Cost-effectiveness of ceftolozane/tazobactam for the treatment of complicated intraabdominal and urinary tract infections in Colombia

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Abstract
Objective: To evaluate the cost-effectiveness of ceftolozane/tazobactam + metronidazole (C/T+M) and ceftolozane/tazobactam (C/T) compared with 8 alternatives used in the treatment of complicated intraabdominal infection (CIAI) and complicated urinary tract infection (CUTI) respectively.

Methods: A Monte Carlo simulation decision model was used for the estimation and comparison of treatment-related costs, and quality adjusted life years for patients with CIAI treated with C/T+M in comparison with cefepime + metronidazole, ciprofloxacin + metronidazole, doripenem, levofloxacin + metronidazole, meropenem, piperacillin/tazobactam, ceftazidime + metronidazole or imipenem/cilastatin and patients with CUTI treated with C/T in comparison with cefepime, ciprofloxacin, doripenem, levofloxacin, meropenem, piperacillin/tazobactam, ceftazidime or imipenem/cilastatin. Local costs were estimated using base cases identified by experts and consulting local databases. Sensitivity values of the PACTS (Program to Assess Ceftolozane/Tazobactam Susceptibility) study in Latin America were used in the model.

Results: C/T+M and C/T obtained incremental cost-effectiveness ratios (ICER) that were below the Colombian cost-effectiveness threshold (3 GDP per capita) in most comparisons, and were dominated by meropenem, considering only gram-negative microorganisms. Sensitivity assessments were also carried out, in which only the population with P. aeruginosa infections was considered, showing positive results for C/T+M and C/T (cost-effective or dominant with regards to all comparators).

Conclusions: C/T+M and C/T could be cost-effective alternatives in the treatment of CIAI and CUTI in Colombia, when there is an adequate and rational use of antibiotics. The results of the sensitivity analyses showed dominance and cost-effectiveness with regards to every comparator in patients infected with P. aeruginosa.

Keywords: Ceftolozane; Tazobactam; cost-effectiveness; urinary tract infections; intraabdominal infections

Costo-efectividad de ceftolozano/tazobactam para el tratamiento de las infecciones intraabdominales e infecciones del tracto urinario complicadas en Colombia

Resumen
Objetivo: Evaluar la costo-efectividad de ceftolozano/tazobactam + metronidazol (C/T + M) y ceftolozano/tazobactam (C/T) en comparación con 8 alternativas utilizadas en el tratamiento de las infecciones intraabdominales complicadas (IAAC) e infecciones del tracto urinario complicadas (ITUc) respectivamente.

Métodos: Se usó un modelo de decisión de simulación de Monte Carlo para la estimación y comparación de los costos relacionados con el tratamiento y los años de vida ajustados por calidad para pacientes con IAAC tratados con C/T + M, en comparación con cefepime + metronidazol, ciprofloxacina + metronidazol, doripenem, levofloxacina + metronidazol, meropenem, piperacilina / tazobactam, ceftazidima + metronidazol o imipenem/cilastatina, y pacientes con ITUc tratados con C/T en comparación con cefepime, ciprofloxacina, doripenem, levofloxacina, meropenem, piperacilina / tazobactam, ceftazidima o imipenem/cilastatina. Los costos locales se estimaron por medio de casos base identificados por expertos y consultando bases de datos locales. Se utilizaron los valores de sensibilidad bacteriana del estudio PACTS (Programa para evaluar la susceptibilidad al ceftolozano/tazobactam) en América Latina para poblar el modelo.

Resultados: C/T + M y C/T obtuvieron razones de costo-efectividad incrementales (RCEI) que estaban por debajo del umbral de costo-efectividad colombiano (3 PIB per cápita) en la mayoría de las comparaciones, y fueron dominados por meropenem, considerando solo microorganismos gran-negativos. También se llevaron a cabo análisis de sensibilidad, en los que solo se consideró la población con infecciones por P. aeruginosa, mostrando resultados positivos para C/T + M y C/T (costo efectivo o dominante con respecto a todos los comparadores).

