ORIGINAL RESEARCH

Acute Uncomplicated UTI and *E. coli* Resistance: Implications for First-Line Empirical Antibiotic Therapy

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ABSTRACT

BACKGROUND: Uncomplicated urinary tract infection (uUTI) typically affects immunocompetent, anatomically normal women. *Escherichia coli (E. coli)* accounts for approximately 80% of cases. Given increased *E. coli*-trimethoprim-sulfamethoxazole (TMP-SMX) resistance, practice guidelines advocate first-line alternatives based on local resistance rates above 10%. This paper provides a model incorporating use of a new extended-release formulation of ciprofloxacin, used once daily, to facilitate revision of uUTI treatment policies by managed care organizations (MCOs) and practitioners.

METHODS: A cost-minimization model was designed from the MCO perspective, assuming an initial office visit with a urinalysis and empiric, 3-day treatment (TMP-SMX 800/160 mg twice daily or ciprofloxacin XR 500 mg once daily). Persistent infections were assumed to require a second visit. Costs were provided by a major employee health and benefit plan provider; clinical data were based on published information. Five case scenarios were used to compare average treatment costs based on varying *E. coli* resistance rates to therapy and to identify rates of TMP-SMX resistance where total treatment costs are equal.

RESULTS: Using national surveillance resistance data, Case 1 demonstrated average cost savings of $9.59 to $10.21 with ciprofloxacin XR. In Case 2, treatment costs ($49.19) were equal at an *E. coli* resistance rate of 4.3% for TMP-SMX and 1.0% for ciprofloxacin. Case 3 assumed empiric telephone prescribing, demonstrating that, at 4.3% TMP-SMX resistance, costs are equal for both treatments ($4.19). Case 4 used real-world data on therapy duration, demonstrating that, at 2.8% TMP-SMX resistance, costs are equal for both treatments ($54.87). Case 5 assumed 10% ciprofloxacin-*E. coli* resistance; at 13.3% TMP-SMX resistance, treatment costs were equal ($57.50). Results from all cases demonstrate that while the per-dose cost of ciprofloxacin XR far exceeds TMP-SMX, average total treatment costs are lower for ciprofloxacin XR at expected local levels of *E. coli* resistance to TMP-SMX.

CONCLUSIONS: The results suggest that in areas where local TMP-SMX *E. coli* resistance exceeds 10% and resistance to ciprofloxacin remains low, (0.5% to 6%) ciprofloxacin XR is an appropriate alternative to standard empiric treatment. The data provide evidence to MCOs that switching to a more expensive per-dose alternative will not necessarily increase total costs when guideline recommendations are followed. Responsible use of antibiotics for uUTI requires selection and administration of the right dosage of the most suitable antibiotic for an appropriate time period to eliminate pathogens quickly and successfully. The decision to use an alternative first-line therapy for uUTI should be driven by local resistance and susceptibility data—not simply per-dose drug acquisition costs.

KEYWORDS: Acute cystitis; Urinary tract infection, uncomplicated; Bacterial resistance; *E. coli* resistance; Antibiotic therapy; Fluoroquinolones; Ciprofloxacin; Trimethoprim/sulfamethoxazole; Cost-effectiveness

J Manag Care Pharm. 2004;10(1):17-25

Urinary tract infection (UTI) is the most common kidney and urologic disease in the United States.[1] UTIs affect approximately 8 million American women and account for approximately the same number of ambulatory care visits per year, making it one of the most common conditions encountered by clinicians.[1-3] UTIs account for more than 100,000 hospital admissions, presumably from acute pyelonephritis.[1] It is estimated that 11% of women report at least 1 physician-diagnosed UTI per year, and between 40% and 50% of women report at least 1 UTI in their lifetimes.[2,4] Uncomplicated UTI (uUTI) typically affects young women who are immunocompetent and have anatomically normal physiology.[5] The most common clinical manifestation is painful urination stemming from uncomplicated urethritis or cystitis.[6]

In addition to the tremendous personal and public health burden, the financial costs associated with UTI are significant. Direct costs are estimated to be more than $1 billion per year.[7] Additional costs stem from lost productivity and reduced quality of life. An epidemiologic study found that a UTI episode prior to treatment with an antibiotic accounts for 6.1 symptom days, 2.4 days of restricted activity, and 1.2 days away from school or work.[4]

The spectrum of causative pathogens for uUTI is well known. *Escherichia coli (E. coli)* is the most common, accounting for approximately 80% of cases. *Staphylococcus saprophyticus (S. saprophyticus)* is the second most common pathogen, accounting for another 5% to 15% of cases.[8-13] A 5-year, cross-sectional survey of antimicrobial susceptibilities in health maintenance organization-enrolled women (aged 18 to 50 years) with acute cystitis, found that *E. coli* and *S. saprophyticus* accounted for 90% of urine isolates studied.[9]

Until recently, the empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) for uUTI was based on the high

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TABLE 1 2001 U.S. Susceptibility Profile for Uncomplicated Urinary Tract Infection in Women of All Ages (38 states reporting)

