Empirical Therapy for Uncomplicated Urinary Tract Infections in an Era of Increasing Antimicrobial Resistance: A Decision and Cost Analysis

Thuan P. Le and Loren G. Miller
Division of Infectious Diseases, Harbor–University of California Los Angeles Medical Center, Torrance, California

Infectious Diseases Society of America guidelines state that uncomplicated urinary tract infections (UTIs) should be treated empirically with trimethoprim-sulfamethoxazole (TMP-SMZ), unless the community resistance among uropathogens exceeds 10%–20%, in which case a fluoroquinolone (FQ) should be used. However, the data to support this threshold are limited. We performed a cost-minimization and sensitivity analysis to determine what level of TMP-SMZ resistance in a community should trigger FQ use. The mean cost of empirical treatment with TMP-SMZ was US$92 when the proportion of resistant *Escherichia coli* was 0%, $106 when it was 20%, and $120 when it was 40%. The mean cost of empirical FQ treatment was $107 at current levels of FQ resistance. When ≥22% of *E. coli* in a community are TMP-SMZ–resistant, empirical FQ therapy becomes less costly than TMP-SMZ therapy. Treatment guidelines for empirical treatment of UTIs may need modification, and the threshold trigger for empirical FQ use should be raised to >20% TMP-SMZ resistance.

Over 7 million uncomplicated urinary tract infections (UTIs [cystitis]) occur every year, contributing nearly $1 billion to health costs in the United States [1]. A variety of antimicrobial agents are efficacious for this condition; however, recent guidelines from the Infectious Diseases Society of America (IDSA) stress use of either trimethoprim-sulfamethoxazole (TMP-SMZ) or a fluoroquinolone (FQ) for empirical treatment of uncomplicated UTIs [2]. Currently, these 2 agents have efficacy superior to that of other available oral antimicrobials such as amoxicillin, first-generation cephalosporins, and nitrofurantoin for the treatment of uncomplicated UTIs [2, 3]. IDSA guidelines recommend that TMP-SMZ should be used for empirical treatment of uncomplicated UTIs, unless the proportion of TMP-SMZ–resistant isolates in the community is >10%–20%, in which case empirical therapy should be switched to an FQ. However, this 10%–20% range is very broad, and there are few published data to support this threshold.

Previous research employing cost-based models of UTI treatment has not addressed the issue of drug-resistant uropathogens. Understanding the impact of drug resistance is of critical importance, because the rates of antimicrobial resistance are continually changing and the prevalence of drug-resistant pathogens has a potentially large impact on the empirical antimicrobial regimen of choice [4, 5].
We have performed a cost-minimization and sensitivity analysis to determine the precise level of TMP-SMZ resistance that should trigger a switch in empirical treatment for uncomplicated UTIs from TMP-SMZ to an FQ. In addition, given potential uncertainties in costs or probabilities inherent in decision analyses [6], we sought to examine which probabilities and costs would most affect the threshold by performing 2-way sensitivity analyses.

**METHODS**

**Decision tree model.** We employed a decision tree model using the DATA software (version 3.5, Tree Age Software). Our model is based on uncomplicated UTIs caused by *Escherichia coli* in women >18 years of age. The model takes a program perspective for determining costs [6, 7]. To obtain information on costs (reported herein in US dollars) and clinical outcomes of uncomplicated UTIs, we performed a systematic review of the literature by searching MEDLINE for articles from 1966 through June 2000 with the key words “urinary,” “urine,” or “cystitis” and crossed these key words with “cost,” “cure,” “success,” “response,” or “efficacy.” We reviewed abstracts, and if an abstract suggested that the article contained data on clinical cure rates of uncomplicated UTIs based on antimicrobial susceptibility, the article was pulled for review. Articles published in non-English languages had only their abstracts reviewed. Clinical response was derived only from prospective clinical trials or investigations. We also contacted representatives from the 3 pharmaceutical firms that manufacture FQs approved for the treatment of UTIs in the United States (Bayer Pharmaceuticals, Ortho-McNeal Pharmaceuticals, and Bristol-Myers Squibb); they provided additional data on rates of clinical response to various antimicrobial agents in cases of uncomplicated UTI.

