A cost-minimization analysis of treatment options for postmenopausal women with dysuria

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BACKGROUND: Empiric therapy for urinary tract infection is difficult in postmenopausal women because of the higher rates of confounding lower urinary tract symptoms and differential resistance profiles of uropathogens in this population.

OBJECTIVE: The objective of the study was to determine the least costly strategy for treatment of postmenopausal women with the primary complaint of dysuria.

STUDY DESIGN: We performed a cost minimization analysis modeling the following clinical options: (1) empiric antibiotic therapy followed by urine culture, (2) urinalysis with empiric antibiotic therapy only if positive nitrites and leukocyte esterase, or (3) waiting for culture prior to initiating antibiotics. For all strategies we included nitrofurantoin, trimethoprim/sulfamethoxazole, fosfomycin, ciprofloxacin, or cephalexin. Pathogens included *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumonaie*, or *Proteus mirabalis*. Pathogens, resistance, treatment success, and medication side effects were specific to postmenopausal women.

RESULTS: Cost minimization modeling with TreeAge Pro assumed 73.4% of urinary tract infections were caused by *Escherichia coli* with 24.4% resistance to nitrofurantoin, trimethoprim/sulfamethoxazole. With our assumptions, empiric antibiotics with nitrofurantoin, trimethoprim/sulfamethoxazole was the least costly approach ($89.64/patient), followed by waiting for urine culture ($97.04/patient). Except for empiric antibiotics with fosfomcyin, empiric antibiotics was always less costly than using urinalysis to discriminate antibiotic use. This is due to the cost of urinalysis ($38.23), high rate of both urinary tract infection (91%), and positive urinalysis (69.3%) with dysuria in postmenopausal women and resultant high rate of antibiotic use with or without urinalysis. Options with fosfomycin were the most expensive because of the highest drug costs ($98/dose), and tornado analyses showed fosfomycin cost was the most impactful variable for model outcomes. Sensitivity analyses showed empiric fosfomycin became the least costly option if drug costs were $25.80, a price still more costly than almost all modeled baseline drug costs. This outcome was largely predicated on low resistance to fosfomycin. Conversely, ciprofloxacin was never the least costly option because of higher resistance and side effect cost, even if the drug cost was $0. We modeled 91% positive urine culture rate in postmenopausal women with dysuria; waiting for the urine culture prior to treatment would be the least costly strategy in a population with a predicted positive culture rate of <65%.

CONCLUSION: The least costly strategy was empiric antibiotics with nitrofurantoin and trimethoprim/sulfamethoxazole, followed by waiting on culture results. Local resistance patterns will have an impact on cost minimization strategies. Empiric fosfomycin would be least costly with reduced drug costs, even at a level at which drug costs were higher than almost all other antibiotics. In a population with high posttest probability of positive urine culture, urinalysis adds unnecessary cost. Antibiotic stewardship programs should continue efforts to decrease fluoroquinolone use because of high resistance, side effects, and increased cost.

Key words: dysuria, postmenopausal, urinary tract infection, women

Urinary tract infections (UTIs) are the most common type of bacterial infection seen in an outpatient setting,[1] accounting for immense morbidity on both an individual and societal level. UTIs account for more than 8 million office visits and 1 million emergency department visits each year in the United States, eventually resulting in approximately 100,000 hospitalizations.[2] UTIs are especially common in women, with an overall lifetime prevalence of greater than 50%, accounting for at least $2.6 billion annual costs in the United States alone.[2]

The factors predisposing postmenopausal women to UTIs and how best to treat UTIs in this population have been significantly less investigated as compared with those for premenopausal women.[3] The treatment of UTIs in older women is especially difficult because of increased variation and antibiotic resistance in the uropathogens that cause UTIs.[4] Furthermore, clinicians typically rely on patient-reported symptoms to diagnose UTI in ambulatory adult women.

Classic UTI symptoms in premenopausal women have high sensitivity and specificity.[5] However, postmenopausal women have higher rates of chronic lower urinary tract symptoms such as urinary urgency and frequency, which have been found to be unreliable in this population for prediction of UTI.[6]

It is well understood that local resistance patterns should be considered when determining empiric therapy for UTI,[7] but again, there are very few data on resistance patterns in postmenopausal women. What data do exist show higher rates of resistance among causative uropathogens in postmenopausal women.[4] Thus, despite scant evidence, patients and clinicians may rely on changes in baseline symptoms to detect UTI (eg, worsened urgency or frequency, dysuria).