State	Number of Isolates	TMP-SMX* % Resistant	Ciprofloxacin % Resistant
Alaska	90	17.78	1.11
Alabama	23	13.04	4.35
Arkansas	51	31.37	0.00
California	788	20.81	2.28
Colorado	133	18.80	0.00
DC	34	17.65	0.00
Delaware	1	0.00	0.00
Florida	1,455	15.40	1.51
Hawaii	231	36.36	1.30
Illinois	270	13.70	1.11
Indiana	156	12.18	1.92
Kansas	1,207	14.00	0.50
Kentucky	204	21.08	0.49
Louisiana	610	15.90	0.33
Massachusetts	157	16.56	1.27
Maryland	11	27.27	27.27
Michigan	4,000	11.30	0.75
Minnesota	44	18.18	2.27
Missouri	331	12.39	1.51
North Carolina	41	12.20	0.00
North Dakota	165	16.36	0.00
Nebraska	124	11.29	0.00
New Jersey	205	10.24	0.98
New Mexico	4,450	17.08	0.65
Nevada	1	0.00	0.00
New York	504	18.65	1.59
Ohio	1,698	9.60	1.06
Oklahoma	275	16.73	2.18
Oregon	1,212	21.62	1.32
Pennsylvania	966	12.42	0.21
South Carolina	104	6.73	0.96
Tennessee	1	100.00	100.00
Texas	324	22.53	4.94
Utah	159	22.01	0.63
Vermont	13	30.77	0.00
Washington	2,592	15.16	1.08
Wisconsin	510	21.96	2.16
West Virginia	378	7.94	0.53
Total	**23,518**	**15.31**	**1.03**

Source: The Surveillance Network, Focus Technologies, 2001.
**TMP-SMX = trimethoprim/sulfamethoxazole.*

level of certainty surrounding both the distribution of causative pathogens involved and the susceptibility patterns of these pathogens.[10] While there is little evidence to suggest that the distribution of causative pathogens has changed appreciably, there are ample data to suggest that resistance to TMP-SMX has risen significantly. Salient risk factors for TMP-SMX resistance include previous exposure to TMP-SMX and other antibiotics.[10,14,15]

The results of several individual studies suggest that TMP-SMX resistance approaches or exceeds 20% in many parts of the United States.[16,17] In a cross-sectional study conducted by Gupta et al., *E. coli* resistance to TMP-SMX increased from 9% in 1992 to 18% in 1996.[9] Similarly, a retrospective cohort study of women with acute cystitis seen at a university health center and primary care clinics showed that the prevalence of TMP-SMX resistance increased significantly ($P = 0.01$) from 8.1% in 1992 to 15.8% in 1999.[14] Recently, one managed care organization (MCO) in California reported a 38% TMP-SMX *E. coli* resistance rate.[18]

Given the marked increase in *E. coli*-TMP-SMX resistance occurring over the last decade, authoritative medical bodies have released evidence-based guidelines advocating a change in first-line therapy of uUTIs based specifically on local resistance rates. The Infectious Diseases Society of America (IDSA) recommends that alternatives to TMP-SMX should be used in communities where resistance rates exceed 10% to 20%.[1] Others have recommended that the threshold level of resistance for abandoning TMP-SMX as a first-line therapy for uUTI should be even lower than the range proposed by IDSA.[19] In addition, the Sanford Guide specifically recommends ciprofloxacin as a treatment alternative in areas of high TMP-SMX resistance.[20]

Resistance patterns are known to vary geographically. To develop guidelines to inform the practice of a particular provider, local data on TMP-SMX resistance data are needed. The Surveillance Network (TSN; MRL, Herndon, VA), a nationwide effort to pool susceptibility data from laboratories across the United States, provides information to clinicians regarding resistance rates in their geographic region of practice.[10] In 2001, there were 270 participating laboratories, up from 43 in 1995.[21] As shown in Table 1, data from the participating 38 states indicate that the average TMP-SMX resistance rate for uUTI specifically was 15.31% in 2001.[22] Table 2 shows resistance rates from another analysis of TSN data in which a broader definition of UTI was used.[21]

The availability of local TMP-SMX resistance data, coupled with the advent of guidelines recommending the use of these data to select the most appropriate first-line therapy for uUTI, means that most MCOs must now determine the level of community resistance at which their current empirical-treatment policies should be modified. They should identify the point at which first-line empirical treatment with TMP-SMX is no longer the most clinically appropriate and cost-effective approach.

To assist managed care professionals in this decision, a number of models have been published addressing the cost-effectiveness of TMP-SMX versus fluoroquinolones at various levels of TMP-SMX-*E. coli* resistance. Le and Miller (2001) found the threshold resistance rate for a switch to a fluoroquinolone was 22%.[23] In a second model, Perfetto and Gondek (2002) identified a threshold TMP-SMX resistance rate between 19% to 21% and included copayments (ranging from $5 to $20) for office visits and prescription drugs.[24] These models, as well as others,[17,18,25,26] demonstrated that, while cost per dose was higher among fluoroquinolone patients, the lower rate of resistance in

these patients rendered this drug more cost effective in average total treatment costs. The models identified the significant cost factors—the direct drug cost of the fluoroquinolone alternative and follow-up care required after a treatment failure occurs.