We based our cost-minimization model on scenarios derived from the systematic review of the literature and clinical experience [2, 3, 8–17]. Our model assumed clinicians would choose to empirically treat uncomplicated UTIs with a 3-day course of either TMP-SMZ or an FQ (figure 1). We assumed that empirical treatment involved a clinic visit and urinalysis to confirm the presence of an uncomplicated UTI and that urine cultures were not performed initially, as recommended by IDSA guidelines [2]. Our model assumed that all infections were ultimately cured, although some treatments for cystitis would initially fail to respond but would later resolve after treatment of a complication (e.g., pyelonephritis) and/or would lead to adverse effects that were subsequently cured (e.g., vaginal yeast infection).

Four main scenarios arose, depending on the agent used and whether the organism had in vitro susceptibility (figure 1). The first subtree examined treatment of a TMP-SMZ–resistant *E. coli* infection with TMP-SMZ, resulting in recovery or initial clinical failure. An initial clinical failure then led to a scenario for a complicated-course outcome. Potential intermediate outcomes included hospitalization for pyelonephritis, outpatient treatment for pyelonephritis, persistence of cystitis symptoms (prompting a return physician visit and performance of a urine culture), and persistence of cystitis symptoms (resulting in a change in antibiotics to an FQ, either before culture results were available [empirical change] or after).

In the second major subtree, we examined the outcomes for a patient treated with TMP-SMZ for infection caused by a TMP-SMZ–susceptible organism using a similar schema. In the third and fourth subtrees, we examined infections caused by an FQ-resistant and an FQ-susceptible organism treated with an FQ. When FQ treatment failed to resolve symptoms, the FQ treatment was either continued until culture results dictated treatment or empirically changed to a regimen aimed against FQ-resistant *E. coli* (see discussion on cost below) for 7 additional days. Not included in figure 1 is the probability of developing a vaginal yeast infection, which was calculated for each outcome. The risk of yeast infection was adjusted to the total duration of antibiotics used to treat the patient [18] and the probability of seeking medical care (as opposed to self-treatment) for vaginitis [19].

**Cost.** Costs used in the decision tree were based on our systematic review of the literature and a survey of local and national costs. For our survey on antibiotic costs, we compiled data in June 2000 from (1) the Red Book price of average wholesale drug prices [20], (2) 2 teaching university hospitals (county-based and community-based), (3) 5 retail pharmacies (Costco, Walgreens, RiteAid, Savon, and Drug Emporium), and (4) 2 Internet pharmacies (1 of which is now defunct) [21–25]. Costs of hospitalization and medical doctor visits were compiled from the literature [26] and a survey of 2 teaching university hospitals. For the cost of an outpatient pyelonephritis treatment, our model assumed that high-dose FQs were used as therapy, except for FQ-resistant *E. coli*, in which case we employed the mean cost of 3 14-day outpatient regimens (ceftixime, 400 mg orally daily; ceftriaxone, 1 g im daily; and gentamicin, 300 mg im daily) [2]. Only costs published during or after 1995 were used to calculate estimates. For each item, we employed mean cost from our sources as the point estimates in our model [27, 28].

To explore the relationship that our model’s cost estimates might have on results, we performed 2-way sensitivity analyses of each cost and the proportion of TMP-SMZ–resistant *E. coli*; the highest and lowest costs from our cost survey served as the limits of the range tested. Table 1 summarizes the costs employed in our model. Because recent evidence suggests that uncomplicated UTIs may be treated effectively without an initial physician visit [29], we considered that an initial office
Therapy for UTIs and Increases in Resistance

![Figure 1. Decision tree diagram that shows intermediate and final outcomes for an uncomplicated *Escherichia coli* urinary tract infection (UTI) treated with either trimethoprim-sulfamethoxazole (TS) or a fluoroquinolone (FQ). After each outcome on the right side of the tree, the probability of developing a vaginal yeast infection was considered in the model (not shown; see text). Abx, antibiotics; MD, medical doctor; R, resistant; Rx, therapy.](image)

visit and urinalysis might not occur; hence, their costs could be as low as $0.

Probabilities. Probabilities of clinical events were taken from published estimates [25, 27, 28, 30–32], with use of the mean value as the point estimate in our model. To explore the relationship that our model’s probabilities might have on results, we performed 2-way sensitivity analyses in the manner described above. To minimize authors’ bias, if there was a paucity of literature (≤1 source) describing the probability of an event, we performed a 2-way sensitivity analysis employing a broad range of probability for a given probability estimate (from at least ≤50% to ≥200% of the point estimates). In table 2, we summarized the list of probabilities used in our model.

