Economic Evaluation of an Updated Guideline for the Empiric Treatment of Uncomplicated Urinary Tract Infection in Women

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Abstract

Background: Until recently trimethoprim-sulfamethoxazole was the drug recommended in the Leumit Health Fund for the empiric treatment of uncomplicated urinary tract infection in women. However, due to increased uropathogen resistance to this drug, the fund has designated nitrofurantoin as its new drug of choice.

Objectives: To evaluate the potential economic impact of implementing this new pharmaco-policy.

Methods: Using data derived from the electronic patient records of the Leumit Health Fund, we identified all non-recurrent cases of women aged 18–49 with a diagnosis of acute cystitis or UTI without risk factors for complicated UTI and empirically treated with antibiotics throughout 2003. The final sample comprised 5,489 physician-patient encounters. The proportion of cases treated with each individual drug was calculated, and the excess expenditure due to non-adherence to the new guideline from the perspective of the health fund was evaluated using 5 days of therapy with nitrofurantoin as the reference treatment.

Results: Ofloxacin was the most frequently prescribed drug (30.24%), followed by TMP-SMX (22.43%), cephalexin (15.08%), and nitrofurantoin (12.59%). The observed net aggregate drug expenditure was 2.3 times greater than expected had all cases been treated with nitrofurantoin according to the guideline duration of 5 days. The cost of treatment in 53% of the cases exceeded the expected cost of the guideline therapy.

Conclusions: Successful implementation of the new drug policy will likely improve quality of care and reduce costs to the health fund.

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Uncomplicated urinary tract infections are among the most common infections in women, with at least 10–20% of women experiencing a symptomatic UTI at least once in their lifetime [1,2]. In the United States, UTIs account for at least 7 million outpatient visits and 1 million hospital admissions annually, with a total cost exceeding one billion dollars [3]. Furthermore, the rapid increase of antimicrobial resistance among uropathogens causing acute uncomplicated community-acquired UTI in women worldwide is becoming a critical problem that poses a significant threat to human health [4–6]. Of the many factors associated with its

UTI = urinary tract infection
TMP-SMX = trimethoprim-sulfamethoxazole

occurrence, the widespread use of antibiotics in clinical medicine – much of it inappropriate or unnecessary [7,8] – has probably had the greatest impact.

The current guidelines for the management of these infections recommend empiric treatment without the use of a urine culture or susceptibility testing to guide choice of drug. The rationale for this strategy is based on the narrow and predictable spectrum of etiologic agents that cause acute cystitis and their susceptibility patterns [9]. In the U.S., recommendations for the treatment of UTIs have not changed significantly over the past decade, with trimethoprim-sulfamethoxazole or selected fluoroquinolones remaining the drugs of choice [10–12].

In Israel, the rising prevalence of uropathogenic resistance to TMP-SMX has prompted reconsideration of the current policies for the treatment of UTI. In a study conducted in northern Israel, 46.8% of *Escherichia coli* found in urine cultures were resistant to TMP-SMX; the lowest resistance was noted for cefuroxime (4.2%), ofloxacin (4.8%), ciprofloxacin (4.8%), and nitrofurantoin (0.4%) [13]. One potential adverse outcome of TMP-SMX resistance is over-prescription of fluoroquinolones [14], which may themselves be eventually limited by the emergence of resistance. Despite the evidence, physicians continue to prescribe TMP-SMX on the assumption that *in vitro* resistance does not necessarily reflect *in vivo* resistance, especially with a drug like TMP-SMX which achieves high urine levels. This assumption has proved to be problematic. In a study designed to evaluate the effectiveness of TMP-SMX in the treatment of uncomplicated UTIs due to TMP-SMX-resistant pathogens in healthy, non-pregnant, premenopausal women in northern Israel, significantly higher clinical cure rates were observed among women with TMP-SMX-susceptible strains as compared to women infected with resistant strains (88% vs. 54%, *P* < 0.001) [15]. Accordingly, the major health management organization in Israel, General Health Services (Kupat Holim Clalit), which provides healthcare to approximately 55% of the population, published a new guideline for its physicians wherein nitrofurantoin is designated the drug of choice for uncomplicated UTI in women [16]. In a study conducted by Leumit Health Fund [17], 22.2% of *E. coli* isolated from positive urine cultures from premenopausal women were found to be resistant to TMP-SMX, with the lowest rate of resistance (0.5%) being observed for the drug nitrofurantoin. The purpose of the present study was to analyze the implications on

drug expenditure of designating nitrofurantoin as the new drug of choice for the empiric treatment of this disease in premenopausal women.

