

# The cost-effectiveness of empirical antibiotic treatments for high-risk febrile neutropenic patients

## A decision analytic model

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### Abstract

**Purpose:** Febrile neutropenia has a significant clinical and economic impact on cancer patients. This study evaluates the cost-effectiveness of different current empiric antibiotic treatments.

**Methods:** A decision analytic model was constructed to compare the use of cefepime, meropenem, imipenem/cilastatin, and piperacillin/tazobactam for treatment of high-risk patients. The analysis was performed from the perspective of U.S.-based hospitals. The time horizon was defined to be a single febrile neutropenia episode. Cost-effectiveness was determined by calculating costs and deaths averted. Cost-effectiveness acceptability curves for various willingness-to-pay thresholds (WTP), were used to address the uncertainty in cost-effectiveness.

**Results:** The base-case analysis results showed that treatments were equally effective but differed mainly in their cost. In increasing order: treatment with imipenem/cilastatin cost \$52,647, cefepime \$57,270, piperacillin/tazobactam \$57,277, and meropenem \$63,778. In the probabilistic analysis, mean costs were \$52,554 (CI: \$52,242-\$52,866) for imipenem/cilastatin, \$57,272 (CI: \$56,951-\$57,593) for cefepime, \$57,294 (CI: \$56,978-\$57,611) for piperacillin/tazobactam, and \$63,690 (CI: \$63,370-\$64,009) for meropenem. Furthermore, with a WTP set at \$0 to \$50,000, imipenem/cilastatin was cost-effective in 66.2% to 66.3% of simulations compared to all other high-risk options.

**Discussion:** Imipenem/cilastatin is a cost-effective strategy and results in considerable health care cost-savings at various WTP thresholds. Cost-effectiveness analyses can be used to differentiate the treatments of febrile neutropenia in high-risk patients.

**Abbreviations:** AKI = acute kidney injury, CI = confidence interval, ESMO = European Society for Medical Oncology, FN = febrile neutropenia, IDSA = Infectious Diseases Society of America, LOS = length of stay, MASCC = Multinational Association for Supportive Care in Cancer, NCCN = National Comprehensive Cancer Network, WTP = willingness to pay.

**Keywords:** antipseudomonal beta-lactams, cost-effectiveness, empirical treatment, febrile neutropenia, hematological malignancies, solid tumors

## 1. Introduction

Cytotoxic chemotherapy suppresses the hematopoietic system, often impairing host protection and defense mechanisms.<sup>[1]</sup> Severe neutropenia results in patients with a neutrophil count less than 500 cells/mm<sup>3</sup>.<sup>[2]</sup> Since the neutrophil-mediated component of the

inflammatory response is attenuated, fever may be the earliest indication of infection.<sup>[3]</sup> Febrile neutropenia (FN) incidence is over 60,000/year in the U.S.<sup>[4]</sup> It encompasses a spectrum of disease severity from low- to high-risk patients, and mortality rates range from 2% to 20%.<sup>[5-8]</sup> Furthermore, the mean cost of FN treatment in high-risk patients is estimated to be \$105,944, including

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*Imipenem/cilastatin is a cost-effective strategy and results in significant health care cost-savings when used for the empirical treatment of febrile neutropenia in high-risk adults.*

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

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treatment, physician office services, chemotherapy, outpatient services, prescriptions, and inpatient hospital services costs.<sup>[9]</sup> More than 1 encounter may be associated with a FN episode.

