Management of Urinary Tract Infections in the Era of Increasing Antimicrobial Resistance

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KEYWORDS

• Urinary tract infection • Acute cystitis • Resistance • Fosfomycin
• Trimethoprim-sulfamethoxazole • Nitrofurantoin • Recurrent UTI

KEY POINTS

- Antimicrobial resistance in common urinary pathogens is increasing at an alarming rate, as a result of overuse and misuse of antibiotics. Resistance patterns vary by geographic location, but are rising nationwide and globally.
- In the properly selected woman with suspected uncomplicated cystitis, evaluation by a symptom-based approach is both cost-effective and may improve patient satisfaction.
- Acute, uncomplicated urinary tract infections (UTIs) should be treated with fosfomycin, nitrofurantoin, or trimethoprim-sulfamethoxazole. Fluoroquinolones are no longer recommended as first-line therapy for uncomplicated UTI.
- Recurrent UTIs are common. Risk factors include recent intercourse, new sexual partner, and contraceptive type.
- Prevention of recurrent UTIs should begin with a history-based approach to identify associated factors. Antimicrobial prophylaxis should be reserved for use when all other considerations have failed.

INTRODUCTION

A previously healthy 32-year-old woman presents to primary care with dysuria and urinary frequency of 2 days' duration. She denies fevers, chills, or flank pain. You have seen her for this reason 3 times in the last 2 years.

This scenario is frustratingly common in modern medicine. The problem is becoming more complex. Despite the availability of oral antibiotics (in fact, because of that

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availability), antimicrobial-resistant gram-negative rods are becoming increasingly important for patients and physicians alike. This article provides an update and practical strategies for the prevention, diagnosis, and treatment of urinary tract infections (UTI) in the contemporary era.

INCIDENCE AND IMPACT

Acute uncomplicated bacterial cystitis is a frequent problem in the American outpatient setting, with an estimated 8.6 million cases annually,[1] accounting for 1.6 billion dollars in health care expenditures.[2] Acute cystitis is associated with an average of 6.1 days of symptoms and 1.2 productive days lost because of illness.[3] Of patients with acute cystitis, an estimated 59% present to primary care and 23% to emergency departments.[1]

MICROBIOLOGY, RESISTANCE MECHANISMS, AND RISK FACTORS

Staphylococcus saprophyticus and any member of the *Enterobacteriaceae* family (including *Escherichia coli*, *Klebsiella pneumonia* and *Proteus mirabilis)* and can cause cystitis. However, *E coli* remains the most common cause, responsible for an estimated 65% to 95% of cases. Because of the predominance of this bacteria, *E coli* resistance is often a focus of epidemiologic resistance studies.[4–6]

The most recent Infectious Disease Society of America (IDSA) guidelines for treatment of uncomplicated cystitis and pyelonephritis focused on the resistance of organisms responsible for uncomplicated cystitis.[7] The guidelines describe the association between antimicrobial prescribing and resistance development as collateral damage. For example, areas with high rates of fluoroquinolone prescribing for all reasons, in particular sinopulmonary infections, show higher *E coli* fluoroquinolone resistance compared with areas with lower prescription rates.[8] Despite clinical practice guidelines for a wide variety of common infections, studies continue to document improper antibiotic prescribing patterns, both in the hospital and in the ambulatory setting.[9,10]

Microbes have developed multiple antimicrobial resistance mechanisms, including alterations of the drug target, enhanced drug efflux, and limitation of drug influx.[11] Many resistance elements are chromosomal point mutations that provide a survival advantage in the setting of selective drug pressure.[12] In contrast, plasmid-mediated genes provide a highly mobile alternative mode of resistance of increasing prevalence. Microbes can exchange plasmids between members of the same or different species. Examples of plasmid-mediated resistance include carbapenem resistance of *Klebsiella pneumoniae* and fluoroquinolone resistance of *Enterobacteriaceae*. Resistant bacteria have increased survivorship under antibiotic selection, leading to increased prevalence.[11,12] Furthermore, plasmids often contain genes encoding for resistance against multiple drugs, and thus bacteria resistant to 1 antimicrobial agent are more likely to also be resistant to others.[5,6]

Resistance caused by extended spectrum β-lactamases (ESBL) deserve special mention. ESBLs are a family of plasmid-borne hydrolytic enzymes that inactivate penicillins and cephalosporins. Original descriptions of ESBL involved *E coli* and *K pneumoniae*, but the plasmids have been detected in a variety of gram-negative rods since then. The current frequency of ESBL expression probably varies substantially from region to region, although national and international numbers are difficult to come by. It is clear that these plasmids are seen routinely in areas where they were previously not found; for example, resistance increased from undetectable to detectable in 8 years' surveillance in Europe, although the overall frequency was low as of

2012.[6] Although penicillins and cephalosporins are rendered inactive by ESBLs, carbapenems are still generally active against them.

However, carbapenem-resistant *Enterobacteriaceae* are also on the increase, thanks to the expression of carbapenemases. Like ESBLs, these are β-lactamases, but they have activity against carbapenems in addition to penicillins and cephalosporins. Two of the most clinically important carbapenemases are the *Klebsiella pneumoniae* carbapenemase (KPC) and the New Delhi metallo-β-lactamase-1 (NDM-1).