It seems that empiric antibiotic therapy is cost effective in younger, premenopausal populations, but it is unclear whether this is true in postmenopausal women.[8] Recent evidence suggests that in women seeking urogynecological care, the presence of frequency and urgency of urination do not confirm a culture-based UTI diagnosis. Instead, clinicians can more readily detect UTI using the presence of dysuria, which more effectively

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AJOG at a Glance

Why was this study conducted?

Urinary tract infections in postmenopausal women are burdensome and unique because of the high rate of concurrent lower urinary tract symptoms unrelated to infection. The least costly management strategy for this population is unclear.

Key findings

The least costly strategies for treatment of postmenopausal women with dysuria is empiric antibiotic therapy with trimethoprim/sulfamethoxazole and waiting on a urine culture prior to treatment.

What does this add to what is known?

Postmenopausal women are a unique population that deserves targeted research and specific recommendations in terms of optimal therapy for urinary tract infections.

discriminates UTI-positive and UTI-negative individuals.[9]

Commonly accepted practices for women presenting with UTI symptoms would be empiric therapy with antibiotics, first checking urinalysis, or waiting on urine culture (UCx) for treatment.[10] Our objective was to determine the least costly strategy for treatment of postmenopausal women with the primary complaint of dysuria.

Materials and Methods

Decision tree model

We performed a cost-minimization analysis using a decision tree model (TreeAge Pro, Williamstown, MA). All models included an index patient who is a postmenopausal woman with a primary complaint of dysuria. We modeled the following clinical options: (1) empiric antibiotic therapy (eABX) followed by confirmatory urine culture, (2) urinalysis (U/A) with eABX only if U/A is positive for nitrites and leukocyte esterase with confirmatory UCx, or (3) waiting for UCx prior to initiating antibiotics.

This model is based on a previous model of UTI treatment caused by *Escherichia coli* in women older than 18 years, and many assumptions were based on the literature cited from this article.[11,12] Additionally, when available, randomized controlled trials were used for other assumptions.[13,14]

For each strategy a tree was constructed with branch points modeling the possibility of different outcomes along different paths. A highly simplified version of the tree is depicted in the Figure. While the simplified diagram contains 14 different total nodes with 7 terminal branches, the actual tree had 1336 nodes demonstrating the level of complexity and nuances of clinical scenarios that we modeled.

In the final model, we included branches for eABX with each of 5 different antibiotics. This included recognized first-line empiric UTI treatments including nitrofurantoin (100 mg PO BID × 5 days), trimethoprim/sulfamethoxazole (TMP/SMX) (800 mg/160 mg PO BID × 3 days), or fosfomycin (3 g PO × 1 dose).[7] We also modeled second-line therapy with cephalexin (500 mg PO BID × 5 days) or ciprofloxacin (500 mg PO BID × 5 days).

For the wait-for-culture arm, the first antibiotic choice was based on resultant uropathogen and antibiotic resistance profiles. The final model also included the typical distribution of uropathogens in postmenopausal women including *E coli*, *Enterococcus faecalis*, *Klebsiella pneumonaie*, or *Proteus mirabalis*. Antibiotic resistance was specific to each bacterium.

We modeled either the 2 most common or the most common and most detrimental side effects for each of the included drugs as follows: (1) TMP/SMX, gastrointestinal and rash; (2) nitrofurantoin, gastrointestinal and pulmonary; (3) fosfomycin, gastrointestinal and rash, (4) cephalexin, rash and candidal infection; and (5) ciprofloxacin, gastrointestinal and achilles tendon rupture.

Women who were prescribed eABX and subsequently underwent a change in antibiotics after UCx results showed they were at risk for side effects from both antibiotics. Additionally, the model accounts for whether the UTI resolves with treatment. Patients with persistent symptoms either progress to pyelonephritis (with outpatient or inpatient treatment) or, in the absence of pyelonephritis, are treated with a different antibiotic.

Similarly, in the wait-for-culture model, the participants who ultimately had a negative UCx would not incur risk of unnecessary antibiotics, and those with a positive UCx would have an appropriately selected antibiotic based on resistance profile probabilities.