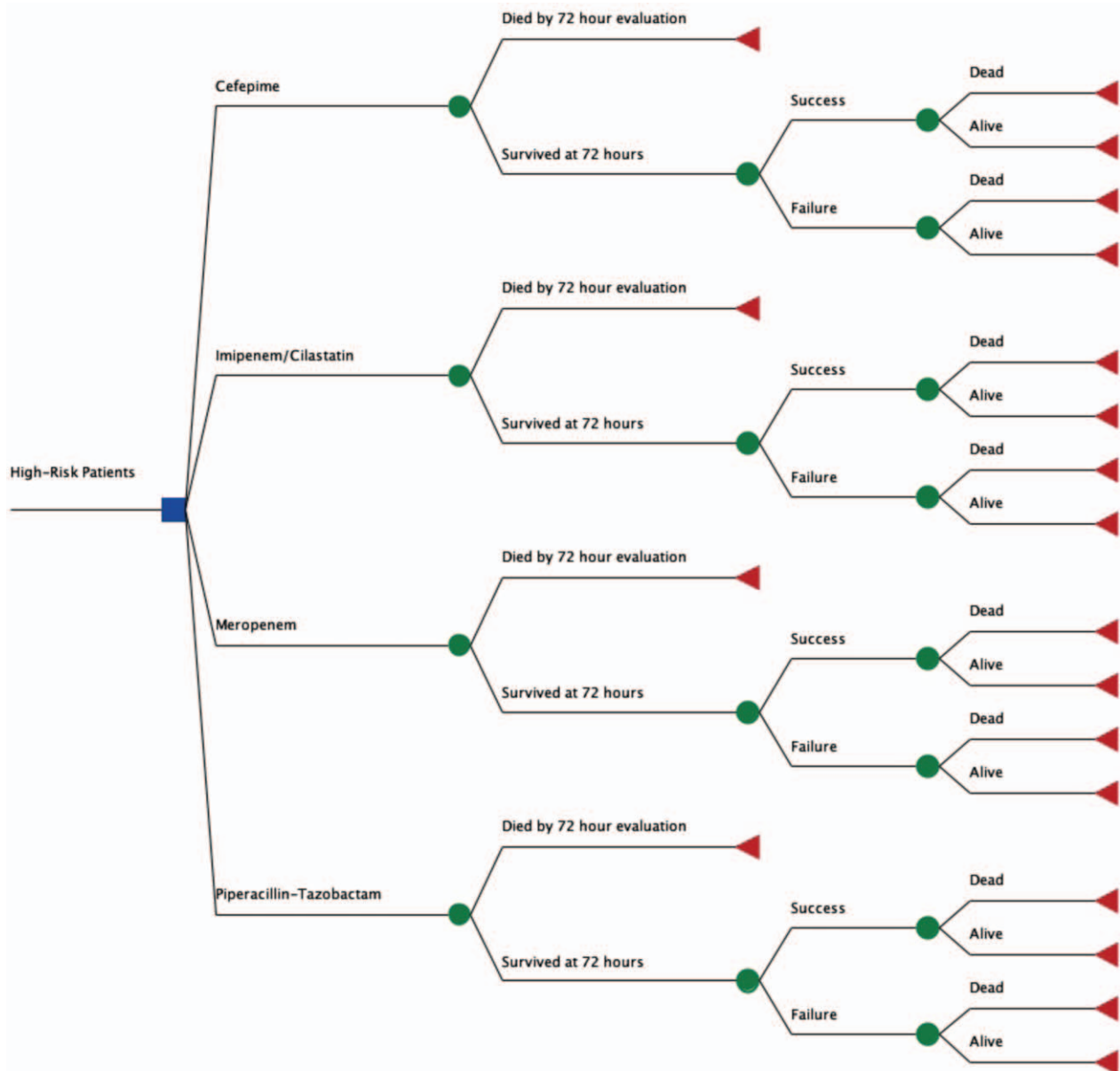
Risk severity is assigned based on the Multinational Association for Supportive Care in Cancer (MASCC) scoring system<sup>[10]</sup> used by the Infectious Diseases Society of America (IDSA) guidelines for the use of antimicrobial agents in neutropenic patients.<sup>[2]</sup> The MASCC scoring index is summarized in Klastersky et al.<sup>[10]</sup> The IDSA guidelines recommend monotherapy with an antipseudomonal beta-lactam agent for high-risk patients, with the addition of other antimicrobials (i.e., vancomycin, antifungals, aminoglycosides) for complications (i.e., pneumonia, hypotension) or suspected or proven antimicrobial resistance.<sup>[2]</sup> The National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) also endorse the use of monotherapy with antipseudomonal agents.<sup>[11,12]</sup>

This study aims to provide a comprehensive cost-effectiveness analysis of empirical antibiotics (cefepime, meropenem, imipenem/cilastatin, and piperacillin-tazobactam) recommended by the IDSA, ESMO and NCCN for the treatment of FN in high-risk patients.

## 2. Methods

### 2.1. Model structure

A decision-analytic model was constructed to assess the cost-effectiveness of various antibiotics used for empirical treatment of high-risk FN (Fig. 1). The analysis was performed from the perspective of U.S.-based hospitals. Subsequently, we relied on U.S. sources to assign costs. The time horizon for this analysis



**Figure 1.** Decision Tree Model for High-Risk Patients. The squares indicate the decision to use cefepime, imipenem/cilastatin, meropenem and piperacillin/tazobactam as treatment for high-risk patients. The circles indicate chance nodes, and the triangles indicate terminal nodes.

was a single FN episode. The clinical progression of the disease guided our models structure.<sup>[13]</sup> After empirical therapy initiation, patients were evaluated at 72 hours and end-of-treatment for death or survival, and treatment modification.<sup>[13]</sup> Outcomes

and costs were calculated from the time a patient was admitted to discharge or death. The analytical model was developed by using TreeAge Pro 2019 modeling software (TreeAge, Williamstown, MA). This study did not require IRB approval. An impact