Subjects and Methods

Data extraction

Using prescription data from the Leumit Health Fund, which has implemented an electronic patient record system for clinic-based primary care physicians, we analyzed physician prescribing behavior in treating this disease. At each patient visit the physician completes an electronic patient record of the visit, detailing the specific clinical services provided during the visit, including diagnosis, drugs prescribed and diagnostic tests ordered. This system has been successfully implemented for the majority of clinic-based primary care physicians. We identified all cases involving female patients aged 18–49 who were diagnosed with an International Classification of Diseases, Ninth Revision (ICD-9) code for either acute cystitis (595.0) or UTI, site unspecified (599.0), in which the physician prescribed an antibiotic (ATC code J01) during the 12 month period January to December 2003 [18–20]. Cases were excluded if they had an additional code for diagnoses suggesting a complicated UTI. Patients who had diagnostic codes listed for additional infectious diseases were also excluded [21]. Patients with underlying urologic structural abnormalities, diabetes, immunosuppression, pregnancy, recent hospitalization, or urologic manipulation are at increased risk of development of pyelonephritis or infection with resistant organisms [4,11]. Since it is necessary to differentiate these women from those with uncomplicated UTI in terms of both workup and treatment, these cases were excluded from the study (cases of underlying urologic structural abnormalities or recent hospitalization were not identified for exclusion due to limited data in the electronic patient record). We also excluded pregnant women since certain antibiotics may be contraindicated at various stages of pregnancy. Cases with a

Table 1. Costs of guideline course of therapy (in shekels)*

Drug and strength	Regimen	Wholesale price	Retail price	Co-payment	Net cost to provider
Nitrofurantoin 100 mg	1 tablet 3 times daily for 5 days	17.22	23.76	12.00	5.22

* 4.5 shekels = $1.00

diagnosis of glucose-6-phosphate dehydrogenase deficiency were excluded since nitrofurantoin is contraindicated in these patients. In order to limit the study to patients receiving empiric treatment, we excluded cases in which a urine culture was performed 3 days prior to, on the day, and 3 days after the date of the physician patient encounter. Also excluded were recurrent cases of UTI (three or more episodes per year or at least two new episodes during the previous 6 months).

Cost analysis

The HMO studied (Leumit) owns and operates 70 pharmacies throughout the country. The cost of drug therapy was therefore calculated from the perspective of the healthcare provider using the wholesale list price of the drug. The expected costs of treatment (in shekels) for the recommended first-line therapy based on the updated guidelines are shown in Table 1. The expected cost of treatment, had all eligible cases been treated with this regimen, was calculated and compared to the costs in all eligible cases in the 2003 data set.

Results

Observed costs

The cost data for the drugs prescribed in this study are presented in

HMO = health management organization

Table 2. Aggregate costs of treatment with specific drugs and excess expenditure due to prescription of non-recommended drugs*

Drug category	No.	%	Mean cost per case	SD	Observed total cost	Expected cost	Observed-expected	Observed/expected
Cefuroxime	83	1.5%	96.11	55.82	7,977.30	433.26	7,544.04	18.41
Other fluoroquinolones	56	1.0%	39.35	51.63	2,203.79	292.32	1,911.47	7.54
Other cephalosporins	94	1.7%	21.02	9.33	1,976.15	490.68	1,485.47	4.03
Other	89	1.6%	17.71	19.11	1,576.15	464.58	1,111.57	3.39
Amoxycillin + clavulanic acid	227	4.1%	42.90	16.29	9,737.38	1,184.94	8,552.44	8.22
Other Penicillin	237	4.3%	2.45	4.91	581.62	1,237.14	-655.52	0.47
Fosfomycin	293	5.3%	27.21	6.28	7,972.28	1,529.46	6,442.82	5.21
Nitrofurantoin	691	12.6%	14.93	8.18	10,318.21	3,607.02	6,711.19	2.86
Cefalexin	828	15.1%	23.28	12.50	19,274.53	4,322.16	14,952.37	4.46
TMP-SMX	1,231	22.4%	0.64	3.84	782.70	6,425.82	-5,643.12	0.12
Ofloxacin	1,660	30.2%	2.75	4.23	4,569.79	8,665.20	-4,095.41	0.53
Total	5489	100.0%	12.20	19.56	66,969.90	28,652.58	38,317.32	2.34

* Wholesale cost to HMO after deduction of patient co-payment in shekels

Table 2. The net costs are the wholesale cost to the provider after deduction of the patient co-payment. During the 12 month study period Leumit spent 66,969.90 shekels on drugs to empirically treat 5,489 premenopausal women with uncomplicated UTI. Prescriptions for nitrofurantoin, the recommended drug, resulted in a net expenditure of 10,318.21 shekels, while prescriptions for the drug ofloxacin, the most commonly prescribed albeit non-recommended drug (30.24% of all cases treated) resulted in a net expenditure of 4,569.79 shekels. Cephalexin, a drug not recommended by the guideline, resulted in a net expenditure of 19,274.53 shekels.