KPC expression has been detected in many *Enterobacteriaceae* including *E coli* and *Proteus*, as well as non-*Enterobacteriaceae* such as *Pseudomonas aeruginosa*. It was first identified in North Carolina in 2001, and since then, has become endemic in many hospitals in the North Eastern United States.[13] In addition to β-lactams, cephalosporins, and carbapenems, these bacteria typically show resistance to quinolones and aminoglycosides.[14] KPC resistance was believed to be isolated to the United States until it was identified in France in 2005 (in a patient recently hospitalized in the United States).[15] This enzyme is encoded by a transposon capable of insertion into diverse plasmids, thereby providing rapid and interspecies transmission.[13] Another worrisome realization is that resistance detection by standard methods is not reliable. Sensitivity testing to meropenem and imipenem is inadequate to evaluate for in vitro carbapenem resistance,[13] because some carrier organisms remain in the susceptible range by in vitro testing. Ertapenem testing has shown better sensitivity than the other carbapenems. Those with increased minimum inhibitory concentrations (MICs) to carbapenems should be tested using the modified Hodge test for further resistance characterization.[14] However, this specialized technique is challenging to perform, and it is possible that many laboratories do not detect KPC expression.

NDM-1 was first recognized in a patient hospitalized in New Delhi, India in 2007.[16] Most cases since that time have been linked in some way to the Indian subcontinent, where prevalence estimates range from 5% to 18%. By August 2010, the resistance was found worldwide, with the exception of Central and South America.[17] By June 2012, a total of 13 cases had been reported in the United States.[16] Organisms with NDM-1 expression are usually sensitive to colistin and may be sensitive to tigecycline and fosfomycin.[17] The NDM-1 gene is transmitted on a variety of plasmids, some highly mobile, even between distantly related gram-negative organisms.[17] Bacterium with NDM resistance can colonize hosts and contaminate water and environmental surfaces.[18]

Regardless of the mechanisms involved, resistance patterns continue to change, in patterns that are geographically distinct and dynamic.[5] For example, overall *E coli* drug resistance is higher in Portugal and Spain when compared with Northern European nations and Canada.[4] There is a pressing need for a unified national American drug resistance surveillance system. One effort, the National Antimicrobial Resistance Monitoring System (available at http://www.NARMS.com), a coalition between the US Centers for Disease Control, Food and Drug Administration (FDA), and Department of Agriculture, monitors the resistance patterns of enteric bacteria cultured from humans and animals. However, this group is largely focused on food-borne illness, and is underfunded to investigate patterns of gram-negative resistance as they pertain to UTI.

Defining one's local resistance patterns is even more difficult. Many hospitals monitor resistance of organisms cultured in their microbiology laboratory. These data may reflect drug-exposed, hospital-acquired organisms more than community-acquired, outpatient-based illnesses. Thus, hospital antibiograms likely overestimate community resistance patterns.[19,20] However, the IDSA recommends avoiding antimicrobial agents when local resistance exceeds 20%,[7] implying that primary care

providers should be familiar with local outpatient resistance patterns. We hope that local health departments will collaborate with outpatient providers and their laboratories to create local ambulatory antibiograms.

EVALUATION

Your patient is calling on Friday afternoon with her usual UTI symptoms. She does not have fevers, back pain, nausea or vomiting. Can empirical treatment be started? Should you obtain a urinalysis or culture before treatment?

Urine culture remains the gold standard to confirm suspected UTI, but bacterial colony count and resistance patterns require more than 24 hours of analysis, and therefore a probable diagnosis must be made by history, examination, and point-of-care diagnostics. Symptoms of dysuria, frequency, hematuria, nocturia, and urgency all increase the probability of UTI, with likelihood ratios between 1.10 and 1.72, whereas vaginal discharge decreases the likelihood of UTI (**Table 1**).[21]

Dipstick analysis is a quick and cheap diagnostic tool. But is it reliable? The positive predictive value is substantial in the setting of both positive leukocyte esterase (LE) and nitrite, but these tests are limited by low sensitivity, and therefore a low negative predictive value as well (**Table 2**).[22] For example, not all uropathogens can convert nitrate into nitrite. With limited negative predictive values, UTI may be difficult to rule out even when all features are negative.[22,23] Dipstick-positive hematuria has been shown to increase the likelihood for UTI and is additive with a positive nitrite.[21] Symptom-based evaluation provides only modest positive predictive value, whereas urine dipstick analysis is unable to effectively rule out UTI when there is moderate clinical suspicion.

Definitive diagnosis of cystitis can be made only with clinical symptoms and bacteriuria. IDSA guidelines recommend a colony-forming unit level of 10^5 or greater as diagnostic of UTI.[7] However, colony counts of 10^2 have shown improved sensitivity and retained specificity among symptomatic women.[24]

In some settings, empirical treatment has been found to be cost-effective and to reduce overall symptom duration when compared with dipstick and culture evaluations.[25] Guidelines have been proposed to help providers reduce expense and inconvenience to patients. **Fig. 1** represents 1 such guideline modified to reflect concerns regarding resistance. These guidelines have reduced the use of urinalysis, cultures,

Table 1
The accuracy of symptoms for diagnosis of UTI

Symptom	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
Dysuria	0.78	0.36	1.22 (1.11–1.34)	0.61 (0.50–0.74)
Frequency	0.90	0.17	1.09 (1.02–1.16)	0.58 (0.32–0.79)
Urgency	0.75	0.36	1.17 (1.04–1.31)	0.70 (0.57–0.86)
Fever	0.10	0.89	0.90 (0.45–1.80)	1.01 (0.93–1.10)
Vaginal discharge[a]			0.65 (0.51–0.83)	1.10 (1.01–1.20)
Hematuria[b]			1.68 (1.06–2.66)	0.89 (0.82–0.98)

[a] Based on $\geq 10^2$ CFU/mL.
[b] Based on $\geq 10^3$ CFU/mL.
Adapted from Giesen LG, Cousins G, Dimitrov BD, et al. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. BMC Fam Pract 2010;11:78.