Conclusiones: C/T + M y C/T podrían ser alternativas costo efectivas en el tratamiento de IAAC e ITUc en Colombia, cuando existe un uso adecuado y racional de antibióticos. Los resultados de los análisis de sensibilidad mostraron dominio y costo-efectividad en relación con todos los comparadores en pacientes infectados con P. aeruginosa.

Palabras clave: Cefotolozano; Tazobactam; rentabilidad; infecciones del tracto urinario; infecciones intraabdominales

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Recibido: 11/05/2018; Aceptado: 24/02/2019
Cómo citar este artículo: F. Hernández, et al. Cost-effectiveness of ceftolozane/tazobactam for the treatment of complicated intraabdominal and urinary tract infections in Colombia. Infectio 2020; 24(1):9-23
Introduction

Intra-abdominal infections (IAI) encompass a wide spectrum of pathological alterations that can be defined as the peritoneal response to the infectious process. They are an important cause of morbidity and mortality and represent the second most common cause of severe sepsis in intensive care units. Complicated intra-abdominal infections (cIAI) extend beyond the affected organ towards the peritoneal space so they are generally associated to diffuse or localized peritonitis. Treatment of these patients requires an adequate control of the infected focus and antibiotic treatment, with the purpose of avoiding spread of the infection.

On the other hand, urinary tract infections (UTI) are among the most common types of infections in clinical practice, with greater prevalence and incidence in women due to the short distance between the urethra and the vaginal opening. Complicated UTI (cUTI) are associated to factors that compromise the host’s immunologic response or the physiology of the urinary tract, such as renal failure, immune suppression, kidney stones, kidney transplant, and others.

The most commonly used antibiotics in the empiric therapy of cIAI are beta-lactam antibiotics due to their wide spectrum and low rate of resistance. According to different studies carried out in Colombia, the most used antibiotics for the treatment of UTI are: ciprofloxacin, ampicillin/sulbactam, nitrofurantoin and trimetoprim/sulfamethoxazole, out of which nitrofurantoin is the antibiotic to which isolated cultures present a higher susceptibility.

However, extended use of wide spectrum antibiotics has increased bacterial resistance during the last decade, decreasing therapeutic options; the need of new therapeutic alternatives has become even more important. Ceftolozane/tazobactam (C/T) is a new cephalosporin associated to a beta-lactam inhibitor that has shown activity in strains that produce extended spectrum beta-lactamases (ESBL) and has proven to be stable to the most common resistance mechanisms to Pseudomonas aeruginosa such as: overexpression of efflux pumps and closing of porins. In Colombia, C/T is approved in combination with metronidazole (M) for the treatment of cIAI caused by the following Gram positive and Gram negative microorganisms: P. aeruginosa, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius. It is also approved for the treatment of complicated urinary tract infections including pyelonephritis caused by the following organisms: P. aeruginosa, E. coli, K. pneumoniae and P. mirabilis.

The objective of this study is to estimate the cost-effectiveness of C/T + M in the treatment of cIAI and C/T in cUTI from the perspective of the Colombian health system.

Methods

Target population and perspective: The population considered in this evaluation are adult patients with a diagnosis of cIAI and cUTI. This evaluation was carried out from a third party payer perspective (Colombian health system).

Comparators: In the case of cIAI, intervention was C/T combined with metronidazole (C/T+M), as approved in the Colombian regulatory agency. Comparators were cefepime + metronidazole, ceftazidime + metronidazole, meropenem, doripenem, imipenem/cilastatin, piperacillin/tazobactam, ciprofloxacin + metronidazole and levofloxacin + metronidazole.

For cUTI, intervention was C/T and comparators were cefepime, ceftazidime, meropenem, doripenem, ertapenem, imipenem/cilastatin, piperacillin/tazobactam, ciprofloxacin and levofloxacin.

