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Cystitis Treatment in Women, Circa 2011: New Role for an Old Drug

Paradigm shifts in patient care all too frequently result in recommendations for more costly medications, procedures, or devices. Clinicians rarely encounter newer therapies that improve outcomes at a lower cost—such as the "rediscovery" of metformin therapy for type 2 diabetes.[1] The article by McKinnell et al[2] in this issue of *Mayo Clinic Proceedings,* coupled with 2011 practice guidelines from the Infectious Diseases Society of America (IDSA) and European Society for Microbiology and Infectious Diseases,[3] provides important and welcome changes in recommendations for cost-effective management of uncomplicated lower urinary tract infection (UTI) in women.

Escherichia coli and other common uropathogens possess unique surface adhesins on fimbriae and other adhesive organelles. These attachment systems promote bacterial adherence to the epithelial cell membrane and subsequent colonization of the vagina, perineum, and periurethral region with colonic bacteria. Bacteria ascend to the bladder from this colonized reservoir, commonly after sexual intercourse. Bladder invasion by bacteria may or may not lead to a symptomatic UTI, depending on the complex interplay of host genetic, behavioral, and biological factors.[4] Women with symptomatic cystitis present with abrupt onset of dysuria, urinary frequency, and urinary urgency. Historical factors that increase the likelihood of UTI include the following: hematuria, suprapubic pain, malodorous or turbid urine, incontinence, prior UTIs, recent sexual intercourse, spermicidal contraception, and recent antibiotic administration.[5]

Although office urine dipstick or laboratory urinalysis demonstrating nitrites (from the bacterial breakdown of urinary nitrates), leukocytes, or blood helps confirm a clinical diagnosis of UTI, these markers are not sufficiently sensitive to exclude the diagnosis in patients with a high pretest probability of infection,[6] in part due to the common practice of "pushing fluids" (with resultant dilution of the urine sample) before seeking medical care.

In 1999, the IDSA recommended empirical therapy for acute cystitis in select patients[7] without ordering a pretreatment urine culture because the clinical outcome (resolution or persistence of symptoms) would be apparent by the time the urine culture results were available 48 to 72 hours after initiation of therapy. Appropriate empirical treatment reduces costs and increases patient convenience.[8] Urine cultures with susceptibility data can be reserved for patients who are pregnant, have symptoms of upper tract disease, have risk factors for a resistant organism, or experience therapeutic failure or early relapse. Clinical algorithms that triage selected patients with cystitis to empirical treatment result in outcomes that compare favorably with office-based therapy (ie, therapy based on the results of urine dipstick testing, urinalysis, or urine culture and sensitivity).[9] The combination of dysuria and urinary frequency without vaginal discharge or irritation has a 96% positive predictive value in diagnosing UTI, eliminating the need for urinalysis or culture.[6] Patients without dysuria, with vaginal symptoms, or with atypical or upper tract symptoms require an office visit and examination for alternative diagnoses such as sexually transmitted diseases, vaginitis, and pyelonephritis.

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Because cystitis is a mucosal infection and most antibiotics achieve high urinary concentrations, administration of an appropriate antibiotic for only a few days results in resolution of symptoms and bacteriuria in 90% to 95% of patients.[10] For the past several decades, 3 days of treatment with twice-daily trimethoprim-sulfamethoxazole (TMP-SMZ) or trimethoprim (TMP) alone has been the accepted first-line therapy for acute uncomplicated cystitis.[7] Trimethoprim-sulfamethoxazole achieves very high urinary concentrations and eliminates bacteria from the vaginal-perineal reservoir due to "ionic trapping" of TMP

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in the acidic vaginal secretions.[11] Single-dose TMP-SMZ therapy has largely been abandoned because of a higher rate of treatment failure, whereas more prolonged courses of therapy increase the frequency of adverse effects without increasing the cure rate.[12]

However, as the use of TMP-SMZ has increased substantially, uropathogens have shown increasing drug resistance.[13] Outpatient isolates of *E coli* in the United States show resistance rates ranging from 15% in the upper midwest to greater than 40% in the southwest and south-central United States.[14] Sulfonamide administration can also be associated with a variety of serious adverse reactions, including the Stevens-Johnson syndrome.[15]

Because of these limitations, many clinicians now prescribe a 3-day course of a fluoroquinolone (FQ) as first-line empirical therapy for uncomplicated cystitis, rather than reserving FQs for treatment failures, resistant organisms, or patients with medication allergies.[16] However, increasing FQ resistance among *E coli* isolates has complicated the management of UTIs.[17] In addition, severe *Clostridium difficile* colitis has increasingly been attributed to FQ use.[18]

