



Revista Mexicana de
UROLOGIA
ÓRGANO OFICIAL DE DIFUSIÓN DE LA SOCIEDAD MEXICANA DE UROLOGÍA

www.elsevier.es/uromx



ORIGINAL ARTICLE

Economic evaluation of ceftibuten in the treatment of uncomplicated urinary tract infections in adult Mexican patients



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Received 14 August 2015; accepted 2 November 2015

Available online 21 December 2015

KEYWORDS

Urinary infection;
Economic evaluation;
Ceftibuten;
Mexico

Abstract

Background: Urinary tract infections are a leading cause of medical consultations in Mexico and the growth of antimicrobial resistance results in increased morbidity and rising costs.

Aim: To make an economic evaluation of ceftibuten as treatment for uncomplicated urinary tract infections in adults, from the perspective of the Mexican private health system.

Methods: A cohort-based decision-making model was developed to compare ceftibuten with TMP-SMX, ciprofloxacin, and cefalexin. Effectiveness was measured using local susceptibility rates of *Escherichia coli*. Costs were obtained from official market value data and converted to 2014 USD values. Incremental analysis was employed to determine if ceftibuten was a worthwhile investment on the part of the private health system in Mexico.

Results: The total expected cost per patient for ciprofloxacin was \$116 USD and the corresponding costs for TMP/SMX and cefalexin were \$92.40 USD and \$74.80 USD, respectively. Ceftibuten had a lower expected cost (\$34.50 USD) and a higher percentage of therapeutic success (99.4%), compared with ciprofloxacin 21%, cefalexin 41%, and TMP/SMX 31.7%.

Conclusions: Even though ceftibuten has a higher market price than other antimicrobials in Mexico, it can represent possible savings by avoiding the costs associated with undesirable results due to antimicrobial resistance to *E. coli*.

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PALABRAS CLAVE

Infección urinaria;
Evaluación
económica;
Ceftibuteno;
México

Evaluación económica del ceftibuteno en el tratamiento de infecciones no complicadas urinarias en pacientes adultos mexicanos

Resumen

Antecedentes: Las infecciones urinarias son una causa principal de consultas médicas en México. La resistencia antimicrobiana creciente incrementa la morbilidad y los costos.

Objetivo: Realizar una evaluación económica del ceftibuteno como tratamiento de infecciones urinarias no complicadas en adultos desde la perspectiva del sistema de salud privado en México.

Material y métodos: Cohorte de modelo de decisión comparando ceftibuteno con TMP-SMX, ciprofloxacina y cefalexina. Medición de efectividad usando rangos de susceptibilidad locales para *Escherichia coli*. Costos obtenidos de datos oficiales de valores de mercado y convertidos en valores en dólares americanos en 2014. Análisis incremental utilizado para determinar la inversión en ceftibuteno desde la perspectiva del sistema de salud privado en México.

Resultados: Los costos totales por paciente con ciprofloxacina fueron US\$116 mientras que los costos correspondientes con TMP-SMX y cefalexina fueron US\$92.4 y US\$74.8 respectivamente. El ceftibuteno resultó con valor más bajo (US\$34.50) y un alto porcentaje de éxito terapéutico (99.4%) comparado con ciprofloxacina (21%); cefalexina (41%) y TMP-SMX (31.7%).

Conclusiones: El ceftibuteno aun teniendo el valor más alto por unidad en México provee de posibilidad de obtener ahorros evitando costos asociados a resultados indeseables por la resistencia antimicrobiana de *Escherichia coli*.

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Introduction

Urinary tract infections (UTIs) are one of the leading causes of medical consultations by adults in Mexico, especially in sexually active women.¹ The incidence of UTIs has increased more than 500% in Mexico, becoming a public health problem that has put pressure on the national healthcare system.¹ A report published by the Mexican Epidemiology Surveillance System revealed a rising incidence of UTIs from 2004 to 2010. The age group of 25–44 years was the most affected with 1,090,886 cases, followed by the group of 50–59 years of age with 386,584 cases. There were 345,152 cases reported for the population 65 years of age and older.¹

Common symptoms of cystitis are dysuria, urinary frequency and/or pollakiuria,² but inappropriate management can result in the complication of pyelonephritis. The impact of UTIs on patient work activities and quality of life makes them a matter of public health.³

UTI treatment

Antimicrobial therapy is central in UTI management and essential for preventing the involvement of the renal parenchyma.⁴ Choosing antibiotics entails factors that must be considered, such as their in vitro activity against the most prevalent uropathogens, urinary concentrations of the chosen antibiotics, the possibility of sub-optimal concentrations, effects of the antibiotic on the vaginal and gastrointestinal flora, adverse events, and the cost of the therapy.