**Table 1**  
**Model inputs and baseline estimates for probabilities, length of stay and costs.**

Input	Mean base-case value (Range)	Type of distribution (range/parameters)	Source
<b>Probabilities</b>			
<i>Success</i>			
Cefepime	0.54 (0.39, 0.69)	Uniform (0.39, 0.69)	[31–38]
Imipenem/cilastatin	0.65 (0.54, 0.75)	Uniform (0.54, 0.75)	[31,34,36,38–40]
Meropenem	0.46 (0.38, 0.55)	Uniform (0.38, 0.55)	[38,41–45]
Piperacillin/tazobactam	0.53 (0.41, 0.65)	Uniform (0.41, 0.65)	[32,40,44,46–51]
<i>Mortality</i>			
Early death	0.00 (0.00, 0.01)	Uniform (0.00, 0.01)	[42,43,47–49,51–56]
Death post success	0.01 (0.00, 0.05)	Uniform (0.00, 0.04)	[43,44,54,55,57]
Death post failure	0.03 (0.01, 0.05)	Uniform (0.01, 0.05)	[34,40,43,51,54,55,57]
<b>Adverse events</b>			
<i>Bacteremia</i>			
Cefepime	0.05 (0.00, 0.13)	Uniform (0.00, 0.13)	[33,54]
Imipenem/cilastatin	0.07 (0.03, 0.17)	Uniform (0.03, 0.17)	[58]
Meropenem	0.06 (0.00, 0.15)	Uniform (0.00, 0.15)	[41–43,45]
Piperacillin/tazobactam	0.04 (0.02, 0.08)	Uniform (0.02, 0.08)	[48,57]
<i>Clostridium difficile infection</i>			
Cefepime	0.08 (0.04, 0.13)	Uniform (0.04, 0.13)	[32–34,36]
Imipenem/cilastatin	0.14 (0.04, 0.26)	Uniform (0.04, 0.26)	[34,36,40,58,59]
Meropenem	0.18 (0.05, 0.36)	Uniform (0.05, 0.36)	[52,59]
Piperacillin/tazobactam	0.03 (0.00, 0.07)	Uniform (0.00, 0.07)	[32,40,47,49]
<i>Nephrotoxicity</i>			
Cefepime	0.01 (0.00, 0.02)	Uniform (0.00, 0.02)	[35,54]
Imipenem/Cilastatin	0.01 (0.00, 0.02)	Uniform (0.00, 0.02)	[40,58]
Meropenem	0.05 (0.01, 0.10)	Uniform (0.01, 0.10)	[43,53]
Piperacillin/tazobactam	0.01 (0.00, 0.05)	Uniform (0.00, 0.05)	[40,57]
<i>Modification with Glycopeptides</i>			
Cefepime	0.60 (0.38, 0.81)	Uniform (0.38, 0.81)	[31–34,36,54]
Imipenem/cilastatin	0.43 (0.11, 0.79)	Uniform (0.11, 0.79)	[31,34,36,39]
Meropenem	0.41 (0.19, 0.65)	Uniform (0.19, 0.65)	[41,43–45,52,53]
Piperacillin/tazobactam	0.62 (0.41, 0.80)	Uniform (0.41, 0.80)	[32,44,46–51,57]
<i>Modification with Antifungals</i>			
Cefepime	0.40 (0.18, 0.63)	Uniform (0.18, 0.63)	[32–35,37,54]
Imipenem/cilastatin	0.28 (0.17, 0.39)	Uniform (0.17, 0.39)	[34,39]
Meropenem	0.50 (0.23, 0.76)	Uniform (0.23, 0.76)	[42–45,52,53]
Piperacillin/tazobactam	0.31 (0.08, 0.60)	Uniform (0.08, 0.60)	[32,44,46,50,51,57]
<b>Hospital length of stay or treatment (in days)</b>			
LOS for early death	3.45 (1.00, 4.00)	Gamma (47.61, 13.80)	[42,43,48,49,52,53]
Successful Treatment LOS	11 (4, 33)	Gamma (5.18, 0.47)	[41]
Failed Treatment LOS	26.5 (25–27.3)	Gamma (4779.02, 180.34)	[50,60]
Early Death DoT	3.45 (1.00, 4.00)	Gamma (47.61, 13.80)	[42,43,48,49,52,53]
Successful Treatment DoT	11.00 (4.00, 33.00)	Gamma (5.18, 0.47)	[41]
Failed Treatment DoT	26.50 (25.00–27.30)	Gamma (4779.02, 180.34)	[50,60]
Vancomycin DoT	12.00 (9.00, 14.00)	Gamma (207.36, 17.28)	[61]
Antifungal Treatment DoT	11.50 (7.50, 13.00)	Gamma (157.39, 13.69)	[62–65]
<b>COSTS (USD)</b>			
Cost of Cefepime/day	76.98 (32.88, 121.08)	Gamma (27.42, 0.36)	[66]
Cost of Imipenem- cilastatin/day	101.04 (45.36, 156.72)	Gamma (29.64, 0.29)	[66]
Cost of Meropenem/day	140.60 (39.60, 241.59)	Gamma (17.44, 0.12)	[66]
Cost of Piperacillin-tazobactam/day	73.34 (36.48, 110.20)	Gamma (35.63, 0.49)	[66]
Cost of Glycopeptide/day	41.32 (25.64, 57.00)	Gamma (62.50, 1.51)	[66]
Cost of therapeutic drug level monitoring	140.3 (70.2, 280.6)	Gamma (16.01, 0.11)	[67]
Cost of Antifungals/day	311.23 (278.63, 383.62)	Gamma (316.35, 1.02)	[66]
Hospitalization cost/day	2,976.68 (1,488.34–5,953.36)	Gamma (16.0, 0.01)	[68]
<i>C. difficile</i> Cost	12,553.63 (10,143.02–15,099.95)	Gamma (230.90, 0.018)	[69]
Acute Kidney Injury Cost	8,211.21 (7,874.81–8,547.60)	Gamma (5362.38, 0.65)	[70]
Bacteremia Cost	23,464.58 (10,782.02–36,147.14)	Gamma (30.81, 0.0013)	[71]

DoT = duration of treatment, LOS = length of stay.

**Table 2**  
Base case analysis results for different treatment strategies.

	Regimen	Cost (\$)	Effect (probability of survival)	Incremental Cost (\$)
High-risk	Imipenem/cilastatin	52,647.24	0.97	Reference
	Cefepime	57,269.60	0.97	4,622.36
	Piperacillin/tazobactam	57,276.76	0.97	4,629.51
	Meropenem	63,777.95	0.97	11,130.71

inventory is provided in the Supplemental Digital Material Table S1, <http://links.lww.com/MD/E157>.