This paper provides an important update to assumptions used in previously reported analyses to aid MCOs and physician leaders in the formulation of treatment policies pertaining to uUTI in light of rising *E. coli* resistance. The model incorporates the use of a new formulation of ciprofloxacin extended-release tablet (Cipro XR), given in 3 single 500 mg doses across 3 days. Since the cost of the fluoroquinolone was identified as a cost driver in previous models, it was hypothesized that the new formulation would lower the total cost for treatment and decrease the threshold rate of TMP-SMX-*E. coli* resistance at which the alternative becomes cost effective.

Methods

Model Perspective

Using a Microsoft Excel spreadsheet, a cost-minimization model was designed from the perspective of an MCO. The structure of the model, in which empiric TMP-SMX was compared with empiric ciprofloxacin XR for the treatment of uUTI, is depicted in Figure 1. Five clinical scenarios are analyzed, including 2 base cases using national averages for *E. coli* resistance, a financial break-even assessment, the use of a telephone treatment protocol, and a worst-case scenario for ciprofloxacin resistance. An effort has been made to provide MCOs with an easy-to-use and transparent model that can be customized to reflect their unique set of clinical and economic conditions.

Model Assumptions

Consistent with a similar model developed by Le and Miller (2001),[23] the model assumed an initial office visit that included an in-office urinalysis but no culture and sensitivity testing. Each initial empiric treatment was given over a period of 3 days, after which all infections were either cured or persistent. As recommended, double-strength TMP-SMX was used twice daily and ciprofloxacin XR was used once daily. Persistent infections were assumed to require a second visit either back to the physician's office or to an emergency room (ER). This return visit was assumed to include a second urinalysis, an initial urine culture and sensitivity test sent to a lab, and a successful 7-day regimen of another antibiotic.

Cost Data

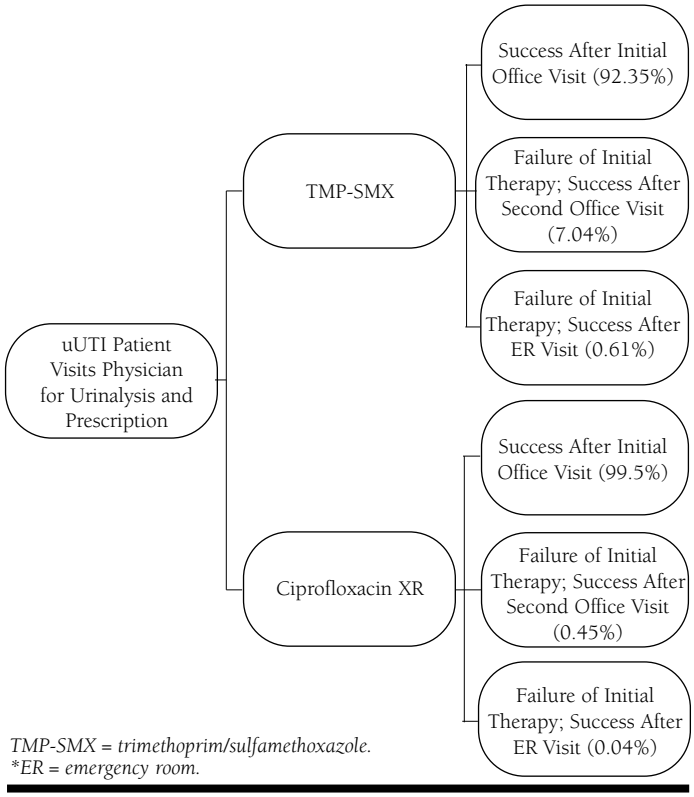
The model incorporates only direct medical costs paid by the MCO or insurer. The cost-related parameters used in the model (Table 3) were derived from reimbursement amounts provided by a major employee health and benefit plan provider (HBPP) based in the mid-Atlantic region of the United States. Using its claims databases, the HBPP reported the range of reimbursements paid, based upon the most common ICD-9 codes for

TABLE 2 2001 U.S. Susceptibility Profile for *E. coli* Urinary Tract Infection Isolates Among Outpatient Women of All Ages

U.S. Census Bureau Region	TMP-SMX* % Resistant	Ciprofloxacin % Resistant
New England (ME, NH, VT, MA, RI, CT)	13.9	1.9
Mid-Atlantic (NY, NJ, PA)	12.7	2.3
South Atlantic (DE, MD, DC, VA, WV, NC, SC, GA, FL)	15.9	6.0
East North Central (OH, IN, IL, MI, WI)	11.8	1.8
East South Central (KY, TN, AL, MS)	17.7	2.0
West North Central (MN, IA, MO, ND, SD, NE, KS)	13.7	1.3
West South Central (AR, LA, OK, TX)	21.8	3.2
Mountain (MT, ID, WY, CO, NM, AZ, UT, NV)	18.3	2.0
Pacific (WA, OR, CA, AK, HI)	20.3	2.3
Nationwide average	**16.1**	**2.5**