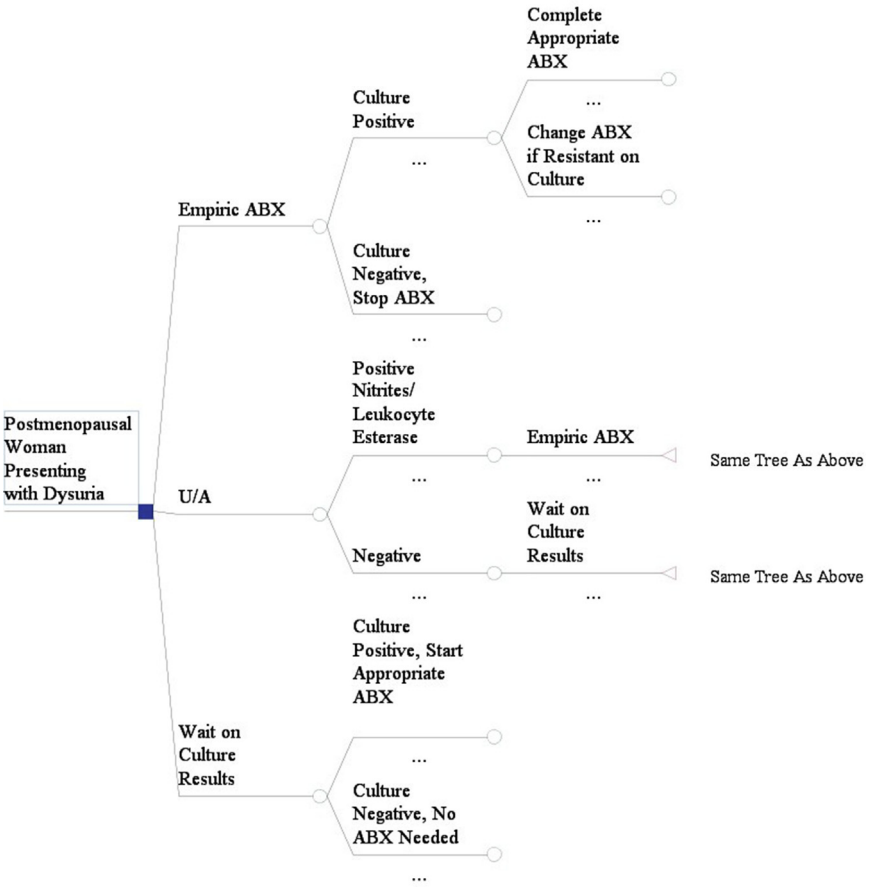
Costs

Drug costs were estimated from GoodRx (www.goodrx.com, accessed 09/2018), and total cost for treatment was based on recommended dosage for the treatment of UTI, as outlined by recent clinical guidelines.[7,15] Data on health care resource use was obtained from the Agency for Healthcare Research and Quality health care cost and utilization project, 2015.[16] For the cost associated with side effects from antibiotics, we estimated costs for treatment of symptoms as per Table 1.

Probabilities

To construct the model, we obtained probabilities from published estimates. The outcome probabilities are contained in Table 2. Probabilities of antibiotic resistance were obtained from either published resources on resistance profiles in postmenopausal women[4] or published antibiograms from the University of Pittsburgh Medical Center. Probabilities for effectiveness were assumed to be equal for all antibiotics.[11,13,17,18] Symptom resolution with incorrect antibiotic was assumed to be reduced by ~50% based on studies showing resolution of symptoms with nonsteroidal antiinflammatories opposed to antibiotics.[14] Probabilities for pyelonephritis risk and outcomes were obtained from different sources.[14,19] Antibiotic side effects were also obtained from different sources (see Table 3).

FIGURE
Simplified decision analysis tree



The tree modeling all possible scenarios is too complex to graphically illustrate here.

ABX, antibiotics; *U/A*, urinalysis.

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Sensitivity analyses

A decision analysis model is based on assumptions and is only as strong as the accuracy of both the assumptions and variables used to create the model. Multiple 1-way sensitivity analyses were performed to test our baseline model assumptions and input values for the variables. Probability variables were assessed at values from 0% to 100% to determine whether a threshold value existed for each variable in which the results of the decision analysis changed from favoring 1 treatment option to another.