**2.2. Decision tree model**

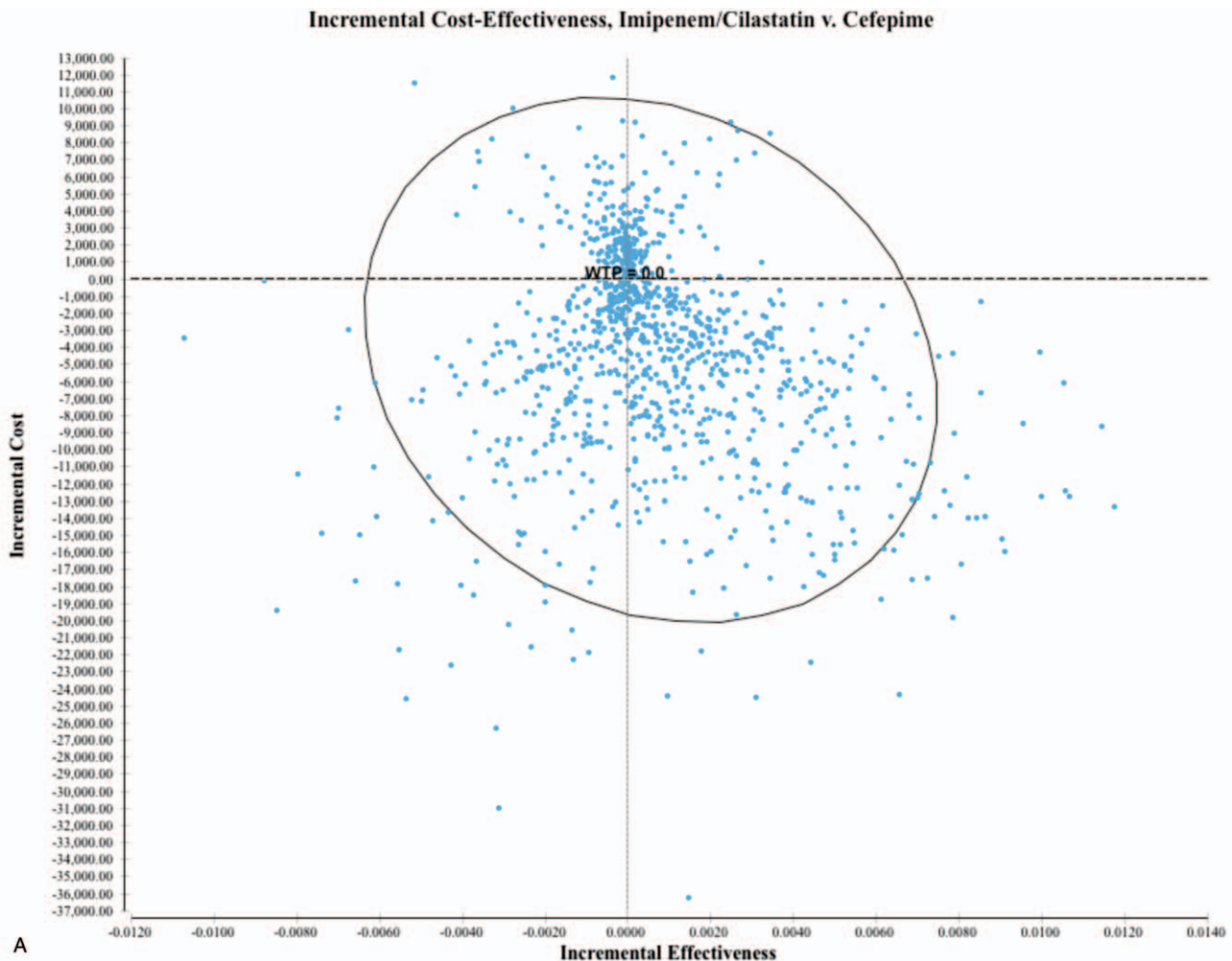
Cefepime, imipenem-cilastatin, meropenem, and piperacillin/tazobactam were included in the analysis. The aforementioned guidelines.<sup>[2,11,12]</sup> also recommend ceftazidime, however, it was not included in the analysis because of infrequent clinical use.<sup>[14,15]</sup> The primary outcomes were all-cause mortality and cost of selected treatments. Model parameters included treatment success/failure, modification with glycopeptides and antifungals, nephrotoxicity, *Clostridioides (Clostridium) difficile* infections,

bacteremia, hospital length of stay (LOS) and duration of antimicrobial treatment.

Model parameters and inputs are detailed in Supplemental Materials (Digital Supplemental Material 1, pages 1-2, <http://links.lww.com/MD/E156>).

**2.3. Outcome and data analysis**

Regimens were presented from most to least cost-effective. Each strategies cost accounted for the costs of antibiotic treatment, hospitalization, *C. difficile* infections, breakthrough bacteremia, and nephrotoxicity, taken as cost of AKI. Cost-effectiveness was estimated for various cost-effectiveness thresholds. To account



**Figure 2.** Incremental Cost-Effectiveness Curves. a: Imipenem Cilastatin vs Cefepime. b: Imipenem/cilastatin vs Meropenem. c: Imipenem/cilastatin vs Piperacillin/Tazobactam.

for random variation in costs and outcome variables, and to evaluate the robustness of our results, we conducted both deterministic (one-way sensitivity) and probabilistic analyses. The incremental effectiveness difference was defined as number of deaths averted. The calculations required for costs are detailed in Digital Supplemental Material 1 page 3, <http://links.lww.com/MD/E156>. Detailed costs and doses of the included drugs are included in the Supplemental Digital Material Table S2, <http://links.lww.com/MD/E158>.