Source: Karlowsky et al. 2002.
**TMP-SMX = trimethoprim/sulfamethoxazole.*

FIGURE 1 Flow Chart of Treatments and Outcomes Incorporated in Model



TMP-SMX = trimethoprim/sulfamethoxazole.
**ER = emergency room.*

TABLE 3 Medical Care Resource Costs Utilized in an Uncomplicated Urinary Tract Infection Treatment Model

Resource	Cost ($)	Copayment ($)	Final MCO Cost After Copayment ($)
Generic TMP-SMX* 800 mg/160 mg bid for 3 days	5.21	5.00	0.21
Ciprofloxacin XR for 3 days	18.23	15.00	3.23
Office visit—physician fee	60.00	20.00	40.00
Urinalysis—physician fee	5.00	0.00	5.00
Urinalysis—physician office processing fee†	5.00	0.00	5.00
Laboratory fee—urinalysis	35.00	0.00	35.00
Laboratory fee—culture and sensitivity	70.00	0.00	70.00
Emergency department visit	145.00	50.00	95.00
Emergency department lab fees—urinalysis	80.00	0.00	80.00
Emergency department lab fees—culture and sensitivity	120.00	0.00	120.00
Second drug for 7 days	38.87	15.00	23.87

** TMP-SMX = trimethoprim/sulfamethoxazole.*

† Fee paid to the physician's office for processing samples that are sent to an outside laboratory.

The most common ICD-9 codes for uncomplicated UTI visits were used to estimate costs (ICD-9 595.000-595.910, 599.000-599.030, 753.100-753.190).

uncomplicated UTI visits (ICD-9 595.000-595.910, 599.000-599.030, 753.100-753.190). To be conservative, the lowest value of each range was selected and rounded to the nearest dollar. The insurer also reported the most common copayment amounts of the health plans it offers. These are typical copayments, not the copayments reported by the insurer. The assumed reimbursement costs as paid by this insurer are reported in Table 3. These estimated costs were based upon those most typically paid by the insurer since the ranges were wide.

As shown in Table 3, the model also incorporated a copayment of $20 for office visits, $5 for a generic TMP-SMX prescription, and $15 for a brand-name prescription. Prescription reimbursements were entered as reported by the HBPP and not rounded. The second drug, used after a failure of either ciprofloxacin or TMP-SMX, was assumed to be a branded product at equal per-dose cost as ciprofloxacin XR and prescribed once daily for 7 days.

This model compares the economic impact of prescribing extended release ciprofloxacin versus generic TMP-SMX. Generic ciprofloxacin (250 mg given twice per day) was not considered because the payer's cost per treated patient was calculated to be $27.45, which is considerably higher than both the brand-name ciprofloxacin XR ($3.23) and generic TMP-SMX ($0.21).

Clinical Data

Clinical success and failure probabilities incorporated in the model were derived from literature sources. The failure rate among TMP-SMX-resistant patients treated with TMP-SMX was estimated to be 50%.[27] Because a similar failure rate for ciprofloxacin resistance could not be identified in the literature, a rate of 50% was assumed, as has been used in previous models.[23] Consistent with a similar model developed by Le and Miller (2001), it was assumed that all TMP-SMX-susceptible infections treated with TMP-SMX and all ciprofloxacin-susceptible infections treated with ciprofloxacin XR were cured.

Among those who fail first-line therapy, it was assumed that 8% would seek further care in an ER and the remaining 92% of patients would return to their physician's office. This is based on data from a study published by the Centers for Disease Control and Prevention that stratified the number of ambulatory care visits in 1997 by diagnosis and setting of care.[28] During that year, there were 2.675 million visits due to cystitis; 261,000 (9.8%) were treated in an ER. Given that a portion of these episodes were likely to be initial visits, an estimate of 8% was used in the model for the second visit. No ER visits were assumed for initial therapy in a conservative estimate of initial costs.

Resistance Rates

Data on TMP-SMX and ciprofloxacin *E. coli* resistance rates were obtained from TSN (Tables 1 and 2). In Table 1, the average resistance rates from the 38 states reporting for uUTI isolates were 15.31% and 1.03% for TMP-SMX and ciprofloxacin, respectively. In Table 2, the average rates for UTI, more broadly defined, were 16.1% and 2.5%, respectively.