Most antibiotics reach high concentrations in urine, above the minimum inhibitory concentration for

common uropathogens, which will influence treatment effectiveness.⁵

Patterns of antimicrobial resistance

Antimicrobial resistance is a growing global concern because of increased morbidity and mortality, and the consequent rising cost. It is a multifactorial phenomenon caused by the unnecessary use of antibiotics and treatment discontinuation.⁶

In Mexico, *Escherichia coli* is the most prevalent bacteria in ambulatory patients, causing 70–95% of the cases, followed by *Staphylococcus saprophyticus* (5–20%), *Klebsiella pneumoniae* and *Proteus mirabilis* (5–20%).⁷

Studies published over the last decade have reported patterns of in vitro bacterial resistance of *E. coli* strains to amoxicillin-clavulanate, ampicillin-sulbactam, cefuroxime, trimethoprim sulfamethoxazole (TMP-SMX), and fluoroquinolones. This resistance pattern involves most of the oral antimicrobials available in Mexico, limiting treatment to ambulatory UTI patients.^{7,8} Other studies have found that TMP-SMX administered 3–6 months prior to the occurrence of a new UTI increases the risk of antibacterial resistance 2.5- to 5-fold, similar to the risk of other factors such as recent hospitalization and diabetes.^{9,10}

Within the framework of these rates of antimicrobial resistance, recent studies have shown that the percentage of resistance of *E. coli* to TMP-SMX in a given community is greater than 22% and empirical therapy with fluoroquinolones would be less expensive than TMP-SMX. However, resistance to fluoroquinolones has increased in the last decade in other countries.¹¹ A specific concern for the present authors is that the Mexican Clinical

Guidelines include fluoroquinolones for UTI treatment.¹ Empirical treatment with TMP-SMX and/or fluoroquinolones would cause 50–60% in vitro antimicrobial resistance with a great potential for clinical failure.¹²

Treatment duration has been another concern in relation to antimicrobial coverage in UTIs. For example, TMP-SMX treatment has been recommended for a 3-day period in some studies, but it would be unhelpful due to the high level of bacterial resistance.^{13,16}

The antimicrobial activity of ceftibuten¹⁴ was originally determined for a wide variety of bacterial species selected for their resistance to oral and parenteral β -lactam antibiotics. Ceftibuten turned out to be an active β -lactam antibiotic against *Enterobacteriaceae* strains because it inhibits 81.6% of the strains to $\leq 8.0 \mu\text{g/mL}$, compared with 75% and 54.8% of the strains inhibited by cefixime and cefuroxime, respectively.

A study in a Mexican population on in vitro antimicrobial susceptibility of gram negative microorganisms related to UTI showed that ceftibuten and netilmicin had the greatest activity against *E. coli*, *Klebsiella* spp., *Proteus* spp., *Serratia* spp., *Morganella morganii*, *Enterobacter*, and *Citrobacter* spp. Antimicrobials with the lowest activity were TMP-SMX, ciprofloxacin, amikacin, and levofloxacin.¹⁵

Economic impact of antimicrobial resistance

The irrational use of antibiotics threatens public health safety because of an increased rate of drug resistance. Before 2008, only 15% of the treatments in Mexico involved the prescription of antibiotics by a physician and it was a known fact that around 80% of the prescriptions were given out by pharmacy employees.¹⁶

Since 2008, the Mexican health authorities highlighted the problem of antimicrobial resistance, regulating the antibiotic markets by making the purchase of antibiotics possible only when prescribed by a physician.¹⁶

Antimicrobial resistance translates into substantial financial burden for the healthcare system, as well as significant morbidity for the patients.¹⁶ Ceftibuten is a good option for the treatment of UTIs due to its lack of resistance. On the other hand, it has a higher market price, compared with other options, making it necessary to assess its cost-effectiveness. Thus, the aim of this study was to perform an economic evaluation of ceftibuten for the treatment of uncomplicated UTIs in adults, from the perspective of the private healthcare system in Mexico.