In one-way sensitivity analysis all variables were allowed to vary within a range of values summarized in Table 1. In the probabilistic model all variables were varied simultaneously. Uniform distributions accounted for probability variations, and gamma distributions for costs, as recommended previously.<sup>[16,17]</sup> LOS was modeled by a gamma distribution to reflect the skewed distribution of the variable. For data provided as median and range, recommendations by Hozo et al were used to convert the median to mean values and the range to standard deviation values.<sup>[18]</sup>

In the probabilistic analysis 10,000 simulations were run.<sup>[17]</sup> A value from the base-case analysis was randomly selected for each variable every time. Resulting simulations were plotted on an incremental cost-effectiveness coordinate plane, where the x-axis

represented incremental effectiveness (probability of survival) and the y-axis represented incremental cost (USD). Points located within the southeast quadrant of the graph were cost-effective and dominant.<sup>[19]</sup> Cost-effectiveness acceptability curves assessed the cost-effectiveness for various WTP thresholds.<sup>[20]</sup>

### 3. Results

The employed model probabilities and costs, as well as their distributions and their distribution parameters are summarized in Table 1. The results of the base-case analysis, including probability estimates, incremental costs and effectiveness values are summarized in Table 2.

#### 3.1. Base-case analysis

The cost-effectiveness analysis suggested imipenem/cilastatin as the most cost-effective regimen. Costs are provided in increasing order. The base-case costs were \$52,647 for imipenem/cilastatin, \$57,270 for cefepime, \$57,277 for piperacillin/tazobactam, and \$63,778 for meropenem. At base-case all treatments were equally effective (0.97 probability of survival) as seen in Table 2.

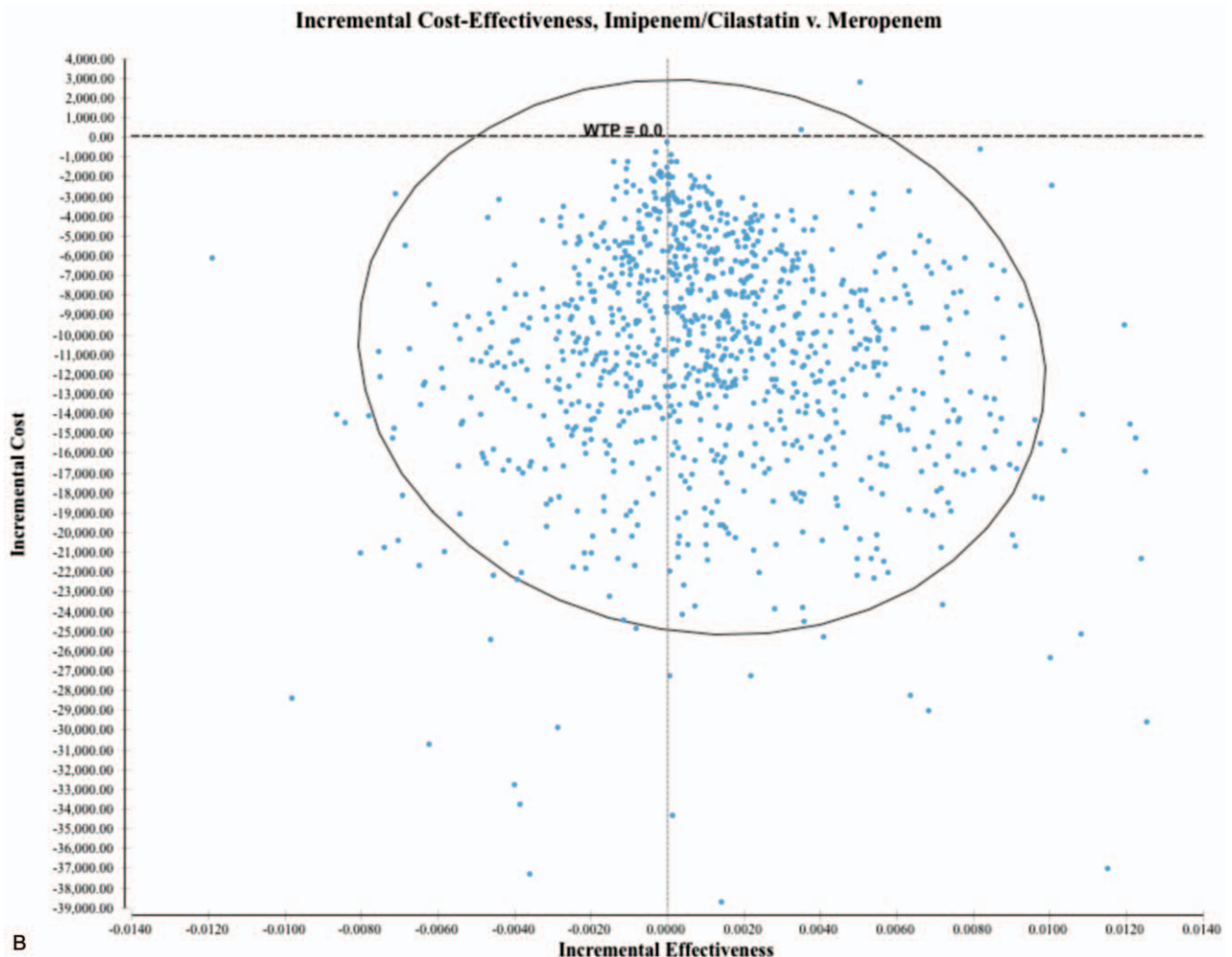


Figure 2. (Continued)