In the setting of increased TMP-SMZ resistance and the need to limit the use of FQs, investigators have reevaluated the role of nitrofurantoin—a nearly forgotten drug—in the treatment of uncomplicated UTIs. A recent large clinical trial demonstrated that a 5-day course of twice-daily nitrofurantoin macrocrystals was equivalent or superior to a standard 3-day course of TMP-SMZ.[19] Most urinary isolates have remained sensitive to nitrofurantoin (97.7% sensitivity among *E coli* in one study[20]), despite decades of clinical use, presumably because of minimal gastrointestinal excretion of the drug (ie, minimal contact with enteric bacteria) and because nitrofurantoin is used almost exclusively to treat UTIs. However, nitrofurantoin has poor activity against *Proteus*, *Serratia*, and *Pseudomonas* species and should not be used to treat UTIs due to these organisms. Nitrofurantoin is inexpensive, safe in early pregnancy, and rarely causes *C difficile* colitis. Although long-term use is associated with pulmonary fibrosis, the only common adverse effects with short-term use are nausea and headache. Hemolytic anemia can be seen in patients with glucose-6-phosphate dehydrogenase deficiency. Rare serious adverse effects include drug-induced hepatitis, hypersensitivity pneumonitis, and peripheral neuropathy (especially in patients with renal insufficiency).

In March 2011, the IDSA and the European Society for Microbiology and Infectious Diseases published joint updated guidelines for treatment of uncomplicated cystitis.[3] The expert panel elevated nitrofurantoin to first-line therapy (along with TMP-SMZ) because of its efficacy, minimal resistance, and lower propensity to cause "collateral damage" (ie, selection of drug-resistant organisms and colonization/infection with multidrug-resistant organisms). When deciding between TMP-SMZ and nitrofurantoin, antibiotic resistance to TMP-SMZ is the most important identified factor for clinicians to consider. Cost factors should also be considered in the management of UTIs.

In this issue of the *Proceedings,* McKinnell et al[2] present the results of a sophisticated decision analysis comparing the cost-effectiveness of nitrofurantoin, TMP-SMZ, and FQs in the treatment of uncomplicated UTIs. Decision analyses help clinicians answer questions about multiple treatment alternatives that would otherwise be difficult to resolve in a clinical trial.[21] The authors based their analysis on an extensive and detailed review of the literature on costs and clinical outcomes of UTIs. They conducted sensitivity analyses for a wide spectrum of costs (eg, for medication, office evaluation, treatment failure, and adverse reactions), antibiotic sensitivities, and treatment outcomes. To our knowledge, this is the first published decision analysis of the use of empirical therapy with nitrofurantoin and confirms its equivalence or superiority in settings in which TMP-SMZ resistance exceeds 17%. Indeed, TMP-SMZ resistance currently exceeds 15% in most of the United States.[13] The McKinnell et al analysis supports and reinforces the following IDSA expert recommendations:[3]

- Consider nitrofurantoin (nitrofurantoin monohydrate/macrocrystals, 100 mg twice daily for 5 days) as first-line therapy for women with signs and symptoms of acute uncomplicated cystitis. Avoid nitrofurantoin use in patients with symptoms of upper tract disease (fever, chills, nausea, vomiting, or flank pain).
- TMP-SMZ remains a viable alternative (if local resistance is low), especially if the patient has not received recent TMP-SMZ therapy or has an infecting strain known to be susceptible.
- Reserve FQ therapy for treatment failures or for patients with suspected upper tract disease.
- Avoid using amoxicillin or ampicillin as empirical therapy because of high rates of antimicrobial resistance and poor efficacy.
- Alternative β-lactam therapies (eg, amoxicillin-clavulanate, cefdinir, cefaclor, cefpodoxime) for 3 to 7 days are appropriate when other agents cannot be used.
- Fosfomycin trometamol (administered as a single 3-g dose).

Note that fosfomycin is active against most gram-positive and gram-negative bacteria, including extended spectrum β-lactamase–producing organisms and compares favorably to other antimicrobial agents.[22,23] However, fosfomycin trometamol is significantly more expensive than nitrofurantoin, TMP-SMZ, and ciprofloxacin.

Nitrofurantoin has evolved as the "metformin" of uncomplicated UTIs: an old drug rediscovered to be an

effective, safe, well-tolerated, and inexpensive first-line therapeutic option for cystitis. Nitrofurantoin has maintained its antimicrobial activity against most uropathogens that cause uncomplicated cystitis, and it is unlikely to induce antibiotic resistance. Clinicians accustomed to using TMP-SMZ for uncomplicated cystitis should consider switching to nitrofurantoin because of increasing TMP-SMZ resistance and treatment failures. Clinicians using FQs in this setting should consider switching to nitrofurantoin in order to reserve FQ use for more serious infections and to further curtail the development of resistant microorganisms.

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