Methods

Study design

This study was conducted following the international Good Research Practices recommendations for cost-effectiveness analysis in healthcare.¹⁷ The analysis was developed simulating a hypothetical cohort of adult men and women with uncomplicated UTI belonging to the Mexican private healthcare system. Four treatment strategies were considered for the management of uncomplicated UTIs in an outpatient setting according to relevant options for decision makers in private local markets: (1) TMP-SMX 160/800 mg;

Table 1 Clinical parameters used in the decision model.

Clinical parameters	Values	
	Basal	Variation ^c
<i>E. coli</i> susceptibility		
Ceftibuten	99.36% ^a	94.39–100%
Cefalexin	41% ^a	38.9–43%
Ciprofloxacin	21% ^a	19.9–22%
TMP/SMX	31.7% ^a	30.11–33.28%
<i>Other parameters</i>		
Pyelonephritis risk	0.05 ^b	0.045–0.055
Hospitalization risk	0.20 ^b	0.18–0.22
% Antibiotic switch for persistent infection	75% ^b	67.5–82.5%

^a Barriga et al.¹⁷

^b Le and Miller.¹⁸

^c $\pm 5\%$ from basal value.

(2) ciprofloxacin 500 mg; (3) cefalexin 500 mg, and (4) ceftibuten 400 mg. Treatment duration was decided by the authors according to drug presentations, which were a box with 14 tablets (1 BID for 7 days), a box with 12 capsules (1 BID for 6 days), a box with 20 tablets (1 BID for 10 days), and a box with 5 capsules (1 QD for 5 days), respectively.

Study setting and population

It was assumed that once a diagnosis of uncomplicated UTI was made, outpatient therapy with the mentioned antimicrobials would be considered, and one of the therapeutic options must be chosen. Since *E. coli* is the main causal agent of UTIs (>80%) in the Mexican population, it was assumed that the therapeutic response of the antibiotics under comparison was a function of *E. coli* susceptibility to them. Susceptibility rates of *E. coli* to different antimicrobials reported by Barriga et al.¹⁵ were used to model the expected UTI resolution or the persistence of UTI symptoms. That trial included 1200 bacterial isolations obtained sequentially during six months from adult outpatients with clinical symptoms of uncomplicated UTI and positive urine culture, having received ambulatory care. Table 1 shows all the clinical parameters used in the model and the corresponding data sources.¹⁸

Decision model

We developed a decision tree model (Fig. 1) to simulate possible outcomes of uncomplicated UTI treated either with TMP-SMX, ciprofloxacin, cefalexin, or ceftibuten, based on a model previously published by Le and Miller.¹⁸ We modeled the following clinical outcomes: UTI resolution or persistent UTI symptoms. Unresolved UTI could derive into pyelonephritis requiring either inpatient or outpatient treatment, or only persistent infection which could give rise to two possible situations: extended treatment according to urine culture or an empirical antibiotic switch. Successful treatment meant that a patient was clinically cured. A time