RESULTS

We found that the mean cost of empirical treatment with TMP-SMZ for an uncomplicated UTI was $92 when the percentage of resistant *E. coli* in the community was 0%; at 10%, the mean cost was $99; at 20%, $106; at 30%, $113, and at 40%, $120. At the current level of FQ resistance among *E. coli* isolates [4], mean cost of empirical treatment with an FQ is $107. On the basis of our model, our sensitivity analysis demonstrated that when the percentage of TMP-SMZ–resistant *E. coli* exceeds 22%, use of empirical FQ rather than TMP-SMZ minimizes the treatment cost of uncomplicated UTIs (figure 2).

In our 2-way sensitivity analyses examining extreme values, the 22% threshold did not differ by >2% for the costs of the following services or treatments: initial medical visit, initial urinalysis, follow-up urinalysis, urine culture, high-dose ciprofloxacin, TMP-SMZ, vaginal yeast infection treatment, hospitalization, and outpatient treatment of FQ-resistant infection. Variables that had more impact included the cost of ciprofloxacin and the cost of a return medical visit (table 1), which changed the threshold by up to ±7% and ±5%, respectively.

In 2-way sensitivity analyses (table 2), extreme values of the following probabilities negligibly affected (<±2%) the threshold: proportion of FQ-resistant *E. coli* infections treated with
Table 1. Cost of antibiotics and medical supplies to treat uncomplicated urinary tract infections (UTIs) caused by *Escherichia coli* that were used in our 2-way sensitivity analysis.

<table>
<thead>
<tr>
<th>Description of therapy</th>
<th>Cost, US$</th>
<th>Data source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin, 250 mg b.i.d.</td>
<td>7.80/day</td>
<td>[20–23, 30, 43]</td>
</tr>
<tr>
<td>Ciprofloxacin, 500 mg b.i.d.</td>
<td>8.80/day</td>
<td>[21, 22, 24, 31, 43]</td>
</tr>
<tr>
<td>Generic TMP-SMZ</td>
<td>1.00/day</td>
<td>[21, 22, 43]</td>
</tr>
<tr>
<td>Generic miconazole</td>
<td>18.50/3 days</td>
<td>15.00–30.00</td>
</tr>
<tr>
<td>Hospitalization for pyelonephritis</td>
<td>1050.00/day</td>
<td>500.00–1500.00</td>
</tr>
<tr>
<td>Initial visit to a physician for UTI</td>
<td>75.00</td>
<td>0–150.00</td>
</tr>
<tr>
<td>Follow-up physician visit</td>
<td>75.00</td>
<td>50.00–150.00</td>
</tr>
<tr>
<td>Urine culture</td>
<td>39.00</td>
<td>25.00–50.00</td>
</tr>
<tr>
<td>Initial urinanalysis</td>
<td>5.25</td>
<td>0–10.00</td>
</tr>
<tr>
<td>Follow-up urinanalysis</td>
<td>5.25</td>
<td>3.00–10.00</td>
</tr>
</tbody>
</table>

**NOTE.** FQ, fluoroquinolone; HS, hospital survey (see Methods); TMP-SMZ, trimethoprim-sulfamethoxazole.

an FQ that were cured, changing antibiotics after lack of clinical response to FQ, seeking medical treatment (medical visit) for a yeast infection, yeast infection with 3 days of antibiotic use, and yeast infection with >3 days of antibiotic use. However, the proportions of FQ-susceptible, TMP-SMZ–susceptible, and TMP-SMZ–resistant *E. coli* infections clinically cured had a relatively larger impact on our break point. When the proportion of ciprofloxacin-resistant *E. coli* in the community increased to 10%, the 22% threshold climbed to 26% (figure 3). When the proportion of TMP-SMZ–susceptible *E. coli* infections cured with TMP-SMZ reached 100%, the threshold increased to 27%. When this proportion was 90%, it lowered the threshold to 8%.