Outcomes of Interest

Costs from each of the 3 possible treatment paths (initial success, failure requiring second office visit, and failure requiring ER visit) were summed to calculate an average treatment cost for both TMP-SMX and ciprofloxacin XR treatment groups. The formula below is used to compare average costs based on resistance rates and also to determine the threshold TMP-SMX-*E. coli* resistance rate at which total average costs become equal for both treatment groups:

Average treatment cost per group =

$$[(1 - (R * F)) * CS] + [(R * F * (1 - F_{ER})) * CF_{No\ ER}] + [(R * F * F_{ER}) * CF_{ER}]$$

where,

R = rate of local antibiotic resistance

F = rate of clinical failure due to resistance

F_{ER} = percentage of failures that result in ER visit for treatment

CS = cost of treatment success

$CF_{No\ ER}$ = cost of treatment failure without an ER visit

CF_{ER} = cost of treatment failure with an ER visit

TABLE 4 Case Scenarios Demonstrating Use of the Model—Calculation of Threshold TMP-SMX-*E. coli* Resistance Rate and Resulting Treatment Costs

	TMP-SMX*			Ciprofloxacin XR		
	Success	Failure		Success	Failure	
		Without ER†	With ER†		Without ER†	With ER†
Case 1a: Base case that uses resistance rates from Table 1 (2001 data from 38 states reporting to The Surveillance Network, Focus Technologies; 15.3% for TMP-SMX and 1.0% for ciprofloxacin)						
Treatment cost	$45.21	$219.08	$364.08	$48.23	$222.10	$367.10
Average total treatment cost	$59.40			$49.19		
Resistance rate	15.3%			1.0%		
Case 1b: Base case that uses resistance rates from Table 2 (regional 2001 data from Karlowsky et al. 2002; 16.1% for TMP-SMX and 2.5% for ciprofloxacin)						
Treatment cost	$45.21	$219.08	$364.08	$48.23	$222.10	$367.10
Average total treatment cost	$60.14			$50.55		
Resistance rate	16.1%			2.5%		
Case 2: Break-even analysis: If ciprofloxacin resistance is held constant at 1%, at what TMP-SMX resistance rate does the average total cost reach equality for both treatments?						
Treatment cost	$45.21	$219.08	$364.08	$48.23	$222.10	$367.10
Average total treatment cost	$49.19			$49.19		
Resistance rate	4.3%			1.0%		
Case 3: Effect of a telephone-based empirical prescribing protocol for uUTI on average total treatment costs						
Treatment cost	$0.21	$174.08	$319.08	$3.23	$177.10	$322.10
Average total treatment cost	$4.19			$4.19		
Resistance rate	4.3%			1.0%		
Case 4: Cost based on reported average duration of use data from Versipan (11.6 days for TMP-SMX and 4.1 days for ciprofloxacin)						
Treatment cost	$52.26	$226.13	$371.13	$53.91	$227.78	$372.78
Average total treatment cost	$54.87			$54.87		
Resistance rate	2.8%			1.0%		
Case 5: The TMP-SMX resistance rate that needs to be exceeded before ciprofloxacin becomes more cost effective in a "worst-case scenario," whereby ciprofloxacin XR resistance reaches 10%						
Treatment cost	$45.21	$219.08	$364.08	$48.23	$222.10	$367.10
Average total treatment cost	$57.50			$57.50		
Resistance rate	13.3%			10.0%		

** TMP-SMX = trimethoprim/sulfamethoxazole. †ER = emergency room.*

Case Scenarios

Case 1a is considered the base case and incorporated national average resistance rates for uUTI for both TMP-SMX (15.31%) and ciprofloxacin (1.03%) (Table 1).[22] Case 1b incorporated the national average resistance rates for UTI (Table 2).[21] Case 2 is considered the "break-even" case. The threshold local TMP-SMX-*E. coli* resistance rate was identified by holding constant the resistance rate for ciprofloxacin XR cited in Case 1a while adjusting the local TMP-SMX-*E. coli* resistance rate until the average total treatment cost for each group was equal.

Since many MCOs may encourage minimal laboratory testing and empiric antibiotic prescribing by telephone,[7,29] Case 3 is a modification of Case 1a to reflect telephone prescribing for all (100%) cases, which obviates the need for an initial office visit and initial urinalysis. Case 4 uses data reported on the average duration of therapy for each antibiotic for treating uUTI.[30] The average durations of 11.6 days for TMP-SMX and 4.1 days for ciprofloxacin XR were applied to Case 1a. Finally, Case 5 uses a 10% rate of ciprofloxacin resistance as a worst-case scenario—10 times the best estimate available for the nationwide average resistance to ciprofloxacin in uUTI shown in Table 1. Again, the 10% rate was applied to Case 1a.

Results

The results are presented in Table 4. In Case 1a, the base case, using national averages for resistance given in Table 1, the aver-

age treatment cost for TMP-SMX ($59.40) exceeded that of ciprofloxacin XR ($49.19) by $10.21. Using 2002 resistance data from Karlowsky et al.,[21] Case 1b shows that the average treatment cost for TMP-SMX ($60.14) exceeded that of ciprofloxacin ($50.55) by $9.59 (19%).