Time horizon and discount rate: The time horizon for this economic evaluation was defined as the patient’s life expectancy, considering that the long-term consequences of an acute event would be modeled (including mortality). A 5% discount rate was considered for costs and utilities, according to the recommendations of IETS, the Colombian health technology assessment agency. The use of a life expectancy time horizon is reasonable in this model, since one of the outcomes included was death due to infection and this event has repercussions in QALY lost due to premature death.

Efficacy measurements and outcomes: The individual patient antibiograms results reported in the PACTS (Program to Assess Ceftolozane / Tazobactam susceptibility) study in Latin America were used as the efficacy measurement. This study measured antimicrobial sensitivity of 2,415 isolated gram-negative bacillus gathered in 12 centers in 4 countries in Latin America (Brazil, Chile, Argentina, and Mexico), between January 1, 2013 and December 31, 2015. Only data from 2015 were used. Infections considered were: blood infections, pneumonia associated to health care, skin infections, intra-abdominal infections, urinary tract infections, and other infections.

Outcomes are expressed in quality-adjusted life years (QALY) that allow to combine the impact of each technology on target population’s quality of life and life expectancy. The utility measurement for survivors in each infection was extracted from Senekjian et al. and Thomas et al. for cIAI and cUTI respectively.

Analytic Model: A Monte Carlo simulation decision model was used for a hypothetical cohort of 1,000 patients in each indication. For cUTI, the patient enters the model after diagnosis, and begins to receive empiric treatment while urine samples are taken for culture. The culture is then assessed to see whether the microorganism is sensitive to the empiric therapy or not. If it is sensitive, the patient may continue with the initial empiric therapy or be de-escalated to the less costly alternative to which the microorganism is sensitive.
Otherwise, the patient will be escalated to the sensitive therapy with the lower cost. In any case, the patient ends up either healed or deceased. As for the cIAI case, the patient follows the same path as for the cUTI. If the patient is a non-responder, imaging analyses and surgical procedures may be considered, ending up in healing or death; if the patient responds to the therapy they may also heal or die. Figure 1 shows the analytical models used. Model parameters values are summarized in Table 1.

**Model assumptions:** The patient will always be de-escalated from the adequate empiric therapy, when there is a less expensive appropriate alternative. Microbial sensitivity to each antibiotic found in the countries included in the PACTS study is similar to the one of Colombian infections isolates (Table S1). There are no differences in the response to antimicrobial therapy, mortality, and length of inpatient stay between men and women.

**Resource use estimation and costs:** The resources used to treat each condition were identified through an expert consultation. Resource cost estimation was carried out using local tariff manuals and databases, according to the recommendations of the Colombian technology assessment agency. Table 2 summarizes the estimated costs for this evaluation.

![Figure 1](image.png)

**Figure 1.** Decision models used in the evaluation. A). Model used in cIAI. B). Model used in cUTI.
Sensitivity analyses: The impact of some parameters on the final results was assessed through one-way and probabilistic sensitivity analyses (supplementary material). Additionally, another sensitivity analysis was carried out, considering only *P. aeruginosa* isolates.

**Results**

C/T+M was a cost-effective option for the empiric treatment of cIAI in the base case compared to cefepime + metronidazole, ceftazidime + metronidazole, ciprofloxacin + metronidazole, levofloxacin + metronidazole, piperacillin/tazobactam, doripenem and imipenem cilastatin, under the of 3GDP per capita for 2017 (18,609 USD; 1 USD = 2,984.5 COP) and is dominated by meropenem in the base case. Likewise, C/T resulted to be a cost-effective option compared with cefepime, ceftazidime, levofloxacin and piperacillin/tazobactam (Supplementary material). Also, when only information from the *P. aeruginosa* isolates was used, the technology was found to be cost-effective or dominant against all comparators in both indications. These results are shown in Table 4.