In the reverse manner, when the clinical cure rate for FQ-susceptible *E. coli* infections cured with FQ therapy was 100%, it lowered the threshold to 20%, whereas when the cure rate was 90%, it raised the threshold to 43%. When the percentage of patients with TMP-SMZ–resistant *E. coli* infections who were clinically cured with TMP-SMZ therapy ranged from 40% to 80%, the threshold changed from 15% to 50%. Finally, the threshold changed by ±2%–5% in the ranges tested on extreme values of the percentage of patients who developed pyelonephritis, the number of days in the hospital for pyelonephritis, and the proportion of patients hospitalized.

**DISCUSSION**

Using a cost-based model, we have performed what we believe to be the first sensitivity analysis to determine what level of TMP-SMZ resistance in the community should trigger a switch of empirical therapy for uncomplicated UTIs from TMP-SMZ to an FQ. To our knowledge, our investigation is also the first to employ decision analysis to explore the relationship between antimicrobial resistance and clinical decision making. Decision analyses are ideal for answering questions that are difficult or impossible to resolve in a clinical trial. Our investigation demonstrated that when the proportion of TMP-SMZ–resistant *E. coli* exceeds 22% in a community, then empirical FQ therapy becomes less expensive than initial therapy with TMP-SMZ.

There are several strengths to our investigation. First, our model employed data obtained by a systematic review of the medical literature, complemented by data from pharmaceutical industry sources. Second, unlike older investigations, we directly addressed the impact of antimicrobial resistance on empirical antibiotic choices for cystitis, building upon previous investigations and employing a more detailed decision tree that incorporated more intermediate health outcomes. Finally, we employed 2-way sensitivity analyses, which have not been used in previous analyses examining the cost of treating uncomplicated UTIs. Older cost analyses that employed only 1 source for costs or probabilities were limited by the values used in their models, which may be imprecise.

Our study has several limitations. First, any decision analysis is potentially limited by its inherent simplicity. Uncommon outcomes like drug allergies or adverse events (e.g., pseudomembranous colitis) were not considered in our model. However, even the cost of an uncommon expensive event (e.g., hospitalization for pyelonephritis) had a minimal impact on our threshold. Another limitation in our model was that we
studied only UTIs caused by *E. coli*. However, this organism causes most uncomplicated UTIs (70%–95%) [3, 16, 30, 33] and thus is responsible for the vast majority of cost. In addition, a recent report demonstrated that the prevalence of TMP-SMZ resistance in non-*E. coli* pathogens causing uncomplicated UTIs is virtually identical to that of *E. coli* [5].

Our model was also limited because published data on clinical response to FQs were confined to studies in which ciprofloxacin was used; data were lacking for other FQs. Therefore, our results may not be valid for FQs other than ciprofloxacin. Finally, our results are derived from an economic model. Clearly, other important factors should help determine the antimicrobial of choice for an uncomplicated UTI, such as potential to alter local resistance patterns. There is evidence that increased use of FQs has raised the proportion of FQ-resistant organisms isolated from patients with common infections [34–36], prompting recommendations to limit FQ use in common infections when other effective agents are available [34, 37]. Therefore, to reduce the selective pressure driving the emergence of FQ resistance in communities, policy makers may wish to use a threshold higher than the level we found, perhaps to 30%. Conversely, arguments could be made for lowering the threshold to <22% to minimize uncommon complications and absenteeism from work and school.

Our 2-way sensitivity analyses led to several important observations. The only costs that significantly impacted our break points (±5%–7%) were those of ciprofloxacin and follow-up physician visits. This supports the adequacy of the model, given the inherent methodological problems with measuring costs of medical services [7]. Probabilities of clinical cure for TMP-SMZ–resistant, TMP-SMZ–susceptible, and ciprofloxacin-susceptible *E. coli* also had significant effects on our break point. Because we found that data on clinical response of TMP-SMZ–susceptible and –resistant infections treated with TMP-SMZ

### Table 2. Probability values for nodes tested with respect to treatment for urinary tract infection (UTIs) caused by *Escherichia coli*.