For Case 2, the break-even point, an average cost of $49.19 for both therapies is reached when the threshold resistance rate of TMP-SMX is 4.3% and the ciprofloxacin resistance rate is 1.0%. Case 3 included no costs for initial office visits or urinalysis, assuming that empirical prescribing was done by telephone. Here, the resistance threshold is also 4.3%, and the average cost per patient at the break-even point drops dramatically to $4.19 for both treatments. Case 4 utilized real-world data reported on average actual duration of these specific therapies in uUTI. In this scenario, the threshold rate of TMP-SMX resistance was 2.8% to achieve equal average costs at $54.87. To test the influence of a "worst-case" scenario for fluoroquinolone resistance, Case 1a was modified in Case 5 to include a 10% local ciprofloxacin-*E. coli* resistance rate. This change increased the TMP-SMX resistance threshold rate to 13.3% to reach an average cost of $57.50 for both groups.

Discussion

This study utilized straightforward clinical assumptions for uUTI. (e.g., cystitis) to demonstrate the treatment and cost implications of increased resistance by *E. coli* to TMP-SMX. It compares typical empirical treatment with double-strength TMP-SMX to ciprofloxacin XR, a new extended-release formulation of ciprofloxacin. The results demonstrate that, while the per-dose cost of the ciprofloxacin XR exceeds the per-dose cost of the TMP-SMX, the net plan costs per *course of therapy*, after accounting for copays, network discounts, and dispensing fees are similar for the 2 drugs (TMP-SMX $0.21 versus ciprofloxacin XR $3.23). Furthermore, at the expected local levels of *E.coli* resistance to TMP-SMX and current levels of ciprofloxacin resistance, the average total treatment costs are actually lower for ciprofloxacin XR.

Results for cases 1a and 1b (Table 4) demonstrate that, at the average rate of *E. coli*-TMP-SMX resistance in the United States, cost savings are achieved using ciprofloxacin XR. Even when using the more conservative national estimates presented by Karlowsky et al. (2002), which may include various types of UTI and not just uUTI, a considerable per-patient cost saving ($9.59) is achieved on average. In Case 2, the TMP-SMX-*E. coli* resistance rate was adjusted until the average total cost for each treatment group was equal. When local *E. coli* resistance rates are below this threshold, the "break-even" point, total cost of therapy for TMP-SMX is less than that of ciprofloxacin XR. When resistance rates reach or exceed the threshold, use of fluoroquinolones becomes cost effective. Case 2 demonstrates that, at *E. coli*-TMP-SMX resistance rates as low as 4.3%, the total average costs would be equal between TMP-SMX and ciprofloxacin XR. At resistance rates higher than 4.3%, the total cost of care for the ciprofloxacin XR group is lower than for TMP-SMX. This case provides reassurance to MCO decision makers that use of the product with higher per-dose costs can be less costly and more effective when resistance rates are considered.

Even if Case 2 assumptions are modified so that one half of all return visits involved urine culture and sensitivity testing and one half of the second courses of antibiotics were handled by telephone prescribing without a second visit and additional medical costs, an average cost of $38.77 for both therapies is reached when the resistance rate of TMP-SMX is 6.8% and the ciprofloxacin resistance rate is 1.0%. Similarly, lowering the office copay in the model to $10 serves only to increase the average total cost for treatment to the MCO by $10. The total average treatment cost increases from $49.19 to $59.23, a difference of $10.04. In this scenario, the threshold TMP-SMX resistance rate drops from 4.3% to 4.1%—a negligible change.

Very low per-patient treatment costs can be achieved by MCOs that have adopted treatment protocols allowing for empiric prescribing by telephone for cystitis. Case 3 suggests that these costs can be as low as $4.19 on average. The threshold *E. coli* resistance rate remains at 4.3% in this case. Even with a substantial reduction in health care service use, this case again demonstrates that the product with higher per-dose costs can be less costly and more effective when resistance rates are considered. When the national average TMP-SMX resistance rate of 15.3% is used in this case, the cost per case for TMP-SMX increases to an average of $14.40 (data not shown) as compared with $4.19 for ciprofloxacin XR.

The recommended duration of empirical therapy—3 days—was used in the base case (Cases 1a and 1b). However, some clinicians may suspect that these recommendations are not always followed. For Case 4, drug costs were adjusted to account for the average number of days of therapy identified in a claims database that included recent information for the new extended-release formulation of ciprofloxacin.[30] When the real-world, average durations of use in uUTI are used (11.6 days for TMP-SMX and 4.1 days for ciprofloxacin XR), the TMP-SMX resistance threshold drops to 2.8% to achieve equal cost for both groups. The per-patient cost for ciprofloxacin XR treatment increased from $3.23 to $8.91, a difference of $5.68. However, the per-patient cost of TMP-SMX increased from $0.21 to $7.26, a difference of $7.05.

Case 5 presents the worst-case scenario for ciprofloxacin resistance, using a rate of 10% in comparison with its current national average of 1% in uUTI patients. Le and Miller also used 10% as an extreme estimate of ciprofloxacin resistance.[23] It is unlikely that any geographic region in the United States will observe such an increase any time soon. This model demonstrates that treatment costs would be the same for both groups if the TMP-SMX resistance rate was 13.3%. A TMP-SMX resistance higher than 13.3% would therefore result in cost savings with use

of ciprofloxacin XR, even at a 10% ciprofloxacin resistance rate.

