tazobactam	222.92			
Cefepime	72.10			
Ceftazidime	8.35			
Ceftriaxone	13.06			
Ciprofloxacin	82.71			
Colistin	42.71			
Imipenem/cilastatin	55.91			
Levofloxacin	53.46			
Meropenem	148.95			
Piperacillin/tazobactam	60.40			
Salvage therapy (fosfomycin)	54.41			

Abbreviations: IAAT, initial appropriate antimicrobial therapy; IIAT, initial inappropriate antimicrobial therapy; NTUH, National Taiwan University Hospital; LOS, length of stay; USD, the United States Dollar.

The probability of ceftolozane/tazobactam being cost-effective was expressed using a cost-effectiveness acceptability curve, calculated as the number of iterations out of the total number of iterations for which the net monetary benefit (NMB) was greatest for a given treatment strategy out of all strategies.[24] The NMB was calculated as the QALYs multiplied by a willingness to pay (WTP) ratio minus the costs, where the WTP is the amount decision makers were willing to pay per additional QALY gained. There is no WTP or cost-effectiveness threshold defined by the Taiwanese public payer, as a result the gross domestic product (GDP) per capita x 3 is commonly used, as advised by the WHO.[25] The GDP per capita for Taiwan in 2017 was 24,408 USD,[26] resulting in a threshold of 73,224 USD.

Analysis of specific scenarios

In many clinical services worldwide, Taiwan included, overuse of carbapenem antibiotics had been reported.[27,28] The introduction of ceftolozane/tazobactam might provide an non-carbapenem choice when treating drug resistance gram-negative bacteria. Therefore, we also performed an analysis based on a specific carbapenem-sparing scenario. In this scenario, a carbapenem was only selected as subsequent therapy if the isolate was resistant to all other non-carbapenem antibiotics. When choosing an agent for de-escalation, if a carbapenem was the cheapest choice, it would be skipped and the cheapest non-carbapenem antibiotic would be assigned as subsequent therapy.

By limiting the selection of Taiwanese isolates from the SMART database, two additional scenarios were explored to address specific high-risk populations. Firstly, a cohort of patients aged 65 years or above were simulated. Secondly, only isolates collected from patients hospitalized for longer than 48 h (healthcare associated UTIs) were included. These two scenarios were designed to focus on potential vulnerable patients with further increased risk of drug-resistance pathogen and were performed by using similar process described above with a subset of the pathogens from the SMART database.

Results

Base case analysis

The analysis was performed on a cohort of 1000 patients with an average age of 70.9 years ranging from 18 to 104 years. The leading causative pathogens used in the simulation included *Escherichia coli* (58%), *P. aeruginosa* (20%), *Klebsiella pneumoniae* (18%), and other gram-negative bacteria (5%).

The key results from the model are summarized in Table 2. In the base case analysis, the susceptibility rate for empiric treatment with ceftolozane/tazobactam was 68.6% compared with 64.6% for piperacillin/tazobactam. No patients required salvage therapy with fosfomycin. The mortality rate was 14.4% and 14.7% in the ceftolozane/tazobactam and piperacillin/tazobactam arms, respectively. Empiric therapy with ceftolozane/tazobactam followed by proper de-escalation could avoid 3.3 death and save 156 hospitalization days in our modeled cohort of 1000 patients.

Empiric treatment with ceftolozane/tazobactam resulted in higher total medical costs than piperacillin/

Table 2 Model estimation of treatment outcome and hospitalization cost[a].

	Ceftolozane/tazobactam	Piperacillin/tazobactam	Difference[b]
Clinical results			
Proportion of IAAT, %	68.6	64.6	4.0
Mortality, %	14.4	14.7	−0.3
Total medical cost per patient, USD (2018)	4199.01	3594.76	604.25
Hospitalization cost per patient (excluding antibiotics), USD (2018)	3176.53	3206.02	−28.48
Cost of antibiotics per patient, USD (2018)	1022.48	388.74	575.77
QALY generated from treatment			
Total QALY gain per patient (undiscounted)	7.02	6.99	0.03
Total QALY gain per patient (discounted)	4.80	4.78	0.02
Resultant effects of empiric ceftolozane/tazobactam treatment			
ICER (Cost per discounted QALY gain), USD (2018)	—	—	32,521.08

[a] The cost and QALY were expressed as the estimate per patient.
[b] Difference: ceftolozane/tazobactam − piperacillin-tazobactam.
Abbreviation: IAAT, initial appropriate antimicrobial therapy; USD, the United States Dollar; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.

tazobactam (4199.01 USD per patient versus 3594.76 USD; respectively), and a greater number of discounted QALYs (4.80 QALYs vs. 4.78 QALYs, respectively) (Table 2).

When examining the results for costs in detail, the cost of antibiotics was significantly higher in the ceftolozane/tazobactam arm than piperacillin/tazobactam arm (1022.48 USD per patient versus 388.74 USD; respectively) and the hospitalization cost was slightly low in ceftolozane/tazobactam arm comparing to piperacillin/tazobactam arm (3176.53 USD per patient versus 3206.02 USD; respectively).