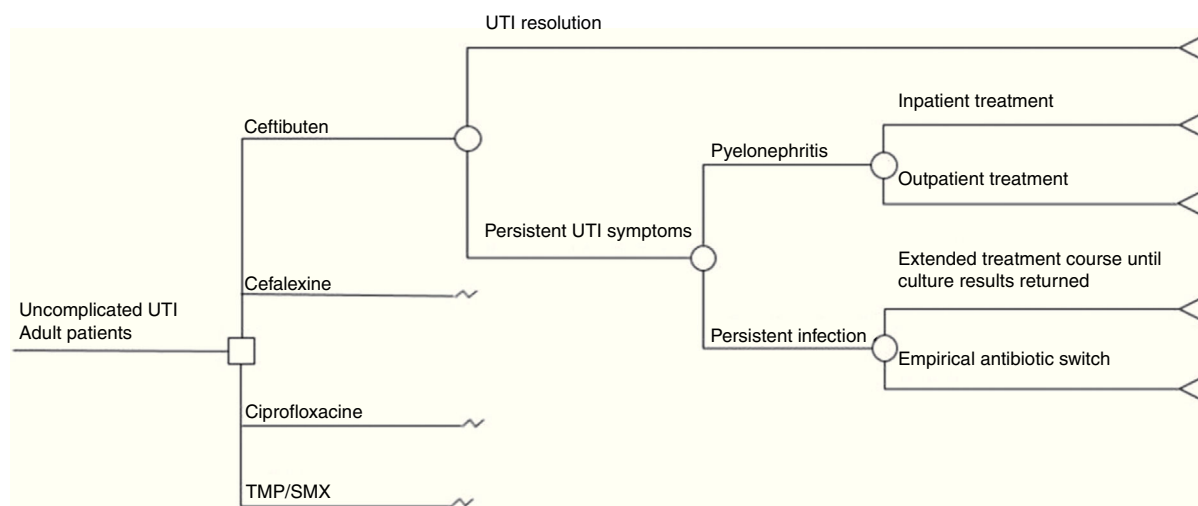


Figure 1 Analytical decision tree model used for the economic evaluation of ceftibuten.

frame less than one year was used in the model, based on the natural history of disease in UTIs.

Model assumptions

The model assumed that there were no fatal events from acute pyelonephritis following a real-life scenario and that there were no recurrences of acute pyelonephritis either. When patients were treated for uncomplicated UTI with TMP-SMX, ciprofloxacin, or cefalexin, and there was persistent infection, the antibiotic was empirically switched to ceftibuten. In turn, if infection persisted after the initial treatment with ceftibuten, the change was made to another option.

Costs

From the perspective of the Mexican private healthcare system, the data on direct medical costs were collected and converted to 2014 U.S. dollars (USD) (Table 2), including the costs of antibiotic therapies, laboratory tests, ultrasounds, hospital stay/day, emergency room (ER) visits, and office visits. The costs of antibiotic therapies were obtained from the market wholesale drug prices. The unit costs of other medical inputs were obtained from the National Institute of Statistics and Geography (INEGI for its Spanish acronym) website.¹⁹ The estimation of inpatient treatment cost of pyelonephritis was made assuming the use of the following resources: ceftriaxone IV 2g daily (unit price: \$41.11 USD; 10-day treatment: \$822.22 USD), 5 hospital days (\$660.56 USD), one ER visit (\$76.14 USD), one office visit (\$33.71 USD), and the following tests: urinalysis, urine culture, chemistry test, blood count, and ultrasound (\$124.71 USD). The total cost of inpatient treatment of pyelonephritis was \$1717.35 USD. The cost of outpatient treatment of pyelonephritis (\$946.93 USD) was estimated using the same amount of resources as with the inpatient scenario, except for hospital stay and ER visit. Costs were not discounted in our analysis because the time horizon used was less than one year.

Table 2 Costs data used in the decision model.

Economic parameters	Values	
	Basal	Variation
<i>Mean prices (US\$) of antimicrobials under comparison</i>		
Ceftibuten	33.76	4.82
Cefalexin	5.19	1.19
Ciprofloxacin	22.79	2.79
TMP/SMX	11.71	1.22
<i>Other inputs (USD)</i>		
		<i>Min–Max</i>
Urine culture	23.53	21.18–25.88
Urinalysis	7.90	5.99–9.81
Blood chemistry	23.65	15.19–32.11
Blood count	17.02	11.18–22.86
Ultrasound	52.61	47.35–57.87
Inpatient day	132.11	91.87–172.35
ER visit	76.14	68.53–83.75
Office visit	33.71	29.55–37.88
Ceftriaxone ^a	41.11 ^b	3.22 ^c

^a Antimicrobial used for the treatment of pyelonephritis.

^b Mean value.

^c Standard deviation.

Effectiveness measure

Since therapeutic response was based on susceptibility rates of *E. coli* to the antimicrobials being compared, the effectiveness measure modeled was the expected percentage of patients cured of uncomplicated UTI with the antimicrobials analyzed.