The model reflects the perspective of the MCO or insurer, after subtraction of copayment (out-of-pocket) costs paid by MCO members. Patients will have to pay a higher copayment in most plans for brand versus generic drugs. This may mean an out-of-pocket cost difference of $10 or more. Some patients may resist paying the higher copayment and request the generic alternative. The health care provider must consider the risk that a patient may not have a prescription filled if the differences are considerable. The MCO or insurer may want to consider waiving the brand-level copayment in this type of clinical scenario. For example, in Case 1a, when the copayment for the patient is reduced to $5.00 for the brand-name ciprofloxacin XR and the second drug, increasing their costs by $10 each, the ciprofloxacin XR group still maintains a $0.93 per-patient average cost advantage over TMP-SMX, with the TMP-SMX resistance rate at 15.3% and the ciprofloxacin resistance rate at 1.0%.

Comparisons With Similar Models

The model presented here has both similarities and differences with past models. This model is simplified to exclude consideration of yeast infections and hospitalization for pyelonephritis. However, the results of Le and Miller (2001) demonstrate that these very low probability events have little impact on total average costs. The models by Le and Miller (2001) and by Perfetto and Gondek (2002) reported a 19% to 22% TMP-SMX *E. coli* resistance threshold range for ciprofloxacin cost-effectiveness to be achieved.[23,24] The thresholds reported in this study are much lower. However, the findings here are consistent with those in previous models in that both reported that the most significant cost drivers were the costs for the fluoroquinolone and for the follow-up physician office visits. Both of these cost drivers are lower in the current model than in past models. The daily cost of ciprofloxacin XR is less than that of ciprofloxacin immediate-release tablets. The cost for the office visit is lower since it is actual reimbursement data from an HBPP and not derived from the literature as was done in previous models.[23,24] Also, past models assumed that a small percentage of failures would go on to hospitalization for pyelonephritis. However, this would account for only a small amount of the differences found. It is important to note that when the health care costs from this study are applied to the Perfetto and Gondek (2002) model, the 19% threshold reported in that study drops to 5.8%, closer to the findings reported here and demonstrating the significant impact of the cost assumptions.

Another previously reported model used prospective data from a randomized clinical trial of elderly women with acute UTI in which ciprofloxacin (250 mg twice daily) was compared with TMP-SMX (160 mg/800 mg twice per day). Of the 261 patients enrolled in the study, 172 (66%) met the criteria to be included in the efficacy analysis (e.g., no protocol violations, no missing data, not lost to follow-up, etc.). For these patients, clinical resolution was achieved in 97% versus 85% of the ciprofloxacin and TMP-SMX groups, respectively. While cost per cure was higher ($98.68 for ciprofloxacin versus $86.17 for TMP-SMX), the differential in the incidence of antimicrobial resistance between groups (1.2% versus 11.2%) rendered ciprofloxacin more cost effective ($64 versus $87, respectively) in terms of average total treatment costs.[26] It should be noted that 1996 Medicare MEDPAR data and 1996 average wholesale drug price data were used to calculate cost in their model, which would not reflect the costs for most managed care providers for younger, more typical cystitis patients today.

Implications for Managed Care Organizations

These cases demonstrate how MCOs can utilize resistance data when making decisions related to formulary management and antibiotic treatment policies. An important point to be stressed is that these data should not be used to suggest that fluoroquinolones be used as the first-line empiric choice at lower rates of TMP-SMX-*E. coli* resistance. This could result in an entirely new spectrum of resistance issues as resistance to fluoroquinolones would begin to increase. Instead, the data should be used to provide assurance to decision makers that switching to a more expensive per-dose alternative at the IDSA-recommended levels of TMP-SMX resistance (greater than 10% to 20%) will not increase costs and may lower the total cost of care. The data offer assurance that a provider can achieve better outcomes at lower costs using local resistance-rate data and clinical guidelines. Responsible use of antibiotics for uUTI requires the selection and administration of the most suitable antibiotic at the right dosage for an appropriate period of time in order to eliminate pathogens quickly and successfully. Therefore, the decision to use an alternative first-line therapy for uUTI should be driven by local resistance and susceptibility data—not drug acquisition costs alone.

Implications for Clinicians

Use of these models implies that local resistance rates are known by clinicians and are being weighed in clinical decision making. Some providers may not give appropriate consideration to resistance rates. They may question: "How large a problem is this?" Given that concentrations of TMP-SMX, as well as most antimicrobials, reach high levels in the urine, many may believe that clinical resolution will be likely despite isolate resistance. Some may not know what percentage of TMP-SMX-treated cases go on to clinical failure when the *E. coli* is resistant. Many clinicians do know that TMP-SMX is an inexpensive alternative and may always try it first, using a fluoroquinolone second-line, only if needed for failures.