In summary, in our cohort of 1000 patients, empiric treatment with ceftolozane/tazobactam generated an additional 18.58 discounted QALYs when compared with empiric piperacillin/tazobactam therapy. The difference in total medical costs was 604,241.66 USD, which resulted in an incremental cost-effectiveness ratio (ICER) of 32,521.08 USD (956,282 New Taiwan Dollar [NTD]) per QALY gained. This ICER was lower than the previously defined WTP threshold (73,224 USD).

Sensitivity analysis

The results of the PSA and the cost-effectiveness acceptability curve are shown in Fig. 2 and Supplement Figure 1. In 89% of the iterations, ceftolozane/tazobactam generated more QALYs and costs (Supplement Figure 1). Also, the probability of ceftolozane/tazobactam being cost effective approached 90% at a willingness to pay threshold of 68,015.64 USD (2,000,000 NTD) per QALY (see Supplement Figure 1).

The results of the OWSA are presented in a tornado diagram (Fig. 3) while the upper and lower bound limits of each parameter were detailed in Supplement Table 2. Varying the duration of empiric therapy (defined as the average turnaround time for culture results) had the largest impact on the ICER. Other input parameters influencing the ICER results included: mortality rate with inappropriate empiric antibiotics, mortality rate with appropriate empiric antibiotics, resistance to piperacillin/tazobactam. Detailed results of the OWSA are provided in Supplement Table 2.

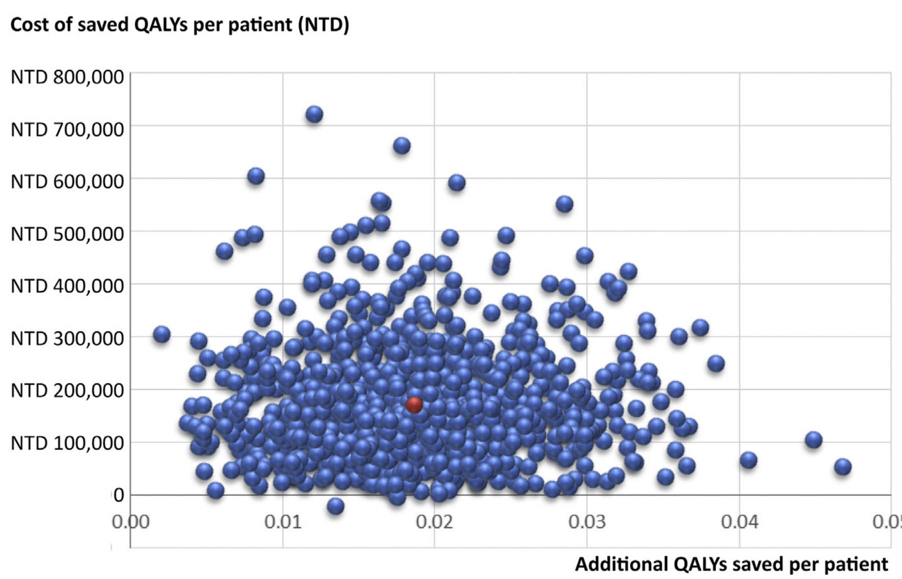

Figure 2. The cost-effectiveness plane in the probabilistic sensitivity analysis. Abbreviations: QALY, quality-adjusted life year; NTD, New Taiwan Dollar.

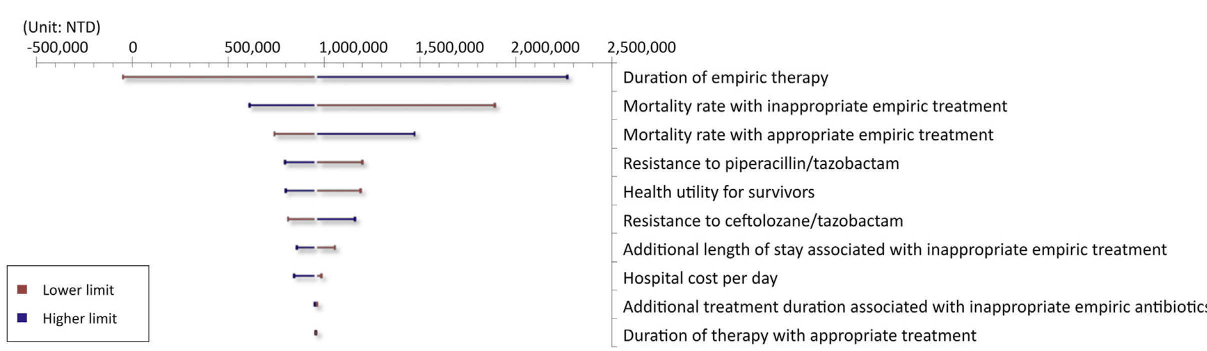

Figure 3. Influence of different variables on the ICER. Abbreviations: ICER, incremental cost-effectiveness ratio; NTD, New Taiwan Dollar.