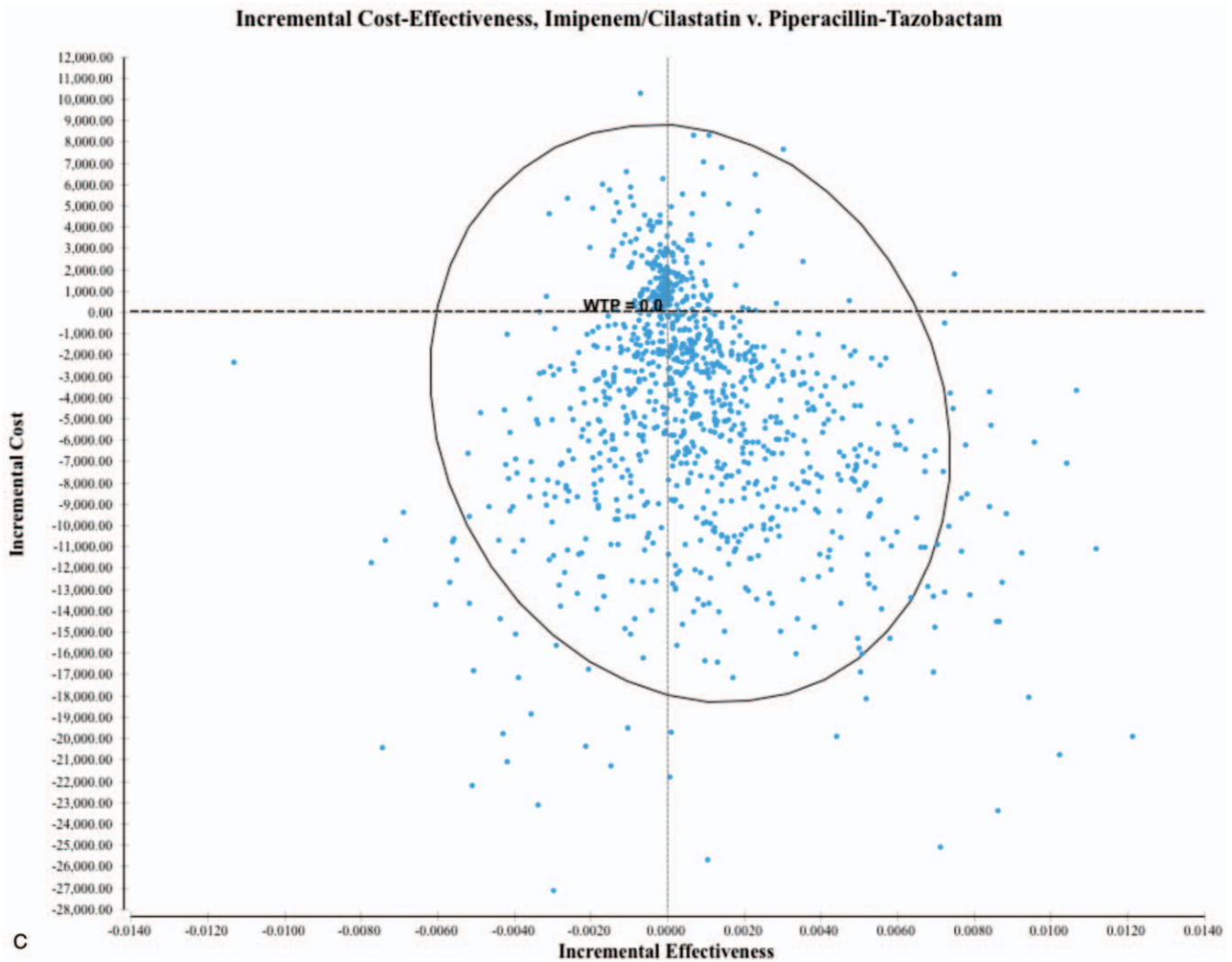


Figure 2. (Continued).

### 3.2. One-way sensitivity analysis

The sensitivity analysis evaluated the impact of fluctuations in each variable within the ranges specified in Table 1. Each individual parameter value was evaluated independently, while all other stayed fixed at the base-case value. Results were robust to one-way sensitivity analysis, with only a few exceptions. Cefepime became dominant for a probability of success  $\geq 0.63$ . Thus, in clinical situations where the probability of success with cefepime equals or surpasses 0.63, cefepime is favored in terms of cost-effectiveness. Furthermore, piperacillin/tazobactam became a dominant strategy, and thus favored in terms of cost-effectiveness, when LOS after successful treatment extended beyond 25.8 days.