<table>
<thead>
<tr>
<th>Description of variable</th>
<th>Probability</th>
<th>Range of probabilities tested</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>FQ resistance</td>
<td>.005</td>
<td>0–1</td>
<td>[3–5, 33, 44]</td>
</tr>
<tr>
<td>Clinical cure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FQ-resistant infection treated with ciprofloxacin</td>
<td>.9</td>
<td>0–1</td>
<td>[28, 30, 38, 39, 45, 46]</td>
</tr>
<tr>
<td>TMP-SMZ-resistant infection treated with TMP-SMZ</td>
<td>.6</td>
<td>0–8</td>
<td>[38, 39]</td>
</tr>
<tr>
<td>FQ-susceptible infection treated with ciprofloxacin</td>
<td>.99</td>
<td>0–1</td>
<td>[13, 24, 32, 46–48]</td>
</tr>
<tr>
<td>TMP-SMZ-susceptible infection treated with TMP-SMZ</td>
<td>.96</td>
<td>0–1</td>
<td>[38, 39]</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>.2</td>
<td>0–5</td>
<td>[25, 31]</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>.04</td>
<td>0–0.8</td>
<td>[2, 25, 31]</td>
</tr>
<tr>
<td>Yeast infection after 3 days of antibiotic therapy</td>
<td>.05</td>
<td>0–2</td>
<td>[5, 18, 30, 31, 52]</td>
</tr>
<tr>
<td>Yeast infection after &gt;3 days of antibiotic therapy</td>
<td>.066</td>
<td>0–2</td>
<td>[18, 31]</td>
</tr>
<tr>
<td>Medical visit because of vaginal yeast infection</td>
<td>.25</td>
<td>0–5</td>
<td>[18]</td>
</tr>
<tr>
<td>Change of therapy due to lack of clinical response to TMP-SMZ (vs. extending TMP-SMZ treatment)</td>
<td>.75</td>
<td>0–1</td>
<td>[25, 31, 43]</td>
</tr>
<tr>
<td>Change of therapy due to lack of clinical response to FQ (vs. extending FQ treatment)</td>
<td>.25</td>
<td>0–1</td>
<td>[25, 31, 43]</td>
</tr>
</tbody>
</table>

**NOTE.** An additional variable used in this model is the duration of hospitalization for pyelonephritis. The value for this variable was 3 days (range tested, 1–5 days) [2, 49-51]. FQ, fluoroquinolone; MD, medical doctor; TMP-SMZ, trimethoprim-sulfamethoxazole.
SMZ were limited to 2 published studies [38, 39] and microbiological susceptibility may correlate weakly with clinical outcomes [40, 41], future research should be aimed at better delineating clinical cure rates based on uropathogens’ antimicrobial susceptibilities.

To further explore the validity of cure rates for infections with drug-susceptible and drug-resistant uropathogens in our model, we performed a post hoc analysis of a large prospective study reporting clinical cures of uncomplicated UTIs [38]. Using our model’s cure rates for TMP-SMZ–resistant and TMP-SMZ–susceptible E. coli (60% and 96%, respectively) and taking into account that 17% of E. coli were TMP-SMZ resistant in that study, we calculated a cure rate of 92%, which is nearly identical to findings published elsewhere [38]. This calculation provides reassurance regarding the accuracy of clinical cure rates employed in our model.

Our results would be enhanced by more reports on the prevalence of resistance in uropathogens causing uncomplicated UTIs [5]. Hospital antibiograms are unlikely to accurately indicate resistance in pathogens causing uncomplicated UTIs. Isolates represented in antibiograms typically originate from patients with nosocomial or complicated infections, groups with a higher likelihood of prior antibiotic exposure and infection with drug-resistant uropathogens [42]. Periodic surveillance of resistance in uropathogens causing uncomplicated UTIs would provide valuable information for clinicians and those developing UTI guidelines.

We conclude that empirical TMP-SMZ therapy is less expensive than FQ therapy for uncomplicated UTIs treated with a 3-day antibiotic course, unless TMP-SMZ resistance exceeds 22% in the community. Our results may have important policy implications. IDSA guidelines may need to be modified, i.e., the threshold for recommending a switch to empirical FQ therapy should probably be raised from 10%–20% to >20% TMP-SMZ resistance. Although our 22% break point is based purely on economic considerations, concerns of inducing further FQ resistance in communities suggest that this threshold may need to be raised further to >30%. The paucity of information on clinical cure rates following treatment against antibiotic-susceptible and antibiotic-resistant pathogens highlights the need for further data on this issue.

Acknowledgments

We acknowledge Arnold Bayer and Donald Sheppard, for their critical review of the manuscript, and Jennifer Yih, Kallpana Gupta, and Walter Stamm, for their help with locating clinical trial results. In addition, we thank Jennifer Tesoro for her technical assistance.

References