Analysis of specific scenarios

Three pre-specified scenarios were performed and the results are shown in Table 3. Among all scenarios, incremental costs were similar, however, the QALYs gained were highest among patients with healthcare associated cUTI. The ICER in all three scenarios remained under the WTP threshold.

Discussion

In this modeling study, the use of ceftolozane/tazobactam compared with piperacillin/tazobactam as empiric therapy for hospitalized patients with cUTI was associated with higher medical costs but a greater number of discounted QALYs. The ICER for ceftolozane/tazobactam was within the WTP threshold and can be considered cost-effective. To our knowledge, this is the first model evaluating the cost-effectiveness of a new antimicrobial agent in Taiwan. To better represent Taiwanese patients and the healthcare system, clinical and microbiological parameters in the model were derived from a cohort of patients with cUTI from the NTUH and Taiwanese isolates from the SMART database.

The increase in the total medical costs in the ceftolozane/tazobactam arm was a result of the increased cost of antibiotics during treatment. Specifically, the cost of empiric antibiotic therapy, since ceftolozane/tazobactam is significantly more expensive than piperacillin/tazobactam in Taiwan. In the OWSA, the duration of empiric therapy had the greatest impact on the ICER. Applying the upper bound value, where the average turnaround time for culture results (duration of empiric therapy) was 9 days, the ICER just exceeded the predefined WTP threshold. However, such prolonged turnaround time seems unlikely in regional hospitals or medical centers in Taiwan. Therefore, proper collection of clinical samples and strategies to accelerate the timing of de-escalation to cheaper, narrow-spectrum antibiotics are important to reduce medical costs. This approach is compatible with current recommendations of AMS programs.

Kauf et al. had published a similar evaluation comparing the cost-effectiveness of ceftolozane/tazobactam and piperacillin/tazobactam as empiric therapy for cUTI in the United States with an ICER of 6128 USD per discounted QALY generated, which was cheaper than our estimation (32,521.08 USD per discounted QALY). In the study by Kauf et al., the difference of initial appropriateness between two empiric antibiotics was 12.4% which was much higher in our study (4%), resulting in a larger discounted QALY generated with ceftolozane/tazobactam as compared with our model (0.06 versus 0.02, respectively). Similarly, the cost-effectiveness of using ceftolozane/tazobactam as empiric antibiotics for cUTI might be affected by different distribution of drug susceptibility among different populations and the interpretation of our results in different setting should be done cautiously.

Our study had some limitations and the results should be interpreted carefully. Firstly, the NTUH cohort only included patients who presented to the emergency room and were then subsequently admitted for cUTI. Therefore, the information may not be applicable to patients with newly developed healthcare associated cUTI. However, we did perform an analysis based on SMART isolates collected 48 h after admission, which showed improved cost-effectiveness of ceftolozane/tazobactam compared with the base case. It should be noted that only 89 isolates (compared with 287 for the overall Taiwanese cohort) were available from the SMART database for this scenario analysis. Secondly, our model did not account for several factors such as the emergence of drug-resistance during treatment, the possibility of antibiotic-related adverse reactions, and the risk of other healthcare associated infections during hospitalization. We also excluded patients presented with gram-positive bacteria in the urine culture, which might lead to potential confounding. Finally, the clinical parameters used in this study were based on a cohort from a tertiary medical center in Taiwan. In the original cohort, 14.1% of included patients had bacteremia upon admission while 32.4% of patients had diabetes mellitus and 31.0% had active malignancy. Therefore, generalization of these results in different clinical setting with less severe patients should be careful. Moreover, some of

Table 3 Results of analysis of specific scenarios.

	Ceftolozane/tazobactam	Piperacillin/tazobactam	Difference[a]
Results of carbapenem-sparing scenario			
Total medical cost per patient, USD	4213.74	3609.62	604.15
Discounted QALYs per patient	4.79	4.77	0.02
ICER	—	—	32,517.23
Results of analysis using isolates from patients ≥65-year-old			
Total medical cost per patient, USD	4247.07	3641.35	605.71
Discounted QALYs per patient	3.78	3.77	0.01
ICER	—	—	43,322.63
Results of analysis using isolates from patients admitted for ≥48 h			
Total medical cost per patient, USD	4233.67	3643.53	590.14
Discounted QALYs per patient	4.80	4.77	0.03
ICER	—	—	21,458.83

[a] Difference: ceftolozane/tazobactam − piperacillin-tazobactam.
Abbreviation: NTD, New Taiwan dollar; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.

the clinical parameters including mortality and utility in our study was adopted from foreign studies and might result in potential bias when used to model Taiwanese healthcare systems.

In conclusion, our study indicates that ceftolozane/tazobactam is a cost-effective choice for the empiric treatment of hospitalized patients with cUTI in Taiwan.

Conflict of interest and funding source

The statistical analyses in this study was performed by the ICON Inc. The ICON Inc. received budgetary compensation from Merck Sharp & Dohme for this study. Other authors had no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2019.04.003.