### 3.3. Probabilistic sensitivity analysis

In probabilistic sensitivity analysis, all parameters can simultaneously depart from base-case values. In the probabilistic analysis, the mean cost was \$52,554 (CI: \$52,242-\$52,866) for imipenem/cilastatin, \$57,272 (CI: \$56,951-\$57,593) for cefepime, \$57,294 (CI: \$56,978-\$57,611) for piperacillin/tazobactam, and \$63,690 (CI: \$63,370-\$64,009) for meropenem.

Incremental cost-effectiveness curves (Fig. 2), which aimed to show the uncertainty around the cost-effectiveness outcomes, demonstrate the uncertainty in estimates of cost-effectiveness for a WTP set from \$0. Imipenem/cilastatin fell on the cost-saving and cost-effective fourth quadrant in 46.2% of simulations when compared to cefepime (Fig. 2a), 59.86% of simulations when compared to meropenem (Fig. 2b), 47.97% of simulations when compared to piperacillin/tazobactam (Fig. 2c).

Finally, the cost-effectiveness acceptability curves (Fig. 3), which show the probability that each strategy was cost-effective for various WTP thresholds, demonstrated that imipenem/cilastatin was cost-effective from 66.22% to 65.25% of simulations, cefepime was cost-effective from 19.11% to 19.14% of simulations, piperacillin/tazobactam was cost-effective from 14.62% to 14.56% of simulations, and meropenem was cost-effective in 0.05% of simulations for a WTP ranging from \$0 to \$50,000.

## 4. Discussion

Febrile neutropenia is a potentially life-threatening infection with high healthcare-associated costs. To date, there is no cost-

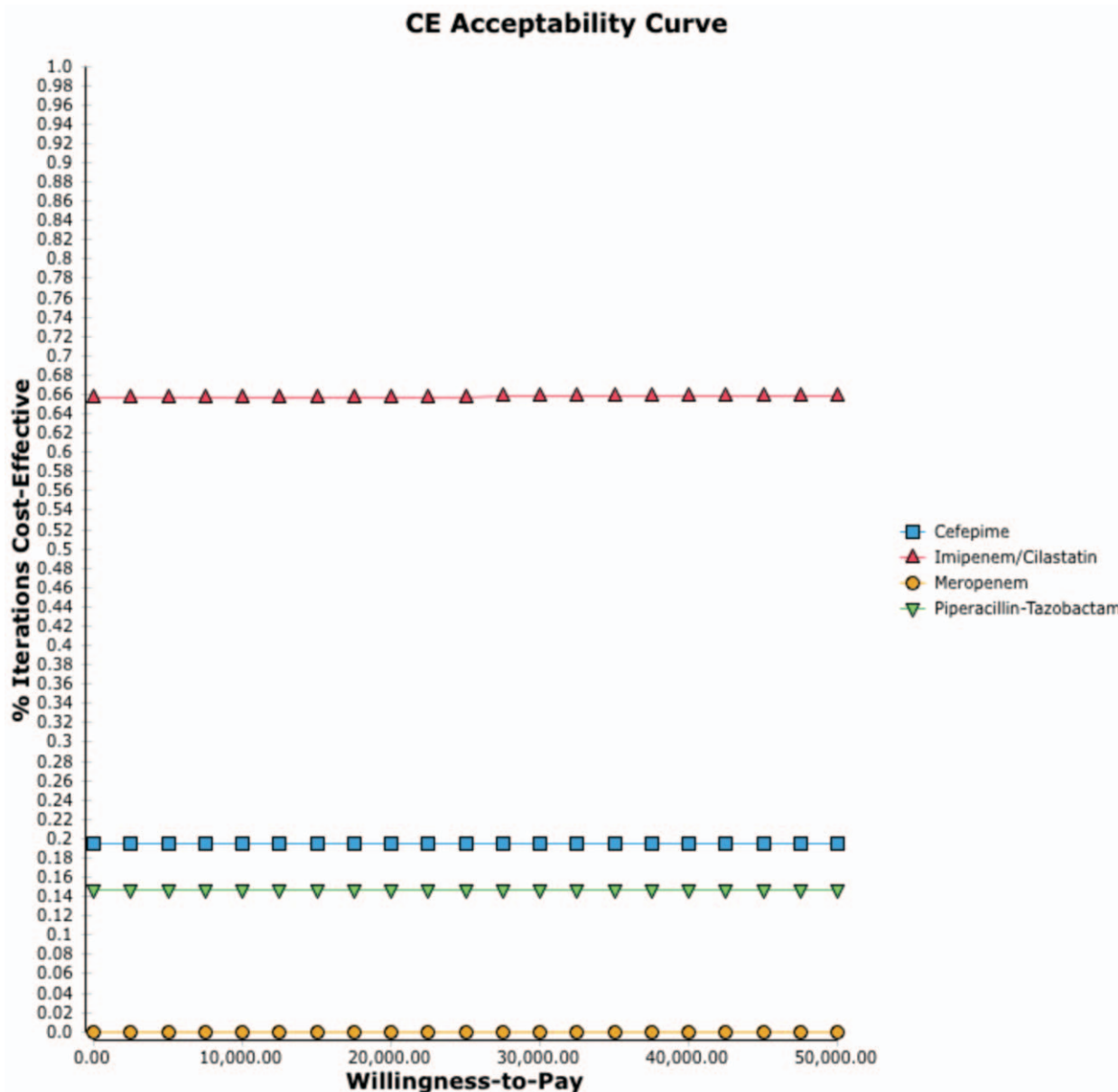


Figure 3. Cost-effectiveness acceptability curves for various willingness-to-pay thresholds for high-risk patients. These curves show the percent of the 10,000 simulations at which each treatment strategy was cost-effective.