Base-case analysis

To determine whether ceftibuten would be a worthwhile investment for the treatment of uncomplicated UTI, we performed the standard incremental analysis of cost-effectiveness ratios using spreadsheets. As a decision rule

Table 3 Base-case results per treated patient.

Options	Total expected cost (USD)	Incremental cost (USD)	Expected % of cured patients	Incremental cost-effectiveness ratio
Ceftibuten	34.50		99.4	Dominant
Cefalexin	74.85	40.35	41.0	Dominated
Ciprofloxacin	116.06	81.56	21.0	Dominated
TMP/SMX	92.43	57.93	31.7	Dominated

to know if the treatment with ceftibuten was cost-effective in relation to the Mexican private healthcare system, we used the cost-effectiveness threshold of one gross domestic product (GDP) per capita per additional health benefit unit, which is generally accepted in Mexico by the health authorities.

Sensitivity analysis

In order to embody the uncertainty of the parameters used in the decision model, we conducted several one-way sensitivity analyses. Basal values of clinical and economic

parameters were varied throughout plausible ranges as shown in [Tables 1 and 2](#).

Results

Base-case results

The total expected costs per treated patient for each therapeutic option, as well as the expected percentage of cured patients, are shown together in [Table 3](#). We can see that ceftibuten exhibits the lower cost and also the higher percentage of therapeutic success compared with the rest of