Table 2
The accuracy of dipstick for diagnosis of UTI

Dipstick	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
Positive LE[a]	0.62	0.70	2.01	0.54
Positive nitrite[b]	0.50	0.82	2.78	0.61
Positive LE or nitrate[b]	0.75	0.70	2.50	0.36
Both LE and nitrate positive[b]	0.45	0.99	45	0.56

Likelihood ratios calculated from published data.
[a] Nonurologic population.
[b] General population.
Data from Deville WL, Yzermans JC, Van Duijn NP, et al. The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. BMC Urol 2004;4:4.

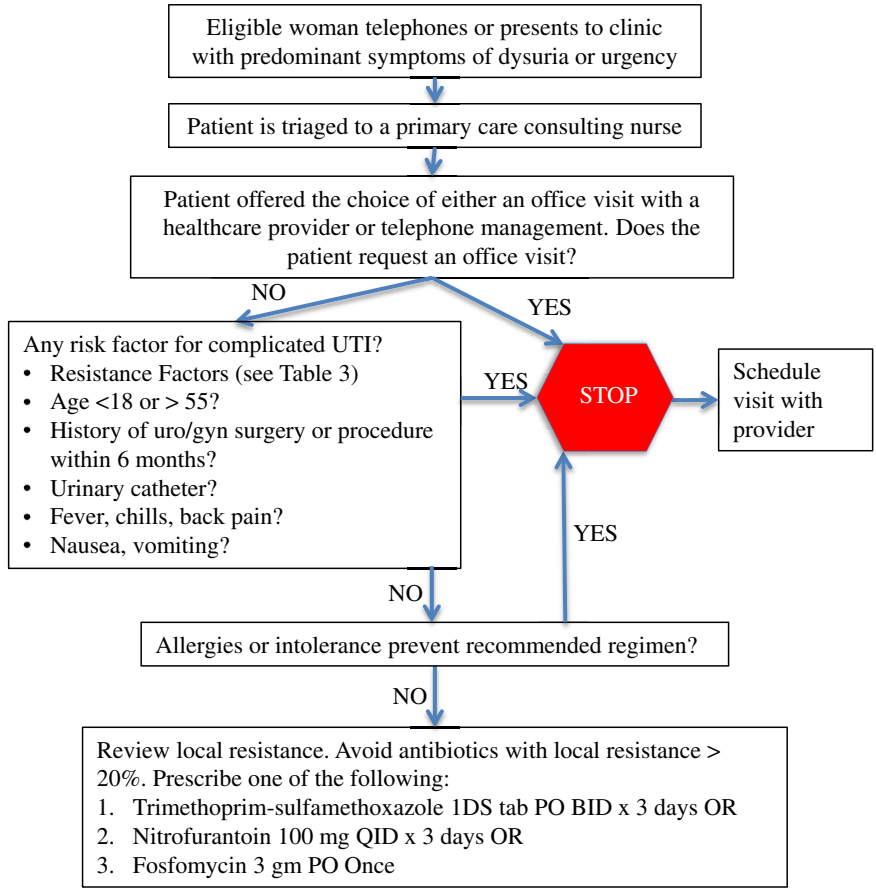

Fig. 1. Evaluation and management of acute, uncomplicated UTI. (*Adapted and modified from* Sanjay S, Scholes D, Fihn SD, et al. The effectiveness of a clinical practice guideline for the management of presumed uncomplicated urinary tract infection in women. Am J Med 1999;106(6):638.)

and office visits and have increased use of recommended antibiotics.[26,27] Cystitis is one of the few, if not the only, infectious diseases in which telephone triage antibiotic prescribing has been shown to be an acceptable option. In indeterminate cases, dipstick or culture should be used to assist with making the diagnosis and reducing antibiotic use for inappropriate cases. Culture is recommended if pyelonephritis is suspected or if the individual patient is at higher risk for resistance.

In cases in which the diagnosis remains unclear, it may be appropriate to delay initiation of antibiotics. In this scenario, the patient submits a urine culture, which is monitored for 48 hours. If positive, a prescription is provided. In a randomized, controlled trial evaluating this approach, patients in the delayed antibiotics arm received antibiotics less often, although those who ruled in for UTI had symptoms for 37% longer than those in the immediate arm. The severity of symptoms was not of significant increased severity in either arm, and there was no increased progression to pyelonephritis among those in the delayed arm.[28]

Because geographic resistance is difficult to estimate, many studies have examined individual factors believed to be predictive for development of resistant UTI. These factors include age older than 60 years,[29,30] recent international travel,[31] previous history of a UTI,[6] chronic medical conditions,[5,6] recent hospitalization,[8] and any recent antibiotic course[6,8,32] (with more recent treatment portraying a higher risk of resistance).[6] Risk factors should be considered when using empirical treatment guidelines (**Box 1**) and when they are present, urine culture should be considered before antibiotic start.

TREATMENT: RECOMMENDED DRUG AND COURSE

In choosing the best antimicrobial agent for uncomplicated cystitis, prescribers must take into account a patient's treatment history, allergies or intolerances, pregnancy or breastfeeding status, insurance coverage, and drug interactions. Because side effects vary by agent, these should be taken into account as applicable. Please see **Table 3**.