effectiveness analysis on empirical antibiotic selection for adult high-risk FN patients. We performed a decision analytic model to optimize selection between recommended drugs.<sup>[2,11,12]</sup> Within the specified assumptions, the cost-effectiveness rankings showed that all regimens were equally effective at base-case, and imipenem/cilastatin had a lower cost, followed by cefepime, piperacillin/tazobactam, and meropenem. In the probabilistic analysis, imipenem/cilastatin outperformed competitors as first drug choice. Finally, imipenem-cilastatin remained dominant at different WTP thresholds.

The total cost of cancer-related FN hospitalizations in the U.S. was as high as \$2.3 billion for adults in 2012 with a mean hospital cost of \$24,770 per stay.<sup>[21]</sup> To this effect, it is crucial to identify an antibiotic regimen that can both improve clinical outcomes and result in cost savings. Guidelines allow us to choose between the 4 different antimicrobial options based on the spectrum coverage of

target infections.<sup>[2,11,12]</sup> Although the effectiveness (probability of survival) of different strategies was equivalent, there was a considerable difference in cost. In this study, different success probabilities were the main contributor to cost. Imipenem/cilastatin had the highest success probability, and thus the lowest probability of failure. This translated to lower LOS for the majority of treated patients, and thus lower costs overall.

The cost of a FN episode in our model was approximately \$53,000 when using imipenem/cilastatin. It did not include physician office services, chemotherapy, or outpatient hospital costs, which were included in the literature.<sup>[9]</sup> Imipenem/cilastatin has been associated with statistically significant higher risk of any adverse event in the recently published meta-analysis by Horita et al, although those events did not lead to drug discontinuation.<sup>[22]</sup> Notably, all adverse events, except for vomiting, nausea, and skin rash were included in our analyses.

Interestingly, imipenem/cilastatin had higher success rates than meropenem in our analyses as seen in Table 1. Guidelines<sup>[2,11,12]</sup> recommend imipenem/cilastatin and meropenem as first-line empirical treatments. A systematic review of 27 randomized controlled clinical trials comparing imipenem/cilastatin and meropenem, resulted in equal clinical and bacteriological effectiveness.<sup>[23]</sup> Other studies showed that 1.5 g/day of imipenem/cilastatin was equivalent to 3 g/day of meropenem in clinical and bacteriological outcomes, and adverse events.<sup>[24]</sup> The doses used in our analysis were in agreement with the recommendations (500 mg four times a day and 1 g three times a day for imipenem/cilastatin and 1 g 3 times daily for meropenem).<sup>[2,11,12]</sup>

Economic analyses demonstrate that imipenem/cilastatin is more effective and less costly than meropenem in intra-abdominal infections.<sup>[25]</sup> Lower dosage of imipenem used (500 mg four times a day vs 1 g three times a day for meropenem), may provide imipenem/cilastatin with a pharmacoeconomic advantage.<sup>[26]</sup> Finally, imipenem/cilastatin has a superior (4 times) in vitro activity against gram-positive pathogens.<sup>[27,28]</sup> It is therefore unclear to us why the probabilities of success of imipenem/cilastatin and meropenem were different in our analysis. However, evidence suggests that imipenem/cilastatin is generally superior to meropenem, especially in gram-positive infections.

Our results are compelling, but the study has some notable limitations. First, our analysis spanned a short time horizon limited to a single FN episode. Since cancer patients undergo multiple chemotherapy cycles, it is possible that they suffer from multiple FN episodes. This renders empirical antibiotic selection more complicated, when we consider prior isolation and infection data, resistance patterns, and cyclical use of broad-spectrum antibiotics. Thus, more episodes might become more complex, therefore leading to higher costs. Second, the included studies did not provide separate outcomes for patients with solid and hematological malignancies, despite their respective differences in FN. For example, the occurrence of FN in solid metastatic tumors is 10% to 50%,<sup>[29]</sup> and can reach 80% in some hematological malignancies, notably acute leukemias.<sup>[2,30]</sup> Furthermore, solid tumors and lymphomas usually have shorter duration of neutropenia after chemotherapy. Therefore, a different setting might be needed to account specifically for patients with acute leukemias and autologous stem cell transplantation, as protracted neutropenias and fever are more common.

In conclusion, our analysis suggests that there are significant cost-effectiveness differences between available empirical treatment for FN. Imipenem/cilastatin appears to be more cost-effective, but in specific populations (i.e., in patients that are likely to respond to cefepime, or those needing longer treatment) other approaches can be cost-effective. In an era of limited resources, future studies should include cost-effectiveness as a potential factor that might differentiate regimens. These cost-effectiveness studies could help personalize treatment for FN.

### Author contributions

KT designed the study, performed the data collection and analysis, prepared tables and figures, participated in data interpretation, wrote and drafted the initial manuscript, and approved the final manuscript as submitted. Ms. Tori had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. GST, DMP, MK and PDZ designed the study, participated in

data collection, extraction and interpretation, revised the manuscript, and approved the final manuscript as submitted. EM conceptualized and designed the study, interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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