Calculation of excess expenditure

The cost of the guideline therapy of nitrofurantoin for 5 days is the referent used for the analysis of excessive expenditure on drug therapy in the empiric treatment of uncomplicated UTI in women. The calculated excess expenditure accrued due to physicians prescribing non-recommended drugs is presented in Table 2. Since the net cost of this regimen to the health fund is 5.22 shekels [Table 1], the expected cost of guideline treatment is calculated by multiplying this cost by the number of cases treated. By this calculation, prescriptions deviating from the recommended therapy resulted in a net excess expenditure of 38,317.32 shekels, with the excess expenditure observed in cases treated with nitrofurantoin due to the treatment exceeding 5 days. The net cost of treatment in 53% of cases exceeded the referent value of 5.22 shekels [Figure 1], and the observed net aggregate drug expenditure was 2.34 times greater than expected had all cases been treated with nitrofurantoin according to the guideline duration of 5 days.

Calculation of excess expenditure corrected for steady supply: best-case scenario

Figure 1. Cumulative percent of cases by cost of treatment.
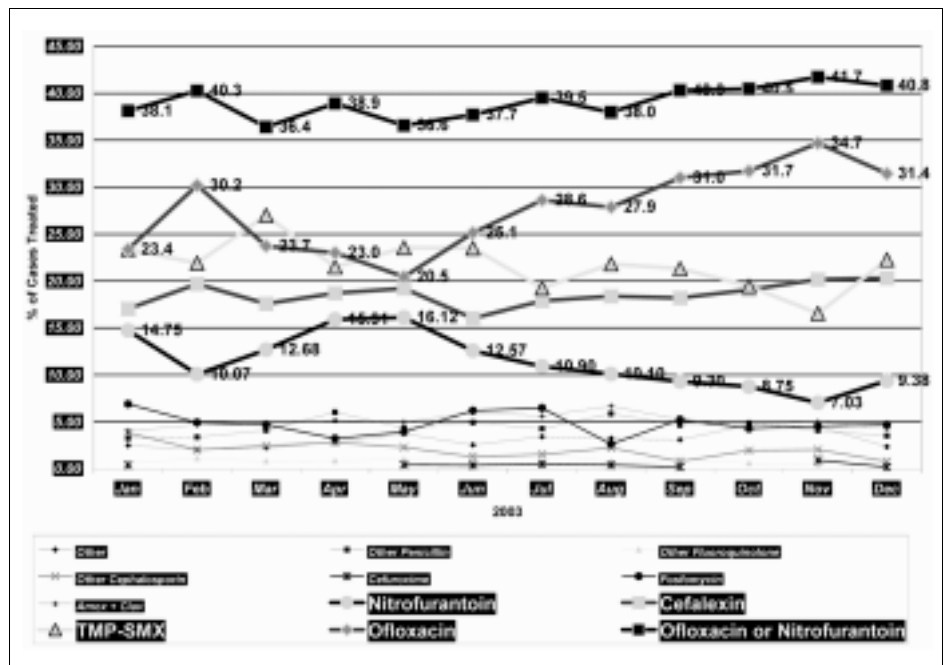
Figure 2. Rate of empiric prescribing UTI, 2003