Nitrofurantoin

Nitrofurantoin is an inactive antiseptic that is largely activated in the urine by microbes. It is produced in 3 formulations that vary by crystal preparation. The smaller crystalline form of nitrofurantoin (Furadatin), is rapidly absorbed, leading to gastrointestinal (GI) upset, and thus it is rarely used.[33] Macrocrystalline nitrofurantoin (Macrodantin), a larger molecule, is more slowly absorbed. The third formulation, monohydrate macrocrystals, also known as modified-release nitrofurantoin (Macrobid), is composed of

Box 1
Risk factors for UTI caused by a resistant organism

Risk Factors for Antimicrobial Resistance

- Age older than 60 years
- Previous history of UTI
- Chronic medical conditions
- Recent hospitalization
- Any recent antibiotic treatment
- Recent travel abroad

Table 3
Commonly used antimicrobial agents and regimens

Drug	Dosing	Side Effects	Other Considerations	Pregnancy Class	Breastfeeding American Academy of Pediatrics[47]/LactMed[39]	Price
Nitrofurantoin	100 mg by mouth twice a day × 5 d	Nausea, vomiting, diarrhea, hypersensitivity reactions including hepatitis	Rare cases of pulmonary fibrosis in long term use	B[a,b]	Hemolysis with glucose-6-phosphate dehydrogenase (G-6PD)-deficient infant/avoid <1 mo old or G-6PD-deficient	100-mg tablets, 20, $70
Trimethoprim-sulfamethoxazole	1 double strength tablet by mouth twice a day × 3 d	Nausea, vomiting, rash including Stevens-Johnson-syndrome in rare cases	Increased bleeding risk with warfarin. Risk of hyperkalemia with low glomerular filtration rate or when combined with angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, aldosterone antagonist. Multiple drug interactions	C[b]	None reported/avoid in ill or premature infants	800-mg to 160-mg tablets, 20, $4
Fosfomycin	3 g by mouth × 1	Nausea, diarrhea, vaginitis	After treatment improvement in symptoms over a few days should be expected	B	Not applicable/limited data, avoid <2 mo old	3-g tablet, 1, $80
Ciprofloxacin	250 mg by mouth twice a day × 3 d	Nausea, vomiting, headache	Risk of *Clostridium difficile* colitis and tendon rupture in those using corticosteroids	C	None reported/little risk	500-mg tablets, 100, $4 1000-mg XL tablets, 50, $465[c]

[a] Contraindicated at term.
[b] American College of Obstetricians and Gynecologists recommends using during first trimester only if no other options.[36]
[c] Prices estimated at http://www.target.com, http://www.walmart.com, and http://www.drugstore.com.

approximately 75% nitrofurantoin monohydrate and 25% macrocrystal, which produce a slow-release preparation by forming a gel matrix in the stomach.[34] The bioavailability is increased when taken with food.[34]

As a result of brisk renal excretion, blood levels rarely reach a therapeutic level, thus reducing effectiveness and making this drug not suitable in pyelonephritis, perinephric abscess, or prostatitis. The rate of clearance is proportional to the creatinine clearance, and dose adjustments are necessary with renal impairment.[35] The urinary excretion of modified-release nitrofurantoin is similar to that of macrocrystalline nitrufurantoin.[34]

The most common adverse effects of using nitrofurantoin are GI in origin, including nausea, vomiting, and diarrhea[35]; the macrocrystalline preparations are better tolerated.[33,35] Nitrofurantoin may color the urine brown. Less common side effects include several hypersensitivity reactions characterized by chills, fever, blood cell dyscrasias, and hepatitis, all of which are treated by discontinuation of the drug. Nerve effects have been reported, with neuropathies being most common in patients with chronic kidney disease. Acute pneumonitis is reported as a rare effect also treated by drug removal.[35]

Chronic nitrofurantoin pulmonary toxicity rates are difficult to estimate but are believed to be rare. For example, chronic lung reactions related to nitrofurantoin were 2.0%, 5.3%, and 3.4% of all adverse reactions reported in the United Kingdom, Sweden, and Holland, respectively, over approximately 3 decades.[36] In a Mayo Clinic retrospective review of cases believed to be secondary to nitrofurantoin, most subjects were women (94%), older (median age of 72 years), and patients who had received a prolonged preventative dosing exposure (median interval of 23 months).[37]

Nitrofurantoin has been associated with a variety of fetal malformations when used in the first trimester. The American College of Obstetricians and Gynecologists recommends using a different agent during this time if an alternative is available.[38] It is also recommended to avoid nitrofurantoin use between 38 weeks' gestation and delivery because of the possibility of hemolytic anemia.[34] Data are limited, but use seems safe for breastfeeding infants older than 1 month and without glucose-6-phosphate dehydrogenase deficiency.[39]

Nitrofurantoin has few drug interactions, probably because of reliance on microbial activation. However, an alternative therapy should be considered when fluconazole is used, because of reports of hepatic and pulmonary toxicity.[40] Antacids containing magnesium may also reduce absorption and subsequent urinary secretion.[34]

Microbes rarely produce new resistance to nitrofurantoin, making this an excellent choice when considering emerging resistance. However, the less common *Proteus*, *Pseudomonas, Enterobacter*, and *Klebsiella* species are usually inherently resistant.[35]

The efficacy of nitrofurantoin compared with other antimicrobials has been studied. When compared with 3 days of low-dose ciprofloxacin, ciprofloxacin showed higher bladder eradication rates but similar rates of clinical resolution.[41] No difference in outcomes was found when a 5-day course of nitrofurantoin was compared with a 7-day course of trimethoprim-sulfamethoxazole.[42]

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole (cotrimoxazole, Bactrim, Septra) was first introduced as a combination drug in the 1970s. It inhibits bacterial production of folate at 2 separate steps, causing a bacteriostatic effect. Trimethoprim-sulfamethoxazole is readily absorbed from the GI tract, has a half-life of approximately 10 hours, and is renally excreted between 25% and 60% in the first 24 hours.[35]