**Discussion**

C/T+M and C/T resulted to be cost-effective alternatives with regards to most comparators for the empiric treatment of cIAI and cUTI, respectively. Even though meropenem was dominant compared with C/T+M and C/T, the difference in utilities and costs between the two alternatives was small. Univariate sensitivity analyses showed that the variation in antibiotic resistance increases, in the range upper limit, the difference in efficacy between the compared alternatives. The sensitivity analysis considering only patients with *P. aeruginosa* isolates showed that C/T + M ends up being cost-effective in comparison to meropenem and cost-saving in comparison with doripenem and imipenem cilastatin. In any case, these results seem to indicate that C/T+M and C/T are valid options for the empiric treatment of patients with cIAI and cUTI, respectively.
In general, the comparators selected for this assessment are not common comparators used in other investigations\textsuperscript{15-17}, taking into account that many of the alternatives evaluated in this study are not considered first choice options in the treatment of cUTI. However, according to the spectrum and the place that C/T will occupy in the therapeutic arsenal for the treatment of cUTI, the evaluated alternatives can be considered reasonable comparators. Likewise, some studies use clinical healing rates directly derived from clinical trials as efficacy measure, which can result in different conclusions for one same comparison\textsuperscript{18-20}.

On the other hand, Kauf et al., (2017)\textsuperscript{21} and Prabhu et al., (2017)\textsuperscript{22} used a similar approach to evaluate the cost-effectiveness of C/T versus piperacillin/tazobactam as initial empiric therapy for the treatment of cUTI and cIAI, respectively, in the United States, obtaining similar results to those of this study.

The main strength of this study is the use of real-world data in the Monte Carlo simulation to model resistance profiles and treatment strategies for cIAI and cUTI. However, the de-escalation assumption to the less costly alternative in all the patients is perhaps one of the model's limitations, since it is slightly distant from the real clinical practice. Even though this can be reasonable practice, it is not necessarily done automatically and in all patients. The use of resistance percentages as a success measure of the antimicrobial therapy is also part of the consideration of the therapeutic response, but it can depend on other factors also. Another potential limitation is the use of Latin American antibiograms, but not Colombian, for this assessment. Considering the importance of the resistance of microorganisms in the sensitivity analysis, a point for future research could be the implementation of Colombian isolate data to improve the reliability of the results.

The calculation of ICER for uncertainty scenarios suggested in the univariate sensitivity analysis shows consistency in the results obtained in the base cases, since in all variations applied, intervention with C/T+M and C/T continue to be a cost-effective alternative with regards to non-carbapenem comparators. In the case of the comparison with carbapenems, ICER showed to be highly sensitive to the variation in the antibiotic resistance, making C/T+M and C/T be dominated in some cases. According to the information included in the model, the variation of the antibiotic resistance has a marked impact on the total QALYs of the entire cohort, in contrast with the minimal change in the cohort's total cost. In the case of the probabilistic sensitivity analysis, for comparisons regarding non-carbapenem alternatives, the simulations are under the cost-effectiveness threshold for the Colombian context.

As for the sensitivity analysis, considering only the population infected by \textit{P. aeruginosa}, the rationale of this scenario is the available evidence indicating that microorganisms of this genus are prevalent in Colombian cIAI isolated elements\textsuperscript{23} and cUTI\textsuperscript{24}. Taking this into account, it is reasonable to assume that there is a population niche where CZT+M and C/T are cost-effective with regards to all comparators. Likewise, according to the model design and the assumptions used, C/T+M and C/T are cost-effective alternatives when antibiotics use is carried out in a rational way.

| Table 2. Hospitalization, surgical and imaging procedures costs for each infection. Costs in USD |
|-----------------------------------------------|----------------|----------------|----------------|---------------|----------------|----------------|
| Infection | Parameter | Base case | Sensitivity analysis | Distribution | Source |
|-----------|-----------|------------|----------------------|-------------|--------|
|           |           |            | Upper | Lower | Gamma | Experts and tariff manual |
| cUTI      | Hospitalization cost per day | $271 | $217 | $320 | Gamma | Experts and tariff manual |
|           | Imaging procedures cost per patient | $39 | $31 | $47 | Gamma | Experts and tariff manual |
| cIAI      | Hospitalization cost per day | $272 | $217 | $327 | Gamma | Experts and tariff manual |
|           | Surgical procedures cost per patient | $199 | $160 | $239 | Gamma | Experts and tariff manual |
|           | Imaging procedures cost per patient | $95 | $76 | $114 | Gamma | Experts and tariff manual |