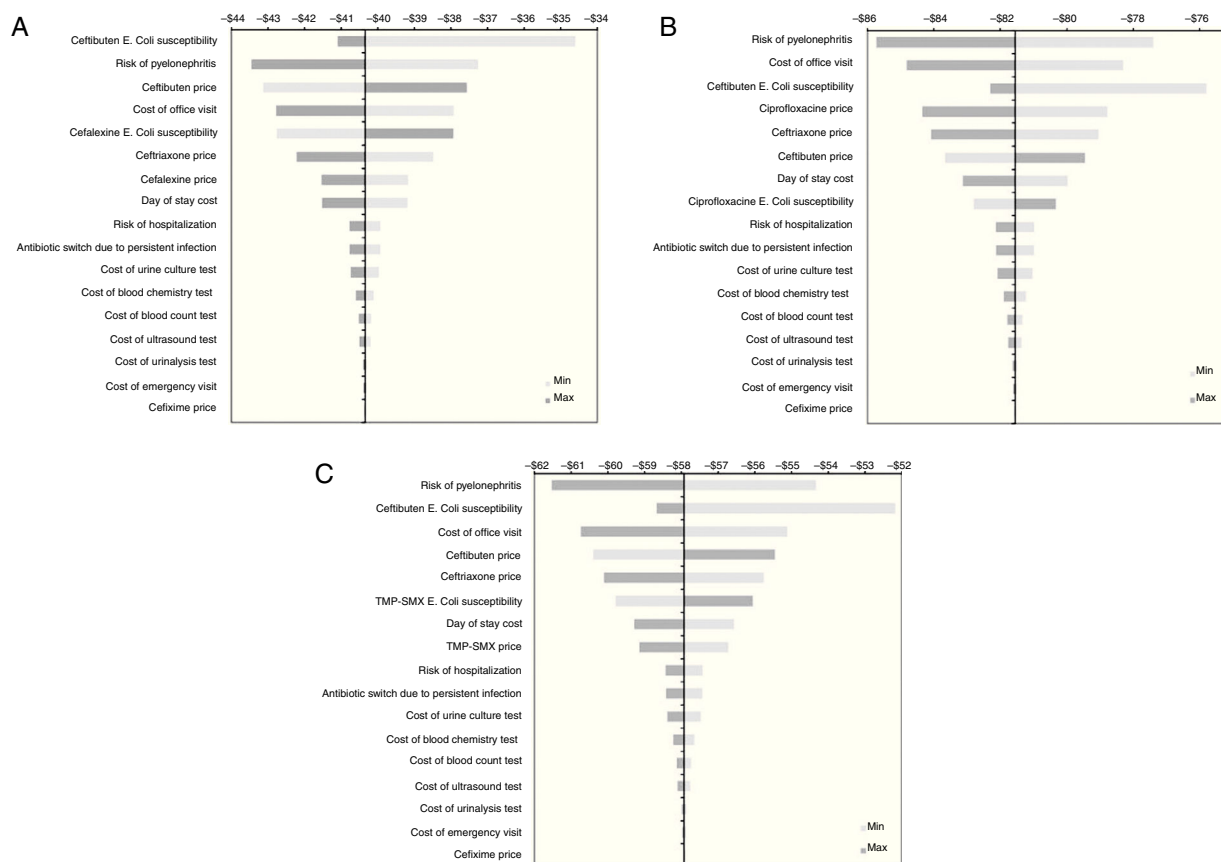


Figure 2 Results of univariate sensitivity analysis of the economic evaluation of ceftibuten. Results of univariate sensitivity analyses are shown by means of tornado diagrams formed by horizontal bars. The name of these types of diagrams comes from the fact that parameters with high uncertainty are located at the top of the diagram, so the parameter with less uncertainty is located at the bottom. Tornado A shows the results for the comparison between ceftibuten and cefalexin. Tornados B and C show the results for the comparison between ceftibuten and ciprofloxacin, and ceftibuten and TMP/SMX, respectively.

the antibiotics. Using the jargon of pharmacoeconomics, we can state that ceftibuten is a 'dominant' option compared with other options, since it is more effective and less costly. Furthermore, under a dominant scenario like that shown for ceftibuten, decision makers do not need any additional analysis, such as the calculation of incremental cost-effectiveness ratios, to know that the dominant therapy (ceftibuten) represents 'good value-for-money'.

Since ceftibuten turned out to be a dominant strategy for the treatment of uncomplicated UTI, the economic analysis must focus on the expected savings per patient treated with ceftibuten, instead of the other three options. Comparison between ceftibuten and ciprofloxacin resulted in a higher savings per patient treated (Table 3), followed by the comparison between ceftibuten and TMP/SMX.

Sensitivity analysis results

Given that the relevant base-case results were focused on savings gained with ceftibuten, hence the objective of the one-way sensitivity analyses was to assess the robustness of the model in terms of expected savings. Fig. 2 shows a series of tornado diagrams represented by means of horizontal bars, from the widest to the narrowest, expressing different degrees of uncertainty from the parameter values into the base-case results. We can see that although some parameters embodied a high degree of uncertainty, the results did not change the dominant profile of ceftibuten.

Discussion

The pharmacoeconomic analysis informs key decision makers about the economic bearings associated not only with the price of the drugs, but also with all the relevant outcomes expected from the use of either therapeutic options. These results enabled us to conclude that despite the fact that ceftibuten has the highest unit market price in Mexico, it can still represent savings, when compared with the other drugs analyzed, by avoiding the costs associated with undesirable outcomes caused by the antimicrobial resistance of *E. coli*, the most prevalent causal agent of uncomplicated UTI in Mexico.

In order to aid the decision-making process with good evidence, the limitations of this study should be mentioned. The bacterial resistance data were obtained from only one source that analyzed in vitro strains from uncomplicated UTI patients from a single healthcare center in Mexico. In addition, information about the resources used was obtained from a review of the Mexican Clinical Guidelines for UTI in order to model the usual treatment path. Another limitation was the simplification of the decision model under a local frame of limited information, although it was driven by broader assumptions in order to facilitate the assessment of therapies. However, the international principles of good practice in pharmacoeconomic research were always followed to enhance the transparency and reproducibility of the results.

Future research will be needed to know if the use of ceftibuten for the treatment of uncomplicated UTI in the Mexican population will modify the antimicrobial resistance patterns of *E. coli*. This will also have economic

consequences, since the expected rate of therapeutic success or failure under a new environment of antimicrobial resistance could represent a different disease burden for the patients, healthcare providers, and payers. For now, the management of uncomplicated UTIs with ceftibuten is a good value-for-money from the perspective of the patients directly paying for the treatment, but also for third party payers, such as the private insurance companies.

Conclusions

Private healthcare systems in Mexico should evaluate current interventions for treatment of uncomplicated UTI that are cost-effective from the resistance perspective. We believe our analysis shows that ceftibuten, previously not fully considered, could be cost-effective. We support the performance of prospective new interventions that would challenge and compare current practice strategies.