Adverse effects of trimethoprim-sulfamethoxazole are variable, but most commonly include GI upset and rash, which vary from transient eruptions to fixed drug reactions to catastrophic exfoliative syndromes (Stevens-Johnson syndrome and toxic epidermal necrolysis). Trimethoprim-sulfamethoxazole can cause a variety of anemias, some related to folate deficiency, as well as thrombocytopenia and rarely methemoglobinemia.[35]

Hyperkalemia may be a concern when prescribing trimethoprim-sulfamethoxazole. It is caused by a reduction in potassium elimination from the distal nephron and is potentiated by reduction in glomerular filtration rate, concomitant use of angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, or aldosterone blockers.[43] Elderly individuals are at greatest risk for hyperkalemia caused by trimethoprim-sulfamethoxazole. Severe hyperkalemia (>5.5 mmol/L) was found in 21% of treated hospitalized patients,[44] but less often in a prospective controlled trial of outpatients, among whom only 6% developed severe hyperkalemia after a 5-day course.[45]

Trimethoprim-sulfamethoxazole deserves special mention with regards to drug interactions. Both components inhibit separate P450 enzymes, leading to multiple interactions. The drug inhibits warfarin metabolism and is associated with a 3-fold higher risk of GI bleeding when used in combination with warfarin compared with use of other antibiotics.[46] Other interactions include sulfonylureas (hypoglycemia),[35,43] methotrexate (pancytopenia), and anticonvulsants (toxicity).[35]

When used in the first trimester of pregnancy, trimethoprim-sulfamethoxazole has been shown to be associated with rare cases of neural tube, cardiovascular, and possibly oral cleft palate and urinary system defects. After 32 weeks' gestation, a theoretic risk of fetal kernicterus exists and so the drug should be avoided if possible.[43] It seems to be safe during breastfeeding.[43,47]

Resistance mechanisms can occur by chromosomal mutation and selection but are largely based on plasmids, likely leading to the known distinct regional resistance patterns.[35] For example, in the ECO-SENS study evaluating European *E coli* resistance, trimethoprim-sulfamethoxazole resistance was found in 26.7% of uncomplicated UTIs in Portugal but only in 9.5% in Austria.[4]

Trials comparing trimethoprim-sulfamethoxazole with other antimicrobials for UTI treatment have shown similar efficacy to nitrofurantoin,[41] ciprofloxacin,[41] and fosfomycin.[48]

Fosfomycin

Fosfomycin is an inhibitor of cell wall synthesis, structurally unrelated to any other antibiotic,[49] and is active against most urinary tract pathogens.[21] It is approximately 40% bioavailable with a 4-hour half-life. The active drug is renally excreted, with excellent urinary concentrations, exceeding most MICs for pathogens.[49,50]

Fosfomycin is approved for a single 3-g dose in uncomplicated UTI.[49,51] With such dosing, no dose adjustment is needed for patients with renal or hepatic dysfunction.[52] Side effects of single 3-g dosing are typically mild and resolve within 1 to 2 days, and include diarrhea, nausea, abdominal pain, headache, dizziness, and vaginitis.[51] In a review of more than 800 patients,[53] side effects occurred in only 6.1% of patients and none was considered severe. Patients should be counseled that urinary symptoms slowly improve over 2 to 3 days, even after a single dose, and that this is not necessarily a sign of failure.[54]

Drug interactions are few, but include balsalazide and metoclopramide, the latter of which when used with fosfomycin may decrease fosfomycin serum and urinary concentrations.[52]

Fosfomycin is safe in pregnancy.[49] The drug is likely excreted in low levels in breast milk, but limited data suggest safety with breastfeeding.[39]

Resistance to fosfomycin is rare,[54] but when present, it is caused by decreased drug transport into the bacterium[50] and enzymatic modification of the drug.[52] Furthermore, many species resistant to other antibiotics, including ESBL-producing *E coli*, are susceptible to fosfomycin.[55]

Single-dose fosfomycin has been compared with a 7-day course of nitrofurantoin and a 5-day course of trimethoprim-sulfamethoxazole. Clinical efficacy was similar between trimethoprim-sulfamethoxazole and single-dose fosfomycin.[48] When fosfomycin was compared with nitrofurantoin, rates of clinical cure (resolution of symptoms) were similar for both treatments. Despite similar early clinical response rates, the microbiological cure rates (resolution of bacteriuria) at the first follow-up visit were lower for fosfomycin (78%) than nitrofurantoin (86%).[56] The drug costs about $80 for treatment course, which is more expensive than the other first-line agents (trimethoprim-sulfamethoxazole and nitrofurantoin). It is also not so easily available, because many pharmacy chains do not carry it.

Fluoroquinolones

Ciprofloxacin and levofloxacin, both fluorinated quinolones, are commonly (and often inappropriately) used for empirical UTI treatment.[10] The bactericidal effects of the drugs come from targeting DNA gyrase and topoisomerase IV.[35] Fluoroquinolones are well absorbed orally, have a half-life of about 4 hours, and are time-dependent and concentration-dependent agents.[35] Given this pharmacokinetic picture, once-daily extended release formations of ciprofloxacin have been found to be equally efficacious to twice-daily[57] dosing, but at a increased price. Ciprofloxacin is largely renally excreted and can lead to increased urinary concentrations.[35]

Side effects are most commonly GI in origin, with up to 17% of patients having nausea or other form of discomfort. Of the fluoroquinolones, ciprofloxacin is the most likely to cause *Clostridium difficile* colitis. Other common side effects include those of the central nervous system (mild headache to rarely seizure, usually when used with theophylline or nonsteroidal antiinflammatory drugs) and rash. Corrected QT interval (QTc) prolongation is usually associated with other drugs in the same class,[35] but should probably be avoided in patients using other prolonging agents or with a history of QTc disorder.