| Table 3. Base case results of the cost-effectiveness analyses for C/T vs. comparators in cIAI and cUTI. *Combined with metronidazole in cIAI. 1000 patients simulated cohort results are shown. Costs in USD |
|-----------------------------------------------|----------------|----------------|----------------|---------------|----------------|----------------|
| Antibiotic | cUTI | cIAI | | | | |
| Incremental cost (USD) | Incremental effectiveness (QALY) | Incremental effectiveness ratio (USD/QALY) | Incremental cost (USD) | Incremental effectiveness (QALY) | Incremental effectiveness ratio (USD/QALY) |
| Ceftolozane/Tazobactam* | - | - | - | - | - |
| Cefepine* | $393,438 | 404.0 | $974 | $96,081 | 327.2 | $294 |
| Ceftazidime* | $479,007 | 317.6 | $1,508 | $313,031 | 256.7 | $1,219 |
| Ciprofloxacin* | $395,185 | 536.6 | $737 | $36,805 | 449,319 |
| Doripenem | $318,927 | 61.7 | $5,171 | $347,806 | 50.8 | $6,838 |
| Imipenem/cilastatin | $356,021 | 67.8 | $5,248 | $405,156 | 39.5 | $10,259 |
| Levofloxicin* | $449,319 | 363.9 | $12,255 | $285,428 | 290.5 | $982 |
| Meropenem | $532,806 | -55.5 | Dominated | $749,559 | -50.8 | Dominated |
| Piperacillin/tazobactam | $431,056 | 293.0 | $1,471 | $271,113 | 248.2 | $1,092 |
Table 4. Sensitivity analyses considering only population infected with \textit{P. aeruginosa} in cIAI and cUTI. * Combined with metronidazole in cIAI. 1000 patients simulated cohort results are shown. Costs in USD

| Antibiotic                      | cUTI | cIAI |
|--------------------------------|------|------|
|                                | Incremental cost (USD) | Incremental cost (USD/QALY) | Incremental effectiveness (QALY) | Incremental cost (USD) | Incremental cost (USD/QALY) | Incremental effectiveness (QALY) |
| Ceftriaxone/tazobactam*         | -    | -    | -    | -    | -    | -    |
| Cefepime*                      | $375,204 | 415.6 | $903 | $64,421 | 335.2 | $192 |
| Ceftazidime*                   | $451,179 | 357.6 | $1,262 | $274,559 | 288.6 | $951 |
| Ciprofloxacin*                 | $352,534 | 470.3 | $750 | $108,036 | 396.5 | $273 |
| Doripenem                      | $158,517 | 592.7 | $267 | $-32,174 | 492.9 | Dominant |
| Imipenem/cilastatin            | $205,453 | 567.0 | $362 | $-188,763 | 469.3 | Dominant |
| Levofloxacin*                  | $386,675 | 541.2 | $714 | $42,134 | 454.8 | $93 |
| Meropenem                      | $367,708 | 492.9 | $746 | $17,285 | 408.1 | $42 |
| Piperacillin/tazobactam*       | $398,568 | 351.1 | $1,135 | $208,803 | 291.5 | $716 |

Conclusions

C/T+M and C/T are cost-effective alternatives for the empiric treatment of complicated intra-abdominal infections and complicated urinary tract infections, respectively, when there is an adequate escalation and de-escalation of antibiotics. In the sensitivity analyses, the model estimates that C/T+M and C/T are cost-effective with regards to all comparators, when only \textit{P. aeruginosa} isolates are considered.

Ethical disclosure

Protection of human and animal subjects. This research do not use animal nor human material or data.

Confidentiality of data. Not applicable

Conflict of interest statement. The authors received grants from MSD Colombia to perform this study. This work was funded by MSD Colombia, however the authors had complete independency on data acquisition and analysis.

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