Ethical responsibilities

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Financial disclosure

An unrestricted grant was received from Merck Sharp & Dohme Mexico.

Conflict of interests

Alfonso Reyes-Lopez has participated as a speaker bureau member and as a consultant for Merck & Co. He works at RCEI Consulting SC, a consulting business, as Research Director.

Virginia Blandón-Vijil is an employee of Merck & Co. Inc. and can own stock or stock options in the company.

References

1. Secretaría de Salud Guía de práctica clínica. Diagnóstico y tratamiento de pielonefritis aguda no complicada en el adulto. México; 2010.
2. Secretaría de Salud. guía de práctica clínica. Diagnóstico y tratamiento de la infección aguda, no complicada del tracto urinario en la mujer. México; 2008.
3. Ellis AK, Verma S. Quality of life in women with urinary tract infections: is benign disease a misnomer? *J Am Board Fam Pract.* 2000;13:392–7.
4. Hooton TM, Stamm WE. Diagnosis and treatment of uncomplicated urinary tract infections. *Infect Dis Clin North Am.* 1997;11:551–81.
5. García-Rodríguez JA, Muñoz Bellido JL, García Sánchez JE. Oral cephalosporins: current perspectives. *Int J Antimicrob Agents.* 1995;5:231–43.

6. Gallardo Luna MG, Magaña Aquino M, Andrade Rodríguez HJ, et al. Resistencia a fármacos empleados en infección de vías urinarias en pacientes de primer contacto en una Unidad de Medicina Familiar del IMSS. *Enf Inf Microbiol*. 2008;28:13–8.
7. Chávez-Valencia V, Gallegos-Nava S, Arce-Salinas CA. Patrones de resistencia antimicrobiana y etiología en infecciones urinarias no complicadas. *Gac Med Méx*. 2010;146:269–73.
8. Ronald AR. The etiology of urinary tract infection: traditional and emerging pathogens. *Dis Mon*. 2002;49:71–82.
9. Goldstein FW. Antibiotic susceptibility of bacterial strains isolated from patients with community-acquired urinary tract infections in France. *Eur J Clin Microbiol Infect Dis*. 2000;19:112–7.
10. Chomarat M. Resistance of bacteria in urinary tract infections. *Int J Antimicrob Agents*. 2000;16:483–7.
11. Sanchez GV, Master RN, Karlowsky JA, et al. In vitro antimicrobial resistance of urinary *Escherichia coli* isolates among U.S. outpatients from 2000 to 2010. *Antimicrob Agents Chemother*. 2012;56:2181–3.
12. <http://www.facmed.unam.mx/deptos/microbiologia/bacteriologia/enfermedades-vias-urinarias.html> [accessed 13.08.15].
13. Pohl A. Modes of administration of antibiotics for symptomatic severe urinary tract infections. *Cochrane Database Syst Rev*. 2007:CD003237, <http://dx.doi.org/10.1002/14651858.CD003237.pub2>.
14. Jones RN, Barry AL. Antimicrobial activity, spectrum, and recommendations for disk diffusion susceptibility testing of ceftibuten (7432-S; SCH 39720), a new orally administered cephalosporin. *Antimicrob Agents Chemother*. 1988;32:1576–82.
15. Barriga Angulo G, Mercado González NF, Arumir Escorza C. Susceptibilidad antimicrobiana in vitro de 1200 microorganismos gramnegativos causales de infecciones de vías urinarias. *Enf Inf Microbiol*. 2008;28:90–8.
16. Dreser A, Wirtz VJ, Corbett KK, et al. Uso de antibióticos en México: revisión de problemas y políticas. *Salud Pública de México*. 2008;50:S480–7.
17. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health*. 2013;16:231–50.
18. Le TP, Miller LG. Empirical therapy for uncomplicated urinary tract infections in an era of increasing antimicrobial resistance: a decision and cost analysis. *Clin Infect Dis*. 2001;33:615–21.
19. <http://www.inegi.org.mx/sistemas/preciospromedio.inpc> [accesses 13.08.15].