Cost variables were assessed in a similar fashion from 0.5 to 2 times the baseline costs. In general, this attempted to show how much less expensive an antibiotic would need to be or how high an antibiotic resistance percentage would have to be to favor a different treatment branch. The protocol of this study was approved by the University of Pittsburgh Institutional Review Board with exempt approval (PRO17110640).

Results

This study used a cost-minimization analysis to identify the treatment option with the lower cost for management of dysuria in postmenopausal women. Because of the complexity of modeling resistance profiles for all other possible bacterial species, we considered only the 4 most common uropathogens. We assumed 73.4% of UTIs were caused by *E coli* with 3 other pathogens responsible for all but 12% of infections. Additional assumptions are present in Table 2.

We modeled an 80% chance of resolution of symptoms with correct antibiotic choice and an assumption of patient compliance with completion of therapy. We utilized bacteria-specific antibiotic resistance probabilities with highest resistance of *E coli to* TMP/SMX and ciprofloxacin (Table 3).

With our assumptions, eABX TMP/SMX was the least costly approach ($89.64/patient, Table 4), followed by waiting for UCx ($97.04/patient). Additional outcomes are presented as incremental cost with eABX TMP/SMX as reference.

Fosfomycin is a very expensive medication ($98/dose) and therefore was the costliest eABX treatment option. Importantly, for any given antibiotic, eABX was always less costly than using U/A to discriminate eABX use. Except for eABX with fosfomcyin, all eABX options were less costly than any options using U/A first. In postmenopausal women with dysuria, this is due to the cost of U/A ($38.23), the high rate of UTI (91%), and the high rate of positive U/A (69.3%).

With these assumptions, the resultant rate of ABX use is high with or without U/A. Again, options with fosfomycin were the most expensive because of the highest drug costs ($98/dose), and tornado analyses showed fosfomycin cost was 1 of the most impactful variables for model outcomes. Other impactful variables included the cost of urinalysis and other antibiotics, the probability that a UCx is positive, and the probability that symptoms resolve with appropriate antibiotics.

In sensitivity analyses, eABX with fosfomycin became the least costly option if drug costs were $25.80, a price still more costly that almost all modeled baseline drug costs. This outcome was largely predicated on low resistance to fosfomycin. Conversely, a sensitivity analysis showed ciprofloxacin was never the least costly option because of higher resistance and side effect cost, even if the drug cost was $0. We initially modeled a

TABLE 1
Cost of antibiotics and health care resources used for the treatment of postmenopausal women with dysuria

Variables	Mean cost per unit time or per item (US$)	References
Antibiotics		
Fosfomycin, 3 g oral dose	98	15
TMP/SMX, 1 DS tablet BID × 3 days	12	
Nitrofurantoin 100 mg PO BID × 5 days	37	
Cephalexin 500 mg PO BID × 7 days	14	
Ciprofloxacin 500 mg PO BID × 5 days	14	
Laboratory testing and health care utilization		
Urinalysis	38	27
Initial urine culture with sensitivities	51	27
Hospitalization for pyelonephritis (ICD-9 590.1)	6,244	16
Outpatient treatment of pyelonephritis (ciprofloxacin 500 mg BID × 7 days or 1 dose ceftriaxone 1 g and then ciprofloxacin)		7
Antibiotic side effects		
Treatment of GI symptoms, Zofran 4 mg oral (10 tablets)	44	15
Treatment of skin reaction, Benadryl 25 mg oral (10 tablets)	6	15
Treatment of achilles rupture, inpatient stay (ICD-9 727.67)	9205	16
Treatment of long-term pulmonary complication, inpatient stay (ICD-9 516.31)	30,123	16
Treatment of candidal infection, Miconazole 3 day treatment	5	15

DS, double strength; *GI*, gastrintestinal; *ICD-9, International Classification of Diseases*, ninth revision; *TMP/SMX*, trimethoprim/sulfamethoxazole; *UTI*, urinary tract infection.
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91% positive UCx rate in postmenopausal women with dysuria. If considering a different population, waiting for the UCx prior to treatment would be the least costly option if you assume a pretest probability of positive UCx of <65%.

Comment

In our cost-minimization analysis in postmenopausal women presenting with dysuria, the least costly strategy was empiric antibiotic therapy with TMP/SMX, followed by waiting on UCx results prior to the initiation of antibiotic therapy.