Fluoroquinolones have long been known to cause tendon rupture. However, this effect is rare. In a case control study,[58] it occurred in approximately 3.2 cases per 1000 and only in patients older than 60 years. Use of corticosteroids was found to be a risk factor for rupture. It is advisable to counsel all patients regarding this risk and to ask them to discontinue treatment and contact their physician with any unexpected tendon or joint pain, especially at the Achilles tendon. Ciprofloxacin is contraindicated in pregnancy because of the risk of fetal arthropathy.[35,59] A review performed by the American Academy of Pediatrics found no evidence for adverse outcome with breastfeeding.[47]

The main drug interaction to recall is that ciprofloxacin can lead to an increase in theophylline levels and subsequent toxicity.[35] It can also lead to increases in international normalized ratio in patients on warfarin.

Resistance to fluoroquinolones occurs secondary to changes in the drug target or to increased drug efflux.[35] Resistance may be mediated by acquisition of genes via plasmids.[59] The increase in fluoroquinolone resistance in *E coli* has occurred at an alarming rate in relation to increased prescribing practices. For example, in the Denver Health System, when the preferred antibiotic for UTI was changed from

trimethoprim-sulfamethoxazole to levofloxacin because of baseline trimethoprim-sulfamethoxazole resistance, the rate of levofloxacin-resistant isolates increased from 1% to 9% in 6 years.[8]

OTHER ANTIBIOTICS

Cefpodoxime has been used for treatment of UTI, given its tolerability and twice-daily dosing. However, cefpodoxime has been found to be inferior to ciprofloxacin[60] and equivalent to trimethoprim-sulfamethoxazole in a study with limited power,[61] questioning overall efficacy. Amoxicillin-clavulanate was compared with ciprofloxacin and found to be inferior, even in cases in which strains were sensitive to amoxicillin-clavulanate. As recommended by the IDSA guidelines, β-lactams should be avoided if possible to avoid resistance and reduce collateral damage.[7]

ORAL CONTRACEPTIVES AND ANTIBIOTICS

Patients with UTI are often women of childbearing age, many of whom rely on oral contraceptive pills (OCPs) for birth control, and so the question of antibiotic interactions with OCPs should be addressed openly. Although more than 200 articles have been published on this question, it is difficult to establish a firm interaction in most cases. Although certain antibiotics that heavily inhibit cytochrome 3A4 (in particular, rifampin) may be expected to increase OCP metabolism, these drugs are virtually never used for UTI. However, based on the serious nature of the consequences, and in light of some continued uncertainty, it is customary to counsel patients to consider using an alternative method of birth control in addition to continuing OCPs until 1 menstrual cycle has completed after antibiotic treatment.[62,63]

PREVENTION AND OTHER CONSIDERATIONS

Another patient recalls that she has had 3 UTIs in the last 12 months and asks about preventative methods, including continuous antibiotics, cranberry juice, and probiotics.

Recurrent UTIs

An estimated 26.6% of women with initial UTI have a recurrence within 6 months.[64] Women with a history of recurrent UTI have an average of 2.6 episodes per patient-year (varying from 0.3–7.6 episodes).[65] Recurrent episodes seem to cluster in time, with the highest risk of recurrence immediately after a previous event.[65]

At first diagnosis, hematuria and urgency may be strong predictors of recurrent UTI.[64] These investigators propose that this finding may indicate that the initial causal bacterium was particularly virulent. Compared with other organisms, when *E coli* caused a first UTI, recurrence was more likely.[66]

Risks for recurrent UTI are similar to those of first UTI. These risks include recent sexual intercourse,[66–68] new sexual partner,[67] and use of diaphragm, cervical cap, or spermicide.[66,69] Other risk factors include age younger than 15 years at the time of first UTI,[67] mother or family with history of UTI,[67,70] and history of previous UTI.[68,71]

Anatomic factors have been implicated. Women with a shorter urethra-anus distance have more frequent UTIs compared with those with longer measurements.[72] Studies have also looked at individual genetic variables, including Lewis blood group[73] and toll-like receptor polymorphisms[74] for further understanding of recurrent UTI susceptibility. These factors remain unproved and are not modifiable.

Behavior and Habits

Evidence of the relationship between habits and recurrent UTI is limited. Habits not associated with a change in recurrence rates include voiding after sexual intercourse,[64,67] delayed voiding,[67,68] wiping patterns, douching, use of hot tubs, or pantyhose.[67] Caution should be exercised when interpreting these data, because in such small trials, a small effect may not be realized until larger studies are performed.

Mode of Contraception

Contraception method is related to acquisition of UTI. Recent condom use, both lubricated and nonlubricated, with or without spermicidal cream or gel, was found to strongly increase the risk of a first and recurrent UTI.[75,76] Diaphragm use is also highly associated with both first and recurrent UTI.[3,66,68]

Spermicide

Spermicide use is associated with increased frequency of first and recurrent UTI.[67,75] Nonoxynol-9, the most commonly used spermicide, is toxic to lactobacilli, and in particular hydrogen peroxide (H_2O_2)-producing lactobacilli including *Lactobacillus crispatus*.[77] The toxic effect to lactobacilli is greater than its toxic effect to *E coli*[77] and may enhance *E coli* attachment to urogenital epithelial cells,[78] with spermicide users more likely to be colonized with *E coli* than nonusers.[79] Unless there are no other options, spermicides should be avoided.