In 2003 the supply of nitrofurantoin to the fund's pharmacies was disrupted repeatedly, due to difficulties experienced by the importer of the generic equivalent in registering the product with the Health Ministry. Consequently, the rate of prescribing this drug was observed to be erratic throughout the study period, with an average annual rate of only 12.6% of eligible cases treated with this drug as opposed to 13.3% in the years 2000–2001. During the study period the rate of eligible cases treated with nitrofurantoin reached a maximum of 16.2% in May, and a minimum of 7.03% ($P < 0.001$) in November after stock levels had been depleted in many of the fund's pharmacies. However, the influence of this flux did not produce an equivalent effect on the rates of prescription of the other drugs used [Figure 2]. Throughout the study period, variance
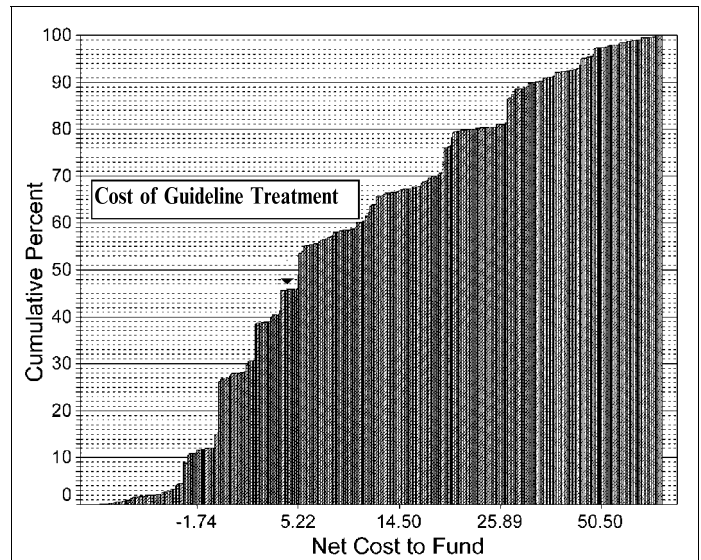
in rates of prescribing parallel and complementary to the fluctuations in the rate of nitrofurantoin was only observed with ofloxacin, peaking in November at a rate of 34.7%, while reaching a minimum of 20.5% in May ($P < 0.001$). Concomitantly, the aggregate rate of cases treated with either one of these two drugs remained constant throughout the study period (36.4% vs. 41.7%, $P = 0.997$). Therefore, had there been an undisturbed, steady supply of nitrofurantoin throughout 2003 facilitating a maximum rate of 16.12% to remain constant throughout the year, an additional 192 cases would have been treated annually with nitrofurantoin instead of ofloxacin. Since the difference in the average cost of treatment with these two drugs is 12.18 shekels [Table 1], the calculated additional expenditure would have been 2,339 shekels, with 1,864

shekels of this expenditure being unwarranted due to unnecessarily long courses of therapy [20].

Discussion

This nationwide study of physicians' prescription behavior in a sample of over 5,000 cases of empirically treated uncomplicated UTI in adult women in the year 2003 shows that successful implementation of the new guideline may reduce the aggregate annual cost of treating this disease. This projected savings can be realized by increasing the rate of choosing a less expensive yet more effective drug and increasing physician awareness to the importance of prescribing the appropriate duration of therapy with the drug of choice. Although the recommended treatment with nitrofurantoin is less expensive than treatment with most other drugs used today, this cost analysis illustrates that encouraging treatment with nitrofurantoin in place of ofloxacin will entail increased expenditure to the fund because the price of ofloxacin has recently plummeted with the introduction of generic equivalents into the market. Despite this, ofloxacin was not designated by the fund as its new drug of choice. This policy decision was made in line with the current international endeavor to curtail the use of fluoroquinolones as part of the effort to stem the growing rate of resistant pathogens. However, in view of the fact that 100% adherence to the guideline is untenable and that rates of physicians prescribing ofloxacin will continue to be significant, we believe that recommendations for the appropriate duration of therapy are imperative to reduce the unnecessary waste in both drugs and money due to inappropriately long treatments with this drug.

Given that our inclusion and exclusion criteria were designed to provide a data set without cases requiring therapy with drugs other than the guideline medication, this calculation assumes a rate of 100% physician adherence. Furthermore, since this study is based solely on empirically treated cases that meet stringent inclusion and exclusion criteria, the actual potential savings of HMO monies annually on the national level is probably much higher.

Conclusions

Most of the simple uncomplicated UTI cases analyzed in this study were not treated according to the new recommendations to be disseminated in the health fund studied. In addition to being suboptimal in terms of evidence-based medicine, the prescribing behavior that we observed indicates a considerable waste of resources due to the use of agents that were not cost-effective. Documentation of adherence patterns accompanied by efforts to explain these outcomes are useful for designing interventions to close the gap between guidelines and physician behavior, thereby reducing costs. Moreover, the health fund needs to implement new methods for promulgating guidelines; these methods should be designed to improve adherence regarding both the choice of drug and the duration of therapy. Considering the magnitude of the resources wasted in the past due to suboptimal adherence to the guidelines, it is plausible that if properly designed and effectively implemented, an educational intervention may prove to be cost-effective.

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