The Infectious Diseases Society of America recommends TMP/SMX, nitrofurantoin, or fosfomycin as first-line therapy for uncomplicated cystitis.[7] Our model supports this practice in terms of cost with empiric TMP/SMX and nitrofurantoin both among the least costly options for management. However, empiric fosfomycin was the most costly option, with a sensitivity analysis demonstrating that the cost of fosfomycin was 1 of the most impactful variables.

Recently a similar cost-minimization analysis performed in Canada[12] concluded that fosfomycin is a safe, effective agent to treat UTI because of a low resistance profile, single-dose treatment administration, and similar cost of the medication. This was not the case in our model because of a significantly higher cost of fosfomycin in the United States.

While most *E coli* isolates associated with UTI remain susceptible to fosfomycin, antibiotic resistance to antibiotics like TMP/SMX is increasing. Because fosfomycin is a recommended first-line therapy for UTI by the Infectious Diseases Society of America but is often cost prohibitive, it is imperative that the source of cost discrepancy is investigated and confronted to provide appropriate care for those suffering from UTIs.

The US Food and Drug Administration has warned about the use of oral fluoroquinolone antibiotics and has strongly advised that health care professionals should not prescribe fluoroquinolones to patients who have other treatment options for bacterial infections, including uncomplicated urinary tract infections, because the risks outweigh the benefits in these patients.[20]

These guidelines have had variable implementation, and fluoroquinolones remain a first-line therapy option in some available published guidelines.[21] Our model demonstrates that use of fluoroquinolones was never the least costly option because of resistance rates and side effect profile (specifically risk of

TABLE 2
Probability values used in the model for decision tree nodes

Variable	Base case	References
Positive urine culture if postmenopausal woman has dysuria	0.90	
Pathogens present in UTI		4,9
Escherichia coli	0.73	
Enterococcus faecalis	0.05	
Klebsiella pneumonaie	0.06	
Proteus mirabalis	0.04	
Other	0.12	
Sensitive isolate: UTI resolution	0.80	11-13,17,18
Resistant isolate: UTI resolution	0.54	14
Sensitive isolate: risk of pyelonephritis	0.00	Assumption
Resistant isolate: risk of pyelonephritis	0.05	14
Hospitalization for pyelonephritis	0.20	19
Positive urine culture if urinalysis negative (no nitrites or leukocyte esterase) with urinary symptoms	0.10	24
Positive urine culture if urinalysis positive (nitrites and leukocyte esterase positive) with urinary symptoms	0.90	24

UTI, urinary tract infection.

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achilles tendon rupture). If fosfomycin remains such a costly medication, providers will continue to be forced to choose between a more costly but superior medication and a cheaper, non-recommended option.

It is commonly accepted that local resistance patterns should guide empiric antibiotic therapy choices for urinary tract infection. There are a myriad of studies evaluating different resistance patterns in the elderly and in different countries.[22,23] We utilized resistance data from the 1 existing paper specifically evaluating postmenopausal women[4] and local resistance data. Further studies are imperative to understand more about causative agents and resistance profiles in this specific population to aid in clinical decision making for postmenopausal women with dysuria.

Finally, in a population of postmenopausal women with dysuria who have a high pretest probability of a UTI, we found that urinalysis adds unnecessary cost. The sensitivity and specifically of urinalysis for discrimination of positive UCx varies greatly in the literature. Turner et al[24] found a high sensitivity and specificity of urinalysis positive for nitrites and leukocyte esterase in a population of women with irritative voiding symptoms, but other studies report low yield.[5] In a population with a lower pretest probability of positive Ucx, urinalyses may provide insight.

TABLE 3
Antibiotic resistance and side effect probabilities

Antibiotic resistance

	Nitrofurantoin	TMP/SMZ	Fosfomycin	Cephalexin	Ciprofloxacin
E coli	0.09	0.24	0.0	0.09	0.20
E faecalis	0.03	—	0.05	—	0.27
K pneumonaie	0.69	0.13	0.06	0.19	0.10
P mirabalis	0.84	0.24	0.10	0.17	0.16

Antibiotic side effects

	Nitrofurantoin (100 mg BID, 5 days)	TMP/SMZ (800/160 mg BID, 3 days)	Fosfomycin (3 g, 1 dose)	Cephalexin (500 mg BID, 5 days)	Ciprofloxacin (500 mg BID, 5 days)
Gastrointestinal	0.050	0.143	0.060	0.390	0.08
Skin reaction/rash	—	0.023	0.016	0.015	—
Achilles tendinopathy/rupture	—	—	—	—	0.003
Long-term pulmonary complication	0.00029	—	—	—	—
Candidal infection	—	—	—	0.004	—

TMP/SMX, trimethoprim/sulfamethoxazole.