Probiotics

The use of probiotics has become popular in the age of increasing antimicrobial use and resistance; however, no probiotic agent has been approved for therapeutic use by the FDA.[80] *Lactobacillus* has been shown to be safe in studies of generally immunocompetent hosts.[81] Evidence for the use of probiotics is diverse and inconsistent, but the proposed mechanisms for prevention of urogenital infection by probiotics include modulating host immunity, preventing adherence of pathogenic organisms to the urogenital epithelium,[82] and modulating growth/colonization of these pathogens.[81] When comparing patients with recurrent UTI with those without UTIs, patients with recurrent UTIs were less likely to be colonized with H_2O_2-producing strains of lactobacilli and more likely to have *E coli* introital colonization, even when controlling for use of spermicide.[83] However, in a 2008 review that evaluated 4 studies looking at the efficacy of *Lactobacillus* for prevention of UTI, only 1 study reported a positive effect (reduction in rate of recurrent UTI), but many were underpowered and used a variety of *Lactobacillus* strains, including those not shown to produce H_2O_2.[84] Most recently, Lactin-V, a product containing an H_2O_2-producing strain of *Lactobacillus crispatus*, was evaluated in a phase 2 clinical study.[85] When used vaginally once per week after antibiotic treatment of UTI, a relative risk reduction of 50% (95% confidence interval, 0.2–1.2) was shown, but the study included only 100 participants, and was likely underpowered to see a statistically significant benefit. In a randomized trial comparing low-H_2O_2-producing *Lactobacillus* and trimethoprim-sulfamethoxazole prophylaxis, the *Lactobacillus* was shown to be inferior to trimethoprim-sulfamethoxazole.[86] Until further evidence is available in larger, randomized trials, using *L crispatus*, probiotics cannot be conclusively recommended. However, they are unlikely to be harmful and may provide benefit to individual patients.

Cranberries

Cranberries are often used for UTI treatment and prevention. Cranberry extract has been shown both ex vivo and in vivo to interfere with *E coli* adherence to the

uroepithelium.[87] Many trials have studied the use of cranberry in various forms and concentrations, but with mixed results. A 2012 Cochrane review, limited because of article diversity, calculated a risk reduction of 0.62, with women, children, and consumers of cranberry juice having the most observed benefit.[88] Most recently, a randomized controlled trial comparing cranberry juice and placebo found no difference in time to UTI; however, this study did note reduction of infections with P-fimbriated *E coli* strains in the cranberry group.[89] Cranberry has been shown to be inferior when compared with trimethoprim-sulfamethoxazole for prophylaxis.[90] Results are discouraging, although patients may safely choose to try cranberry; those who cannot tolerate the sugar and acidity of juice might try extract capsules instead, although again the supporting evidence has been underwhelming.

Urinary Additives

Methenamine salts are proposed to prevent UTI by producing formaldehyde from hexamine, leading to urinary acidification, and thus making the bladder more hostile to microbial invasion. Few large trials have evaluated the efficacy of these additives. The salts come in 2 forms: methenamine hippurate and methanamine mandelate; the latter is not widely available. Typically well tolerated, methenamine salts were examined by a Cochrane review in 2012. With great study heterogeneity, subgroup analysis showed a relative risk (RR) of 0.24 when used by patients without renal tract abnormalities, a finding not shown in patients with such abnormalities. Furthermore, treatment duration of 1 week showed an RR of recurrent UTI of 0.14.[91] These medications are generally well tolerated, although some women discontinued use because of a sensation of urethral burning caused by chemical irritation.

Estrogen for Postmenopausal Women

After menopause, women are believed to lose the UTI-protective benefits of estrogen, with resultant increases in vaginal pH[92] and decrease in introital *Lactobacillus* colonization,[93] among other effects. Investigations of estrogens to prevent recurrent UTI have varied by dose, route (oral vs vaginal), and control group (placebo vs antimicrobial). In a 2008 Cochrane review, oral estrogen replacement was not found to reduce recurrent UTI, whereas vaginal estrogens showed a reduced risk (RR of 0.25 and 0.64 in 2 trials). Studies comparing estrogen replacement with prophylactic antibiotics were again heterogeneous in design and showed conflicting results.[94] Topical estrogen treatment could be considered in motivated, postmenopausal women with recurrent UTIs, especially when the risk of prophylactic antibiotic use is high.

Evaluation of Recurrent UTIs

The purpose of recurrent UTI workup is to evaluate and eliminate any cause that might predispose the patient to morbidity related to recurrent UTIs. The workup should start with a thorough history, including possible predisposing factors, such as temporal relationship to intercourse and method of contraception. Symptoms such as vaginal discharge or odor may point toward an alternative diagnosis. The physical examination should focus on vaginal and urethral disease, and in particular uterine or rectal prolapse.[95] Residual urinary volume should be measured with either bladder ultrasonography or catheterization to rule out retention (**Fig. 2**).[96]

After these tests are completed, imaging may be considered, although in many cases, it yields no information to change management. Cystoscopic or radiologic evaluation should be considered in patients with complicated, persistent, or febrile infections.[95] Patients without fever, flank pain, or hematuria can usually be managed without imaging.[96] In a prospective study of 100 patients referred for urologic work