Clearly, the data provided through TSN demonstrate the magnitude of the TMP-SMX-*E. coli* resistance problem. Of the 38 states reporting isolates (Table 1), one quarter report TMP-SMX resistance rates of 20% or greater. Approximately half

report rates higher than 15%. The model demonstrated through the case scenarios in this study can help a provider understand the implications of failing to respond to increasing *E. coli* resistance rates and the costs involved.

This means that health care providers, especially primary care physicians, nurse practitioners, physician assistants, and pharmacists must be educated and knowledgeable with regard to pathogen resistance and susceptibility in their geographic area of practice. They must understand the implications of resistance in clinical decision making, formulary selections, and treatment protocol applications. However, it has become difficult for some organizations to have a clear understanding of what their own resistance rates are due to the rise in empiric treatment and a decline in the acquisition of urine cultures and sensitivities in uncomplicated cases. Managed care cost-containment efforts, which may result in a reduction in urine culture laboratory orders for uncomplicated cases, may be contributing to an increasing scarcity of outpatient resistance rate data.[29] This may impact the monitoring of resistance and failure rates in the future. MCOs may need to conduct more internal surveillance in order to better understand resistance and its implications in their own, eligible populations. In the absence of specific internal data on resistance, inpatient *E. coli* susceptibility data for uUTI is a reasonable basis for decision making.[9]

Practitioners must also be concerned about rising fluoroquinolone resistance. As indicated in Tables 1 and 2, national rates for ciprofloxacin-*E. coli* resistance range from 1.03% to 2.5% on average. Other authors have indicated rates as low as .5%, and isolated areas of the country have reported rates as high as 6%.[21,23] While these rates remain low, practitioners must be mindful of the implications of increasing bacterial resistance. Following guidelines and monitoring local resistance rates must become a routine part of clinical practice to keep resistance in check.

Patients may prefer once-per-day dosing. Convenient and short-course dosing can enhance patient compliance, which can result in increased effectiveness.[19,31] It must also be considered that the model does not account for any of these kinds of differences between therapies (e.g., increased effectiveness due to better compliance, therapeutic effectiveness).

Limitations

It is important to note the limitations of any modeling exercise. The clinical assumptions and costs used in this model were derived from various sources and may not reflect the actual situation for any specific MCO. It is important that each organization use its own local resistance rates, clinical parameters, cost data, and copayments to derive meaningful information that can guide clinical decision making in a given health system.

Also, two primary objections have been noted regarding the use of publicly available resistance data to determine whether TMP-SMX is the most appropriate first-line therapy for uUTIs. First, some argue that the resistance data in these databases historically pertain to isolates from hospitalized patients instead of community pathogens. However, several studies have found no differences between pathogens isolated from these 2 patient populations.[9] Second, there is a concern that microbiological resistance may not translate to adverse clinical outcomes.[15,32] However, a growing body of literature indicates that this objection to the use of surveillance data may also be unfounded. Specifically, resistant *E. coli* has been shown to have a greater likelihood of treatment failure.[10,11,16,27,33] That is, a 50% clinical failure rate is expected for UTI patients with TMP-SMX-resistant uropathogens who are treated with TMP-SMX.

It should be noted that the model described in this study compares ciprofloxacin XR with 1 therapeutic alternative. Other common first-line therapies such as nitrofurantoin or second-line agents such as cephalexin were not considered.

Conclusions

A straightforward economic model was used to compare empiric antibiotic therapies for uncomplicated urinary tract infections. Standard empiric therapy, double-strength TMP-SMX administered twice daily for 3 days, was compared with a new option, ciprofloxacin XR administered once daily for 3 days. The model demonstrated that, when using costs typical of an MCO and national estimates of resistance, the total average cost for ciprofloxacin XR-treated patients is less than that of TMP-SMX-treated patients. It can be concluded that ciprofloxacin XR is an appropriate alternative to standard empiric treatment in areas where local *E. coli* resistance to TMP-SMX exceeds guideline-recommended levels.

Local resistance-rate data can provide assurance to MCO decision makers that switching to a more expensive per-dose alternative at the IDSA-recommended levels of resistance (greater than 10% to 20%) will not increase costs and may lower the total cost of care. The data offer assurance that a provider can achieve better outcomes at lower costs using local resistance rates and clinical guidelines.

The decision to use an alternative first-line therapy for uUTI should not be made based on drug acquisition costs alone. Local resistance and susceptibility data should be factored into this decision making. Accordingly, efforts should be focused on improving the availability of local susceptibility data to clinicians to help guide patient care.

DISCLOSURES

Funding for this research was provided by Bayer Pharmaceuticals, Inc., and was obtained by authors Eleanor M. Perfetto and Brian R. Nichols. Authors Karen Keating and Sanjay Merchant are employed by Bayer, and Perfetto and Nichols are employed by The Weinberg Group, consultants to Bayer. Perfetto served as principal author of the study. Study concept and design were contributed by Perfetto, Keating, and Merchant. Analysis and interpretation of data and drafting of the manuscript were contributed by Perfetto, Nichols, and Keating. Critical revision of the manuscript was the work of Keating and Merchant. Statistical expertise was contributed by Perfetto, Nichols, and Merchant.

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