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TABLE 4
Treatment options for postmenopausal women with dysuria ranked by cost

Strategy	Cost (2018 $US)	Incremental cost ($US)	Increase from eABX TMP/SMX, %
eABX TMP/SMX	89.64	Reference	Reference
Wait on UCx to treat	97.04	7.39	8.24
eABX cephalexin	97.45	0.41	8.70
eABX nitrofurantoin	109.83	12.38	22.51
eABX ciprofloxacin	113.76	3.93	26.90
U/A, then TMP/SMX	121.63	7.87	35.68
U/A, then cephalexin	126.64	5.01	41.26
U/A, then nitrofurantoin	134.81	8.17	50.38
U/A, then ciprofloxacin	138.00	3.19	53.94
eABX fosfomycin	161.51	23.50	80.16
U/A, then fosfomycin	170.65	9.14	90.36

eABX, empiric antibiotic therapy; *TMP/SMX*, trimethoprim/sulfamethoxazole; *U/A*, urinalysis; *UCx*, urine culture.
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Dysuria has been found to be the most discriminating symptom of a UTI in urogynecological patients,[9] and therefore, we modeled a high rate of UTI in this population. Importantly, this paper did not report an exact percentage of UTI in women specifically with dysuria, and the 91% proportion is related to women with self-reported UTI. The median dysuria score in the non-UTI group was dysuria. Multiple other studies have noted that specifically acute dysuria most effectively predicts laboratory confirmation of UTI.[25]

We know that interpreting the probability of urinary tract infection based on symptoms and testing allows for greater accuracy in diagnosis of urinary tract infection, decreasing overtreatment and encouraging antimicrobial stewardship.[26] Because older women have a higher chance of chronic lower urinary tract symptoms, like urgency and frequency, and higher rates of asymptomatic bacteriuria, it is possible that the strategy of waiting for a UCx prior to treatment is less costly than empiric therapy in many other women presenting with symptoms other than dysuria.[25] Again, we ultimately found that waiting for the UCx prior to treatment would be the least costly option if one assumes a pretest probability of a positive urine culture of <65%.

Strengths of our study include the unique and specific population that the cost minimization was created for because this population is particularly afflicted by UTIs. We modeled detailed clinical pathways including population-specific infective organism distributions and resistance patterns. We included side effects of medications and symptom resolution after treatment. We took 2–3 of the most common or costly antibiotic side effects into account in our model. Other common cost-analysis of antibiotics for UTI do not model cost associated with side effects. Although we did not include all possible side effects, we believed it was important to take these variables into account, especially in terms of the cost of rare but significant complications.

Our study limitations include those inherent to a cost-minimization analysis. We utilized existing probabilities in the literature and performed sensitivity analyses to investigate variation in probability and cost and how these variations affected the model. Antibiotic efficacy was assumed to be equal based on meta-analysis data and other existing literature. However, the meta-analysis was focused only on comparing fosfomycin with other antibiotics. Meta-analyses providing efficacy comparisons between the other antimicrobial agents were not identified in the literature. Similarly, we were unable to locate sources for the efficacy of each agent in susceptible vs resistant infections but decided to use resolution of symptoms without antibiotics as a proxy.[14]

Another consideration is that we did not model utility values or quality-adjusted life-years. Our focus of this cost-minimization analysis was to investigate cost discrepancy between treatment options as a primary investigation, but future studies that investigate utility values are warranted.

Finally, this cost-minimization analysis is specific for postmenopausal women with dysuria. We did not utilize specific resistance patterns in women with recurrent UTIs; therefore, our model cannot be generalized to women with recurrent UTI.

In conclusion, in a specific population of postmenopausal women with dysuria, the least costly strategy is empiric TMP/SMX. This result may change when local resistance patterns, probability of positive UCx, and drug costs are all considered. ■

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