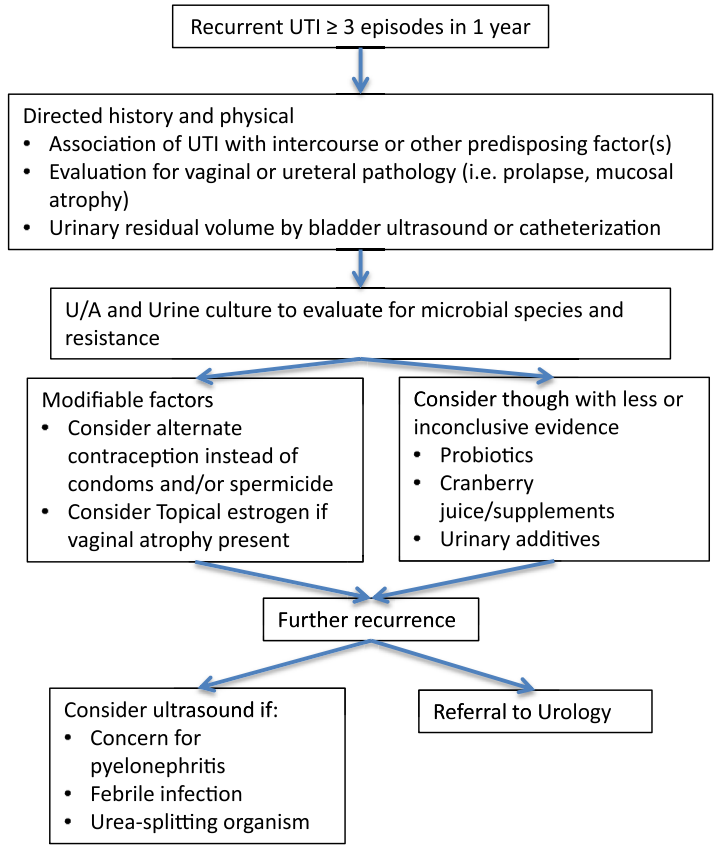

Fig. 2. Recommended management of women with recurrent cystitis.

up in the setting of UTI, the usefulness of imaging and subsequent findings was evaluated. Abdominal radiographs were performed in all 100 patients without an abnormal finding in any case. Renal ultrasonography was performed in 90 cases, with 5 abnormalities found, and in 16 intravenous urograms, 2 were abnormal. In total, 6 abnormalities were found, but only 1 was considered related to recurrent UTIs.[97] Those with pyelonephritis caused by urea-splitting organisms such as *Proteus vulgaris* should be considered for ultrasonography or plain radiography to rule out nephrolithiasis, because of the association between these bacteria and struvite calculi.[96]

Cystoscopy has been used in the evaluation of recurrent UTI to evaluate for structural abnormalities not found with imaging, such as urethral stricture, bladder calculus, or colovesicual fistula. In a study of 118 patients with recurrent UTI undergoing cystoscopy, all of whom had some form of previous imaging, only 8% of the women had a significant abnormality detected radiographically. Most of these abnormalities were in women older than 50 years. Furthermore, negative imaging before cystoscopy carried a negative predictive value of 99% for finding an abnormality.[98] Given these findings, in women without risk factors for structural abnormalities and with negative imaging, cystoscopy can usually be deferred. Furthermore, given the association of

abnormal findings with age, it is likely not necessary to evaluate women younger than 40 years with cystoscopy.[97,98]

Antibiotic Prevention

When conservative, nonantimicrobial measures fail to prevent recurrent UTI, antibiotics are relied on. In a recent Cochrane review,[99] the effectiveness, safety and administration schemes of antibiotic prophylaxis were reviewed. This database defined recurrent UTI as 3 or more episodes within 1 year or 2 or more episodes within 6 months. Antibiotic prophylaxis prevented recurrence after treated UTIs with an RR of 0.21 and a number needed to treat to prevent 1 recurrence of 1.85. As expected, the rate of side effects was higher in the treatment group (RR 1.58 for severe side effects), with high dropout overall (exceeding 20% in some studies). Dropout was highest amongst the nitrofurantoin groups. After prophylaxis was discontinued, the protective effect was no longer evident. However, the investigators were unable to pose a best antibiotic, duration, or other mode because of the heterogeneity of the studies.

Prophylactic regimens are used in many schedules, including daily, weekly, monthly, and postcoital. With the pressure of antibiotic resistance, regimens with limited duration offer the benefit of less exposure. Postcoital administration of trimethoprim-sulfamethoxazole was more effective than placebo at preventing UTI (0.3 events per patient-year compared with 3.6 events per patient-year), although this was a small study,[100] and postcoital ciprofloxacin showed similar efficacy compared with daily administration in another study.[101]

Patient-initiated regimens have also been studied. In a randomized trial in 2011,[102] patients were randomized to continuous prophylaxis or patient-initiated treatment. The patient-initiated arm was instructed to take a single dose after an event known to be associated with recurrence in the individual's circumstance (eg, intercourse, delayed micturition, diarrhea). Groups had similar efficacy but fewer side effects in the patient-initiated arm (9.1%) compared with the continuous group (30%). Limitations of this study included inclusion of only postmenopausal women and a rotation of the continuous antibiotic every 2 to 4 weeks. Because recurrence is known to cluster near the time of initial UTI,[64,65] duration of prophylaxis might continue for 6 to 12 months, regardless of the method chosen.[99]

SUMMARY

In the era of increasing microbial resistance, caution should be taken when prescribing both for the individual patient's risk of resistant infection and for reducing community antimicrobial resistance. Practice guidelines have been shown to reduce cost and increase the rate of appropriate antibiotic use. Antibiotics with less potential for promoting resistance (nitrofurantoin, fosfomycin) should be used preferentially. Trimethoprim-sulfamethoxazole remains an important first-line agent in most settings. Fluoroquinolones and broad-spectrum antibiotics should be reserved as second-line agents. Some host factors may be modified to reduce risk of recurrence. Prophylactic antibiotics should be minimized and (if needed) used in a patient-initiated scheme.

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